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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
June 26-27, 2019
Atlanta, Georgia

Final - June 17, 2019

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Centers for Disease Control and Prevention

1600 Clifton Road, NE, Tom Harkin Global Communications Center, Kent "Oz" Nelson Auditorium

Atlanta, Georgia 30329

June 26-27, 2019

	AGENDA ITEM	PRESIDER/PRESENTER(s)
Wednesday, June 26		
8:00	**Welcome & Introductions**	Dr. José Romero (ACIP Chair) Dr. Amanda Cohn (ACIP Executive Secretary, CDC)
8:30	**Human Papillomavirus Vaccines**	
	Introduction	Dr. Peter Szilagyi (ACIP, WG Chair)
	Background	Dr. Lauri Markowitz (CDC/NCIRD)
	9vHPV Immunogenicity and Safety Trial in Mid-Adult Females	Dr. Alain Luxembourg (Merck & Co.)
	Overview of Health Economic Models for HPV Vaccination of Mid-Adults	Dr. Harrell Chesson (CDC/NCHHSTP)
	Evidence to Recommendations (EtR) Framework	Dr. Elissa Meites (CDC/NCIRD)
	Work Group Considerations and Proposed Policy Options	Dr. Lauri Markowitz (CDC/NCIRD)
10:00	***Break***	
10:15	**Pneumococcal Vaccines**	
	Introduction	Dr. Grace Lee (ACIP, WG Chair)
	Considerations for PCV13 use among adults 65 years or older and summary of the Evidence to Recommendations (EtR) Framework	Dr. Almea Matanock (CDC/NCIRD)
	Proposed policy options	Dr. Almea Matanock (CDC/NCIRD)
11:45	***Lunch***	
1:00	**Combination Vaccines**	
	Introduction	Dr. Kelly Moore (ACIP, WG Chair)
	Summary and Relevant Evidence to Recommendation Information	Dr. Sara Oliver (CDC/NCIRD)
1:30	**Public Comment**	
2:10	***Break***	
2:25	**VOTES**	
	Human Papillomavirus	Dr. Lauri Markowitz (CDC/NCIRD)
	Pneumococcal Vaccines	Dr. Almea Matanock (CDC/NCIRD)
	VFC VOTES	
	Diphtheria, Tetanus, & Pertussis	Mr. Frank Whitlatch (CDC/NCIRD)
	Haemophilus influenzae type b	
	Hepatitis B	
	Polio	
3:25	***Break***	
3:40	**Measles Update**	TBD
3:55	**Zoster Vaccines**	
	Introduction	Dr. Kelly Moore (ACIP, WG Chair)
	Update: Safety Monitoring and Surveillance for Recombinant Zoster Vaccine (RZV)	Dr. Tom Shimabukuro (CDC/NCEZID)
	Herpes Zoster Work Group Summary	Dr. Kathleen Dooling (CDC/NCIRD)
4:30	**Pertussis Vaccines**	
	Introduction	Dr. Henry Bernstein (ACIP, WG Chair)
	EtR Framework, Work Group Considerations and Proposed Policy Options	Dr. Fiona Havers (CDC/NCIRD)
5:00	**Rabies Vaccine**	Dr. Sharon Frey (ACIP, WG Chair)
5:10	**Adjourn**	

Final - June 17, 2019

Thursday, June 27

8:00	**Unfinished Business and Agency Updates**	
	CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NIH, NVPO	
8:30	**Influenza Vaccines**	
	Introduction	Dr. Chip Walter (ACIP, WG Chair)
	2018-19 U.S. Influenza Activity	Ms. Lynette Brammer (CDC/NCIRD)
	2018-19 Influenza Vaccine Effectiveness	Dr. Brendan Flannery (CDC/NCIRD)
	2018-19 Influenza Vaccine Safety	Dr. Tom Shimabukuro (CDC/NCEZID)
	Proposed Recommendations for 2019-20	Dr. Lisa Grohskopf (CDC/NCIRD)
9:45	***Break***	
10:00	**Hepatitis A Vaccines**	
	Introduction	Dr. Kelly Moore (ACIP, WG Chair)
	Proposed Recommendations for Use of Hepatitis A	Dr. Noele Nelson (CDC/NCHHSTP)
11:15	***Break***	
11:30	**Meningococcal Vaccines**	
	Introduction	Dr. David Stephens (ACIP, WG Chair)
	Review of Immunogenicity and persistence data, GRADE, EtR, and policy options for MenB booster doses	Dr. Sarah Mbaeyi (CDC/NCIRD)
	Proposed recommendations for use of meningococcal vaccines	Dr. Sarah Mbaeyi (CDC/NCIRD)
12:30	***Lunch***	
1:30	**Public Comment**	
2:10	**VOTES & VFC VOTES**	
	Influenza Vaccines	Dr. Lisa Grohskopf (CDC/NCIRD)
	Influenza VFC	Mr. Frank Whitlatch (CDC/NCIRD)
	Hepatitis A Vaccines	Dr. Noele Nelson (CDC/NCHHSTP)
	Hepatitis A	Mr. Frank Whitlatch (CDC/NCIRD)
	Meningococcal Vaccines	Dr. Sarah Mbaeyi (CDC/NCIRD)
	Meningococcal VFC	Mr. Frank Whitlatch (CDC/NCIRD)
2:55	***Break***	
3:10	**Dengue Vaccine**	
	Introduction	Dr. Robert Atmar (ACIP, WG Chair)
	Dengue Epidemiology in the U.S.	Dr. Gabriela Paz-Bailey (CDC, NCEZID)
	Dengvaxia Phase III Clinical Trials and Long Term Follow Up	Dr. Gustavo Dayan (Sanofi Pasteur)
	Work Group Considerations and Next Steps	Dr. Steve Waterman (CDC, NCEZID)
4:10	**Adjourn**	

Acronyms

AI/AN	American Indian/Alaska Native
AVA	Anthrax vaccine absorbed
CDC	Centers for Disease Control & Prevention
CMS	Centers for Medicare and Medicaid Services
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
Hib	*Haemophilus influenzae* type b
HRSA	Health Resources and Services Administration
IHS	Indian Health Service
MenB	Serogroup B meningococcal vaccine
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]
NVPO	National Vaccine Program Office
PCV13	13-valent pneumococcal conjugate vaccine
RZV	Recombinant zoster vaccine
WG	Work Group

Acronyms

9vHPV	9-valent HPV
AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core Surveillance
ACA	Affordable Care Act
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
ADE	Antibody-Dependent Enhancement
ADEM	Acute Disseminated Encephalomyelitis
ADVISE	Agent-based Dynamic model for Vaccination and Screening Evaluation
AE	Adverse Event
AFHSB	Armed Forces Health Surveillance Branch
AFIX	Assessment, Feedback, Incentive and eXchange of information
AGW	Anogenital Warts
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
ALTS	Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study
Anti-HAV	Serum Antibody to Hepatitis A Virus
Anti-HBsAg	Hepatitis B Surface Antigen
Anti-PA IgG	Anti-Protective Antigen Immunoglobulin G
AOA	American Osteopathic Association
APhA	American Pharmacists Association
APN	Advanced Practice Nurse
APRN	Advanced Practice Registered Nurse
aQIV	Adjuvanted Quadrivalent Influenza vaccine
ARFI	Acute Respiratory or Febrile Illness
ARI	Acute Respiratory Illness
ASTHO	Association of State and Territorial Health Officers
ATS	American Thoracic Society
BLA	Biologics License Application
BMI	Body Mass Index
CAP	Community-Acquired Pneumonia
CAPiTA	Community-Acquired Pneumonia Immunization Trial in Adults
CDC	Centers for Disease Control and Prevention
CDSi	Clinical Decision Support for Immunization
CER	Cost-Effectiveness Ratio
CFR	Case Fatality Ratio
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CIN	Cervical Intraepithelial Neoplasia
CISA	Clinical Immunization Safety Assessment
CISNET	Cancer Intervention and Surveillance Modeling Network
CLD	Chronic Liver Disease

CLIA	Clinical Laboratory Improvement Amendments
CMS	Center for Medicare and Medicaid Services
COI	Conflict of Interest
COID	Committee on Infectious Diseases (AAP)
COPD	Chronic Obstructive Pulmonary Disease
CSTE	Council of State and Territorial Epidemiologists
DC	District of Columbia
DENV	Dengue Virus
DFO	Designated Federal Official
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DSTDP	Division of STD Prevention
DTaP	Diphtheria and Tetanus Toxoid and Pertussis
DVA	Department of Veterans Affairs
DVD	Division of Viral Diseases
EB	Empirical Bayesian
ED	Emergency Department
EGL	External Genital Lesions
EHR	Electronic Health Record
EIS	Epidemic Intelligence Service
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EMR	Electronic Medical Record
EtR	Evidence to Recommendation
EU	European Union
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FFS	Medicare Fee-For-Service
FHA	Filamentous Hemagglutinin
FQHC	Federally Qualified Health Center
GBS	Guillain-Barré Syndrome
GCC	(Tom Harkin) Global Communications Center
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HAIVEN	Hospitalized Adult Influenza Vaccine Effectiveness Network
HAN	Health Alert Network
HAV	Hepatitis A Virus
HBIG	Hepatitis B Immune Globulin
HCAP	Healthcare-Associated Pneumonia
HCUP	Healthcare Cost and Utilization Project
HCP	Healthcare Personnel / Providers
HCW	Healthcare Workers
HepA	Hepatitis A
HepB	Hepatitis B
HHS	(Department of) Health and Human Services
HI	Hemagglutinin Inhibition

Hib	Haemophilus Influenzae Type B
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HPV-IMPACT	HPV Vaccine Impact Monitoring Project
HRSA	Health Resources and Services Administration
hSBA	Human Serum Bactericidal Activity
HZ	Herpes Zoster
ICD	International Classification of Diseases
IDCRP	Infectious Disease Clinical Research Program
ICER	Incremental Cost-Effectiveness Ratio
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IDSA	Infectious Disease Society of America
Ig	Immunoglobulin
IHB	Immunization Healthcare Branch
IHS	Indian Health Service
IIS	Immunization Information Systems
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
ILINet	Influenza-like Illness Surveillance Network
IM	Intramuscular
IND	Investigational New Drug
IOM	Institute of Medicine
IPD	Invasive Pneumococcal Disease
IPV	Inactivated Poliovirus
IRB	Institutional Review Board
ISD	Immunization Services Division
ISO	Immunization Safety Office
ITT	Intention-To-Treat
IV	Intravenously
IVE	Influenza Vaccine Effectiveness
IVIG	Intravenous Immunoglobulin
JE	Japanese Encephalitis
LTFU	Long-Term Follow-Up
MAM	Mid-Adult Men Study
MedDRA	Medical Dictionary for Regulatory Activities
MenB	Meningococcal B
MMP	Medical Monitoring Project
MMWR	*Morbidity and Mortality Weekly Report*
MSM	Men Who Have Sex With Men
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization Canada
NAP	National Action Plan
NAPNAP	National Association of Pediatric Nurse Practitioners
NBPP	Non-Bacteremic Pneumococcal Pneumonia
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

NCI	National Cancer Institute
NCIRD	National Center for Immunization and Respiratory Diseases
NDCs	National Drug Codes
NEJM	*New England Journal of Medicine*
NFID	National Foundation for Infectious Diseases
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHRC	Naval Health Research Center
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIP	National Immunization Program
NIPP	Non-Bacteremic Pneumococcal Pneumonia
NIS-Child	National Immunization Survey-Child
NIS-Teen	National Immunization Survey-Teen
NNDSS	National Notifiable Diseases Surveillance System
NNV	Number Needed to Vaccinate
NP	Nasopharyngeal
NPCR	National Program of Cancer Registries
NVSN	New Vaccine Surveillance Network
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
NVSN	New Vaccine Surveillance Network
NVT	Non-Vaccine Types
NYC	New York City
OASH	Office of the Assistant Secretary for Health
OB-GYN	Obstetrician-Gynecologist
OHAIDP	Office of HIV/AIDS and Infectious Disease Policy
OID	Office of Infectious Disease
OIDP	Office of Infectious Disease Policy and HIV/AIDS
OP	Oropharyngeal
PA	Protective Antigen
PCP	Primary Care Physician
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PEP	Post-Exposure Prophylaxis
PhRMA®	Pharmaceutical Research and Manufacturers of America®
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
PK	Pharmacokinetics
PPS	Philippine Pediatric Society
PPV	Positive Predictive Value
PrEP	Pre-Exposure Prophylaxis
PREVENT	Pregnancy Influenza Vaccine Effectiveness Network
PRNT	Plaque Reduction Neutralization Test
PRP	Polyribosyl Ribitol Phosphate
PRR	Proportional Reporting Ratio
PT	Preferred Terms (MedDRA)
PRDH	Puerto Rico Department of Health

PWHIV	Persons Living With HIV
PWID	People Who Inject Drugs
QALY	Quality-Adjusted Life-Year
QIV	Quadrivalent Influenza Vaccine
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RDT	Rapid Diagnostic Test
RIV	Recombinant Influenza Vaccine
RNA	Ribonucleic Acid
ROA	Route of Administration
RPMS	Resource and Patient Management System
RR	Relative Risk
rRT-PCR	Real-Time Reverse Transcription Polymerase Chain Reaction
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
RZV	Recombinant Zoster Vaccine
S. pneumoniae	*Streptococcus pneumoniae*
SAB	Spontaneous Abortion
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunization (WHO)
SAHM	Society for Adolescent Health and Medicine
SBA	Serum Bactericidal Assay
sBLA	Supplemental Biologics License Application
SC	Subcutaneous
SCC	Squamous Cell Carcinoma
SCRI	Self-Controlled Risk Interval
SDOH	Social Determinants of Health
SES	Socioeconomic Status
SGA	Small for Gestational Age
SIDS	Sudden Infant Death Syndrome
SLIPE	Sociedad Latinoamericana de Infectologia Pediatrica
SME	Subject Matter Expert
SNiPP	Surveillance for Non-invasive Pneumococcal Pneumonia
SNS	Strategic National Stockpile
SSUAD	Serotype-Specific Urinary Antigen Detection
STI	Sexually Transmitted Infections
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis
TECs	Tribal Epidemiology Centers
TIV	Trivalent Influenza Vaccine
TND	Test Negative Design
TPP	Target Product Profile
UK	United Kingdom
US	United States
USCS	United States Cancer Statistics
USAFSAM	Air Force School of Aerospace Medicine
US Flu VE	US Influenza Vaccine Effectiveness Network
USPHS	US Public Health Service
USU	Uniformed Services University
UTD	Up-To-Date

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
VLP	Virus-Like Particles
VRBPAC	Vaccine and Related Blood Products Advisory Committee
VRC	Vaccine Research Center
VSD	Vaccine Safety Datalink
VT	Vaccine Type
VT-CAP	Vaccine-Type Community-Acquired Pneumonia
WG	Work Group
WHO	World Health Organization
YF	Yellow Fever
ZVL	Zoster Vaccine Live

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

José Romero, MD, FAAP
ACIP Chair

Amanda Cohn, MD
Executive Secretary, ACIP / CDC

Dr. Romero called to order the June 2019 Advisory Committee on Immunization Practices (ACIP) and welcomed those present.

Dr. Cohn welcomed everyone to the June 2019 ACIP meeting. She indicated that the proceedings of this meeting would be accessible to people not in attendance via the World Wide Web, and welcomed those who could not attend the meeting in person. She pointed out that multiple Centers for Disease Prevention and Control (CDC) staff were present at the entrance to the room and at the desk outside the room to assist members of the public with questions.

She noted that handouts of the presentations were distributed to the voting ACIP members and were made available for others on the tables outside of the auditorium. Additionally, slides were made available through a ShareFile link for liaison and *ex-officio* members. Slides presented during this meeting will be posted on the ACIP website approximately three to four weeks after the meeting. The live webcast also will be posted in about four 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 2018 meeting were scheduled to be posted shortly after the June 2019 meeting.

To ensure the health and safety of all individuals attending this meeting, Dr. Cohn reviewed a few safety regulations. She explained that in the event of an emergency resulting in an evacuation, the procedures would be as follows:

- Those sitting in the back of the room behind the ropes were instructed to exit out the rear doors and across the bridge the way they came in.
- Those sitting in the front of room were instructed to exit through the rear of the room, turn left, then proceed right down the stairs.
- Everyone should locate the blue building marker sign labeled “Conference and Meeting Space—GCC, 2nd floor” and group together to ensure all attendees are accounted for.
- Once the premises have been secured and an “all clear” has been issued, participants would be permitted to re-enter the building and the meeting would resume.

The next ACIP meeting will be convened at CDC on Wednesday and Thursday, October 23-24, 2019. Registration for all meeting attendees is required and will open on the ACIP website when the *Federal Register* notice is posted. As a reminder, registration is now being limited so that all members who have registered for the meeting can participate in the meeting room. Registration will close when room capacity has been reached. Registration is not required for webcast viewing.

Dr. Cohn announced the following new and substitute Liaison Representatives:

- Jeffrey Duchin, MD will be a new Infectious Disease Society of America (IDSA) representative along with Carol Baker, MD and the two will be alternating meetings
- Clement Lewin PhD, MBA would be representing Pharmaceutical Research and Manufacturers of America® (PhRMA®) during this meeting
- Marcus Plescia, MD, MPH would be representing the Association of State and Territorial Health Officers (ASTHO) during this meeting

Dr. Romero observed that this was a bittersweet meeting for those on the committee because it was time to say goodbye to individuals with whom they have worked for the last 4 years. He recognized the following retiring ACIP members:


Dr. Echezona Ezeanolue

Dr. Ezeanolue, from the University of Nevada, has been with ACIP since 2015. He has served on the General Best Practices Work Group (WG) and Hepatitis WG. He was Dr. Romero's mentee during his first year. Dr. Ezeanolue said that it had been an honor for him as someone who did not grow up in this environment to see how policies are made in a way that allows science to trump politics. For him, serving on ACIP for the past 4 years has been a great learning experience.


Dr. Kelly Moore

Dr. Moore, from Vanderbilt University, is a rival for Art Reingold for the award for most Chairmanships on ACIP having served as chair on the Combination Vaccines, Hepatitis, Mumps, and Zoster WGs and as a member of the General Best Practices and Meningococcal WGs. Dr. Moore has tremendous experience in public health and has brought that perspective to ACIP. Dr. Moore said that she attended her first ACIP meeting in 2005 as a member of the audience and has not missed a meeting since. Serving as a liaison representing Association of Immunization Manager (AIM) for 5 years and the last 4 years as a voting member has been the best privilege of her professional life. She said that it has been a delight to get to know each of them, and emphasized that she always will be proud of the quality of the work they have done.

Dr. David Stephens

Dr. Stephens, from Emory University School of Medicine, has served as Chair of the Anthrax and Meningococcal WGs. While Dr. Stephens has a very quiet demeanor, he has had a very strong influence on the group bringing his thoughtful and measured perspective to topics ACIP has addressed. Dr. Stephens thanked ACIP and the members for the last 4 years, which he said was wonderful to be a part of. ACIP is comprised of a fine set of individuals and he appreciated the opportunity to have been a part of the group. He also thanked CDC and the ACIP leadership and said he looked forward to continuing to promote vaccines and vaccine policy.

Dr. Chip Walter

Dr. Walter, from Duke University School of Medicine, has served as Chair of the Influenza and Flavivirus WGs and as a member of the Dengue WG. The Influenza WG is one of the most complicated, has had to analyze a lot of data, and has had to make decisions based on very little data sometimes. Dr. Walter said that it has been a honor and a highlight of his professional career to have served as a member of ACIP for the past 4 years. He believes that ACIP does fantastic work evaluating all of the available information and trying to make the best recommendations for the use of vaccines for controlling vaccine-preventable diseases. He recognized that throughout the past 4 years, he has had the opportunity to work with incredible people from CDC who have provided information and resources to assist ACIP with its deliverables. Furthermore, he recognized the fantastic opportunity to have worked alongside of a number of talented and diverse ACIP members. He expressed his gratitude for having had this once in a lifetime experience.

Dr. Cohn noted that these 4 members began their ACIP experience at the same time that she started her experience in the role of Executive Secretary, so she felt like she “grew up” with them and appreciated their leadership and mentorship of her over the last 4 years. She presented each with a framed Dr. Seuss vaccine poster.

As stated in the ACIP charter, Dr. Cohn reminded everyone that the purpose of the ACIP committee is as follows:

- “Committee deliberations on the use of vaccines to control disease in the U.S. shall include consideration of disease epidemiology and burden of disease, vaccine efficacy and effectiveness, vaccine safety, the quality of evidence reviewed, economic analyses, and implementation issues.”

- "The committee may revise or withdraw their recommendations regarding a particular vaccine as new information on disease epidemiology, vaccine effectiveness or safety, economic consideration or other data become available."

- "Under provisions of the Affordable Care Act (ACA) . . . immunization recommendations of the committee that have been adopted by the Director of the CDC must be covered by applicable health plans"

Dr. Cohn indicated that to improve the clarity of ACIP's recommendations, recommendations based on clinical decision-making between the patient and provider will be referred to beginning with this meeting as "shared clinical decision-making" recommendations. This differs slightly from the previous phrasing of "individual clinical decision-making," but the intent is the same. "Shared clinical decision-making" is a better understood concept among clinicians and better describes that this is not a decision made by an individual, but instead is a decision made between two people for an individual.

ACIP is, at its heart, a public body. Engagement with the public and transparency in ACIP's processes is vital to the Committee's work. As part of ACIP's commitment to continuous improvement, ACIP recently 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. Dr. Cohn indicated that for this meeting, there would be oral public comment periods prior to the votes for each day. The oral public comment were scheduled to occur at 1:30 PM each day of the meeting.

To create a fairer and more 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. Dr. Cohn requested that the public comment speakers identified for this meeting sign in at the information table outside the main auditorium to confirm their presence.

For written public comments, ACIP is using a docket on regulations.gov where any member of the public can submit a written comment. This process allows for the ability to submit longer comments and the ability to include attachments, comments to be visible to the public, and a longer window for comment submission. Comments may now be submitted up to 48 hours following the end of the meeting, and all comments submitted by 72 hours of the meeting will be made available to the ACIP members prior to the meeting. At the time of this meeting, the written comment docket was still open. Using docket ID CDC-2019-0028, those interested were invited to submit a comment at regulations.gov. Dr. Cohn indicated that the docket would remain open for 48 hours following the end of the meeting. This information also can be found in the *Federal Register* notice announcing ACIP meetings and on the ACIP meeting website. She encouraged everyone to access and read the public comments posted.

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 session, ACIP members will state any COIs.

Detailed instructions for submission of names of potential candidates to serve as ACIP members is available on the ACIP website. Applications for ACIP membership originally were due no later than July 1, 2019 for the 4-year term beginning July 2020. However, that has been extended to August 1, 2019.

Dr. Cohn announced that Dr. Narayan Nair would be retiring as a CAPT in the United States Public Health Service (USPHS) as well as his position as Division Director/Chief Medical Officer in the Division of Injury Compensation Programs in the Healthcare Systems Bureau of the Health Resources and Services Administration (HRSA). Therefore, this would be his last ACIP meeting. He has served in the role as the HRSA liaison for the last 5 years. CDC and ACIP have appreciated his participation.

Dr. Romero conducted a roll call to determine whether any ACIP members had COIs. No member had any COI to declare. 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 2019 ACIP meeting.

Human Papillomavirus (HPV) Vaccines

Introduction

Peter Szilagyi, MD, MPH
Chair, ACIP HPV Vaccines WG

Dr. Szilagyi reminded everyone that these are the current recommendations for HPV vaccination in the US:

- Routine vaccination
  - Age 11 or 12 years
  - Vaccination can be started at age 9 years
- Catch-up vaccination
  - Females through age 26 years
  - Males through age 21 years
  - Certain populations through age 26 years*
- Males aged 22 through 26 years may be vaccinated

[*Men who have sex with men (MSM), transgender persons, and persons with certain immunocompromising conditions; *MMWR* 2014;63 (RR05); *MMWR* 2015;64:300-4; *MMWR* 2016; 65:2105-8]

He indicated that the following policy questions for HPV vaccination would be presented to ACIP for a vote during this session:

- Should catch-up HPV vaccination be recommended for primary prevention of HPV infection and HPV-related disease for all persons through age 26 years?

- Should catch-up HPV vaccination be recommended for primary prevention of HPV infection and HPV-related disease for all persons aged 27 through 45 years?

The reason the WG is considering these two issues is that with regard to harmonization, the WG had discussions in 2017 and 2018 related to simplification of the vaccination schedule. Related to vaccination of adults older than 26 years of age, the manufacturer filed an application in April 2018 to expand the age indication for 9-valent HPV vaccine (9vHPV) from age 9-26 years to age 9-45 years. This was approved by the Food and Drug Administration (FDA) in October 2018.

HPV vaccine sessions at 3 ACIP meetings have focused on the expanded age indication. In June 2018, there was an overview and presentation on the history of application for the expanded age licensure, a review of HPV epidemiology, and the natural history and burden of disease. The manufacturer presented clinical trial data submitted in the Supplemental Biologics License Application (sBLA) for 9vHPV in adults aged 27-45 years.

In October 2018, presentations included a review of the regulatory basis for licensure for the expanded age range, several aspects of the US HPV vaccination program, including vaccination coverage and current evidence of impact on infection and disease. There was a review of HPV epidemiology, sexual behavior, and post-licensure effectiveness. In addition, there was a brief update on global HPV vaccination and vaccine supply, highlighting the current demand/supply imbalance. Grading of Recommendation Assessment, Development and Evaluation (GRADE) was presented for efficacy, immunogenicity, and safety of HPV vaccine for adults older than 26 years of age. There also was a summary of the health economic analyses, and initial policy considerations discussed by the HPV Vaccines WG were presented. At that time, the WG introduced the option of a recommendation for individual clinical decision-making.

In February 2019, the WG presented an overview of natural history, the impact and cost-effectiveness of mid-adult HPV vaccination using the HPV Agent-based Dynamic model for Vaccination and Screening Evaluation (ADVISE) model, and health economic results from 5 models being considered for this policy question. In addition, the WG presented information on patient values and acceptability and findings from program and vaccine provider surveys about the expanded age indication for HPV vaccination. Updated considerations and policy options, based on continued WG discussions and deliberations, were presented as well.

Since the February 2019 ACIP meeting, the WG has continued to review updated results from models of HPV vaccine impact and health economics. They heard an industry presentation on the global HPV vaccine supply and the current shortage. They had a preliminary review of data on HPV vaccination in HIV-infected adults, as well as data on HPV vaccination post-treatment for anogenital disease. Both topics require additional review of data and discussion, which the WG will consider in the future. Data from the recently completed 9vHPV vaccine immunogenicity and safety trial in adults were presented to the WG in May 2019, which the ACIP will hear during this session. The WG also reviewed the Evidence to Recommendations (EtR) documents and continued to discuss recommendation options.

Regarding recommendations for vaccination of adults older than age 26 year, during the February 2019 meeting, the options presented by the WG for consideration included *Clinical Decision-Making* or *Not Making a Recommendation*. Importantly, no members of the WG were in favor of a *Routine Universal Recommendation*. Therefore, this was not discussed as an option. After the February 2019 ACIP meeting, there were discussions with the ACIP Secretariat, EtR consultants, and the WG. Options being proposed during this session included *Shared Clinical Decision-Making* or *Do Not Recommend the Intervention.*

The WG reached consensus on the first question, "Should catch-up HPV vaccination be recommended for primary prevention of HPV infection and HPV-related disease for all persons through age 26 years?" For vaccination of adults older than 26 years of age, two options would be proposed: a majority and a minority opinion from the WG.

This session included the following presentations: Background, 9vHPV Immunogenicity and Safety Trial in Women Age 27-45 Years, Overview of Health Economic Models for HPV Vaccination of Mid-Adults, Evidence to Recommendations, and WG Considerations.

Background: HPV Vaccines Session

Lauri Markowitz, MD
Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

In this presentation, Dr. Markowitz provided some additional background for this session. Specifically, she provided background for the two policy issues being considered: harmonization of catch-up vaccination through age 26 years and vaccination of adults older than age 26 years. She also included an update on the global HPV vaccine landscape.

This table shows vaccines licensed in the US, the manufacturer, and licensure ages before October 2018:

Vaccine	HPV Types	Manufacturer	Licensure Ages
Bivalent (2vHPV)	16,18	GlaxoSmithKline	Females 9-25 years
Quadrivalent (4vHPV)	6,11,16,18	Merck & Co.	Females and males 9-26 years
9-valent (9vHPV)	6,11,16,18, 31,33,45,52,58	Merck & Co.	Females and males 9-26 years

Although three vaccines are licensed, since the end of 2016, only 9vHPV vaccine has been distributed in US. However, 2vHPV and 4vHPV vaccines continue to be available in other countries. In October 2018, 9vHPV vaccine was licensed through age 45 years. Dr. Markowitz emphasized that although 9vHPV vaccine was recently licensed through this age in the US, all three HPV vaccines have been licensed through age 45 or older in other countries. However, no country has a public health HPV vaccination program targeting adults older than age 26 years. She again reviewed the current recommendations.

Vaccination for females was recommended in 2006. At that time, HPV vaccine was licensed only in females. Routine vaccination of males was recommended in 2011. Vaccination was first recommended as a 3-dose schedule. A 2-dose schedule was recommended in 2016 for those starting the vaccination series before age 15 years. 4vHPV was the first vaccine licensed and recommended in 2006, bivalent in 2009, and 9-HPV in 2015. Almost all vaccine used in the US was 4vHPV vaccine through 2015. After 2016, as mentioned earlier, only 9vHPV vaccine has been distributed in the US.

Data from the National Immunization Survey (NIS)-teen among adolescents aged 13-17 years showed coverage increasing gradually in females from 2006-2017. Up-to-date (UTD) is the measure that has been used since the 2-dose recommendation for persons starting vaccination before age 15. In 2017, at least 1-dose coverage for females was 69% and UTD was 53%. Coverage for males has increased more rapidly than for females since the 2011 recommendation. At least 1-dose coverage was 63% in 2017, almost similar to females, and UTD coverage was 44%. [Adapted from Walker et al. *MMWR* 2018; NIS-Teen; Revised definition of adequate provider data in 2013].Understanding coverage is important, as this impacts some inputs to the models. In spite of coverage being lower than target goals, dramatic decreases in vaccine type HPV prevalence and other endpoints have been observed in the US. These were detected within 4 years of the program introduction and further reductions have been observed in subsequent years

In terms of why there are different catch-up ages in the current recommendations for males and females, routine vaccination for males was considered after 4vHPV vaccine was licensed for use in males and data were available on efficacy for prevention of anal precancers in males. ACIP considered policy for males using GRADE, including health economic analyses. These health economic models showed that inclusion of males in the vaccination program was less cost-effective than female vaccination and that vaccination becomes less cost-effective with increasing age at vaccination. Vaccination of males was recommended at age 11 or 12 years, as for females, but catch-up was recommended through age 21. ACIP considered health economic modeling data when recommending the age for catch-up vaccination.

There has been increasing interest from partners and stakeholders in harmonizing the upper age for catch-up recommendations across genders for simplification of the vaccination schedule. In 2017-2018 before CDC awareness of the manufacturer application to FDA for the 9vHPV vaccine expanded age range, the ACIP HPV Vaccines WG was considering harmonization of catch-up recommendations across genders through age 26 years. The WG delayed consideration of harmonization after the FDA agreed to an expedited review for the expanded age application in April 2018. At that time, it was unclear what health economic analyses would show for adult vaccination, and they wanted to avoid multiple recommendation changes in one year. The health economic analyses have been much more challenging than anticipated; however, the WG now is ready to move forward on both harmonization and adult vaccination decisions.

Regarding the WG's deliberations on the second policy question being considered during this session pertaining to vaccination of adults older than age 26 years, the WG also considered this policy decision harmonized across genders. Over the past year, the WG reviewed a wide range of data. Dr. Markowitz highlighted that, as presented during past ACIP meetings, there is uncertainty about some aspects of HPV natural history. The WG considered the results from 5 health economic models. Three models were used initially and 2 additional models were included to inform policy after October 2018. CDC's desire to include additional models was due to the disparate results obtained across the models initially considered. Modelers and the

ACIP/CDC economic team have been working hard over the past year to understand the modeling results. Of the 5 models, 4 predict high cost per quality-adjusted life-year (QALY) for expanding the catch-up age. The presentations for this session were intended to summarize data presented to ACIP over the last year, much of which is summarized in the following EtR presentation. The only new data were in the health economic presentation, which includes some new modeling data and new data from a 9vHPV vaccine immunogenicity and safety trial.

As a reminder, licensure of 9vHPV vaccine for use through age 45 years was based on results of a randomized controlled trial (RCT) of 4vHPV vaccine that included women aged 27-45 years; observational follow-up through 10 years in a subset of women in the base study; a cross-study immunogenicity analysis showing statistical non-inferiority of immune responses to 4vHPV vaccine in males aged 27-45 years compared with males aged 16-26 years, the age in which efficacy was demonstrated; and extrapolation of these data to 9vHPV vaccine in individuals aged 27-45 years [Munoz et al. *Lancet* 2009; Castellsague et al. Br J *Cancer* 2011 (end of study results); Luna et al. PLoS One 2013 (6 year follow-up); Luxembourg (10 year follow-up presented at ACIP June 2018); Giuliano et al. *Vaccine* 2015; Giuliano et al. *N Engl J Med* 2011; Palefsky et al. *N Engl J Med* 2011; https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM622941.pdf].

GRADE for adult vaccination was presented to ACIP in October 2018. The GRADE evidence tables included data for 2vHPV and 4vHPV immunogenicity, efficacy, and safety in adults aged 27-45 years*. The WG updated the GRADE tables in June 2019 to include data from the 9vHPV immunogenicity and safety trial in women age 27-45 years described in the next presentation [GRADE: Grading of Recommendations, Assessment, Development and Evaluation https://www.cdc.gov/vaccines/acip/recs/grade/about-grade.html; *Meites, presentation at October 2018 ACIP meeting; +Luxembourg, presentation at June 2019 ACIP meeting].

To end, Dr. Markowitz mentioned some aspects of the global landscape for HPV vaccines. This also was discussed briefly during the October 2018 ACIP meeting. There were just 96 (50%) of countries with HPV vaccine in the National Immunization Program (NIP) as of early 2019. Most of the countries with the highest burden of cervical cancer have not yet introduced vaccine.

There is a global HPV vaccine demand/supply imbalance, which is outlined in a World Health Organization (WHO) publication. As background, the WHO issued HPV vaccination recommendations for the first time in 2009 for a single age cohort of girls. In 2016, this recommendation was modified to include multi-age cohort vaccination for girls aged 9-14 years in the first year of vaccine introduction for greater and faster impact of the vaccination program. This recommendation, along with more country interest in introduction of HPV vaccine, has increased demand. Gavi funding for HPV vaccination for eligible countries started in 2012. Gavi procures bivalent and quadrivalent HPV vaccines. The current HPV vaccine demand/supply imbalance is projected to last for 3-5 years until there is more manufacturing capacity by the two current manufactures and until other manufactures in late stages of vaccine development can bring their products to market. This will delay introduction in some low, middle, and high income countries and will prevent multiage cohort vaccination. No vaccine shortage is anticipated in the US.

The global HPV vaccine supply was discussed during the WHO Strategic Advisory Group of Experts on Immunization (SAGE) meeting in October 2018. The following statement was included in the published SAGE report:

> "Concerned about the impact of a constrained HPV vaccine supply forecast until at least 2024, SAGE urged that a globally more equitable distribution of the available doses be encouraged to ensure optimal global public health access to the vaccine."

There are ongoing discussions at WHO and Gavi about vaccination strategies and allocation of vaccine during the supply shortage [*Weekly Epidemiological Record* 2018;93:661-80].

Dr. Markowitz indicated that this short update on the global demand/supply imbalance was presented to ACIP during this session for general awareness, and because some WG members considered this in discussions of policy options for vaccination of adults older than 26 years.

In closing, she reminded everyone that the two policy issues to be considered during this session included harmonization of catch-up vaccination through age 26 years, and vaccination of adults older than age 26 years.

9vHPV Immunogenicity and Safety Trial in Mid-Adult Females

Alain Luxembourg, MD, PhD
Director, Clinical Research
Merck Research Laboratories

Dr. Luxembourg briefly recapped what was presented to ACIP a year ago as well as Merck's new clinical trial, Protocol 004, which is a trial of the 9vHPV vaccine among women 16-45 years of age.

In terms of clinical trial information, the 4vHPV vaccine is highly efficacious to prevent HPV6/11/16/18-related persistent infection and disease regardless of age. The women tested were 16-45 years of age. There was high efficacy across the entire age range, which is a very consistent feature of the clinical trials. Also shown was that protection is durable. In women 27-45 years of age, protection lasts at least 10 years based on clinical trials. Regulatory agencies have concluded that data from the 4vHPV vaccine efficacy and immunogenicity results can be extrapolated to the 9vHPV vaccine. This is based on the fact that both vaccines are manufactured using the same process, share the same virus-like particles (VLPs) for HPV6/11/16/18 and are manufactured using similar processes and show consistent success in efficacy and immunogenicity bridging studies of 4vHPV and 9vHPV vaccines across age and gender.

Based on clinical trial results, the FDA and other regulatory agencies have granted an indication for the 9vHPV vaccine in adults over 26 years of age. In the US, the 9vHPV vaccine age indication was expanded from 9-26 years to 9-45 years in October 2018 following priority review by the FDA based on 4vHPV vaccine efficacy data.

9vHPV vaccine is indicated in girls/women 9-45 years of age in Canada and Australia and individuals from the age of 9 years in the European Union (EU). The European Medicines Agency (EMA) requested a clinical study to compare 9vHPV vaccine safety and immunogenicity in women 27-45 years of age compared to women 16-26 years of age as a post-licensure commitment, which Dr. Luxembourg presented during this meeting.

High efficacy of 4vHPV vaccine was shown across the entire 24-45 year age range in the FUTURE III Study for the endpoints of HPV6/11/16/18-related 6-month persistent infection, cervical intraepithelial neoplasia (CIN), and condyloma and HPV6/11/16/18-related Pap test abnormalities. Similar efficacy was shown in both the 24- to 34-year and the 35- to 45-year age strata. There was no statistical difference between the efficacy in these two ages for two different endpoints. There are a substantial number of endpoints in the placebo groups showing a high number of cases of infections [Castellsague et al. *Br J Cancer* 2011; 105:28-37].

Protocol 004 was a 9vHPV vaccine immunogenicity and safety study in women 16-45 years of age split into 2 cohorts: 1) 642 women 27 to 45 years of age; and 2) 570 women 16 to 26 years of age (control group). This was an open-label, 7-month study in which all participants received 9vHPV vaccine at Day 1 and Months 2 and 6. The goal was to examine the immunogenicity of the 3-dose regimen at Day 1 and Month 7. Safety was assessed in the same way it has been in other studies of the 9vHPV vaccine. The primary objective was to demonstrate non-inferiority of geometric mean titers GMTs at Month 7 (one month after the last dose) for the 7 high-risk types in the vaccine. The non-inferiority criterion required a less than a 2-fold decrease in women 27-45 years of age compared to women 16-26 years of age. This study design was agreed to with the regulators.

Regarding the analysis of the primary objective, the non-inferiority criterion was met for all 7 high-risk HPV types with GMT ratios (women 27-45 yrs / women 16-26 yrs) at approximately 0.7 for each HPV type, similar to what has been observed for 4vHPV vaccine. The lower bound of the 95% confidence interval of the GMT ratio was approximately 0.6 for each HPV type. The non-inferiority criterion required that the lower bound be greater than 0.5, so this criterion was met and the primary objective was met. Seropositivity rates at Month 7 were greater than 99% for the 9 HPV types in the vaccine. Analyses by age strata showed that immunogenicity was very robust regardless of age. There was a trend for GMTs to decrease with age at vaccination, which is common with many vaccines and also has been seen with the 4vHPV vaccine previously. As mentioned earlier, efficacy of 4vHPV vaccine in clinical studies was always high across the 16-45-year age range.

In terms of safety, there was no substantial difference between the two age groups. Most adverse events (AEs) were injection-site AEs. There were no vaccine-related serious adverse events (SAEs) or deaths. The most common injection-site events were pain, swelling, and erythema. The frequencies of AEs at the injection site were similar between the two age groups and there was no statistical difference between the two groups.

In conclusion, most women 27-45 years of age are susceptible to infection by HPV types covered by the 9vHPV vaccine. The 4vHPV vaccine is highly efficacious in women 16-45 years of age, regardless of age and provides durable protection up to at least 10 years. The 9vHPV vaccine is highly immunogenic in women 27-45 years of age. Seroconversion rates were greater than 99% for the 9 HPV types. The 9vHPV vaccine induces HPV antibody responses in women 27-45 years of age that are non-inferior to responses in women 16-26 years of age. Efficacy in women 27-45 years of age was previously inferred based on the overall 4vHPV and 9vHPV vaccine clinical data. This result further supports the efficacy of the 9vHPV vaccine in women 27-45 years of age. The 9vHPV vaccine is generally well-tolerated in women 27-45 years of age. The overall conclusion is that collectively, all of these data support the clinical benefit of the 9vHPV vaccine in individuals 27 to 45 years of age.

Overview of Health Economic Models for HPV Vaccination of Mid-Adults

Harrell Chesson, PhD
Division of STD Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Dr. Chesson reminded everyone of the history of the health economic analyses of mid-adult HPV vaccination for ACIP. In October 2018, there was a summary presentation of the results from 3 models (HPV-ADVISE, Simplified, Merck) that illustrated great differences in the model results. Subsequently, there was a post-meeting request to the Cancer Intervention and Surveillance Modeling Network (CISNET) modeling group to help try to understand the differences. In February 2019, there were two health economics presentations. Dr. Brisson presented the HPV-ADVISE model and there was a summary presentation of the results from 5 models, 3 from October plus 2 from the CISNET group. Since February 2019, all of the models have completed the CDC economic review process in accordance with the *ACIP Guidance for Health Economic Studies* and there is now a better understanding of the differences in the model results.

During this session, Dr. Chesson presented an overview of the 5 available models; showed results from these models that could inform both policy considerations (harmonization of catch-up vaccination through age 26 years; vaccination of adults older than age 26 years); and discussed the reasons for the differences in the model results. The models available to inform mid-adult HPV vaccination policy decisions in the US include the following:

- ❑ HPV-ADVISE model (Laval University / CDC)
- ❑ Simplified model (CDC)
- ❑ Merck model
- ❑ CISNET Harvard model
- ❑ CISNET Policy1-Cervix (Cancer Council New South Wales)

All 5 models include a wide range of health outcomes that can be prevented by HPV vaccination, including cervical precancers and cancer, other HPV-associated cancers (anal, vaginal, vulvar, penile, oropharyngeal), and anogenital warts. All incorporate current medical cost estimates for HPV-associated cancers, account for “herd effects” on mid-adults from the existing vaccination program, examine a long time horizon (~100 years or more), and exclude productivity costs. The 5 models differ in terms of structure, calibration to fit available data, cervical cancer screening assumptions, vaccine uptake assumptions for mid-adults, natural history of HPV parameters (e.g., natural immunity after HPV acquisition and clearance), and in how HPV transmission dynamics are characterized (e.g., rate of acquisition of new sex partners by age).

Regarding calibration, one important point is that the HPV-ADVISE model uses the 50 best-fitting parameter sets used for analysis and the other models use a single best-fitting parameter set used for analysis. Regarding natural immunity assumptions, the models differ in the percent of people who have natural immunity after infection and clearance and in the degree and duration of protection of natural immunity.

In terms of the current program, all 5 models give a relatively favorable cost-effectiveness estimate. The cost per QALY gained by vaccination ranges from less than zero in the HPV-ADVISE model, indicating that the program is cost-saving, to just under $35,000 in the CISNET Harvard model.

With respect to the comparisons that were made to inform the policy considerations for this session, for harmonization of catch-up vaccination through age 26 years the models assessed vaccination through age 26 years for all persons versus the current program. For vaccination of adults older than age 26 years, two key comparisons were made. First, the model looked at expanding vaccination to age 30 years versus maintaining the current program. Second, the model considered vaccination through age 45 years versus the current program. The modelers examined a wide range of other scenarios, such as incremental analyses and increasing the cutoff age from 30 to 35 and 40. However, Dr. Chesson did not show those results during this session.

In terms of harmonization of catch-up vaccination through age 26 years focusing primarily on results from the HPV-ADVISE model, the estimated number needed to vaccinate (NNV) in the current program versus no vaccination is 9 for anogenital warts, 22 for CIN, and 202 for HPV-associated cancers. For harmonization of catch-up vaccination through age 26, when all 50 parameter sets are applied, the NNV is 140 for anogenital warts, 430 for CIN, and 7590 for HPV-associated cancers. Using the 22 sets with faster progression and lower natural immunity the NNV is 40 for anogenital warts, 450 for CIN, and 3260 for HPV-associated cancers. Using the 28 sets with slower progression and higher natural immunity, the NNV is 840 for anogenital warts, 340 for CIN, and 8200 for HPV-associated cancers. The results are more favorable for harmonization at age 26 when using the parameter sets with faster progression and lower natural immunity.

Regarding the cost-effectiveness of harmonization of HPV vaccination, the HPV-ADVISE model predicts that the current program is cost-saving. When the analysis is limited to the parameter sets with fast progression and lower natural immunity, the cost per QALY gained is roughly $178,000 for harmonization at age 26 and over $400,000 at age 30 years. When the analysis is limited to the slower progression and higher natural immunity scenarios, no cost per QALY could be estimated for harmonization at age 26 because the model could not consistently find significant health benefits at the population level with this strategy. In this scenario, the cost per QALY gained by harmonization at age 30 was about $2.3 million. In terms of the estimated impact on the cost of the HPV vaccination program, the long-term costs are expected to increase by only 5% or less based on estimates from the Simplified Transmission Model under the uptake assumptions used in that model.

In terms of vaccination of adults older than 26 years of age, the NNV to prevent one case of disease from the HPV-ADVISE model in the current program versus no vaccination is again 9 for anogenital warts, 22 for CIN, and 202 for HPV-associated cancers. For harmonization of catch-up vaccination through age 45, when all 50 parameter sets are applied, the NNV is 390 for anogenital warts, 860 for CIN, and 7690 for HPV-associated cancers. Using the 22 sets with faster progression and lower natural immunity the NNV is 120 for anogenital warts, 800 for CIN, and 6500 for HPV-associated cancers. Using the 28 sets with slower progression and higher natural immunity, the NNV is 870 for anogenital warts, 880 for CIN, and 8580 for HPV-associated cancers. The results are much higher than for the current program.

Regarding the estimated impact of HPV vaccination in terms of the percentage in disease incidence, presented by Dr. Brisson in February 2019, there is very little incremental benefit at the population level in terms of the impact of the current program and the impact when extending the current program to include mid-adults through age 45 years. For example, for cervical cancer the model estimates that current program over 100 years will avert about 650,000 cases and that adding the mid-adult strategy through age 45 would avert an additional 3000 cases.

This table shows the cost-effectiveness of vaccination of adults through 30 years of age versus the current program and through 45 years of age versus the current program for all 5 models:

Adult Vaccination Strategy	**Model**				
	HPV-ADVISE	**Simplified**	**Merck**	**CISNET (Harvard)**	**CISNET (Policy1-Cervix)**
Through age 30 years (vs. current program)	$830,000	$587,600	$81,200	$627,700	$341,100
Through age 45 years (vs. current program)	$1,471,000	$653,300	$117,500	$440,600	$315,700

As a reminder, the HPV-ADVISE model uses results from the 50 parameter sets. However, if it is limited to the parameter sets that have the faster progression and lower natural immunity, the cost per QALY gained is lower. Conversely, when limited to the parameters that have slower progression and higher natural immunity, the costs per QALY estimates are higher. As noted in February 2019, a distinguishing feature of the CISNET model results is that the cost per QALY gained from vaccination through age 45 years is lower than through age 30 years. This arises likely because of herd effects of the existing program on mid-adults.

The estimate in the Simplified model has changed since the February 2019 presentation. The Simplified model now takes into account the ongoing HPV vaccination program. The cost per QALY gained through age 30 was $265,200 and now is $587,600 and through age 45 was $417,200 and now is $653,300. The magnitude of this increase is consistent with what would be expected based on the other models, showing the importance of accounting for historic vaccination coverage. The Merck model results are now somewhat lower than presented in February 2019, owing to a series of minor changes. The cost per QALY gained through age 30 was $105,100 and now is $81,200 and through age 45 years was $149,100 and now is $117,500.

Identified factors that may account for differences in model results include uncertainties about HPV natural history, including natural immunity following clearance of infections and burden of disease caused by new HPV infections after age 26 years; degree of herd protection from the existing HPV vaccination program; cervical cancer screening assumptions; health economic assumptions; and deaths from undiagnosed cancer. The first three factors were discussed during the February 2019 meeting. In the interest of time, Dr. Chesson did not revisit them and referred everyone to the supplemental slides for additional information. However, he did further discuss health economic assumptions and deaths from undiagnosed cancer.

ACIP/CDC economic reviewers asked the modelers to examine a set of results when using a standardized list of health economic parameters regarding medical treatment costs of the HPV-associated outcomes and QALY assumptions. In terms of the cost-effectiveness of vaccination of adults through age 45 years versus the current program, there was a somewhat large relative increase in the Merck estimate (base case of $117,500 versus $172,000 using standard health economic parameters). However, in terms of the absolute differences across the models, these parameters did not make that much of a difference.

Deaths from undiagnosed cancer was recently identified as a factor that may be accounting for some of the differences across the models. In the Merck model, each year in the absence of vaccination, there would be almost 10,000 deaths due to diagnosed HPV cancers. These results are fairly consistent with the other models. The Merck model also estimates that about 24,000 deaths would be attributable to undiagnosed HPV cancer each year. That works out to about 71% of the HPV cancer deaths being attributable to undiagnosed cases. With the exception of the CISNET Harvard cervical cancer model in which 16% of the cervical cancer deaths were attributable to undiagnosed cancers, none of the other models had undiagnosed cancer deaths in the analysis. It is important to note that the 71% Merck value and the 16% CISNET Harvard value are outputs of these models; whereas, the 0% values arise from assumptions of the modelers in the HPV-ADVISE, Simplified, and CISNET Policy1-Cervix models that there are no deaths due to undiagnosed cancers.

A lot of the data about cancer incidence in the models come from cancer registries. If the registries have good completeness, a large number of deaths due to undiagnosed cancers would not be expected. CDC's US Cancer Statistics (USCS) website has a quote stating that, "After years of analyzing completeness of case ascertainment, CDC has determined that NPCR registries consistently deliver high-quality, complete data."

In terms of the results from the Merck model regarding the cost-effectiveness of vaccination through age 45 years versus the current program, the base case result is $117,500 per QALY gained. The cost per QALY is $202,200 when deaths due to undiagnosed cancer are excluded and $428,900 when deaths due to undiagnosed caner are excluded and the standardized health economic parameters are applied. Undiagnosed cancer deaths do account for some of the differences across the model results, but this does not account for all of the differences. Even when assumptions are standardized regarding undiagnosed cancer deaths and health economic parameters, there are still some differences that continue across the models.

To summarize, the cost per QALY gained by the current vaccination program is less than $35,000 and is cost-saving in the HPV-ADVISE model. In all of the models, adult vaccination is much less cost-effective than the current program. However, there are notable differences in the cost-effectiveness estimates across models. Uncertainties in HPV natural history and transmission dynamics preclude a precise estimate of the cost-effectiveness of vaccination of adults. However, the results are more consistent when standardizing health economic assumptions and assumptions regarding deaths due to undiagnosed cancer. In the context of the existing program, vaccinating adults over age 26 years would produce relatively small additional health benefits. The NNV to prevent one case of disease is approximately 40 times higher for adults through age 45 years than the current program for anogenital warts, CIN 2/3, and cancer.

The cost per QALY gained by harmonization of catch-up vaccination through age 26 years versus the current program in the HPV-ADVISE model is $178,000 using faster progression and lower natural immunity assumptions. There is no significant gain in QALYs using slower progression and higher natural immunity assumptions. The results are not so favorable or unfavorable as to make a strong economic case for or against harmonization through age 26 years. The cost per QALY gained by adult vaccination through age 30 years exceeds $300,000 in 4 of the 5 available models and exceeds $800,000 in the median of the 50 parameter sets in the HPV-ADVISE model. The cost per QALY gained by adult vaccination through age 45 years exceeds $400,000 in 3 of the 5 available models and exceeds $1,400,000 in the median of the 50 parameter sets in the HPV-ADVISE model.

Discussion Points

Dr. Elbasha (Merck Modeling Group) thanked Dr. Chesson and CDC for a thorough review of the Merck model. They reviewed several lengthy documents, including dense mathematical equations, and detailed results from many modeling scenarios during several rounds. They asked several important questions and provided feedback that helped and will continue to help in refining the model, its inputs, and its predictions. Merck will continue to refine the Merck model and its predictions, and will continue to conduct analyses to address natural history, health economics, and other important inputs. The model results are still different and do not align with the other models, which requires further investigation. The models align when evaluating the current program of vaccinating younger cohorts, but exhibit a wide variety of results when vaccinating older cohorts. The understanding of the differences in the models have improved, but what accounts for the major differences is still not fully understood. Because the models are simplifications of a complex reality, all models have limitations. Merck thinks it is important for all modelers to work together to fully understand what might be driving the major differences in model results. This would include sharing equations, inputs, and other technical details of the models and harmonizing critical assumptions and inputs. Merck welcomes any further input from the CDC team and any opportunity to work with other modeling groups, including participation in comparative modeling societies and face-to-face meetings. This would greatly help decision-makers not only in the US, but also in jurisdiction around the work to accurately assess the public health impact and the true economic value of expanding vaccination to 45 years of age.

Dr. Moore requested clarification from Dr. Chesson regarding whether the incremental difference in the new version of the NNV was among those currently not recommended or if it was across the whole cohort adding in the small number of men 22 through 26 years of age not currently recommended for routine catch-up.

Dr. Chesson clarified that it focuses on the benefits of vaccinating the men in this age group, but technically it looks at the additional number vaccinated when these men are included and the additional number of cases averted. These cases could be averted through herd effects of vaccinating these men, but it is based on the benefits of extending the vaccination to include these men.

Dr. Hunter inquired as to whether Dr. Quach could comment on the 9vHPV vaccine being indicated up to age 45 in Canada, and whether the Canadian National Advisory Committee on Immunization (NACI) deliberated on this decision. In addition, he wondered whether different provinces had different approaches.

Dr. Quach (NACI Canada) replied that this recommendation was made a while back not looking at the cost-effectiveness. They did not delve into other details such as Dr. Chesson described. It was more of a permissive indication than a solely publicly funded program. The provinces do employ different approaches. For example, Quebec is moving completely toward a mixed schedule and not providing public coverage up to even 26 years of age. Quebec's program is based on 4th graders and teenagers. There is not a publicly funded program in Quebec or most of the other provinces.

Dr. Stephens requested clarity on the undiagnosed cancers in two of the models in terms of where those data originated, as they did not appear to be real.

Dr. Chesson clarified that the estimates of deaths due to undiagnosed cancers were outputs of the model. They are not inputs into the model based on a specific data source. He requested that a representative from the Merck Modeling Group explain how they arrived at these estimates in their model.

Dr. Elbasha (Merck Modeling Group) indicated that death is an outcome in all of the models. It depends on assumptions regarding the natural history as well as many factors in the inputs on transmission, progression, diagnosis, and prevention efforts. When they calibrated the Merck model, meaning that they included certain inputs to match outcome data, they match to age-specific and HPV type-specific prevalence. They matched the data on cervical cancer incidence by age from the registry. Then they started looking at the overall number of deaths that occurred among vaccinated and unvaccinated. As Dr. Chesson mentioned, the registries capture all deaths if someone is diagnosed. However, registries by definition include only individuals who are diagnosed with cancer. The Merck model also accounts for the fact that someone can be dying from cancer but not be diagnosed. Merck is looking at data for more cancer mortality statistics to make sure that by matching inputs in the model, they match overall deaths from cancer whether it is diagnosed or not because they think that deaths can occur from undiagnosed cancer.

Evidence to Recommendations (EtR) Framework

Elissa Meites, MD, MPH
Medical Epidemiologist, Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Meites presented two EtR summaries, one for each policy question. First, the EtR for Harmonization of Catch-Up HPV Vaccination through age 26 years. As a reminder, the elements of the ACIP EtR framework are the PICO (Population, Intervention, Comparison, Outcomes) Question and Background, Problem, Benefits & Harms, Values, Acceptability, Resource Use, Feasibility, and Balance of Consequences; the WG discusses each of these before arriving at a policy option for ACIP consideration. For each criterion, the WG summarized the evidence and considerations and offered the judgments of the HPV Vaccines WG.

The first PICO question was, "Should catch-up HPV vaccination be recommended for primary prevention of HPV infection and HPV-related disease for all persons through age 26 years?" The population is males age 22 through 26 years since that is the group for whom the recommendations would change. The intervention is catch-up vaccination with 3 doses of HPV vaccine. The comparison is existing HPV vaccination recommendations. The outcome is primary prevention of HPV infection and HPV-related disease.

Regarding background, ACIP routinely recommends HPV vaccination for adolescents at age 11 or 12 years. “Catch-up” vaccination recommendations apply to people who were not vaccinated at the routine age. Since 2006, ACIP has recommended vaccination for females at the routine age of 11 or 12 years, and catch-up vaccination for females through age 26 years. In 2011, ACIP added routine recommendations for males at age 11 or 12 years, with catch-up vaccination through age 21 years. Also, catch-up vaccination has been recommended through age 26 years for MSM (including men who identify as gay, bisexual, or who intend to have sex with men), for transgender persons, and for persons with certain immunocompromising conditions such as HIV. HPV vaccination coverage has been increasing among US adolescents, but remains low among young adults, and coverage in males is lower than coverage in females. In 2017, at-least-one-dose coverage among 13-17 year-olds was 69% in females and 63% in males. For 22-26 year-olds, it was 51% in females and 15% in males [Walker TY, et al. *MMWR*. 2018;67(33):909-917, and https://www.cdc.gov/nchs/nhis/index.htm].

Regarding the problem, HPV is common in both women and men and causes over 33,000 cancers annually in the US, including over 20,000 cancers in women and over 13,000 cancers in men. The existing HPV vaccination program for US adolescents has the potential to prevent the majority of these cancers. However, it is uncertain how much HPV-related morbidity and mortality is related to new HPV infections acquired by men at ages 22 through 26 years. The WG feels that that HPV-related disease is a problem of public health importance, and that preventing new HPV infections among 22-through-26 year-old males is probably of public health importance.

Regarding desirable anticipated effects (benefits), efficacy has been demonstrated in this age group. Clinical trials have shown that HPV vaccines are effective against infection and related disease due to HPV types that recipients are not infected with at the time of vaccination. The additional benefit of vaccinating males in this age range would be small compared with the benefit of the existing program. The NNV to prevent one case of anogenital warts, CIN 2+, or cancer is 9, 22, and 202, respectively, under the existing program. For expanding recommendations for males through age 26 years to harmonize catch-up vaccination across genders, the NNV would be 40, 450, and 3260, respectively, in a subset of analyses in the HPV-ADVISE model with more favorable model assumptions for adult vaccination.

As for undesirable anticipated effects (harms), in 9vHPV clinical trials, there were no serious vaccine-related events among males aged 9-26 years. AEs were generally less common among males than among females. HPV vaccines have an excellent safety profile based on large clinical trials and post-licensure effectiveness data. Over 100 million doses of HPV vaccine have been given in the US. The additional benefit of vaccinating males in this age range would be small compared to the existing program. However, small desirable effects outweigh minimal undesirable effects of HPV vaccination. Thus, the judgment of the WG is that this favors intervention.

Full grading of recommendations, assessment, development, and evaluation (GRADE) for use of 4vHPV and 9vHPV in males have been publicly available since these ACIP recommendations were made in 2011 and 2015, respectively. For males through age 26 years, GRADE evidence level, or certainty of the evidence, is 2 (moderate) for benefits of 4vHPV and 3 (low) for benefits of 9vHPV, and 2 (moderate) for safety of 4vHPV and 2 (moderate) for safety of 9vHPV [GRADE for HPV Vaccine for Males [https://www.cdc.gov/vaccines/acip/recs/grade/hpv-vac-males.html. Linked from *MMWR*; December 23, 2011 / 60(50);1705-8; GRADE for Use of 9vHPV in

Females and Males. https://www.cdc.gov/vaccines/acip/recs/grade/hpv-9v.html. Linked from *MMWR*; March 27, 2015 / 64(11);300-304].

Regarding values and acceptability to the target population, a systematic review of 22 published studies found that the overall mean acceptability of HPV vaccine was moderate at 57 on a 100-point scale. In the 9 studies reporting sexual orientation, there was no significant difference in acceptability between gay, bisexual, or other MSM and heterosexual men. In terms of whether the target population feels that the desirable effects are large relative to undesirable effects, the judgment of the WG is "probably yes." As for whether there is important uncertainty about or variability in how much people value the main outcomes, the judgment is "No Important Uncertainty or Variability."

Next the WG considered acceptability to key stakeholders, including programs and vaccine providers. In a 2018 survey conducted by AIM, 51 immunization programs responded and 50 (98%) were in favor of harmonizing the recommended age for catch-up vaccination to include everyone through age 26 years. Reasons the majority of programs favored harmonization were:

- ❑ Easier to implement (92%)
- ❑ Easier to explain to patients (88%)
- ❑ Will simplify health department recommendations and guidelines (84%)
- ❑ Easier to explain to providers (84%)
- ❑ Facilitate reaching high-risk populations (84%)
- ❑ To create equity between genders (78%)
- ❑ Reduce the burden on health care providers (76%)

In a 2018 survey of primary care physicians (pediatricians, family physicians, and internal medicine physicians), 93% were in favor of a change to harmonize the recommended age for catch-up vaccination to include everyone through age 26 years, and 27% agreed that current catch-up recommendations with different upper ages for males and females have caused challenges or confusion. Reasons the majority (n=713) of physicians favored harmonization included:

- ❑ Simplify the vaccination schedule (99%)
- ❑ Easier to implement (97%)
- ❑ Easier to explain to patients (96%)
- ❑ Facilitate reaching high-risk populations (88%)
- ❑ Reduce burden on health care providers (80%)
- ❑ Create equity between genders (61%)

The judgment of the WG is that yes, the intervention is acceptable to key stakeholders.

Regarding resource use, health economic analyses were conducted. In the context of the existing program for adolescents and catch-up, the incremental cost per QALY gained for expanding male vaccination through age 26 years was $178,000 in a subset of analyses in the HPV-ADVISE model with more favorable model assumptions for adult vaccination. Although less cost-efficient, absolute costs of vaccination would likely increase by less than 5% in the long-term under the expanded recommendation. These results are not so favorable or unfavorable as to make a strong economic case for or against harmonization through age 26 years. As for whether the option is a reasonable and efficient allocation of resources, the judgment of the WG is that this is uncertain.

Regarding feasibility, this intervention is a simplifying modification to an existing vaccination program and is considered feasible to implement. ACIP already recommends catch-up HPV vaccination for some people aged 22 through 26 years, including those who are female and certain special populations. A simplified adult immunization schedule is expected to be easier to explain and to remember [Meites E, Kempe A, Markowitz LE. Use of a 2-dose schedule for HPV vaccination—Updated recommendations of the ACIP. *MMWR*. 2016;65:1405–1408]. The judgment of the WG is that this option is feasible to implement.

After weighing the evidence, the judgment of the WG about the overall balance of consequences is that desirable consequences probably outweigh undesirable consequences in most settings. The WG feels there is sufficient information to move forward with a recommendation at this time. Based on the evidence and considerations discussed, the policy option for consideration is to recommend the intervention. The next presenter, Dr. Markowitz, will offer the proposed recommendation text.

In the second half of this presentation, Dr. Meites presented the EtR for HPV vaccination of adults older than age 26 years. The WG's second PICO question was, "Should catch-up HPV vaccination be recommended for primary prevention of HPV infection and HPV-related disease for all persons ages 27 through 45 years?" The population is persons age 27-45 years, the intervention is catch-up vaccination with 3 doses of HPV vaccine. The comparison is persons age 27-45 years with no catch-up HPV vaccination. The outcome is primary prevention of HPV infection and HPV-related disease.

Regarding background, HPV is a commonly sexually transmitted infection. Persistent HPV infections can develop into cancers, usually several decades later. Vaccination against HPV is recommended to prevent new HPV infections and subsequent disease. In October 2018, based on results from quadrivalent vaccine clinical trials in women through age 45 years and bridging immunogenicity and safety data in women and men, the FDA approved 9vHPV for use in US women and men through age 45 years [Food and Drug Administration. Prescribing information [package insert]. Gardasil 9 [human papillomavirus 9-valent vaccine, recombinant] Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2018].

Regarding the problem, over 33,000 cancers are caused by HPV annually in the US, including cervical, vaginal, vulvar, penile, anal, and oropharyngeal cancers. Again, the existing HPV vaccination program for US adolescents has the potential to prevent the majority of these cancers. It is uncertain how much HPV-related morbidity and mortality are related to new HPV infections acquired at ages 27 through 45 years [https://www.cdc.gov/cancer/hpv/statistics, and Saraiya M, et al. U.S. assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *J Natl Cancer Inst.* 2015 Apr 29;107(6):djv086]. The mean age of acquisition of causal HPV infection for cancers is unknown, but estimated to be decades before cancer is diagnosed. [Schiffman M, et al. Carcinogenic human papillomavirus infection. *Nat Rev Dis Primers*. 2016 Dec 1;2:16086] HPV incidence is highest among people in the age range of teens to early 20s. First HPV infections are acquired soon after first sexual activity, so most sexually active adults have been exposed to HPV already. Nevertheless, at any age, having a new sex partner is a risk factor for acquiring new HPV infections. Exposure to HPV decreases among older age groups, as the percentage of people reporting a new sex partner within the past year is lower in older age groups than among younger age groups. [Winer RL, et al. Incident Detection of High-Risk HPV in a Cohort of High-Risk Women Aged 25-65 Years. *J Infect Dis.* 2016 Sep 1;214(5):665-75.] The existing US HPV vaccination program has resulted in significant declines in prevalence of vaccine-type HPV infections, anogenital warts, and cervical precancers. Declines have been observed among both vaccinated and unvaccinated

persons, suggesting protective herd effects [Markowitz LE, et al. Ten Years of Human Papillomavirus Vaccination in the United States. *Academic Pediatrics*. 2018]. Based on the most recent national data on prevalence of HPV infections under the existing vaccination program, compared to the pre-vaccine era, 2013-2016 prevalence of quadrivalent vaccine-type HPV infection declined 86% (from 11.5 to 1.8%) among 14-19 year-olds and declined 71% (from 18.5 to 5.3%) among 20-24 year-olds. Declines seen in older age groups were not significant, but over time, further declines are anticipated in the older age groups as vaccinated women age into these groups [McClung NM, et al. HPV prevalence among females in the United States, NHANES. 68th EIS Conference; April 2019; Atlanta, GA]. The WG agrees that HPV-related disease is a problem of public health importance. However, the amount of HPV-related disease that could be prevented by vaccinating 27-45 year-olds is small, compared with the amount of disease that can be prevented by vaccinating at younger ages. Preventing new HPV infections among 27-45 year-olds is of uncertain public health importance.

Regarding desirable anticipated effects (benefits), clinical trials have shown that HPV vaccines are effective against infection and related disease due to HPV types that recipients are not infected with at the time of vaccination. In the FUTURE III trial of quadrivalent vaccine in adult women, against a combined endpoint of persistent HPV infection, extragenital lesions, and/or CIN 1+, per-protocol efficacy was 88.7% with a confidence interval of 78% to 95%. Intention-to-treat (ITT) results were lower, since these included women with previous HPV exposures and prevalent HPV infections at baseline even before they were vaccinated. The ITT efficacy was 47.2% with a confidence interval of 33% to 58%. In the 9vHPV trial presented earlier in this session, antibody titers were non-inferior in women age 27-45 years compared to women age 16-26 years. Over 99% of women in both groups seroconverted to all 9-valent vaccine types [Castellsagué X, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. *British Journal of Cancer*. 2011;105:28-37; Luxembourg A. 9vHPV immunogenicity and safety trial in mid-adult females. Presentation to ACIP, Atlanta, GA. June 2019]. Desirable anticipated effects vary. HPV vaccines are most effective when given before exposure to any HPV. The population benefit of adult vaccination would be minimal in the context of the existing program, yet some individuals in this age range might be able to benefit from vaccination. Recall that under the existing program, the NNV to prevent one case of anogenital warts, CIN 2+, or cancer, is 9, 22, and 202, respectively. For expanding vaccination to include adults through age 45 years, the NNV would be substantially higher at 120, 800, and 6500, respectively, according to a subset of analyses in the HPV-ADVISE model with more favorable model assumptions for adult vaccination [Castellsagué X, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. *British Journal of Cancer*. 2011;105:28-37; NNV results from HPV-ADVISE, per Chesson HW, Overview of Health Economic Models for HPV Vaccination of Mid-Adults, presentation to ACIP, Atlanta, GA, June 2019].

Regarding undesirable anticipated effects (harms), there is abundant evidence for safety of HPV vaccines. In 9 clinical trials of 9vHPV, 4vHPV, or 2vHPV vaccine in adults older than age 26 years (n=14,057), there were few SAEs and no vaccine-related deaths [Meites E, GRADE for HPV Vaccination of Mid-Adults. ACIP, Atlanta, GA. October 2018; and http://www.cdc.gov/vaccines/acip/recs/grade/table-refs.html]. Yet from a public health perspective, some WG members felt that adult vaccination might detract from the adolescent vaccination program, which remains the main focus for HPV prevention. Unanticipated harms could occur if vaccination of previously exposed or ill adults were to cloud data on vaccine safety or efficacy, or if communication messages were to focus on sexual transmission rather than HPV disease prevention.

The judgment of the WG is that desirable anticipated effects vary. Compared with the benefit of the existing HPV vaccination program for adolescents and young adults through age 26 years, the additional population-level benefit of vaccinating people age 27 through 45 years would be minimal. Yet some individuals in this age range might be able to benefit from vaccination against HPV types they have not yet encountered. Undesirable anticipated effects are also minimal, given abundant evidence for safety of HPV vaccines. The WG acknowledges that there could be concerns about potential undesirable unanticipated effects on the program as well. As for whether the desirable anticipated effects outweigh the undesirable anticipated effects, the judgment of the WG is that this is unclear.

Full GRADE tables with detailed assessment of the certainty of the evidence were presented to ACIP in October 2018. The only change is that the WG is adding the new results from the 9vHPV observational trial that was presented during this session. Therefore, the number of studies has increased by one for immunogenicity and safety, but the overall certainty of the evidence has not changed. The certainty of the evidence on benefits, based on 3 RCTs of 4vHPV or 2vHPV efficacy and immunogenicity and 6 observational trials of immunogenicity, was GRADE evidence level 2 (moderate quality evidence). The certainty of the evidence on harms, based on 5 RCTs and 4 observational trials, was also GRADE evidence level 2 (moderate quality evidence). The certainty of the evidence was level 2 or moderate for both effectiveness and safety of the intervention. Note that the evidence presented in the GRADE tables has to do with individual-level outcomes on vaccine safety and effectiveness; outcomes in GRADE do not speak to population-level outcomes or any programmatic concerns [Meites E, GRADE for HPV Vaccination of Mid-Adults. ACIP, Atlanta, GA. October 2018; and http://www.cdc.gov/vaccines/ acip/recs/grade/table-refs.html].

Regarding values and acceptability to the target population, in 9 published studies of adults, acceptability varied across studies, yet overall was moderate to high. Acceptability was higher when vaccine was assumed to be free and/or a health care provider made a recommendation. Acceptability varied by study population and methodology. Regarding whether the target population feels that the desirable effects are large relative to undesirable effects, the judgment of the WG is “probably yes.” As for whether there is important uncertainty about or variability in how much people value the main outcomes, the judgment of the WG is that there is possibly important uncertainty or variability.

For acceptability to key stakeholders, the WG notes that there are no recently published data assessing US stakeholder acceptability of routine HPV vaccination among 27 through 45 year-olds. However, vaccines for other conditions are routinely given to adults in this age range. In a 2019 survey about HPV vaccination recommendations based on shared clinical decision-making for individuals, among 45 immunization programs, the majority (27 programs, or 60%) anticipated that it would be either very challenging or somewhat challenging for immunization programs to communicate a recommendation for clinical decision-making to vaccine providers in their jurisdiction. Another 16 programs (36%) said it would be not challenging. Almost half (19 programs, or 42%) thought it would be either easy or somewhat easy for vaccine providers to determine patients in this age group who might benefit from vaccination, while another 19 programs (42%) said it would be not easy. Most (31 programs, or 69%) anticipated challenges to implementing such a recommendation. [Association of Immunization Managers (AIM) survey, January-February 2019]. It is uncertain whether this amounts to an option acceptable to key stakeholders.

Regarding resource use, five health economic models of HPV vaccination in the US were reviewed. In these models, the cost-effectiveness ratio for the current HPV vaccination program ranged from cost-saving to about $35,000 per QALY gained. In the context of the existing program, expanding vaccination to adults through age 45 years would produce relatively small additional health benefits and less favorable cost-effectiveness ratios. For example, the incremental cost per QALY for also vaccinating adults through age 30 years exceeded $300,000 in 4 of the 5 models. Variation in results across models was due to factors such as uncertainties about HPV natural history, as presented earlier in this session [Chesson HW. Overview of Health Economic Models for HPV Vaccination of Mid-Adults. Presentation to ACIP, Atlanta, GA. June 2019].

Also regarding resource use, globally, there is an HPV vaccine shortage as production capacity is not adequate to meet demand currently. The demand/supply imbalance is expected to last for the next 3 to 5 years. In some countries, including those with Gavi and UNICEF support, national introductions and multi-age cohort vaccination are unable to proceed due to lack of vaccine availability. Although no domestic vaccine shortage is anticipated, some WG members had serious concerns about HPV vaccination recommendations being extended to 27 through 45 year-olds in the US in this context. As for whether this option is a reasonable and efficient allocation of resources, the judgment of the WG was probably not.

Regarding feasibility, delivering any adult vaccination can be challenging in the US. Programs and funding for adult vaccination are not available in all jurisdictions, and adult immunization is performed primarily in the private sector. For shared clinical decision-making, identifying individuals likely to benefit from adult HPV vaccination could be challenging. Some vaccine providers do not regularly assess sexual behaviors. However, in a 2015 survey of obstetrician-gynecologists, 81% reported that they already stock and administer HPV vaccine [O'Leary et al. Vaccination Practices among Obstetrician/ Gynecologists for Non-Pregnant Patients. *Am J Prev Med* 2019]. Regarding health disparities and equity concerns, in general, it is not clear whether any recommendation for HPV vaccination in this age range would lead to greater uptake among individuals who are likely versus unlikely to benefit. Some WG members felt that recommending vaccination in this age range might reduce health disparities by increasing access to vaccination among adults with health insurance coverage. On the other hand, other WG members felt that recommending vaccination in this age range might enhance health disparities, as underinsured adults would be less likely to have access to vaccination since states have limited funds for adult vaccination programs. The overall judgment of the WG is that shared clinical decision-making for adult vaccination is probably feasible to implement, although there were a number of uncertainties about the potential consequences.

After weighing the evidence, the judgment of the WG is that the overall balance between desirable and undesirable consequences is closely balanced or uncertain. Taking into account ACIP's role in providing timely guidance for vaccines with an indication from FDA, the WG would like to move forward with a recommendation. The HPV Vaccines WG was unanimous that HPV vaccination should not be routinely recommended for 27 through 45-year-olds. A majority felt that ACIP should recommend the intervention for individuals based on shared clinical decision-making, while a large minority felt that ACIP should not recommend the intervention in this age range. Thus, two policy options for this question are presented to ACIP for consideration. In the next presentation, Dr. Markowitz will offer the proposed recommendation text.

WG Considerations and Proposed Policy Options

Lauri Markowitz, MD
Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

During this session, Dr. Markowitz reviewed the proposed recommendation text for the policy options to be voted on by ACIP. As heard from Dr. Meites, there was consensus on the WG for the first policy issue regarding harmonization of catchup through age 26 years. The WG consensus is "recommend the intervention." This is the current text for routine and catch up vaccination:

- "ACIP recommends routine HPV vaccination at age 11 or 12 years; vaccination can be given starting at age 9 years."
- "ACIP also recommends vaccination for females through age 26 years and for males through age 21 years who were not adequately vaccinated previously. Males aged 22 through 26 years may be vaccinated. (See also: Special populations, Medical conditions)."

The proposed recommendation text would not change the routine recommendation, and would simplify catch-up recommendations to read:

- "ACIP also recommends catch-up vaccination for persons through age 26 years who are not adequately vaccinated."

Due to the limited length of the *Policy Notes*, there will be several footnotes in the proposed Policy Note referring to past recommendations. Specifically for the above statement, there will be a footnote stating the definition of *adequately vaccinated*:

- "Definitions of persons considered adequately vaccinated are unchanged from the prior recommendation."

This is the footnote that will refer to text from 2016 policy that states:

- "Persons who initiated vaccination with 9vHPV, 4vHPV, or 2vHPV before their 15th birthday, and received 2 doses of any HPV vaccine at the recommended dosing schedule (0, 6–12 months), or 3 doses of any HPV vaccine at the recommended dosing schedule (0, 1–2, 6 months), are considered adequately vaccinated."
- "Persons who initiated vaccination with 9vHPV, 4vHPV, or 2vHPV on or after their 15th birthday, and received 3 doses of any HPV vaccine at the recommended dosing schedule, are considered adequately vaccinated."

Text in other sections would be impacted by the proposed harmonization text. In "Special Populations," there is current text for MSM and for transgender persons stating recommendations for vaccination through age 26 years. The proposed harmonization text would replace the current text, which would no longer be needed:

- ~~"For men who have sex with men, ACIP recommends routine HPV vaccination as for all males, and vaccination through age 26 years for those who were not adequately vaccinated previously.~~

- ~~For transgender persons, ACIP recommends routine HPV vaccination as for all adolescents, and vaccination through age 26 years for those who were not adequately vaccinated previously."~~

Similarly, for medical conditions, the current text about catch up through age 26 years for persons with immunocompromising conditions would no longer be needed:

- ~~"ACIP recommends vaccination with 3 doses of HPV vaccine (0, 1–2, 6 months) for females and males aged 9 through 26 years with primary or secondary immunocompromising conditions..."~~

For simplicity, the WG proposed a combined section header and one sentence for special populations and medical conditions reading:

- Special Populations and Medical Conditions
  "The above recommendations for routine and catch-up age groups and for individuals older than the catch-up age group also apply to MSM, transgender people, and people with immunocompromising conditions."

For the second policy issue regarding vaccination of adults older than age 26 years, two options were proposed by the WG: 1) recommend shared clinical decision-making (the majority opinion); or 2) do not recommend the intervention (the large minority opinion). The proposed recommendation text options were:

1) Shared clinical decision-making (majority opinion) option, which will include a footnote defining *adequately vaccinated*:

- "ACIP recommends HPV vaccination based on shared clinical decision making for individuals ages 27 through 45 years who are not adequately vaccinated. HPV vaccines are not licensed for use in adults older than age 45 years."

2) Do not recommend the intervention (minority opinion) option:

- "ACIP does not recommend HPV vaccination for adults older than age 26 years."

In discussions in the WG, some members who favored shared clinical decision-making also mentioned these factors as contributing to why they favor the first option ("shared clinical decision-making"):

- ❑ There are some people in this age range who could benefit from vaccination
- ❑ Public health messages and guidance can be provided
- ❑ Clinicians faced with individual patient requests may do clinical decision-making anyway
- ❑ Health insurance coverage for vaccination might reduce health disparities
- ❑ Communicating who might benefit from vaccination will be fundamentally different for this age range; it is easier for clinicians to discuss sexual risk behaviors with adults than with adolescents
- ❑ This type of recommendation from ACIP would allow flexibility

However, some people felt that recommending vaccination in this age range might enhance disparities and equity concerns, as underinsured adults would be less likely to have access to vaccination since states have limited funds for adult vaccination programs. In discussions on the WG, some members mentioned these factors as contributing why they favor the second option ("Do not recommend"):

- Little public health benefit is expected from vaccinating people in this age range
- Better stewardship of resources
- Adult vaccination might detract from the adolescent vaccination program which is the main focus of the vaccination program
- Communicating who might benefit from vaccination in this age range would emphasize sexual behavior instead of HPV disease prevention, which is not consistent with messaging for adolescents
- Shared clinical decision making is programmatically difficult
- Concern about equitable use of vaccine given the global vaccine shortage

The WG acknowledged the challenges of shared clinical decision-making. Considerations drafted for a *Policy Note* if there is a recommendation for shared clinical decision-making could include:

- HPV is a very common sexually transmitted infection. Although new HPV infections are most commonly acquired in adolescence and young adulthood, some adults are at risk for acquiring a new HPV infection.

- Ideally, vaccination should be given in early adolescence. Vaccination before exposure to HPV through sexual activity will result in the greatest efficacy.

- Vaccine efficacy is high among people who have not been exposed to HPV.

- Vaccine efficacy is lower among people previously exposed to vaccine-type HPV, likely including adults who are considered to be at high risk for HPV-related disease given multiple lifetime sex partners and/or certain immunocompromising conditions.

- Most sexually active adults have already been exposed to some types of HPV, although not necessarily all of the HPV types targeted by vaccination.

- At any age, having a new sex partner is a risk factor for acquiring a new HPV infection.

- No clinical antibody test can determine whether a person is already immune or still susceptible to any given HPV type.

- People who are in a long-term, mutually monogamous sexual partnership are not likely to acquire a new HPV infection.

- HPV vaccines are prophylactic (i.e., they prevent new HPV infections) and do not prevent progression of HPV infection to disease, decrease time to clearance of HPV infection, or treat HPV-related disease.

The WG will continue to review data on vaccine efficacy and effectiveness in special populations, additional modeling results, post-licensure safety, and population impact and effectiveness of vaccination.

The proposed recommendation options for ACIP discussion and vote:

Vote #1:
Routine and Catch-Up Age Groups
"ACIP recommends routine HPV vaccination at age 11 or 12 years; vaccination can be given starting at age 9 years. ACIP also recommends catch-up vaccination for persons through age 26 years who are not adequately vaccinated."

Vote #2:
Shared Clinical Decision-Making Option
"ACIP recommends HPV vaccination based on shared clinical decision making for individuals ages 27 through 45 years who are not adequately vaccinated. HPV vaccines are not licensed for use in adults older than age 45 years."
Do Not Recommend the Intervention Option
"ACIP does not recommend HPV vaccination for adults older than age 26 years."

Discussion Points

Dr. Moore indicated that she shared the WG's position regarding harmonization of the schedule through 26 years of age. While she recognized that there are individuals older than 26 years of age who could benefit from this vaccine and that there is not a current shortage domestically, the potential expansion of this recommendation to include millions more Americans gave her great pause in terms of the supply question. She would not want to do anything that would compromise the supply for the pre-teen and adolescent priority populations. She inquired as to whether they should consider deferring the age 27 through 45 years question and remain silent for a few years until supplies have stabilized, and they can be more confident that the decisions about this age group will not adversely affect access among priority populations where great benefit already has been demonstrated.

Dr. Markowitz replied that the WG heard a presentation from the manufacturer because of similar concerns. She invited a Merck representative to comment.

Rick Haupt (Global Medical Affairs, Merck) said he thought it was important to talk about the global supply in the context of the discussion during the morning. Merck recognizes that there is an imbalance globally in the demand and supply for GARDASIL®9, which they take very seriously. As Dr. Markowitz mentioned earlier, HPV vaccine recommendation goals have changed quite dramatically in the last few years. There have been new indications and recommendations for expanded use of the vaccine in many countries around the world, which has created an unprecedented demand on the GARDASIL®9 supply. As part of Merck's global commitment to support global public health, they are making substantial investments to improve that supply. It will take a few years to manage that, but in the short-term they are working with countries around the world to try to provide vaccine adequately and equitably across both high- and low-resource settings. As it pertains to the US, Merck fully anticipated the recommendations being discussed during this session in terms of the harmonization through 26 years of age and potential recommendations for shared clinical decision-making for those 27 through 45 years of age and have the supply to be able to manage those recommendations if voted on during this session. It is important to note, particularly in the 27 through 45 year olds, there are individuals in that age group who remain susceptible to one or more of the HPV types that are in GARDASIL®9. Many individuals are at risk for new infections in this age group. A shared clinical decision-making recommendation would be the appropriate recommendation to allow

individuals the opportunity to have access to the vaccine so that they can be protected from HPV-related disease, including cancer.

Dr. Ezeanolue observed that when the FDA approves a vaccine, it gives clinicians the power as physicians to use shared decision-making. If that is the case, ACIP's role is different from FDA's role, and ACIP should consider all of the other things that are of public health importance. From what he was hearing based on the presentations was that there is little public health importance in expanding the HPV vaccine recommendation to 27 through 45 year olds. He wondered what the policy implication would be if ACIP recommended shared decision-making, which seems already to be possible for physician with the FDA approval except for the issue of who pays for the vaccine. If ACIP does not make the recommendation, clinicians will still be able to use shared decision-making, but it would not be paid for. He just wanted to ensure whether this interpretation of the difference was correct. Dr. Markowitz confirmed that this was basically a correct interpretation. If a vaccine is licensed by the FDA, an individual can have a discussion with a provider and make a decision about whether they want the vaccine. If it did not have an ACIP recommendation for even shared clinical decision-making, her understanding was that it would not be covered by insurance.

Dr. Messonnier emphasized that this is complicated; they needed to step back to think about this in the context of all of the clinical decisions that are shared between a clinician and a patient. She thought the problem with ACIP remaining silent would be that among certain cadres of clinicians, it would be interpreted that basically ACIP thinks there should not be a conversation.

Dr. Cohn added that an ACIP recommendation for shared clinical decision-making would be reflected on the Adult Immunization Schedule; whereas, it would not be reflected there if ACIP stayed silent. Being on the schedule alerts providers and raises their awareness that they need to bring this to their patients to discuss.

Dr. Romero added that this also is an issue of equity in terms of the cost of the vaccine and who will have access.

Dr. Bernstein asked whether they knew how many individuals 27 through 45 years of age have commercial insurance and how many would have to self-pay to get the vaccine.

Dr. Markowitz reminded ACIP members that not everyone on the WG felt that clinical decision-making would lead to equity. Because there is not a lot of funding for adult vaccination, for those who do not have insurance, it would not necessarily increase equity.

Dr. Ezeanolue said he understood the rationale for ACIP making a shared clinical decision-making recommendation, but he felt that then ACIP would never make a recommendation that is "do not recommend" because the default recommendation would always be shared decision-making. There is an uncertain public health importance to expand this particular recommendation. Based on that, he thought ACIP should say "do not recommend" based on the lack of public health importance, irrespective of payment issues. There is a science to evidence-based decision making, and here the science says that there is uncertain public health importance.

Dr. Talbot did not foresee HPV vaccination being expanded to all women through 45 years of age. However, there are women at risk, perhaps those who are recently divorced or are getting married for the first time at 40 and have not been vaccinated who might be able to benefit from getting immunized. She did not want that opportunity only to be for wealthy women. It needs to be for all women.

Dr. Atmar added that this vaccine is immunogenic and appears to be effective in the age group under consideration. There are many clinicians who look at the ACIP recommendations to determine what should be given to their patients. If ACIP votes for "do not recommend" rather than the default shared decision-making, that will have a significant impact, particularly for some patient groups who may have risk factors for new infections and are not protected but may well be susceptible and at risk. While he agreed that shared decision-making is the default for any licensed drug, the effect that ACIP has on practice throughout the US is substantial.

Dr. Szilagyi thought that within the WG, the vast majority think that a small number of men and women might benefit from this vaccine. He did not hear anybody in the WG talk about large numbers of people benefitting. The challenge regards how to identify high risk individuals. To him there are two groups of high risk individuals, those who were high risk for HPV when they were younger and are continuing to be very high risk for new infections or those who were not as high risk and now have a new sexual partner or for behavioral reasons now are high risk. Shared decision-making is done all of the time in the adult world and is standard of care. He personally is worried about equity issues, and to him the important thing would be to try to identify and then perhaps vaccinate the very small number of individuals who would benefit from vaccine and not vaccinate the vast majority of women and men 27 through 45 years of age. Guidance from ACIP that could follow a recommendation of shared decision-making could help that. He also thinks more research is needed to determine who the very high risk patients are.

Dr. Walter echoed that and said that if they do adopt a shared decision-making recommendation model, the guidance that will follow will be important for the individual provider in discussing issues of risk with their patients.

Dr. Frey agreed with the majority of what had been said. She pointed out that it is more likely that an insurance company would pay for vaccination if it was recommended by ACIP.

Dr. Lee said she thought she was hearing that with population-level considerations there is a "yes" or "no" vote, such as occurred with RotaShield®. It sounded to her like shared clinical decision-making was really about the individual and clinician decision, recognizing that there is benefit to certain people but that perfectly identifying every individual in a general recommendation is a challenge. This would allow them some flexibility to be able to protect those who they think are interested in protection and may be at higher risk, which only could be assessed in a conversational setting. That said, she specifically asked the WG whether they need to formally assess and evaluate the impact of any recommendation they make on disparities. That would be incredibly helpful, particularly as they move into the shared clinical decision-making world. These decisions are no longer as straightforward as a simple "yes" or "no."

Dr. Wharton answered Dr. Bernstein's earlier question by indicating that according to the Census Bureau data from 2017, approximately 15% of individuals 26 through 45 years of age are uninsured. Medicaid is probably considered insured, but the degree to which Medicaid would cover this is likely to vary by state.

Dr. Szilagyi added the highest age at which young adults can be on parents' insurance is 26 years, so the issue of 27 through 45 does not involve that age group. Among those who have either private insurance or Medicaid, the majority have private insurance.

Dr. Moore pointed out that they had not seen anything presented about what the potential economic issues would be in terms of shared clinical decision-making. They only heard estimates for a routine recommendation for this group. While she agreed with Drs. Szilagyi and Talbot that among men and women in this age group, there are a small proportion who would benefit, they have not seen what shared clinical decision-making guidance would look like and what that implies in terms of the proportion of the population in this age group who would fall under those categories. She would feel more comfortable voting to recommend a shared clinical decision-making if she knew what that guidance would look like and for which people in this population it would apply. Thus, her preference was to delay voting on that component until later.

Dr. Hunter stressed that they should be careful to avoid making recommendations that inadvertently emphasize vaccinating adults more than children for certain infections, often because the benefit is greater in the children and adolescents. He also expressed concern about the list of considerations for shared decision-making. While he thought they were quite good for general reflection in an academic setting, but they may be very difficult to implement in clinical practice.

Dr. Fryhofer (AMA) said that speaking as a practicing physician and as a member of the WG, as Dr. Markowitz indicated, this was a very difficult decision for this WG. There was a majority decision, but there also was a very strong minority decision. She thought Dr. Moore raised some very important points, and she was very impressed by the deliberations she had heard during this session. One of her great concerns as a practicing physician, as an internist who sees children and adults of all ages, is that there is only a certain amount of vaccine. It is known that this vaccine works best in children. She also was concerned about mixed messaging. Having seen what has happened in the public arena in the past when a recommendation is made and the shared decision-making items are not so clearly defined is that it may be expanded to people who do not necessarily need it, which is not a great use of resources. This is not an inexpensive vaccine. It is a wonderful vaccine and to her is one of the most important things ACIP has addressed. In fact, ACIP voted to give HPV vaccine during her first ACIP meeting. This is a very tough decision and the details of the shared clinical decision-making need to be made very clear. This is not needed for every patient 27 through 45 years of age.

Dr. Messonnier reminded everyone that there had been recent discussions during previous ACIP meetings about how the decisions CDC was asking them to make were becoming harder than in a previous generation of decisions. She thought the second issue fell into that category. CDC recognized that there were gaps in the information ACIP had and that this made it hard to make a decision. However, it was not like they would have answers to these questions in the short-term. She made the commitment that whatever decision ACIP made, CDC would make the appropriate research questions a priority. If ACIP decided not to recommend this right now, CDC would work hard to determine what groups potentially would benefit from additional vaccination and bring the issue back a couple of years from now. If they decided to approve the shared clinical decision-making, CDC could figure out how that would be implemented and what the implications would be in terms of who is getting the vaccine, whether it is exacerbating equity issues, if there are going to be supply issues, et cetera. Given that no additional data are anticipated in the next 6 months, CDC preferred that ACIP come to some type of consensus or

conclusion on the second issue with the understanding that like anything, they will continue to research the issue.

In terms of the comment about the considerations she showed and whether they would be helpful, Dr. Markowitz said the WG realized that those were not guidance and they changed the term from “guidance” to “considerations.” It is true that it is very difficult to identify patients who might benefit. She agreed that those descriptions needed to be further refined, and they do have plans to try to review efficacy and effectiveness in special populations and do some modeling to determine whether they can identify people who would benefit. In terms of what Dr. Fryhofer mentioned, she confirmed that there was much discussion within the WG. There was a strong minority opinion opposed to shared clinical decision-making because of the difficulty identifying people, among other reasons, and concerns that a recommendation for shared clinical decision making would give license to some groups to be more actively promoting the vaccine.

Dr. Middleman (SAHM) expressed appreciation for this conversation. With the potential vote for shared clinical decision-making, she thought it was very important to have very clear guidance. She was somewhat concerned about the use of gender identity as an identification of risk. Gender identity is distinct from sexual behaviors. If they did vote on shared clinical decision-making, she thought they should create guidance that is as specific as possible about behaviors rather than groupings of people.

Dr. Eckert (ACOG) assured the voting members that from ACOG’s perspective, they already have had extensive internal discussions about how they would try to provide guidance for shared clinical decision-making, knowing that many women in their patient population could benefit from this vaccine and at the same time knowing that not everybody in this age group needs this vaccine. She thought this would be a very active area and that ACOG would engage heavily in trying to assist its providers with guidance.

Dr. Rockwell (AAFP) said she felt like they were almost giving clinical and shared decision-making too much discussion and weight. In her clinical practice, she sees children and adults and has been doing so for over 25 years. She felt that it would not be difficult for her to recognize who might benefit from HPV vaccination, such as a newly divorced woman or a 28-year old patient who has never had sex and is now getting married. Therefore, she did not think ACIP needed to be that explicit in these recommendations. It seemed that they were giving HPV more attention than it actually needed compared to other vaccination recommendations. In terms of the recommendations for boys or young men for shared clinical decision-making, they did not have this type of discussion.

Dr. Szilagyi said he agreed that it is much easier in the adult world to identify behaviors and internist and family physicians do this all of the time. It is much more difficult in the pediatric world to identify current behaviors or behaviors in the next year or two. He agreed that this is about identifying behaviors rather than demographic characteristics.

Dr. Ezeanolue said he thought HPV vaccine did require the attention that it was getting. He has family members who have died from this cancer.. He wants people to get the HPV vaccine when it is most efficient, most cost-effective, and when it is of public health importance. The idea was not about limiting people from getting HPV vaccine. It was actually about increasing the number of people getting HPV vaccine by focusing on the target group where they get the best “bang for the buck.” What he was challenging was that shared decision-making is different from focusing on target groups. The woman who gets divorced may have received the vaccine

at 16. The idea is that if someone already received the vaccine on time, it does not matter if they get divorced or have a new sex partner later. The idea is to get people to receive it on time in the first place. The challenge he has was that if ACIP made this decision today, he could not imagine any other scenario where ACIP would be able to say "no" to any vaccine. Once FDA approved it, they were saying this vaccine is safe for use in individuals. However, that is not the role of ACIP. It is the role of the FDA. Once FDA approves it, what goes through his mind as a clinician in practice is that he now has the shared clinical decision making background. He thought that scenarios when ACIP could say "no" is where there were other considerations for example, use of resources. Should we use the resources to target more HPV immunizations at age 10 to 26 years, where there will be a public health benefit, or should we use those resources to focus on an older age group where there is questionable public health importance?

Dr. Markowitz said the point Dr. Ezeanolue was making was exactly why no one on the WG favored a routine catch-up recommendation for adults through age 45 years, and also was one of the reasons some WG members had concerns about even shared clinical decision-making. These issues certainly entered into the decision about not extending routine catch-up through 45 years of age.

Dr. Romero indicated that unless there were further comments, they needed a motion and second for each of the two recommendations to prepare for the vote following public comment.

Dr. Szilagyi made a motion, which Dr. Walter seconded, to approve the proposed recommendation text for harmonization reading:

> Routine and Catch-Up Age Groups
> "ACIP recommends routine HPV vaccination at age 11 or 12 years; vaccination can be given starting at age 9 years.
> ACIP also recommends catch-up vaccination for persons through age 26 years who are not adequately vaccinated."

Dr. Frey made a motion, which Dr. Lee seconded, to approve the proposed recommendation text option for vaccination of adults older than age 26 years based on shared clinical decision-making reading:

> "ACIP recommends HPV vaccination based on shared clinical decision-making for individuals ages 27 through 45 years who are not adequately vaccinated. HPV vaccines are not licensed for use in adults older than age 45 years."

Dr. Hunter inquired as to whether he could make a motion instead that HPV vaccination for adults older than age 26 is not recommended.

Dr. Romero clarified that he could not, as they must vote on the first motion and then if necessary take up Dr. Hunter's motion.

Dr. Hunter did not think this made sense logically. He objected to this pointing out that the order not to recommended HPV vaccination for adults older than age 26 would make more sense.

Dr. Cohn emphasized that the motion already had been placed on the table for shared clinical decision-making, following which another motion could be placed on the table if it did not pass. She clarified that they were making the motions for the votes and then staying the vote until the

afternoon sessions subsequent to the Public Comment period. The votes are included here for continuity.

Motion/Vote #1: Harmonization of Catch-Up Vaccination Through 26 Years

Dr. Szilagyi made a motion to approve the proposed recommendation text for harmonization reading, Routine and catch-up age groups: "ACIP recommends routine HPV vaccination at age 11 or 12 years; vaccination can be given starting at age 9 years. ACIP also recommends catch-up vaccination for persons through age 26 years who are not adequately vaccinated." Dr. Walter 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, Bernstein, Ezeanolue, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
0 Opposed: N/A
0 Abstained: N/A

Prior to the vote pertaining to shared clinical decision-making, Dr. Markowitz shared the main discussion points made by WG members who favored "shared clinical decision-making" and those who favored "do not recommend."

Discussion: WG Members Who Favored "Shared Clinical Decision-Making"
- There are some people in this age range who could benefit from vaccination
- Public health messages and guidance can be provided
- Clinicians faced with individual patient requests may do clinical decision-making anyway
- Health insurance coverage for vaccination might reduce health disparities
- Communicating who might benefit from vaccination will be fundamentally different for this age range; it is easier for clinicians to discuss sexual risk behaviors with adults than with adolescents
- This type of recommendation from ACIP would allow flexibility

Discussion: WG Members Who Favored "Do Not Recommend"
- Little public health benefit is expected from vaccinating people in this age range
- Better stewardship of resources
- Adult vaccination might detract from the adolescent vaccination program which is the main focus of the vaccination program
- Communicating who might benefit from vaccination in this age range would emphasize sexual behavior instead of HPV disease prevention, which is not consistent with messaging for adolescents
- Shared clinical decision making is programmatically difficult
- Concern about equitable use of vaccine given the global vaccine shortage

Motion/Vote #2: Shared Clinical Decision-Making

Dr. Frey made a motion to approve the proposed recommendation text option for vaccination of adults older than age 26 years based on shared clinical decision-making reading, "ACIP recommends HPV vaccination based on shared clinical decision-making for individuals ages 27 through 45 years who are not adequately vaccinated. HPV vaccines are not licensed for use in adults older than age 45 years." Dr. Lee seconded the motion. No COIs were declared. The motion carried with 10 affirmative votes, 4 negative votes, and 0 abstentions. The disposition of the vote was as follows:

10 Favored: Atmar, Ault, Frey, Lee, McNally, Romero, Stephens, Szilagyi, Talbot, Walter
4 Opposed: Hunter, Moore, Ezeanolue, Bernstein
0 Abstained: N/A

Discussion After HPV Votes

Dr. Romero invited members to share their rationale for how they voted.

Dr. Ault noted that he is a new member of ACIP and the WG, and he thought Dr. Szilagyi summarized what he was thinking earlier in the day when he said that they did not have a consensus for a broad recommendation, but there may be a few individuals in this age group who would benefit from vaccination.

Dr. Szilagyi emphasized that he voted "yes" because of what he said earlier about believing that the proportion of patients who would benefit is small but exists, high risk individuals can be identified, guidance following the vote would be very helpful for clinicians, and the majority of patients in this age group should not receive the vaccine.

Dr. Bernstein indicated that he voted "no" because he was concerned about potential disparities, difficulty in implementing this in clinical practice, concern about the vaccine supply in the US and worldwide, and lack of clarity regarding how this may negatively impact immunization rates of teenagers and young adults.

Dr. Ezeanolue said that he voted "no" because he supports HPV vaccine and does not want the focus to change and move away from the target audience where the vast majority of benefits occur, which is among those younger than 26 years of age. Considering that there already is a global shortage, diversion to a smaller group where there is little demonstrated effectiveness or public health value does not seem prudent. He was concerned that there is always a pressure on the imbalance between supply and need, and that the focus may be shifted away from millions of young girls in countries that may not be able to stock these vaccines because of a shifting focus. This runs the risk that some countries may delay administration of HPV vaccine. He supports HPV vaccine, but wants to reach the greatest majority of people who will benefit from it.

Dr. Stephens indicated that he voted "yes" because he thinks this is an effective and safe vaccine. He does believe that "shared clinical decision-making" in this case needs to be well-defined by the guidance, because this is an area in which there are certain situations where this vaccine could be effective.

Dr. Moore said that she voted “no” because there were no details on the shared clinical decision-making, for whom they would be suggesting this vaccine would be appropriate, or what size of the population of men and women in that large age group would be suggested. In the absence of any information on the details of what that means and in the presence of supply questions, she did not feel comfortable expanding a recommendation to such a huge population. She also was concerned that despite assurances from the manufacturer, supply could become a problem that distracts from the priority recipients and she did not want to do anything to compromise that.

Dr. Hunter said he voted “no” because he was worried that this would send a negative message that vaccinating at a younger age is not as important and effective as it is. Because of that and because the guidance might not be as clear or effectively communicated by the public sector, the private sector may communicate this in a way that meets their best interests, and that clinicians may choose the easy way out based on their perception that most parents have a problem with this vaccine though the data show that that is not true.

Dr. Walter indicated that he voted “yes” to allow for shared clinical decision-making to allow those at risk to get the vaccine, but he does believe that additional guidance needs to be provided.

Dr. Frey said she voted “yes” because she appreciated the concern about perhaps missing earlier HPV vaccination at the recommended age range. The guidance included in the ACIP recommendation statement will provide support for the idea that young children should get vaccinated to prevent cancer and those who missed vaccinations would have the opportunity to receive the vaccine later.

Dr. Romero indicated that he voted “yes” for all of the reasons state previously. He observed that this is likely to be a frequent issue in the future that the ACIP will be dealing with as vaccines become more complex and more targeted for certain populations.

Pneumococcal Vaccines

Introduction

Grace Lee, MD, MPH
Pneumococcal Vaccines WG Chair
Advisory Committee on Immunization Practices

Dr. Lee reminded everyone that the Pneumococcal Vaccines WG’s terms of reference are to: 1) Review current data on efficacy, effectiveness, immunogenicity, and cost-effectiveness of pneumococcal vaccines; 2) Review current recommendations considering up-to-date evidence, including epidemiological studies conducted post-licensure, and assess strength of the evidence; and 3) Revise or update recommendations for pneumococcal vaccine use, as needed.

ACIP recommended pneumococcal conjugate vaccine (PCV)7 for children in 2000, followed by PCV13 in 2010 when that became available. In 2012-2013, ACIP recommended PCV13 for individuals with immunocompromising conditions. In 2014, ACIP recommended PCV13 in series with PPSV23 for adults ≥65 years of age. The WG is currently re-evaluating the use of PCV13 in adults ≥65 years of age. When ACIP recommended PCV13 in series with PPSV23 for adults ≥65 years of age in 2014, the rationale was that the recommendation was in the short-term because there was still a significant burden of disease among older adults, particularly due to pneumococcal pneumonia. The long-term public health benefits at that time were expected to be limited since the indirect effects from the pediatric PCV13 use were expected to increase. Thus, the recommendation was made in 2014 with a commitment to re-evaluate this policy 4 years later and revise it as needed.

The policy question the WG has been examining is, "Should PCV13 be administered routinely to all immunocompetent adults aged ≥65 years in the context of indirect effects from pediatric PCV use experienced to date?" The population of interest is immunocompetent adults ≥65 years of age. The intervention is PCV13 in series with PPSV23 in the context of indirect effects. The comparison is PPSV23 alone in the context of indirect effects. The core outcomes are invasive pneumococcal disease (IPD), pneumonia, mortality, and safety.

Again, the population covered by the policy question are immunocompetent adults ≥65 years of age. Not included in the current policy discussion are adults ≥19 years old with an immunocompromising condition, including:

Chronic renal failure	Generalized malignancy
Nephrotic syndrome	Hodgkin disease
Immunodeficiency	Leukemia or Lymphoma
Iatrogenic immunosuppression	Multiple myeloma
HIV	Solid organ transplants
Cochlear implants	Congenital or acquired asplenia
CSF leaks	Sickle cell disease or other hemoglobinopathies

Adults ≥19 years old with one of the above immunocompromising condition are still recommended to receive PCV13 in series with PPSV23 based on ACIP's 2012 recommendations.

The proposed policy options for a vote during this meeting:

A. ACIP recommends PCV13 for all adults ≥65 years who have not previously received PCV13. PCV13 should be given first, followed by a dose of PPSV23 (2014 recommendation as currently stated).

B. ACIP recommends PCV13 based on shared clinical decision-making for adults ≥65 years who do not have an immunocompromising condition and who have not previously received PCV13. All adults ≥65 years should receive a dose of PPSV23.

C. ACIP no longer recommends PCV13 for adults ≥65 years who do not have an immunocompromising condition. All adults ≥65 years should receive a dose of PPSV23 (pre-2014 policy).

In terms of the WG rationale, the goal was to re-evaluate the 2014 policy to recommend PCV13 in series with PPSV23 for adults ≥65 years. The WG began with this thinking about continuing the 2014 recommendation and thought that the answer should be "yes" or "no." The WG proposed to focus on whether to continue the current recommendation as the goal of its re-evaluation. Further discussions among the WG members revealed that "no" could mean two different things, shared clinical decision-making or no longer recommending. Dr. Lee expressed her hope that based on Dr. Matanock's presentations and the discussion, ACIP would recognize the diversity among the WG members, who were split amongst the three options and there was no clear consensus as this is such a complex decision.

Dr. Lee indicated that during this session, presentations and discussion would focus on the following topics:

- ❑ Considerations for PCV13 use among adults 65 years and older and a summary of the EtR
- ❑ Proposed policy options
- ❑ Feedback from liaison and *ex-officio* members on the policy options proposed
- ❑ Discussion about the considerations for PCV13 use among adults ≥65 years old

Considerations for PCV13 Use Among Adults ≥65 Years Old and A Summary of the EtR Framework

Almea Matanock, MD, MS
National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Matanock summarized the considerations for PCV13 use among adults ≥65 years of age, as well as the EtR Framework. In re-evaluating PCV13 use, the following key questions were considered:

- ❑ What **indirect effects** from pediatric PCV13 use were observed among adults aged ≥65 years before 2014?

- ❑ What **effects** from PCV13 use have we observed among adults aged ≥65 years since 2014?
- ❑ What **additional benefits** are expected from continued PCV13 use among adults aged ≥65 years given the remaining disease burden?

As a reminder, the population covered by the policy question are immunocompetent adults ≥65 years of age. Not included in the current policy discussion are adults ≥19 years old with an immunocompromising condition as identified by Dr. Lee, who are recommended to receive PCV13 in series with PPSV23 per the 2012 ACIP policy. The 2012 policy is not part of the current re-evaluation.

In terms of the first key question regarding indirect effects, since PCV's first introduction in 2000, there was a 9-fold reduction observed in PCV13-type IPD from 2000 through 2014. This included a 3-fold reduction in PCV13-type IPD after PCV13 introduction for children from 2010-2014. PCV13-type disease incidence among adults 65 years and older declined through indirect effects from 45/100,000 before 2000 to 5/100,000 in 2014[1]. Reductions in all-cause pneumonia in adults ≥65 years old were demonstrated after pediatric PCV7 introduction in 2000[2]. Analysis of Healthcare Cost and Utilization Project (HCUP) data between 2010-2014 presented to ACIP did not observe any reductions in all-cause pneumonia, but demonstrated that there were

declines from indirect effects in pneumococcal pneumonia of 35% (-40% to -17%) for adults 65-74 years of age and 20% (-40% to 8%) for adults ≥75 years of age[3] [[1]Active Bacterial Core Surveillance, unpublished data; [2]Tsaban et al. 2017; [3]Lessa ACIP October 2018].

An inquiry was posed during the last ACIP meeting regarding what indirect effects from pediatric PCV13 use have been observed among older adults by age, race, ethnicity, and underlying chronic medical conditions. Indirect effects were observed for all age groups. Disparities by age in PCV13-type disease were reduced but not eliminated. Indirect effects reduced PCV13-type IPD among adults of black race[1], Navajos[2], and Alaska Natives[3]. Disparities in PCV13-type IPD for Alaska Natives and Navajos versus the general population have been reduced but not eliminated. In terms of indirect effects by underlying medical conditions, there has been a similar percent reduction in PCV13-type disease amongst adults ≥65 years old with chronic medical conditions, including chronic heart, liver, and lung disease; diabetes, alcohol abuse, and cigarette smoking as compared to healthy adults[1] [[1] Active Bacterial Core Surveillance, unpublished data; [2] John Hopkins Center for American Indian Health, unpublished data; [3]CDC, Arctic Investigations Program, unpublished data].

For PCV13 individual-level effectiveness and PCV13 safety, it was known in 2014 that PCV13 was efficacious in prevention of IPD and non-bacteremic pneumonia. Results from the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) showed a 75% reduction in vaccine type IPD and a 45% reduction in vaccine type non-bacteremic pneumonia. Additionally, PCV13 safety had been demonstrated in clinical trials. In 2014, the GRADE evaluation demonstrated a strong quality evidence supporting PCV13 use in series with PPSV23 for all adults ≥65 years. Post-licensure data were incorporated into GRADE this year and similar conclusions were observed about PCV's benefits and harms. PCV13 is effective against PCV13-type IPD with a VE of 47% to 75%, PCV13-type non-bacteremic pneumonia VE of 38% to 71%, and all-cause pneumonia VE of 6% to 11%. There are limited data for PCV13-type disease mortality. However, no VE has been demonstrated for this outcome. For harms, no new safety signals or unexpected patterns have been observed in terms of SAEs associated with PCV13.

PCV13 uptake among adults ≥65 years is now 47%, with 30% of adults ≥65 years having received both PCV13 and PPSV23. PCV13 coverage among this age group was 36% in 2016 and 47% in 2018 [Bardenheier. CDC/Immunizations Services Division—Centers for Medicaid and Medicare, unpublished data].

In terms of the combined direct and indirect population-level impact on disease since 2014, there have been no changes in IPD incidence among adults ≥65 years based on data from 2013-2017. No continued direct or indirect effects have been observed at the population level since 2014. Additionally, non-PCV13 serotypes now make up the majority of the disease burden. No population-level impact on mortality has been associated with PCV13-type IPD since 2014, nor have there been any changes in the case fatality ratio (CFR)[1]. Trends in non-invasive pneumococcal pneumonia (NIPP) incidence[2] were evaluated from 2013-2016, and trends evaluated in NIPP were compared to invasive pneumococcal pneumonia from ABCs[1]. The trends in the two are similar. Incidence was higher for adults ≥65 years as compared to the younger age groups, but the trends in the two groups were similar. A decline was observed in non-invasive pneumonia between 2013 and 2014 during a period of only indirect effects, but no further population-level impact has been seen on non-invasive or invasive pneumonia since 2014 [[1]Active Bacterial Core Surveillance, unpublished data; [2]Gierke. ACIP October 2018. Surveillance for Non-Invasive Pneumococcal Pneumonia (SNiPP), unpublished data].

A population-level impact on PCV13-type pneumonia was observed in the Pfizer Louisville Cohort Study. Reductions of 35.1% in PCV13-type pneumonia and 13.8% in all-cause pneumonia were demonstrated between the 2014-2015 year and the 2015-2016 year. PCV13-type pneumonia was measured to be 4% of all-cause pneumonia versus the 10% that it was estimated to be in 2014 [Swerdlow. ACIP June 2018. Pfizer, Louisville Cohort Study, unpublished data].

Regarding additional benefits expected from continued PCV13 use among adults ≥65 years given the remaining disease burden, PCV13-type IPD disease has remained stable since 2014 with an incidence of 5/100,000 representing 20% of all IPD. Serotype 3 is not only the most common PCV13 serotype, but also is the most common overall for IPD[1]. For PCV13-type pneumonia, incidence ranges from 17/100,000[2] to 76/100,000[3]. Again, PCV13-type pneumococcal pneumonia is 4% of all-cause pneumonia and serotype 3 is the most common [[1]Active Bacterial Core Surveillance (ABCs), unpublished data; [2]Gierke. ACIP October 2018. Surveillance for Non-Invasive Pneumococcal Pneumonia (SNiPP), unpublished data; [3]Swerdlow. ACIP June 2018. Pfizer, unpublished data].

Two economic models estimated the public health impact and cost-effectiveness of PCV13 in series with PPSV23 as compared to PPSV23 alone, the CDC model included two different assumptions about the effectiveness of PCV13 against serotype 3 disease. The estimated cases averted for PCV13-type IPD were 76 to 175 cases, and 4000 to almost 11,000 for PCV12-type pneumonia in a single cohort of 65 year olds. Applying the cost to QALY, the estimated cost-effectiveness ratio is between $200,000 and $560,000 per QALY. The annual NNV for adults ≥65 years would be 26,000 vaccinated to prevent 1 case of IPD; 3000 to 14,000 vaccinated to prevent one case of in-patient pneumonia; and 2600 vaccinated to prevent 1 case of outpatient pneumonia per year.

There were a few additional important considerations from the EtR framework. First, there are limited data regarding the values and preferences of older adults regarding PCV13 use. In 3 patient-focused studies, participants perceived pneumonia as severe and sometimes fatal[1-3]. However, there was low perceived personal susceptibility to pneumonia[1-2]. The WG's perspective was that the potential protection against pneumonia likely outweighs the effects of PCV13 for older adults [[1] Doshi et al. 2016; [2] Brown et al. 2017 (PPSV23 only); [3] Kaljee et al. 2017].

There also are limited data on assessing acceptability among stakeholders. Based on the studies reviewed, some found that current recommendations are confusing for providers[1] and reimbursement for vaccine is still a programmatic issue for some[3]. However, in other studies, providers recommended continuing with the current recommendation[2]. Keeping the current recommendations also was noted to be a preference programmatically if higher valency conjugate vaccines were going to be available soon[3]. In addition to these study results, the WG also noted that frequent changes in recommendations may negatively impact the perceived importance of future adult vaccine recommendations. On one side of the argument, continued PCV13 use provides individual-level protection for the remaining PCV13 disease burden. But on the other side of the argument, continued PCV13 use provides minimal public health benefit due to the low remaining disease burden [[1] Hurley et al. 2018; [2] Pfizer sponsored provider survey, unpublished, 2018; [3] Association of Immunization Managers (AIM) survey, unpublished, 2018].

When considering feasibility, a number of issues were raised. The current recommendations are complex, but have been integrated into many health care and public health systems. Frequent changes to recommendations could present implementation challenges. Universal age-based recommendations are easier to implement effectively than risk-based recommendations. Effective communication strategies will be needed if a policy change occurs.

In summary, this table compares the key issues favoring continued PCV13 use versus no longer using PCV13:

Element	Favoring Continued PCV13 Use	Favoring No Longer using PCV13
Burden of Disease	• PCV13-type disease reduced, but not eliminated through indirect effects from pediatric PCV use	• Indirect effects from pediatric PCV use have reduced the burden of PCV13-type disease to historic lows
Benefits	• PCV13 effective in preventing PCV13-type pneumococcal disease	• Impact from PCV13 use in older adults observed to date is minimal; no impact on IPD and inconsistent findings across studies for impact on pneumonia • Benefits from continued PCV13 use are expected to be minimal
Acceptability	• Frequent changes in recommendations may negatively impact the perceived importance of future adult vaccine recommendations	• Credibility comes from evidence-based recommendations
Resources Used	• A recommendation change would incur a cost to update electronic medical records, decision support tools, etc.	• Economic analyses results do not favor continued PCV13 use
Feasibility	• Universal prevention strategies are easier to implement effectively than risk-based ones • Frequent changes in recommendations present implementation challenges	• Simplifies the recommendations—current recommendations have been confusing and difficult to implement

In conclusion, the WG agrees that by far, PCV13's greatest impact for adults has been through indirect effects from pediatric use. Since 2014, consistent population-level impact has not been observed from PCV13 use amongst older adults. Continuing PCV13 would not be cost-effective by usual standards. On the other hand, frequent changes and recommendations may negatively impact the perceived importance of adult pneumococcal vaccine programs and present implementation challenges. Some WG members weighted more heavily the former strong scientific rationale in favor of changing the recommendation, while others weighted more heavily the latter acceptability and feasibility issues in favor of maintaining the current recommendation.

Dr. Matanock posted the proposed Policy Options for review and discussion:

A. Recommend PCV13: "ACIP recommends PCV13 for all adults 65 years or older who have not previously received PCV13. PCV13 should be given first, followed by a dose of PPSV23."

B. Shared clinical decision making: "ACIP recommends PCV13 based on shared clinical decision making for adults 65 years or older who do not have an immunocompromising condition and who have not previously received PCV13. All adults 65 years or older should receive a dose of PPSV23."

C. No longer recommend PCV13: "ACIP no longer recommends PCV13 for adults 65 years or older who do not have an immunocompromising condition. All adults 65 years or older should receive a dose of PPSV23."

Discussion Points

Dr. Szilagyi said it seemed to him that in this context of immunocompetent persons ≥65 years of age, shared decision-making would not depend on an observable behavior or something that could be discerned from an interview. This is very different from the previous discussion about shared decision-making for HPV vaccine. It was not clear what guidance would be offered to clinicians for shared decision-making in this context other than patient values. As a primary care physician (PCP), although he does not take care of adults, simplifying something is less disruptive and less of a challenge than adding something. That is, this seems like less of a challenge than other decisions ACIP has made.

Drs. Frey and Walter also questioned how shared decision-making would be accomplished with this vaccine in this context.

Dr. Lee said she thought there was a recognition that the population-level benefit is minimal in the context of the indirect effects from the pediatric vaccination program, and that the pediatric vaccination program has been the most impactful on adult burden of disease. That said, there also is a recognition that there is some individual benefit to patients who may be exposed to PCV13-type pneumonia. The challenge is that the burden of disease due to PCV13 specific serotypes is low compared to all-cause pneumonia. That particular construct came up because of the tension the WG members were having between population-level decision-making versus individual-level decision-making. There also is the challenge of recognizing that there is a distinction between a risk-based recommendation versus shared clinical decision-making. Because they were unpacking this construct during this session, she invited everyone to weigh in and comment on it. She could imagine that there are certain populations, such as the American Indian/Alaska Native (AI/AN) population, for whom that latitude in decision-making may be appropriate to think about populations in which there are higher endemic risk. In that situation, it would make sense for a clinician to target that particular population.

Dr. Ezeanolue stressed that there always would be the challenge of population-based benefit versus individual-based benefit for vaccines. There always will be some population, however small, who will benefit. He did not think that when ACIP said "do not recommend" they were passing judgment on whether one person or a small percentage of people may be affected. He thought ACIP was tasked to look at the bigger picture and larger perspective and whether chasing a smaller population would draw away from the target population. When vaccine is available, he thinks everyone should have an opportunity to have it, including the one person that it might affect. But the world is a global place. When they expand to smaller populations, they draw vaccines away from those who cannot get this vaccination because it is not available to them. There is a shift that happens globally when ACIP makes these recommendations for a smaller group of people that will pull from what is needed for a very large group of people who need the vaccine. In the end, they are not doing the general public good. He asked again

whether there is an anticipated shortage of this vaccine, which should help them in making the decision.

Dr. Walter thought that the individual-level falls upon the strength of the provider recommendation more than shared decision-making in this case. This is not a risk-assessment with a patient. It is a provider assessment for their practice in this case.

Dr. Talbot pointed out that it is important to note that there will be newer, better, and more comprehensive conjugate vaccines in the near future. Therefore, it may become more complicated to remove and then try to add back. In terms of adding back, adults ≥65 years of age who are not immunocompromised per se have some immunosenescence, and the conjugate vaccines provide B-cell and T-cell responses. Removing the conjugate and allowing just the polysaccharide will blunt the future conjugate responses. Therefore, she worried about removing PCV13 from an immunologic standpoint for a period of time and leaving a population naive.

Dr. Stephens noted that they had previously discussed a prime boost strategy and how that may benefit a future platform. He requested an update on the future expanded multi-valent conjugate. He agreed with Dr. Talbot about what constitutes immunocompromised. A 65 year old with diabetes or chronic obstructive pulmonary disease (COPD) would be considered immunocompetent in this group as opposed to a 30-year old individual who is immunocompromised, which should be considered in this discussion. One of the challenges has been getting any vaccine into the adult population. Vaccination among the eligible group with polysaccharide alone was 45% or so, and now the combination vaccine is at almost 60%. Some progress has been made with at least getting a vaccine into the adult population with the current platform.

Dr. Atmar also expressed interest in knowing when the new conjugate vaccine would become available. It seemed to him that this was the kind of discussion about a vaccine that did not appear to have public health impact in this population based on the information presented. However, the Louisville data clearly show effectiveness of the vaccine in this population. In terms of shared decision-making, it is basically about the clinician talking to their patients to let them know that the vaccine is effective though not routinely recommended for this age group. Some clinicians may promote it more than others in the context of a general pneumonia discussion. The default is shared decision-making once a vaccine is licensed, but shared decision-making would be a step back from the current recommendation. He did not think vaccine availability would be an issue. Because of the effectiveness data, he could not see no longer recommending the vaccine in accordance with Policy Option C. While he was moving toward the second option, he could be strongly swayed by the implementation issue if a new significantly higher multi-valent vaccine would soon become available.

Dr. Hunter said he did not see how things would change by having a higher valent vaccine. They still would work better if given to children in terms of protecting adults than giving them directly to adults. As a clinician for the past 19 years and now as a public health practitioner for the past 10 years, he was very concerned that he had gone from making decisions based on individual patient characteristics and how his clinic personally operates to looking at a wide variation of clinical practice styles and quality in practice styles across the community and country when he gives presentations. He has come to recognize that what really influences the decisions clinicians and patients make are the policies that are set up, especially with regard to insurance decisions that are made and that those can have population-level effects. As somebody who was in the minority on 2 of 3 preferential votes that went in favor of the

recombinant zoster vaccine, he has watched with concern as the unexpected lack of supply of that vaccine has resulted in missing the second dose of vaccine. For both PCV and HPV, he was concerned that emphasizing vaccines for adults over vaccinating children will divert resources to the less beneficial, more expensive interventions. If there is not clear guidance or suggestions to clinicians about how to do individual clinical decision-making and shared guidance for patients, vaccine manufacturers are going to have a vested interested in using their significant resources to educate clinicians and patients in a way that might not align with public health goals. Unfortunately, there are also significant resources that give information directed toward parents of children that is emotionally convincing to them to choose not to vaccinate children, which also will detract from the most benefit that can come from these vaccines. He thought they needed to be realistic about what they were deciding and not just focus on the individual-level, patient-by-patient decisions.

Dr. Bernstein pointed out that the indirect effects of the PCV13 pediatric program on adults 65 and older is highly impressive. He wondered whether there were any data about decreasing rates of PCV13 immunization in children versus current uptake in terms of how that might impact adults ≥65 years of age.

Dr. Moore said that striking to her was the estimated 26,300 NNV of those ≥65 years of age to prevent one case of IPD. That number is so incredibly high that shared clinical decision-making reflects an uneasiness about dismantling the PCV13 program as it currently exists. Perhaps a clearer and more decisive risk-based recommendation might be more appropriate in terms of its ability to prevent disease in that group. She shared the thought that it is easier to remove the vaccine for a time and introduce a new higher valent at a later date in the near future than it is to maintain complex recommendations that have been quite difficult to implement. She also expressed concern that if they maintain a PCV13 recommendation until a higher valent vaccine is available, consideration would have to be given to whether those ≥65 years of age who received PCV13 would also be recommended to receive the higher valent vaccine.

Dr. Messonnier requested that Dr. Lee show the information regarding the two new near future pneumococcal conjugate vaccines that are in Phase 3 trials, PCV15 and PCV20. She pointed out that all of the companies could tell them when they plan to submit to FDA, but how long things may take after that is not knowable.

Dr. Lee shared information showing that both vaccines are conjugated to CRM_{197} and both manufacturers are working toward licensure in adults first. PCV15 includes PCV13 plus 22F and 33F serotypes and is currently in adult Phase 3 trials. The manufacturer is projecting adult Phase 3 completion in approximately the 3rd quarter of 2020 based on clinicaltrials.gov. PCV20 includes PCV13 plus 8, 10A, 11A, 12F, 15B, 22F, and 33F serotypes. This vaccine is currently in adult Phase 3 trials. According to clinicaltrials.gov, the manufacturer is projecting adult Phase 3 completion by approximately the end of 2019 or early 2020. Dr. Lee emphasized that this information was based on the clinicaltrials.gov website, which does not indicate real-time updates.

Dr. Luis Jodar (Chief Medical Officer, Pfizer) indicated that Pfizer has stated publicly that they are now in Phase 3 clinical trials for the 20-valent and that they are going to file with the FDA by the end of 2020. He emphasized that the FDA has given Breakthrough Therapy Designation (BTD) to PCV20 for adults. There should not be too much skepticism about the filing or approval dates, because these vaccines are based on immunogenicity and non-inferiority. After Phase 2 they already knew the kind of responses that the common and additional serotypes will have. Regarding the comment about PCV20 having the same effect as PCV13 in terms of herd effect,

PCV20 will be licensed in adults first and will take a few years before the pediatric indication is licensed. It will take 5 to 6 years before herd protection will kick off. The Phase 3 clinical trial with a 3+1 in pediatrics takes much longer than a single dose vaccine that will just need to be non-inferior to PCV13 and then to PPSV23.

Dr. Richard Haupt (Merck) confirmed that the timelines are accurate. As Dr. Jodar noted, these are immunogenicity studies, so they are not event-driven and are predictable in terms of the timeline. The adult indication will come before the pediatric indication, so discussions about how to apply a 15-valent vaccine in an adult will come before ACIP before there is a licensed pediatric age group vaccine.

In terms of shared clinical decision-making, Dr. Schmader (AGS) pointed out that the health of older adults is quite heterogeneous. There are individuals for whom shared decision-making is more challenging. For the record, the AGS supports the continued use of PCV13 in older adults for all of the reasons listed in favor of PCV13 use.

Dr. Rittle (ANA) indicated that he had communication with the National Black Nurses Association (NBNA) and the National Association of Hispanic Nurses (NAHN) in the past couple of weeks. Both organizations feel that the current recommendation should be continued. The President of the NBNA, Eric Williams, mentioned that there is limited awareness in these communities about adult vaccination. There are missed opportunities among healthcare providers, payment complexities, financial risks to stock and store vaccines, and limited funding for uninsured patients. Norma Cuellar, President of the NAHN, feels that the 2014 National Health Interview Survey (NHIS) data coverage information showed that the Hispanic population has lower pneumococcal vaccination rates than the non-Hispanic white population, increasing the burden of disease among Hispanics. The Hispanic population is often under-represented in both statistics and studies completed about the effectiveness of vaccines, and access to vaccines in the Hispanic population is often burdened due to social determinants of health (SDOH), provider trust, higher insurance rates, and adequate access to care among other factors.

Dr. Foster (APhA) commended CDC and the WG for the amount of work put into this. It was quite a burden in 2014 when the recommendation was made, and they considered many angles. Clinicians like to follow guidelines, particularly in the setting with pharmacy. Pharmacists play many roles, and they specifically think about the community pharmacists in terms of vaccines. By having a guideline, they know what to do and how to implement it. Pharmacists are very busy, so decision-making or confusing issues will result in them not vaccinating. APhA has spent a lot of time and resources educating them so that they do understand the current guidelines. The problem with too many changes in the guidelines, particularly if a change is made again in one more year, is that this will add another difficulty. He was asked to assess the opinion of pharmacists. He had the opportunity at the APhA to informally poll a group of about 300 pharmacists. He went through EtR framework that the WG discussed and presented the data to them. Overwhelmingly, these pharmacists felt that because new vaccines are coming, it would be much easier and preferred to keep the same guidelines and then revise them when the new vaccines are available so that it is not as confusing. The main issue from the pharmacist standpoint is the programmatic costs to implement guidelines changes versus the scientific changes.

Dr. Grogg (AOA) indicated that the AOA favors keeping the present guidelines. He gives an annual update to their national meeting about ACIP, and he has spent a great deal of time over the last 3 years teaching them about the two pneumococcal vaccines. He quipped that if changes are made now, they will probably throw things at him when he discusses it.

Dr. Zahn (NACCHO) indicated that NACCHO designated the NACCHO Immunization WG to review these data and provide comments to ACIP. Based on their review of the data, the NACCHO Immunization WG recommends that at this point, ACIP should no longer recommend PCV13 for persons ≥65 years of age who are immunocompetent. The rationale was similar to the reasons enumerated, particularly lack of evidence of population-based disease prevented. One of the NACCHO Immunization WG's recommendations was that with any change in the recommendation, there should be aggressive communication to providers and local health departments to ensure that everyone is providing accurate information and education to providers and their patients.

Dr. Whitley-Williams (NMA) indicated that NMA is in support of keeping the current guidelines. In spite of the impact from PCV13, she inquired as to whether the data regarding population-level impact on IPD and IPD-associated mortality were broken down by ethnicity. She shared some of the same ideas as the APhA in that sometimes people of color do get both influenza and pneumococcal vaccination at their pharmacies. She suspected that the percent of the population would be lower than the numbers who receive these vaccines at a provider's office. She is concerned about risk-based decisions being determined at alternative sites outside of the medical home. The assessment of risk, particularly for people in that age group with diabetes and other chronic medical conditions, is a concern. Consideration must be given to the fact that a change to no longer recommending PCV13 for persons ≥65 years of age may inadvertently affect persons of color.

Dr. Rockwell (AAFP) said that AAFP had a divided opinion, so they did not come to consensus. However, she gave her word that she would say something on behalf of the COPD Foundation. She was approached by the Chief Science Officer to say something about community-acquired pneumonia (CAP). She also personally agreed with this in that they are not really looking at the effects of this vaccination on the patients who are presenting to the outpatient world and maybe never getting to the hospital, or who may be getting treated and getting better because they did not get a severe pneumonia.

Dr. Fryhofer (AMA) reported that the AMA as an organization honors the ACIP process in making these evaluations. Speaking as an individual practicing physician, she recalled the emergency meeting during which this recommendation was made and the CAPiTA study was reviewed. When that recommendation was made, it was with the caveat that the information be re-evaluated in 2018, which was now done. As a practicing physician, every time a vaccine is available that is licensed by the FDA, she has the opportunity for a shared decision-making discussion with her patients. However, practicing physicians and the public depend upon ACIP to do exactly what the WG did—review all of the studies to determine effectiveness and to tell the practicing physicians who do not have time to do all of this whether a vaccine really works. She would like to know the estimated cost of continuing a vaccine for which there is no evidence for another two years. She agreed that it is easier to stop than to add something, but she wants her patients to be protected from pneumococcal disease and looks forward to the PCV20 vaccine being available. Between now and then, they must distribute their resources wisely. There is a healthcare crisis in terms of the amount of money being spent on healthcare, and thought must be given to how to best use resources. She expressed appreciation for all of the

time that was put into reviewing the studies and her trust that they would make the right decisions for patients and the country.

Dr. Duchin (IDSA) thanked the CDC team as someone who previously had the privilege of service on ACIP and acknowledged that it is critically important for CDC and ACIP to be data-driven and evidence-based in their guidance and recommendations. The IDSA also produces recommendations and re-assesses them over time as new data become available and as the epidemiology of disease changes, and adjustments are made to their guidance as appropriate. He read the official response from IDSA which was asked to weigh in on whether PCV13 should be administered routinely to all immunocompetent adults ≥65 years of age in the context of indirect effects from pediatric PCV use experienced to date, after careful consideration of the evidence and robust discussions made possible by the presentations and sharing of information heard during this session with IDSA, a majority of IDSA's Public Health Committee and Board of Directors concluded that, "Given the beneficial indirect effects of pediatric PCV13 vaccination on adult pneumococcal disease in the US resulting in a markedly decreased burden of PCV13-preventable disease, administration of PCV13 routinely to all immunocompetent adults ≥65 years of age should not be recommended. The key evidence IDSA considered in support of this conclusion included that there has been no change in population-level IPD and IPD-related mortality or pneumococcal pneumonia incidence after the 2014 recommendation beyond that attributable to the indirect effects from the PCV13 childhood program; the majority of pneumococcal disease burden is comprised of non-PCV-type disease currently, which limits the benefit from PCV direct effects; that Serotype 3 is the most common cause of remaining PCV-type disease for which the benefit of vaccine is uncertain; that the NNV to prevent one case is approximately 26,000 adults and approximately 2600 to prevent one case of outpatient pneumonia per year; and the very high cost of continuing the current recommendation. The minority of IDSA representatives who did not support the majority decision raised many of the concerns already discussed, particularly that potentially increased vaccination rates would result in more noticeable reductions in IPD and IPD-related mortality. However, they recognized the low burden of PCV13-type disease that is preventable currently. They were concerned about the potential for confusion related to discontinuation of a recommendation, the administrative burdens, and the subsequent impact on recommendations for a new vaccine. However, in closing, the IDSA's conclusion is a reflection of the tremendous success of the pediatric PCV13 vaccination program and its corresponding population health benefits in reducing pneumococcal disease burden among adults. IDSA respectfully requests that if ACIP agrees and votes to no longer recommend PCV13 be administered routinely, we urge a robust and proactive communication strategy for healthcare providers and the public that clearly describes the rationale and evidence base for this decision. Thank you for giving IDSA the opportunity to provide an official opinion on this important topic."

Dr. Weiser (IHS) indicated that since the last ACIP meeting, he had a chance to review some IHS data and was invited to sit in on some of the discussions with the ACIP Pneumococcal WG. IHS has PCV13 coverage of AI/AN ≥65 years of age that has been reported to the IHS immunization reporting system. Nationally, about 48% have received the vaccine. This ranges by area from less than 20% to 67%. There is either a lack of data or differential uptake. They also got to witness some updates to the work that Johns Hopkins has been doing, but there still seems to be a lack of data specific to AI/AN to suggest a benefit of PCV13 vaccination to immunocompetent adults ≥65 years of age. Limited data on AI/AN subgroups do not demonstrate any increase in protection from PCV13 vaccine-type pneumonia or IPD beyond the indirect effects achieved with the use of PCV13 in infants. However, those studies are limited to Alaska Native, Navajo, and White Mountain Apache Tribes and may not be generalizable to all AI/AN. Any changes to the ACIP recommendation for the use of PCV13 in adults ≥65 years of

age would have a minimal impact on PCV13 vaccine availability for those high-risk AI/AN adults served by IHS who should still receive PCV13. IHS conducted a quick survey of its Immunization Coordinators and learned that overall, PCV13 vaccination of adults ≥65 years of age has been effectively implemented according to ACIP recommendations per their opinions. By a large majority of 92%, the Immunization Coordinators responded that changes to this recommendation might have a negative impact on AI/AN adults ≥65 years of age. That reflected some of the discussion they heard from others about the implementation issues. IHS did not feel that they had enough information to go out on a limb as an agency to say "yes" or "no" for which recommendation should be followed.

Dr. Szilagyi pointed out that with regard to the economic analyses and the NNV or the cost per QALY, when these models are being done, they do not assume 100% vaccine rates and are independent of risk. They are not really modeling shared decision-making. If in shared decision-making they can identify high risk patients, the NNV would decrease and the cost per QALY would be much lower. If they cannot identify high risk patients, the models would still apply. He was worried that in the context of this vaccine, it would be difficult to identify high risk patients in shared decision-making, so that the NNV or the cost per QALY would remain what was in the model. He was not sure whether that was clear at all.

Dr. Matanock indicated that these models assumed the current vaccination rate. They did assess some differential in that they had separate subgroups for those who were healthy, though she recognized that "healthy" was not always great term for describing an 85+ year old. But, they did separate that group [healthy] into those with chronic medical conditions (heart, lung, liver disease; alcohol abuse; et cetera) that are not covered in the immunocompromising recommendation. This is the group that should receive PPSV23 based on the 2012 recommendation.

Dr. Lee commented that in trying to understand the construct of shared clinician decision-making across a series of decisions more broadly, from the pharmacy perspective, it is true that it is shared decision-making. On the other hand, if a patient walks into a pharmacy and says that they know they want PCV13, it seems reasonable to administer the vaccine if the patient feels well-informed and wants to receive it. She did not necessarily have a problem with that, but thought it depended upon how the construct of "shared clinical decision-making" is defined. Does it require a conversation between two people? There are multiple ways people can be informed. People are not informed only through their HCP. From the influenza perspective, there was a nice summary of recommendations that spoke to the fact that while ACIP recommends universal influenza vaccine for anyone 6 months of age and older, there is a framework for thinking about how to prioritize people who might be at higher risk (in no particular order) in resource-constrained settings. In any given season, they are essentially doing this for all patients based on when influenza vaccine becomes available, who the patient is seeing, et cetera. Therefore, the dynamic decision-making is essentially happening. As Dr. Lee was looking at the influenza construct, it made her realize that they treat vaccines in isolation. However, they need something like the adolescent vaccine platform Dr. Middleman mentioned years ago for the adult pneumonia prevention platform. There is a lot of interrelatedness. Even though they treat vaccines separately and are trying to make decisions separately, they are trying to protect the same populations.

Ms. McNally said that she was struggling with the public trust in this organization in that they were making decisions based on current data. She did not want the current data to erode the trust that they have in other vaccines and the importance of them at the time. She appreciated the concern about the use of resource and the fact that they do not anticipate that future introduction of vaccines will change the outcome in terms of the population-level impact.

Dr. Stephens said that in his view, the issue was about prevention of pneumonia. Data were provided in the handouts indicating that the estimated cases averted of pneumonia for the cohort of adults ≥65 years of age was 4,000 to 10,000 for PCV-type pneumonia.

Dr. Matanock clarified that what was in the package was that 4,000 to 10,000 cases of PCV13-type pneumonia are the cases averted for a cohort of adults ≥65 years of age, while what was in the presentation was the annual NNV. It is important to note that the annual NNV is different from the NNV for a cohort. For a cohort, there is the benefit of that vaccine for whatever the assumptions are in the model. Those come from the same health economics model. The 4000 to 10,000 cases averted was over the lifetime of the cohort. That is the difference between using PCV13 + PPSV23 in series versus PPSV23 alone.

Dr. Foster (APhA) commented that it is important to keep in mind that state practice determines what pharmacists are permitted to do. Every state has its own board that makes these decisions. Pharmacists operate under Standing Orders that dictate what they can or cannot do, and typically Standing Orders instruct them to follow ACIP guidelines. If Standing Orders do not state to follow ACIP guidelines, someone who walks in requesting a vaccine may not receive it.

Dr. Moore commented that as she had more time to reflect, it seemed that part of their dilemma was that there were two main choices: 1) prioritize operational concerns by not changing anything, which prioritizes the operational evidence; and 2) remove the recommendation, which prioritizes the epidemiologic evidence. She thought their struggle was that both were legitimate points of view with very legitimate questions to be answered. She thought the shared clinical decision-making was an attempt to split the difference, but she had some concern that it could inadvertently make things more complicated.

Dr. Maldonado (AAP) pointed out that they were looking at two different things, vaccine efficacy/effectiveness versus the population benefits. If it is an FDA-approved vaccine, it is efficacious. The question regarded vaccine efficacy and the direct effects of the vaccine subtracted from the indirect effects. For example, is there a population for which the direct effects are actually stable or increasing? There may be additional information that they were not seeing with regard to direct effects, which may be masked by the indirect effects. A control group is needed that is comprised of people who were vaccinated and did not get sick in order to show the direct effects, but she did not think they had seen that. She worried about that in terms of identifying populations, especially with regard to populations who may not be vaccinated appropriately and whether there are pockets where direct effects are showing some impact on the disease. She also looked at a recent meta-analysis of the effect of herd immunity on adult IPD, which suggested that it takes about 2 to 3 years for PCV13 to reach a 50% reduction in disease, but it would take about 8 to 9 years to get to a 90% rate. She wondered whether perhaps it was too early to see the what is actually occurring and if that number would decrease even further. Even that does not clarify the issue of the direct versus indirect effects. Those are two separate issues.

Dr. Matanock replied that effectiveness studies have shown effectiveness of this vaccine. No impact has been observed at the population-level, meaning that no continued indirect effects or direct effects have been seen at the population-level and they are now close to 10 years post-PCV13 introduction and more since conjugate vaccines have been used for children.

Dr. Mahon (NCIRD) mentioned that in the space of shared clinical decision-making, it would be possible to identify some groups that would be at higher risk that would provide assistance to clinicians if ACIP decided to go in that direction. The group that meets the definition of immunocompromising conditions is not part of this policy decision. That group will be recommended to receive both vaccines regardless. There are additional data about groups who are at higher risk that could be identified to assist practitioners in clinical decision-making.

Dr. Messonnier clarified that she was trying to draw a parallel between the HPV discussion and the clinical considerations language that the HPV WG showed, with the idea being that that language would be provided in a different fashion to clinicians in order to provide some help to them in how to think about this. The Pneumococcal WG did not display that kind of language, but there are clinical considerations that could be provided if Policy Option B was approved.

Regarding the point raised about disparities, Dr. Matanock indicated that they do have information about this and shared it with ACIP previously. Disparities were presented to ACIP by race and ethnicity, which showed that disparities amongst older adults of black race have been eliminated through indirect effects. The disparities for AI/AN have been reduced through indirect effects, but not completely eliminated. She agreed that this important point should continue to be assessed, because there are other factors such as access involved.

Dr. Luis Jodar (Chief Medical Officer, Pfizer) agreed that the discussion had been about the epidemiology viewpoint versus programmatic and implementation issues. As a representative of the manufacturer, he wanted to discuss the epidemiology viewpoint. Dr. Matanock showed PCV13 vaccine effectiveness of 6% to 11% in all-cause pneumonia, which represents approximately 30,000 hospitalizations in the CDC data. That was not included in any of the cost-effectiveness calculations. He thought it was important to recognize that this is a gigantic public health impact rather than no public health impact. This is not isolated in that it has been corroborated in Germany and the Netherlands. There also were a lot of technical discussions about NNV. In all of the models, the NNV was for one year. This conjugate vaccine has shown at a minimum 5 years of protection. The NNV might need to be divided by 5 to reflect the real picture of NNV. When talking about public health impact, this should be taken into consideration by ACIP.

Dr. Lee said that while this was a difficult decision and there were three differing viewpoints on table, because of the way the PICO question was asked and the way the evidence was reviewed, it made sense to her to make a motion to approve Policy Option A to recommend PCV13 for all adults 65 years or older who have not previously received PCV13. PCV13 should be given first, followed by a dose of PPSV23.

Dr. Hunter made a motion to approve Policy Option C to no longer recommend PCV13 for adults 65 years or older who do not have an immunocompromising condition. All adults 65 years or older should receive a dose of PPSV23.

Dr. Romero clarified that when this happens, ACIP refers to *Roberts Rules of Order* such that the motion that would move forward for seconding would come from the Chair of the Pneumococcal WG, which would be Dr. Lee. However, she already made the motion to approve Policy Option A. Therefore, Dr. Romero called for anyone who wished to second Dr. Lee's motion. Dr. Atmar seconded the motion made by Dr. Lee.

Dr. Cohn reminded everyone that they would stay the motion, which would be voted on subsequent to public comment, and that further votes could be considered if the first motion did not pass. For continuity, the vote and related discussion are included here.

Motion/Vote #1: Continue to Recommend PCV13 for All Adults ≥65 Years of Age Not Previously Vaccinated with PCV13

Dr. Lee made a motion to approve the proposed recommendation text for Policy Option A to continue the current recommendation reading, "ACIP recommends PCV13 for all adults 65 years or older who have not previously received PCV13. PCV13 should be given first, followed by a dose of PPSV23." Dr. Atmar seconded the motion. No COIs were declared. The motion failed with 6 affirmative votes, 8 negative votes, and 0 abstentions. The disposition of the vote was as follows:

6 Favored:	Bernstein, Ezeanolue, Moore, Stephens, Talbot, Walter
8 Opposed:	Atmar, Ault, Frey, Hunter, Lee, McNally, Romero, Szilagyi
0 Abstained:	N/A

Discussion Following The Vote

Dr. Romero invited the members to share the rationale for their votes.

Dr. Lee said that she voted "no" because looking at the overall evidence in terms of burden of disease, preventability, cost-effectiveness, and population-level benefit, she felt that it was challenging to continue this recommendation. While she recognized and very much appreciated the implementation challenges and agreed with all of the comments made by all of the members and liaisons, she felt the need to focus on the evidence base in this instance.

Mc. McNally echoed Dr. Lee's comments. This was a very difficult decision, but for those reasons she chose to vote "no."

Dr. Ault said that he had very mixed feelings about this vote as well. It has been known for more than a century that pneumococcus is a killer of men and women, especially in this age group. However, he felt that he needed to follow the evidence and vote "no." He also echoed what Dr. Lee said.

Dr. Szilagyi indicated that he voted "no" for the same reasons, including the epidemiologic data/evidence, the remarkable success of the pediatric program in terms of indirect benefits, and the overall public health implications.

Dr. Talbot said that she voted “yes” because she likes the prime boost, especially in the population with immunesenescence. The current polysaccharide vaccine does not prevent pneumonia in older adults. This is very important because pneumonia can take away a person’s independence.

Dr. Atmar said he voted “no” for many of the reasons already stated. He was not ultimately persuaded that implementation difficulties that would accrue, if and when there is a higher valent vaccine, would occur soon enough to outweigh the evidence of lack of effect for the general public at large.

Dr. Bernstein indicated that he voted “yes” because it was incredibly impressive how ACIP has handled this issue over the years since the recommendation was first made in 2014 and the intent to reassess the recommendation after a number of years. He was almost swayed by the evidence and certainly the indirect impact of the pediatric PCV13 program. However, there is still a significant amount of disease in those 65 years of age and older. He also believes there will be potential implementation issues as well.

Dr. Ezeanolue said that he voted “yes” because there is still a significant amount of disease in those older than 65 years of age. The vaccine has been shown to be very effective in this age group. The reason they are not seeing a difference is because there is herd immunity from the pediatric population. The herd immunity could decrease and this would put older adults at risk. They should have the opportunity to get a vaccine that is known to work very well, and there is a public health need for it. There is not an impact because of herd immunity, but they are counting on that when it may not be there for a long time.

Dr. Stephens said he voted “yes” because this was a retreat from the platform they have had for a number of years that he thought was the right platform moving forward (e.g., conjugate followed by polysaccharide). He was swayed by the evidence that this vaccine does prevent pneumonia in adult patients, though perhaps not significant IPD. As mentioned earlier, the term “immunocompromised” in this particular population is a difficult one and one that ACIP should address in the future. Though the current platform may not be ideal and broader conjugates are needed since most IPD and pneumonia is caused by non-PCV serotypes due to the remarkable impact of the pediatric vaccine. Conversely, this is a message that ACIP is retreating from the conjugate platform that has been effective in the older population.

Dr. Moore said that she voted “yes” to retain the current recommendation not because she felt like it was obviously the choice. It was a very difficult choice with evidence on both sides, epidemiologic and evidence of operational disruption. They did not really talk about the cost associated with transforming every heath system in the country to adjust to a change in this recommendation. She would rather spend that money on vaccine where there might be some epidemiologic evidence missing that the studies simply have not yet captured. Knowing how disruptive a change in recommendation is, she would rather have all of the disruption take place at once with the advance of a new more multi-valent conjugate vaccine. Weighing those two very narrowly calculated risks and benefits, she erred on the side of not making a change, leaving things alone until a later data, and making all of the changes at once.

Dr. Hunter said he voted “no” for very similar reasons. As with HPV, he thought they were diluting the message that vaccinating children is important. He was interpreting the advent of the higher valent vaccines as positive, but felt the need to send a message to the manufacturers because while it is easier to conduct the studies with adults due to Institutional Review Board (IRB) issues, that is not where the public health “bang for the buck is.” It is among children and that is what they should be doing.

Dr. Walter said that he voted “yes” due to the potential for direct benefit to prevent pneumonia and due to the potential operational issues discussed.

Dr. Frey indicated that she voted “no” because the indirect effects of vaccinating children is quite strong. This vaccine is effective and she does have concerns about immunocompromised hosts, but they were not voting on them. She does have concerns about older adults with other underlying co-morbidities. She leaned more toward the epidemiology than the logistics because she does not want to give a vaccine to someone if it is not necessary.

Dr. Romero said that he voted “no” for all of the reasons previously stated.

Motion/Vote #2: No Longer Recommend PCV13 for All Adults ≥65 Years of Age Not Previously Vaccinated with PCV13

Dr. Hunter made a motion to approve the proposed recommendation text for Policy Option C to continue the current recommendation reading, “ACIP no longer recommends PCV13 for adults 65 years or older who do not have an immunocompromising condition. All adults 65 years or older should receive a dose of PPSV23.” Dr. Ault seconded the motion. No COIs were declared. The motion failed with 1 affirmative vote, 13 negative votes, and 0 abstentions. The disposition of the vote was as follows:

1 Favored:	Hunter
13 Opposed:	Atmar, Ault, Frey, Bernstein, Ezeanolue, Lee, McNally, Moore, Romero, Szilagyi, Stephens, Talbot, Walter
0 Abstained:	N/A

Discussion After The Vote

Dr. Romero invited members to share their rationales for their votes.

Dr. Hunter indicated that he voted “yes” for no longer recommending PCV13 for adults 65 years or older who do not have an immunocompromising condition because he thinks that clinicians need a clear message, and it is going to be very difficult to clinical decision-making that is going to be implemented. This would have been easier to explain to clinicians than the clinical decision-making.

Motion/Vote #3: Recommend Shared Clinical Decision-Making for PCV13 for Adults ≥65 Years of Age Not Previously Vaccinated with PCV13

Dr. Lee made a motion to approve the proposed recommendation text for Policy Option B implement shared clinical decision-making reading, "ACIP recommends PCV13 based on shared clinical decision-making for adults 65 years or older who do not have an immunocompromising condition and who have not previously received PCV13. All adults 65 years or older should receive a dose of PPSV23." Ms. McNally seconded the motion. No COIs were declared. The motion carried with 13 affirmative votes, 1 negative votes, and 0 abstentions. The disposition of the vote was as follows:

13 Favored: Atmar, Ault, Frey, Bernstein, Ezeanolue, Lee, McNally, Moore, Romero, Szilagyi, Stephens, Talbot, Walter
1 Opposed: Hunter
0 Abstained: N/A

Discussion After The Vote

Dr. Romero invited members to share their rationales for their votes.

Dr. Messonnier acknowledged that this was complicated and difficult, and CDC will think about how to simplify it. They need to make sure that in the ACIP statement this is not communicated as an 11 to 1 vote, because that misses the sequences of votes that ACIP went through.

Dr. Bernstein said that he considered it to be shared clinical decision-making with all vaccines. He voted "yes" initially, so this was a compromise. He agreed that it would be important to explain the sequence of the votes in the *MMWR* guidance.

Dr. Lee thanked the WG and ACIP members. Even with this decision, she was feeling a heavy weight upon her. She does think that there is strong individual benefit to patients, so she feels like having access to this vaccine is very important. She also strongly believes that a better pneumonia prevention program is needed, and that they need to be thoughtful about how to approach this from a broader perspective.

Dr. Szilagyi agreed with both of the statements Dr. Lee made and noted that he really struggled with this decision. As discussed before, he thought a lot more research and thought were needed in the area of shared decision-making and identifying high risk groups. The group of individuals 65 years and older who are not immunocompromised is not a homogeneous group. He was swayed by the AI/AN subgroups and there may be additional subgroups. Like many things, there is a lack of optimal evidence. That is part of clinical care.

Dr. Ezeanolue said that he voted "yes" because he was concerned about reliance on herd immunity and he wanted to ensure that people who live in places where herd immunity is low or decreased have an opportunity for a shared decision to get the vaccine.

Combination Vaccines

Introduction

Kelly Moore, MD, MPH
Chair, Combination Vaccines WG
Vanderbilt University School of Medicine

Dr. Moore reported that the Combination WG has been focusing on a pediatric hexavalent vaccine over the last couple of months. This vaccine is a joint venture with Merck and Sanofi Pasteur that combines the following antigens:

- Diphtheria, tetanus, pertussis (DTaP5)
- Polio (IPV)
- *Haemophilus influenzae* type b (Hib; PRP-OMP)
- Hepatitis B (Hep B)

The official abbreviation is DTaP-IPV-Hib-HepB. The dashes in between indicate that each component is liquid. This vaccine is intended to be given in a 3-dose series at 2, 4, and 6 months. The Biologics License Application (BLA) was approved and licensed by the FDA on December 21, 2018. It is important to note that the manufacturer has stated that this vaccine will not be available commercially prior to 2021 in order to assure adequate supply to meet demands.

In terms of the policy topics under consideration initially by the WG, the first was to consider whether the new pediatric hexavalent vaccine should be preferentially recommended for the AI/AN population. The second was to consider whether the new pediatric hexavalent vaccine should be included as an option in the Vaccines for Children (VFC) Program for the infant series at 2, 4, and 6 months of age. The preferential recommendation would have required an ACIP policy vote. There was discussion during the February 2019 meeting regarding some of the reasons the WG had not advised moving forward on that. The recommendation to add this vaccine to the VFC Program requires only a VFC vote.

As a reminder, February 2019 ACIP presentations included: 1) Immunogenicity and Safety of Pediatric Hexavalent Vaccine by Andrew Lee, Merck; 2) Hib Epidemiology and Vaccines in AI/AN Population by Laura Hammitt, Center for American Indian Health, Johns Hopkins; and 3) Summary and Review of Work Group Considerations by Sara Oliver, CDC/NCIRD.

Since then, the WG has had a number of calls during which they reviewed safety and immunogenicity data, Hib epidemiology and Hib vaccines among the AI/AN population, and use of combination vaccines in an infant series and discussed policy options. Later in 2019, they will publish the *MMWR* Policy Note related to this new vaccine.

The agenda for this meeting included a presentation summarizing WG discussions, relevant components to the EtR recommendations framework for this vaccine, and VFC votes.

Summary and Relevant EtR Framework

Sara Oliver MD, MSPH
CDC WG Lead, *Haemophilus Influenzae* Subject Matter Expert
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Oliver first briefly reviewed the topics under consideration and then presented the relevant aspects of the EtR Framework and the WG interpretation. As a reminder, the two policy topics under deliberation include consideration of whether the new pediatric hexavalent vaccine should be preferentially recommended for the AI/AN population and whether the new pediatric hexavalent vaccine should be included as an option in the VFC Program for the infant series at 2, 4, and 6 months of age.

In the pre-vaccine era, Hib disease occurred at a younger age among the AI/AN population compared to the general US population. Dr. Hammitt's February 2019 presentation showed a peak of Hib meningitis at 4-5 months of age among Native American children, compared to 6-9 months in the general US population. In addition, PRP-OMP vaccines can achieve protective immunity in a majority of infants after the first dose. Dr. Hammitt also highlighted the ability of PRP-OMP vaccines to achieve protective immunity in 91% of infants after the first dose, much higher than what was seen with other Hib vaccines. It is because of these factors, to provide necessary protection early in infancy, that PRP-OMP vaccines are preferentially recommended for the AI/AN population. That preferential recommendation was based on immunogenicity data after the first dose. The available data after the second and third dose for the new hexavalent vaccine show a robust response. However, there are no data post-dose 1, which would provide important information for the window of vulnerability seen in this population.

Because of this, the WG and ACIP members felt that immunogenicity data post-dose 1 are needed before ACIP could consider a preferential recommendation for the AI/AN population. Given that, Dr. Oliver indicated that she would be presenting only the relevant EtR framework on the second topic (e.g., to consider whether the new pediatric hexavalent vaccine should be included as an option in the VFC Program). She explained that at this time, there was no proposed ACIP vote that would change current ACIP policy. The only vote would pertain to adding an additional vaccine option to the VFC Program. Because of this, the full EtR Framework was not undertaken. However, to present evidence in a standard and transparent format, there are aspects of the EtR Framework that are relevant for the new combination vaccine: Benefits and Harms, Values, Acceptability, and Feasibility. Dr. Oliver presented available evidence related to these aspects.

In terms of potential benefits, given that all components of the pediatric hexavalent vaccine are currently licensed and recommended, the immunogenicity studies conducted were non-inferiority studies comparing each antigen in the new vaccine to currently licensed vaccines. Overall, non-inferiority criteria were met, with 2 exceptions. First, non-inferiority was not met for the geometric mean concentrations (GMCs) for one of the 5 pertussis antigens, filamentous hemagglutinin (FHA), at the post-dose 3 time point. However, it was achieved with the percent that met a pre-specified vaccine response. Next, 1 of the 13 pneumococcal antigens, 6B, missed the pre-specified non-inferiority endpoint post-dose 3. However, it would have met the non-inferiority endpoints used in the PCV13 studies.

As mentioned in February, antigen or serotype-specific correlates of protection are unknown, so it is unclear whether these differences are clinically relevant. However, there are 5 pertussis antigens included in the vaccine, and only one antigen at one time point did not meet the pre-set non-inferiority criteria. In addition, the non-inferiority criteria were met for all other PCV13 antigens. Serotype 6B rarely causes invasive pneumococcal disease among US children in the post PCV13 era. Regarding the benefits of combination vaccines in general, combination vaccines merge equivalent component vaccines into a single product to prevent more than one disease. An increased number of vaccine doses due is associated with deferring doses, leading to missed opportunities and decreased coverage[1]. However, the receipt of at least 1 combination vaccine has been found to be associated with improved coverage rates, both among individual vaccines as well as for completion of the full infant vaccine series[2] [[1]Meyerhoff et al. *Preventative Medicine* 2005; 540-544; [2]Marshall et al. *Pediatr Infect Dis J* 2007; 496-500].

In terms of potential harms of the new hexavalent vaccine, the vaccine has an overall safety profile consistent with the licensed component vaccines. There was a higher rate of fever, particularly when compared to pentavalent regimens. However, there was no increase in fever-related medical events, such as hospital visits or febrile seizures. With regard to potential harms of combination vaccines in general, as stated in ACIP's *General Best Practice Guidelines for Immunization*[1], potential disadvantages of combination vaccines include AEs that might occur more frequently after administration of a combination vaccine compared with administration of separate antigens; confusion and uncertainty about selection of vaccine combinations and schedules for subsequent doses, especially when vaccinations are given by multiple providers who might be using different products; reduced pathogen coverage if the combination product covers fewer types of one particular vaccine-preventable disease-causing agent; extra doses of certain antigens could be given in the combination product; and there is potential for a shorter shelf-life than in individual component vaccines. Not all of these potential disadvantages would apply to the specific hexavalent vaccine [[1]General Best Practice Guidelines for Immunization. Best Practice Guidance of the ACIP. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html].

Regarding values and preferences, there are no specific data about the new hexavalent vaccine and values of the target population. However, ACIP and the American Academy of Pediatrics (AAP) have statements regarding the value of combination vaccines. The ACIP *General Best Practice Guidelines for Immunization* states that, "Use of combination vaccines can reduce the number of injections patients receive and alleviate concern associated with the number of injections. The use of a combination vaccine generally is preferred over separate injections of the equivalent component vaccines. Considerations should include provider assessment, patient preference, and the potential for adverse events[1]." In addition, the 2018 *Red Book* states that, "Combination vaccines represent one solution to the issue of increased numbers of injections during single clinic visits and generally are preferred over separate injections of equivalent component vaccines[2] [[1]General Best Practice Guidelines for Immunization. Best Practice Guidance of the ACIP. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html; [2]American Academy of Pediatrics. Red Book 2018 Report of the Committee on Infectious Diseases. 31st Edition].

Moving to acceptability, there have been no specific studies regarding the new hexavalent vaccine and acceptability among stakeholders. However, there have been evaluations for the acceptability of combination vaccines overall. A prior evaluation of combination vaccines in 2003 among Medicaid patients in Georgia showed that 85% of children received at least 1 combination vaccine in the first year of life [Marshall et al. Pediatr Infect Dis J 2007; 496-500].

For a more recent assessment, the frequency of combination vaccines and single vaccines for the infant series in multiple birth cohorts from 2014 to 2018 was evaluated using data from the Immunization Information Systems (IIS). The evaluation assessed 2 different antigens: DTaP and Hib. This evaluation was conducted at 6 IIS sentinel sites. The IIS systems have provider-submitted, population-based data that are timely and cover all pediatric ages. However, given that it is only 6 sites, the information may not always be generalizable. There are 2 pentavalent combination vaccines that contain DTaP. Over 90% of DTaP doses over this timeframe were given in a combination vaccine. When assessed with Hib antigen, which is included in only 1 pentavalent vaccine, 40% to 60% of Hib doses were given in a combination vaccine [Michelle Lin, CDC's Immunization Services Division].

In terms of feasibility, the additional combination vaccine will not alter the established vaccination schedule. As the vaccine is licensed only for the primary series at 2, 4, and 6 months of age and not a booster dose, there will need to be consideration for having additional product or products available for booster doses. As mentioned earlier, the new vaccine will not be commercially available prior to 2021.

In summary, the WG reviewed relevant evidence to consider whether the new pediatric hexavalent vaccine should be included as an option in the VFC Program for the infant series at 2, 4, and 6 months of age. The balance of benefits and harms would support making the vaccine an available option. The target population appears to value combination vaccines in general, and this seems acceptable to key stakeholders. Therefore, the overall interpretation of the evidence was that the WG unanimously supported the inclusion of this vaccine in the VFC Program as one of the available options.

Discussion Points

Dr. Atmar requested clarification regarding whether there still would be a preferential recommendation for AI/AN populations if the new vaccine was added to the VFC schedule.

Dr. Oliver indicated that the preferential recommendation would remain for the single antigen Hib PRP-OMP vaccine unless post-dose 1 data become available. Essentially, there would be no change in the vaccine schedule for the AI/AN population at this point.

Dr. Moore added that the WG is very hopeful that there will be post-dose 1 data available for their review close to the time the vaccine is anticipated to enter the marketplace.

Ms. Hayes (ACNM) inquired as to how this combination vaccine would impact the birth dose of HepB vaccine.

Dr. Oliver replied that the birth dose is still recommended. The combination vaccine is not licensed for the birth dose and would be given at 2, 4, and 6 months.

Given that this vaccine will not become available until 2021, Dr. Hunter inquired as to whether ACIP voting now was going to help AIM and other groups be prepared when it is available.

Ms. Finley (AIM) replied that this was correct and that it also would allow time to consider what educational information they would provide.

VFC Resolution Updates: New DTaP-IPV-Hib-Hep B Vaccine

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

Mr. Whitlatch presented the VFC resolution updates for the new DTaP-IPV-Hib-HepB vaccine. He reminded everyone that in December 2018, a new combination vaccine was licensed: DTaP-IPV-Hib-Hep B. In order to include this vaccine in the VFC program, updated VFC resolutions had to be prepared for each of the affected vaccine types (DTaP, IPV, Hib, and Hep B) for review and consideration by ACIP. The impetus of the resolution updates was to incorporate the new combination vaccine into the list of currently available vaccines in the VFC program. Additionally, they took this opportunity to update portions of the resolution language to more closely reflect the current ACIP recommendations when appropriate. Yellow highlighting was used to indicate changes to the resolution in comparison to the prior approved version.

The first VFC resolution update was for diphtheria, tetanus, and pertussis vaccines. The purpose of this resolution was to update the “Recommended Schedule and Intervals” section using tables and language adapted from the most recent ACIP recommendations, and to reflect the currently available vaccines that can be used to prevent diphtheria, tetanus, and pertussis. No changes were proposed to the eligible groups, which include children and adolescents aged 6 weeks through 18 years.

Two new tables were added to the Recommended Schedule and Intervals section that were adapted from the current ACIP recommendations, with the new combination vaccine incorporated into the first of these tables.

Vaccines containing tetanus toxoid, diphtheria toxoid, and acellular pertussis antigens and age for approved use by vaccine type for persons aged < 7 years:

Vaccine Type	Vaccine	Brand (1)	Age for approved use in the routine schedule (2)				
			2 mos	4 mos	6 mos	15-18 mos	4-6 yrs (3)
DTaP	DTaP (4)	Daptacel	X	X	X	X	X
	DTaP (4)	Infanrix	X	X	X	X	X
Combination vaccines with DTaP	DTaP-HepB-IPV (4, 5)	Pediarix	X	X	X		
	DTaP-IPV/Hib (4, 6)	Pentacel	X	X	X	X	
	DTaP-IPV-Hib-HepB (4, 7)	Vaxelis	X	X	X		
	DTaP-IPV (8)	Kinrix					X
	DTaP-IPV (8)	Quadracel					X
DT	DT (4, 9)	None	X	X	X	X	X

The notes remain the same as in the existing resolution except for those shown in yellow. The second table note was added to show minimal intervals, the seventh table note provides specific information about VAXELIS™, and the ninth table note updates language about the use of TD vaccine from the existing VFC resolution using language from the current ACIP recommendations:

(1) The use of brand names is not meant to preclude the use of other comparable licensed vaccines.

(2) Minimal intervals: Dose 1 to 2: 4 weeks. Dose 2 to 3: 4 weeks. Dose 3 to 4: 6 months. Dose 4 to 5: 6 months. For more information on age for use in catch-up immunization schedules please see: **https://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html**

(3) The fifth dose is not necessary if the fourth dose was given after the fourth birthday.

(4) FDA approved for use in infants as young as 6 weeks.

(5) FDA-approved for use through age 6 years (prior to 7th birthday). The combined DTaP-HepB-IPV vaccine may be used when any component of the combination is indicated, and if the other components are not contraindicated. Approved for the primary series only (Doses 1-3). For adequate immune response, the last dose of hepatitis B vaccine should be given at ≥24 weeks of age and therefore this combination vaccine should not be administered as a complete primary series on an accelerated schedule at 4-week intervals for prevention of pertussis.

(6) FDA-approved for use through age 4 years (prior to 5th birthday). The combined DTaP-IPV/Hib vaccine may be used when any component of the combination is indicated, and if the other components are not contraindicated. Approved for the primary series and first booster dose (Doses 1-4). The combined DTaP-IPV/Hib vaccine is not indicated for children 5 years of age and older.

(7) FDA-approved for use through age 4 years (prior to 5th birthday). The combined DTaP-IPV-Hib-HepB vaccine may be used when any component of the combination is indicated, and if other components are not contraindicated. Approved for the primary series only (Doses 1-3). For adequate immune response, the last dose of hepatitis B vaccine should be given ≥24 weeks of age and therefore this combination vaccine should not be administered as a complete primary series on an accelerated schedule at 4-week intervals for prevention of pertussis.

(8) The combined DTaP-IPV vaccines may be used when any component of the combination is indicated, and if the other components are not contraindicated. Only approved for the booster dose at age 4 through 6 years. Earlier doses should use another vaccine.

(9) Use diphtheria and tetanus toxoids vaccine if encephalopathy not attributable to another identifiable cause occurs within 7 days of administration of previous dose of pertussis-containing vaccine.

The second new table shows the vaccines approve in persons aged 7 to 18 years and also is adopted from the current ACIP recommendations:

Vaccines containing tetanus toxoid, diphtheria toxoid, and acellular pertussis antigens and age for approved use by vaccine type for persons aged 7-18 years:

Vaccine Type	Brand	Age for Approved Use
Tdap (1, 2, 3, 4)	Adacel	10 - 18 years
	Boostrix	10 - 18 years
Td (4, 5)	Tenivac	7 - 18 years
	TDVAX	7 - 18 years

The first table note has been updated to reflect the guidance about the use of Tdap as included in the current ACIP recommendations. The second table note was included in the existing VFC resolution, but it was updated with information about additional Tdap vaccination in children who received a dose of Tdap as part of the catch-up series. This information is taken from the current ACIP recommendation. The third table note has been updated and table notes 4 and 5 were not part of the existing resolution, but were included to reflect the current ACIP recommendations. The update in item 3 provides information about the timing of Tdap vaccination during pregnancy, while new notes 4 and 5 provide guidance for tetanus prophylaxis, wound management, and language related to contraindications for Td vaccine:

1) Tdap is indicated for a single booster dose at age 11 or 12 years. Adolescents who did not receive Tdap at age 11 or 12 should receive a single dose of Tdap. Tdap can be administered regardless of interval since the last tetanus or diphtheria containing vaccine.

2) Tdap should be given to children aged 7-18 years of age who have received tetanus and diphtheria containing vaccine (DT or Td) instead of DTaP for some or all doses of the childhood series; have received fewer than 5 doses of DTaP or 4 doses if the fourth dose was administered at age 4 years or older; or have never been vaccinated against tetanus, diphtheria, or pertussis (no doses of pediatric DTaP/DT or Td). The preferred schedule is a single Tdap dose, followed by a dose of Td four weeks after the first dose and a second dose of Td 6-12 months later. If not administered as the first dose, Tdap can be substituted for any of the other Td doses in the series. For persons aged 7–10 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap vaccine dose should be administered at age 11–12 years. More information about the catch-up is available at: https://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html#note-tdap

3) Adolescents who are pregnant should receive Tdap, irrespective of past history of Tdap receipt. Tdap should be administered between 27 and 36 weeks' gestation, preferably during the earlier part of this time period, although it may be administered at any time during pregnancy. If an adolescent did not receive Tdap during her current pregnancy and did not receive a prior dose of Tdap ever, then Tdap should be administered immediately postpartum. If an adolescent did not receive Tdap during her current pregnancy but did receive a prior dose of Tdap, then she should not receive a dose of Tdap postpartum.

4) A tetanus toxoid-containing vaccine may be indicated for tetanus prophylaxis for wound management. For more details, see: https://www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm.

5) Td should be used if encephalopathy not attributable to another identifiable cause occurs within 7 days of administration of previous dose of pertussis-containing vaccine.

No changes were made to "Recommended Dosages, Contraindications, and Precautions" or the Statement Regarding Update Based on Published Documents":

Recommended Dosages, Contraindications, and Precautions
Recommended Dosages
- Refer to product package inserts.

Contraindications and Precautions
- Contraindications and precautions can be found at: https://www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm.

Statement Regarding Update Based on Published Documents

[If an ACIP recommendation regarding vaccination against diphtheria, tetanus, and pertussis 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.]

Discussion Points

Regarding the schedule, Dr. Moore thought the final dose for HepB was ≥24 weeks of age versus >24 weeks as shown on the schedule.

Dr. Oliver confirmed that this should be ≥24 weeks of age and would be revised.

Regarding pregnant teenagers and Tdap on the table notes for the second table, Ms. Hayes (ACNM) thought the sentence at the end of note 3 reading "If not administered during pregnancy, Tdap should be administered immediately postpartum" should be removed as postpartum vaccines are no longer being recommended. She emphasized the importance of this being consistent for adults and pregnant teens.

Dr. Havers, the Pertussis WG lead indicated that the current recommendation states that it can be administered postpartum and it is recommended if the woman has not previously received a Tdap vaccine. The wording could be amended to clarify that.

Regarding table note 2 for the first table, Dr. Bernstein pointed out that the minimal intervals should be Dose 1 to 2: 4 weeks, Dose 2 to 3: 4 weeks, Dose 3 to 4: 6 months, and Dose 4 to 5: 6 months rather than Does 5 to 6: 6 months.

Dr. Frey requested clarification on whether this should be preferentially recommended.

Dr. Cohn clarified that they were not making a policy change. When there is a new type of vaccine product, ACIP must vote to include it in the VFC program. This is an option to be used to follow the schedule. They would not be voting on any recommendation related to the AI/AN population.

Motion/Vote #1: Changes to the VFC Resolution for DTaP

Dr. Moore made a motion to accept the revised VFC Resolution for DTaP as corrected with the comments made during the discussion period with respect to intervals and other errors. Dr. Walter 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, Bernstein, Ezeanolue, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
0 Opposed: N/A
0 Abstained: N/A

VFC Resolution Update: Hib Vaccines

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

Mr. Whitlatch presented the VFC resolution updates for *Haemophilus influenzae type b* (Hib) vaccines. The purpose of this resolution was to update the "Recommended Vaccination Schedule and Intervals" section to reflect the list of currently available Hib-containing vaccines that can be used to prevent Hib disease and to add a clarifying footnote about the timing of the booster dose that is included in the most recent recommendations. Yellow highlighting indicates changes to the resolution in comparison to the prior approved version.

No changes were proposed to eligible groups, which include all children 6 weeks to 18 years of age, to prevent Hib disease.

The recommended schedule includes 3 or 4 doses of a Hib-containing vaccine, depending on the specific vaccine. The "Recommended Schedule/Dosage Intervals" Table 1 was updated to include VAXELIS™, table note 4 was included to clarify the timing of the booster dose for PENTACEL®, table notes 5 and 6 were added for VAXELIS™:

Vaccine	Brand (1)	Components	Primary Series	Booster Dose
Monovalent vaccines				
PRP-OMP (2,3)	PedvaxHIB	PRP conjugated to OMP	2, 4 months	12 – 15 months
PRP-T	ActHIB	PRP conjugated to tetanus toxoid	2, 4, 6 months	12 – 15 months
PRP-T	Hiberix	PRP conjugated to tetanus toxoid	2, 4, 6 months	12 – 15 months
Combination vaccines				
DTaP-IPV/Hib	Pentacel	DTaP + IPV + PRP-T	2, 4, 6 months	15 – 18 months (4)
DTaP-IPV-Hib-HepB (5)	Vaxelis	DTaP + IPV + PRP-OMP + HepB	2, 4, 6 months	Not licensed (6)

(1) Use of brand names in Table 1 is not meant to preclude the use of other licensed Hib vaccines with similar active components.

(2) If a PRP-OMP vaccine is not administered as both doses in the primary series or there is uncertainty about which products were previously administered, a third dose of Hib conjugate vaccine is needed to complete the primary series.

(3) Preferred for American Indian/Alaska Native children.

(4) The booster dose may be administered as early as age 12 months, provided that at least 6 months have elapsed since the third dose.

(5) Not preferred for AI/AN children due to lack of immunogenicity data after the first dose.

(6) DTaP-IPV-Hib-HepB is not licensed for a booster dose; any other Hib conjugate vaccine licensed for the booster dose can be used.

No updates were made to Table 2 “Minimum Age and Intervals for Hib Vaccines” or the associated notes:

Minimum Age	Minimum Intervals Primary Series (Up to 12 months)	Minimum Interval Booster dose (12 months and older)
6 weeks	4 weeks	8 weeks

- ❑ The ACIP recommends Hib vaccine for all children through 5 years of age. In addition, children less than 24 months of age who develop invasive Hib disease should be considered unvaccinated and receive Hib vaccine doses according to the age-appropriate schedule for unimmunized children. Vaccination or re-vaccination of children <24 months of age who develop invasive Hib disease should begin 4 weeks after disease.

- ❑ If Hib vaccination is not initiated by 6 months of age, use the following schedule shown in Table 3. (next slide)

No updates were made to Table 3 “Catch-Up Vaccination Schedule”:

Age at First Vaccination	Primary Series	Booster
7-11 months	2 doses, at least 4 weeks apart	Age 12-15 months at least 8 weeks after the second dose*
12-14 months	2 doses, at least 8 weeks apart	N/A
15-59 months	1 dose	N/A

*A booster dose at 12 - 15 months of age is only necessary if 2 or 3 primary doses (depending on vaccine type used) were administered before age 12 months.

No updates were made to Table 4 “Guidance for Hib Vaccination in High-Risk Groups” or its footnotes:

High-Risk Group*	Hib Vaccine Guidance
Patient <12 months of age	Follow routine Hib vaccination recommendations
Patients 12-59 months of age	If unimmunized or received 0 or 1 dose before age 12 months: 2 doses 2 months apart If received 2 or more doses before age 12 months: 1 dose If completed a primary series and received a booster dose at age 12 months or older: no additional doses
Patients undergoing chemotherapy or radiation therapy, age <59 months†	If routine Hib doses given 14 or more days before starting therapy: revaccination not required If dose given within 14 days of starting therapy or given during therapy: repeat doses starting at least 3 months following therapy completion
Patients undergoing elective splenectomy, >15 months-18 years	If unimmunized§: 1 dose prior to procedure ‡
Asplenic patients, >59 months–18 years	If unimmunized§: 1 dose
HIV-infected children, >59 months -18 years	If unimmunized§: 1 dose
Recipients of hematopoietic stem cell transplant, through18 years	Regardless of Hib vaccination history: 3 doses (at least 1 month apart) beginning 6-12 months after transplant

Footnotes for Table 4:

**Patients with functional or anatomic asplenia, HIV infection, immunoglobulin deficiency including Immunoglobulin G2 subclass deficiency, or early component complement deficiency, recipients of a hematopoietic stem cell transplant (HSCT), and those receiving chemotherapy for malignant neoplasms.*
† Some experts suggest conducting serologic testing for these patients.
‡Some experts suggest vaccination at least 14 days before the procedure; some experts suggest administering a dose prior to elective splenectomy regardless of prior vaccination history.
§ Patients who have received a primary series and booster dose or at least 1 dose of Hib vaccine after 14 months of age are considered immunized.

No changes were made to “Recommended Dosages, Contraindications, and Precautions” or the Statement Regarding Update Based on Published Documents.”

Motion/Vote #2: Changes to the VFC Resolution for Hib Vaccines

Dr. Moore made a motion to accept the revised VFC Resolution for Hib vaccines as presented. Dr. Szilagyi 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, Bernstein, Ezeanolue, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
0 Opposed: N/A
0 Abstained: N/A

VFC Resolution Update: Hepatitis B Vaccines

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

Mr. Whitlatch presented the VFC resolution updates for Hepatitis B Vaccines. The purpose of this resolution was to update the "Recommended Vaccination Schedule and Intervals" section to reflect the currently available hepatitis B-containing vaccines that can be used to prevent hepatitis B. Yellow highlighting indicates changes to the resolution in comparison to the prior approved version.

No changes were made to eligible groups, which include all children and adolescents from birth through 18 years of age. The tables listing the acceptable vaccination schedules for children and adolescents from birth through 18 years of age was not changed:

		Single Antigen Vaccine		Single-antigen[1] and combination vaccine[2,3,4]	
Birth weight	Maternal HBsAg status	Dose	Age	Dose	Age
≥2000 g	Positive	1	Birth (≤12 hrs)[1]	1	Birth (≤12 hrs)[1]
		2	1-2 months	2	2 months
		3	6 months	3	4 months
				4	6 months
	Unknown	1	Birth (≤12 hrs)[1]	1	Birth (≤12 hrs)[1]
		2	1-2 months	2	2 months
		3	6 months	3	4 months
				4	6 months
	Negative	1	Birth (≤24 hrs)[1]	1	Birth (≤24 hrs)[1]
		2	1-2 months	2	2 months
		3	6 -18 months	3	4 months
				4	6 months

<2000 g	Positive	1	Birth (≤12 hrs)[1]	1	Birth (≤12 hrs)[1]
		2	1 month	2	2 months
		3	2-3 months	3	4 months
		4	6 months	4	6 months
	Unknown	1	Birth (≤12 hrs)[1]	1	Birth (≤12 hrs)[1]
		2	1 month	2	2 months
		3	2-3 months	3	4 months
		4	6 months	4	6 months
	Negative	1	Age 1 month or at hospital discharge[1]	1	Age 1 month or at hospital discharge[1]
		2	2 months	2	2 months
		3	6 -18 months	3	4 months
				4	6 months

For the table notes, additional information was added to the PEDIARIX® [DTaP-IPV-HepB] to match the PEDIARIX® footnote in the DTaP VFC resolution, which provides guidance about minimum intervals. Table note 3 was added for VAXELIS™ [DTaP-IPV-Hib-HepB]:

1. Only a single antigen hepatitis B vaccine (ENGERIX-B or RECOMBIVAX HB) can be given at birth.

2. Pediarix [DTaP-IPV-HepB] is licensed for children 6 weeks through 6 years of age. For adequate immune response, the last dose of hepatitis B vaccine should be given ≥24 weeks of age and therefore this combination vaccine should not be administered as a complete primary series on an accelerated schedule at 4-week intervals for prevention of pertussis.

3. Vaxelis [DTaP-IPV-Hib-HepB] is licensed for children 6 weeks through 4 years of age. For adequate immune response, the last dose of hepatitis B vaccine should be given ≥24 weeks of age and therefore this combination vaccine should not be administered as a complete primary series on an accelerated schedule at 4-week intervals for prevention of pertussis.

4. Use of brand names is not meant to preclude the use of other comparable US licensed vaccines.

No changes were made to “Table 2: Children and Adolescents” or its table notes:

Age	**Schedule[1, 6]**
Children (1 through 10 years)	0, 1, and 6 months[2] 0, 2, and 4 months[2] 0, 1, 2, and 12 months[2,4]
Adolescents (11 through 18 years)	0, 1, and 6 months[2] 0, 1, and 4 months[2] 0, 2, and 4 months[2] 0, 12, and 24 months[2] 0 and 4-6 months[3] 0, 1, 2, and 12 months[2,4] 0, 7 days, 21-30 days, 12 months[5]

Table Notes
1. Children and adolescents may be vaccinated according to any of the schedules indicated, except as noted. Selection of a schedule should consider the need to optimize compliance with vaccination.
2. Pediatric/adolescent formulation.
3. A two-dose schedule of Recombivax-HB Adult Formulation is (10 micrograms) is licensed for adolescents aged 11 through 15 years. When scheduled to receive the second dose, adolescents aged > 15 years should be switched to a three-dose series, with doses 2 and 3 consisting of the pediatric formulation administered on an appropriate schedule.
4. A four-dose schedule of Engerix B is licensed for all age groups.
5. Twinrix can be administered to persons 18 years of age before travel or any other potential exposure on an accelerated schedule at 0, 7, and 21-30 days, followed by a dose at 12 months.
6. Use of brand names is not meant to preclude the use of other comparable US licensed vaccines.

No changes were made to the "Interrupted Schedules and Minimum Dosing Intervals" or "Revaccination" sections:

Interrupted schedules and minimum dosing intervals

- When the HepB vaccine schedule is interrupted, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose should be administered as soon as possible, and the second and third doses should be separated by an interval of at least eight weeks. If only the third dose has been delayed, it should be administered as soon as possible.

- The final dose of vaccine must be administered at least eight weeks after the second dose and should follow the first dose by at least 16 weeks; the minimum interval between the first and second doses is four weeks. Inadequate doses of hepatitis B vaccine or doses received after a shorter-than-recommended dosing interval should be re-administered, using the correct dosage or schedule.

- Vaccine doses administered ≤4 days before the minimum interval or age are considered valid. Because of the unique accelerated schedule for Twinrix®, the four-day guideline does not apply to the first three doses of this vaccine when administered on a 0 day, 7 day, 21-30 day, and 12 month schedule.

- In infants, administration of the final dose is not recommended before age 24 weeks (164 days).

Revaccination

Revaccination (i.e., booster dose, challenge dose, or revaccination with a complete series) is not generally recommended for persons with a normal immune status who were vaccinated as infants, children, or adolescents. Revaccination when anti-HBs is <10 mIU/mL is recommended for the following:

- Infants born to HBsAg-positive mothers
  - HBsAg-negative infants with anti-HBs <10 mIU/mL should be re-vaccinated with a single dose of HepB vaccine and receive post vaccination serologic testing 1-2 months later. Infants whose anti-HBs remains <10 mIU/mL following single dose revaccination should

receive two additional doses of HepB vaccine, followed by PVST 1-2 months after the final dose.

- Based on clinical circumstances or family preference, HBsAg-negative infants with anti-HBs <10 mIU/mL may instead be revaccinated with a second, complete 3-dose series, followed by post vaccination serologic testing (PVST) performed 1-2 months after the final dose of vaccine.

- ❑ Hemodialysis patients. For hemodialysis patients, the need for booster doses should be assessed by annual anti-HBs testing. A booster dose should be administered when anti-HBs levels decline to <10 mIU/mL.

- ❑ Other immunocompromised persons. For other immunocompromised persons (e.g., HIV-infected persons, hematopoietic stem-cell transplant recipients, and persons receiving chemotherapy), the need for booster doses has not been determined. When anti-HBs levels decline to <10 mIU/mL, annual anti-HBs testing and booster doses should be considered for persons with an ongoing risk for exposure.

- ❑ Persons with postvaccination serologic testing results that do not demonstrate protection. This includes children and adolescents through age 18 years who are chronic hemodialysis patients, HIV-infected, otherwise immunocompromised (e.g., hematopoietic stem-cell transplant recipients or persons receiving chemotherapy), or sex partners of HBsAg-positive persons. Persons in these groups found to have anti-HBs concentrations of <10 mIU/mL after the primary vaccine series should be revaccinated.

No changes were made to "Recommended Dosages, Contraindications, and Precautions" or the Statement Regarding Update Based on Published Documents."

Motion/Vote #3: Changes to the VFC Resolution for Hepatitis B Vaccines

Dr. Moore made a motion to accept the revised VFC Resolution for Hepatitis B vaccines as presented. Dr. Frey 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, Bernstein, Ezeanolue, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
0 Opposed:	N/A
0 Abstained:	N/A

VFC Resolution Update: Polio Vaccines

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

Mr. Whitlatch presented the VFC resolution updates for polio vaccines. The purpose of this resolution was to update the "Recommended Vaccination Schedule and Intervals" section to reflect the currently available inactivated polio vaccine (IPV) and IPV-containing vaccines that

can be used to prevent polio. Yellow highlighting indicates changes to the resolution in comparison to the prior approved version.

No changes were made to eligible groups, which include all infants and children aged at least six weeks of age.

VAXELIS™ was added to the recommended schedule, which identifies single antigen and combination vaccines licensed and currently available for routine use to prevent polio and a link was added for additional details:

Vaccine	Brand(s)	Schedule	Comments
IPV	Ipol	2,4,6-18 mos; 4-6 yrs	Approved for use in infants and adults
DTaP-HepB-IPV	Pediarix	2,4,6 mos	Approved for first 3 doses of IPV through 6 yrs
DTaP-IPV/Hib	Pentacel	2,4,6 and 15-18 mos	Approved for 4 doses of IPV through 4 yrs
DTaP-IPV-Hib-HepB	Vaxelis	2,4,6 mos	Approved for first 3 doses of IPV through 4 yrs
DTaP-IPV	Kinrix, Quadracel	4-6 yrs	Approved for booster dose at age 4-6 yrs

Additional details can be found at:
https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5830a3.htm?s_cid=mm5830a3_e*
No changes were made to "Recommended Dosages, Contraindications, and Precautions" or the Statement Regarding Update Based on Published Documents."

Motion/Vote #4: Changes to the VFC Resolution for Polio Vaccines

Dr. Moore made a motion to accept the revised VFC Resolution for Polio vaccines as presented. Dr. Walter 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, Bernstein, Ezeanolue, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
0 Opposed: N/A
0 Abstained: N/A

Measles Update

Thomas Clark, MD, MPH
Deputy Director, Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Clark provided an update on the current measles outbreaks in the US. For context, the implementation of single dose of measles-containing vaccine dramatically reduced the burden of morbidity and mortality associated with measles in the US. However, a resurgence of disease in the late 1980s resulted in both a second dose recommendation prior to school entry and contributed to the formulation of the VFC Program to reduce disparities due to socioeconomic status (SES) in vaccination.

Coverage with measles-containing vaccine overall has been sustained at high levels in the US. One plus dose coverage among toddlers is 90% to 91% nationwide, but ranges from about 82.5% to over 98%. Drivers of under-immunization nationally are related to access. Within states, pockets of under-immunization exist in communities that are under-immunized by choice. Those communities are not reflected in state-level maps [Source: National Immunization Survey-Child (NIS-Child), 1995 through 2017 available online through CDC ChildVaxView at https://www.cdc.gov/vaccines/imz-managers/coverage/childvaxview/data-reports/index.html].

To date in 2019, there have been 1077 cases of measles confirmed in 28 states. This is the greatest number of cases reported in the US since measles was declared eliminated in 2000. In fact, this is the highest number since 1992 at the tail-end of the resurgence of measles. There are currently five ongoing measles outbreaks associated with New York State, Rockland County; New York City; California, Butte County; Pennsylvania, Allegheny County; and Washington, King County. In the last three of these, it has been more than 21 days since the last case onset. Therefore, CDC is hopeful that these outbreaks will be over soon. However, the New York City and New York State outbreaks are ongoing. Those outbreaks began at the end of September 2018 and have been sustained through 2019.

Because measles has been eliminated, all cases and all outbreaks are associated with importations due to travel overseas. High 2-dose coverage has been critical in eliminating or limiting transmission when cases are imported. However, when cases are imported into communities with low coverage, measles can spread and expose individuals who are unvaccinated. There have been 13 outbreaks reported in the use this year. Of these, 94% of the total case count have been associated with outbreaks. Of the 13 outbreaks, 6 were in under-immunized, close-knit communities such as in Rockland County and New York City. Those two outbreaks have contributed 77% of the case counts nationwide. Since the end of 2018, there have been over 640 cases in New York city and over 340 in Rockland County. Of the cases, 64 (6%) were internationally imported. Of those cases, 44 (69%) were US residents and 20 (31%) were foreign visitors. The 3 most common source countries from which importations have occurred are the Philippines (15 imports), Ukraine (10 imports), and Israel (9 imports). The global context for these importations is a 3-fold increase in measles globally. Measles are endemic in much of the world, and there are large outbreaks in many parts of the world. The countries that have imported cases reflect to some degree the burden of disease globally, but especially reflect travel patterns and the likelihood of exposing under-immunized communities.

Since early April 2010, CDC has been operating in an Incident Management Structure operated out of NCIRD. Over 100 staff are working on the response. Case counts and outbreak information are updated on the website weekly. They are working especially to promote vaccination of travelers and prevention of importations, especially through air contact investigations. They have provided technical assistance to states reporting measles cases, including prevention and control measures, and vaccine implementation and work to support case confirmation and genotyping, especially through the vaccine-preventable disease collaborations with the state public health laboratories. They are able to provide on-ground assistance when requested, and have had over 25 staff deployed to Rockland County, New York to assist the state and county with their outbreak. They have been especially working to provide evidence-based information and targeted communications resources to promote awareness of measles and of the benefits of vaccination, and to establish collaborations with key stakeholders in affected communities (e.g., Rabbis/Rabbinical organizations, healthcare providers, health centers, and summer camps). At the end of April, they published an *MMWR* report the experience with measles with the 704 cases to date that describes the clinical presentation, complications, et cetera.

In summary, the US remains in measles elimination status, although there are prolonged outbreaks in close-knit communities that CDC is working to bring under control. Vaccination coverage remains high, but communities with low vaccination coverage are at risk for outbreaks. In the context of increased global measles activity, risk of continuing importations is expected.

Discussion Points

Dr. Schaffner (NFID) asked what could/would put the US's status of having eliminated measles at risk.

Dr. Clark replied that measles elimination was declared after more than a year of no endemic transmission. A year of sustained endemic transmission would put the status at risk, so CDC is working hard to support getting ahead of these outbreaks before that happens.

Dr. Kimberlin (AAP) noted that when children under a year of age travel internationally, they are recommended to receive MMR if they are between 6 through 11 months of age. He wondered what the recommendation within the US would be.

Dr. Clark indicated that in general, everyone could be reassured that the risk of measles in most of the US is low. CDC is recommending that travelers who intend to go to communities where there is sustained transmission and where they are likely to be exposed to populations in which measles are being transmitted to follow the recommendations made by the local health departments. There is a narrow circumstance, with most people not being at high risk for measles in the US or from travel across the US.

Dr. Lee thought it would be interesting for ACIP to hear about how CDC has tailored implementation strategies depending upon the contextual factors and what they have found to be most effective.

Dr. Stephens inquired about the level of vaccine coverage in communities where there have been sustained outbreaks.

Dr. Clark said that in some cases, it has been a challenge to understand coverage in these communities. These are very local phenomena and the immunization registries are not always optimal. Even in New York and Rockland County, it has been a challenge to understand the denominators. They do not absolutely know prior coverage in these communities. Many doses have been delivered in New York City and Rockland County, so they appear to be improving coverage.

Dr. Hahn (CSTE) commented that it is challenging for state and local health departments to message the need for immunization when outbreaks are going on. She wondered whether there might be other language they could use, such as "transmission has been interrupted." It is difficult to say, "It has been eliminated, but it is here and we have more cases."

Dr. Clark said that they have bridged this by stating that all cases of measles in the US are associated with travel, which puts the communities travelers come into at risk.

Dr. Hunter asked whether there are any administrative or logistical implications of losing elimination status such as insurance coverage or ability to use 317 vaccines in certain situations.

Dr. Clark said that there should not be. Of course, it is important to re-establish elimination status, but this should not have practical implementation implications for the vaccination program.

Dr. Bernstein asked what relationship CDC has with the countries that have thousands to tens of thousands of cases of measles, and how the agency is working with those countries if at all.

Dr. Clark indicated that CDC's Global Immunization Division works closely on measles globally with many countries. CDC is in constant communication with PAHO and WHO regarding the US's status and with respect to situational awareness with these countries. In certain circumstances, CDC is trying to promote specific travel-associated prevention measures with travel from some specific countries.

Zoster Vaccines

Introduction

Kelly Moore, MD, MPH
ACIP Chair, Zoster WG
Vanderbilt University School of Medicine

In terms of the Zoster WG's activities, Dr. Moore reminded everyone that in October 2017, ACIP voted to recommend recombinant zoster vaccine (RZV) for adults ≥50 years of age. In June 2018, plans were described to monitor the safety, effectiveness, and uptake of RZV. In February 2019, preliminary results were presented of uptake and safety, including a statistical signal for Guillain-Barré Syndrome (GBS). She indicated that the purpose of the presentation for this session was to present a follow-up on the results for RZV safety monitoring.

Update on Post-Licensure Safety Monitoring of RZV (SHINGRIX)

Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
Centers for Disease Control and Prevention

Dr. Shimabukuro provided an update on safety monitoring from the Vaccine Adverse Event Reporting System (VAERS), Rapid Cycle Analysis (RCA) from the Vaccine Safety Datalink (VSD), FDA assessment of GBS following recombinant zoster vaccine (RAV) from Medicare data, and next steps. He first clarified a few of the terms that are used in the context of vaccine safety monitoring and research, which are shown in the following table:

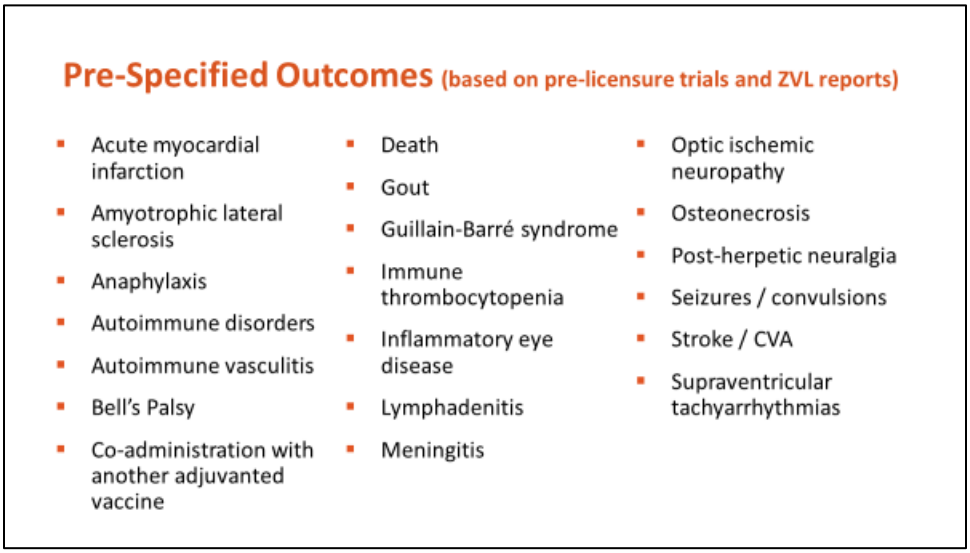
Vaccine safety monitoring and research terms

Term	Explanation
Adverse event	An adverse medical or health event following vaccination (a temporally associated event), which may or may not be related to vaccination (i.e., coincidental).
Adverse reaction	An adverse health event following vaccination where substantial evidence exists to suggest the event is causally related to vaccination.
MedDRA	A clinically-validated international medical terminology used by regulatory authorities to describe health outcomes and events.
ICD-10 and 9	A system used by physicians and other healthcare providers to classify and code diagnoses, symptoms and procedures associated with healthcare.
Automated analysis	Analysis on administrative or claims data or non-chart/health record confirmed data.
Chart confirmed/ medical record confirmed case	A case where review of medical charts and records by physicians or medical personnel confirms the diagnosis as valid and with accurate onset relative to timing of vaccination.
Incident case	A new case occurring for the first time ever or during a specified time period.
Prevalent or non-incident case	A case that has been diagnosed in the past prior to vaccination or prior the study period that has become part of the patient's past medical history and therefore is not new.
Biologically plausible risk interval	The time interval following vaccination where it is biologically plausible, based on the best available science, that an observed adverse event could be related to vaccination.
Statistical signal	A finding from an analysis where a calculated value (i.e., the test statistic) exceeds a specified statistical threshold; a statistical signal does not necessarily represent a vaccine safety problem and requires further assessment before conclusions can be drawn.

As a reminder, RZV is an adjuvanted ($AS01_B$) glycoprotein vaccine that was licensed in October 2017 and is preferentially recommended by ACIP for adults ≥50 years. Initial post-licensure safety data was presented during the February 2019 ACIP meeting. Overall, the safety profile of RZV was consistent with pre-licensure clinical trial data. A statistical signal was detected for GBS in VSD RCA monitoring based on a small number of GBS cases using automated data. Signal assessment is in progress, including a FDA analysis of Medicare data.

Beginning with VAERS monitoring, VAERS is a spontaneous reporting system that is co-managed by CDC and FDA. As a spontaneous reporting system, its main limitation is that generally causality cannot be assessed from VAERS data alone. VAERS accepts all reports from all reporters without making judgments on causality, irrespective of clinical seriousness. As a hypothesis generating system, VAERS identifies potential vaccine safety concerns that can be studied in more robust data systems.

CDC performed a descriptive analysis of RZV reports from October 2017 through April 2019 and estimated reporting rates based on 11.89 million RZV doses distributed for the US market through March 2019. FDA colleagues conducted Empirical Bayesian (EB) data mining to detect disproportional reporting for vaccine-AE pairings. A clinical review was performed of reports for the 20 pre-specified outcomes shown below:



During the analytic period, there were 18,418 total reports. Of those, 12,431 (67.5%) were in females and 17,919 (97.3%) were non-serious. In 94% of reports, RZV was given alone without other vaccines. The reporting rates for all reports were 154.3 per 100,000 doses distributed and 3.9 per 100,000 doses distributed for serious reports. Those are similar to what was reported in February 2019 and similar for other vaccines given in this age group. Systemic signs and symptoms and injection site reactions were the most commonly reported AEs, and no unexpected patterns were detected by physician reviewers of reports of pre-specified outcomes. EB data mining identifies AEs that are reported more frequently than expected, adjusting for age, sex, and the year in which reports are received. There has been one empirical EB data mining finding to date for RZV, which was "product administered to patient of inappropriate age" when looking at individuals 19 through 44.9 years of age.

In summary, RZV post-licensure safety monitoring findings in VAERS are generally consistent with the safety profile observed in pre-licensure clinical trials. Self-limited systemic signs and symptoms and injection site reactions were the most commonly reported adverse events. SAEs were rarely reported (2.7% of reports), which is similar to other vaccines given in the same age group. There have been no EB data mining findings for any RZV-AE pairings except for "product administered to patient of inappropriate age."

Regarding the RCA in the VSD, there are 8 participating integrated healthcare organizations in the VSD collaborating with CDC: Kaiser Permanente Washington, Kaiser Permanente Northwest, Kaiser Permanente Northern California, Kaiser Permanente Southern California, Kaiser Permanent Colorado, HealthPartners, Marshfield Clinic Research Institute, and Harvard Pilgrim. The VSD has medical care and demographic data on over 12.1 million persons per year (~3.7% of U.S. population), including data on immunizations, encounters with the healthcare systems, hospital discharge codes, procedure codes, and demographic information all linked by unique study IDs. CDC also has access to electronic files and paper charts. RCA in the VSD is

a powerful and sophisticated tool for near real-time vaccine-safety monitoring using sequential monitoring techniques. It employs an automated analysis that uses ICD-coded diagnoses from administrative data. It is a surveillance activity (signal detection and signal refinement), which is not the same as an epidemiologic study (signal evaluation, causality assessment). It is designed to detect statistical signals, which are values above specified statistical thresholds. When a statistical signal occurs, CDC conducts a series of evaluations using traditional epidemiologic methods. Chart-confirmation of diagnoses to confirm or exclude cases as true incident cases is a key part of statistical signal assessment. Importantly, not all statistical signals represent a true increase in risk for an AE.

For RZV RCA, a historical comparator design is used to compare current RZV recipients to zoster vaccine live (ZVL) recipients from 2013 to 2017 for the risk window of 1 to 42 days. Monthly near real-time sequential monitoring is done of pre-specified outcomes. During this session, Dr. Shimabukuro presented data from the 7th of 18 planned analyses. The test statistic is an adjusted likelihood ratio test (H_0: RR=1 versus H_A: RR>1). These are the 10 high priority pre-specified RZV RCA outcomes:

High Priority Pre-Specified Outcomes	Risk Interval in Days
Acute myocardial infarction	1-42
Anaphylaxis	0-1
Bell's palsy	1-42
Convulsion	1-42
Giant cell arteritis	1-42
Guillain-Barré syndrome	1-42
Optic ischemic neuropathy	1-42
Polymyalgia rheumatica	1-42
Stroke	1-42
Supraventricular tachycardia	1-42

Other outcomes for descriptive analysis include: gout, keratitis, non-specific adverse effects, stroke subtypes, pneumonia, keratitis, uveitis and retinitis, zoster ocular disease, systemic reactions, local reactions, and urgent care or emergency department visits.
A secondary analysis also is being done using two concurrent comparators comparing RZV recipients to those who: 1) had an ICD-10 coded well-visit during RZV uptake period; and 2) received another vaccine that was not influenza (e.g., PPSV23, PCV13, Td, Tdap, et cetera) during the RZV uptake period. For the 7th analysis, just over 211,000 doses had been administered in the VSD through December 2018 with follow-up for outcomes through April 2019. This is a summary table of the RCA results for the high priority outcomes:

RZV RCA Results: Statistical Signals for Bell's Palsy and GBS Detected

High priority outcomes	Obs events	Exp events	Obs rate (per 100K)	RR	Statistical signal (which analysis)
Stroke	109	126	51.6	0.87	No
Acute MI	106	125	50.2	0.85	No
Polymyalgia rheumatic	35	53	16.6	0.66	No
Supraventricular tachycardia	34	42	16.1	0.82	No
Convulsion assoc. terms	45	40	21.3	1.11	No
Bell's palsy[1]	40	31	18.9	1.31	Yes (at #5)
Anaphylaxis	7	5	3.3	1.32	No
Giant cell arteritis	10	17	4.7	0.61	No
Optic ischemic neuropathy	14	17	6.6	0.83	No
Guillain-Barré syndrome (GBS)[2]	5	1.6	2.4	3.18	Yes (at #2)

[1]Bell's palsy signaled at 5th analysis (36 obs events vs. 24 exp; RR=1.51, adjusted p=0.03)
[2]GBS signaled at 2nd analysis (3 obs events vs. 0.6 exp; RR=5.25, adjusted p=0.02)

No statistical signals were detected for any of the high priority outcomes with the exception of Bell's Palsy and GBS. GBS signaled previously, which was presented to ACIP during the February meeting.

Bell's Palsy signaled at the 5th analysis. At that time, there was a relative risk (RR) of 1.51 with 36 observed events versus 24 expected events (p=0.03). By the 7th analysis, it had attenuated somewhat to an RR of 1.31 with 40 observed events versus 31 expected events. Importantly, the RR are not consistently elevated for the concurrent comparator groups. The RR are actually 0.98 in the well-visit comparator group and 0.74 in the other non-influenza vaccine recipients. Chart review adjudication was performed on the 36 RZV cases from the 5th analysis, which ruled out 21 cases (11 prevalent/non-incident; 5 miscoded; 2 diagnosis overturned; 3 outside 1-42 day risk window) and classified 15 cases as definite with onset within the 1 to 42 day window. That is a chart confirmation rate of about 40%. Bell's Palsy reports that came into VAERS also were reviewed. There were no EB data mining findings or proportional reporting ratio (PRR) findings for Bell's Palsy. After review and adjudication of the Bell's Palsy reports, a reporting rate of 1.2 cases per million RZV doses distributed was estimated.

GBS signaled at the 2nd analysis at which time there were 3 observed events versus 0.6 expected for a RR of 5.25. Currently at the 7th analysis, there are 5 observed events compared to 1.6 expected events for a RR of 3.18. Of the 5 events, 2 were ruled out due to prior diagnosis of GBS so they were not true incident cases and 1 was ruled out due to GBS symptom onset prior to vaccination. Of the 2 confirmed cases, 1 was a Brighton Criteria level 2 GBS case with onset in the risk window who also received simultaneous PCV13 and 1 was a Brighton Criteria level 3 GBS case with onset in the risk window and probable respiratory infection prior to GBS symptom onset.

As part of the statistical signal assessment for GBS, all of the GBS cases in the historical ZVL comparators were reviewed. Upon chart review of these 5 cases in the historical comparator, 2 cases were ruled out, 1 due to prior diagnoses of GBS and 1 who was given an alternative diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Medical records were not available for 1 case, so it was not possible to confirm/rule out. There were 2 Brighton Criteria level 2 confirmed GBS cases with onset in the risk window. So that is 2 confirmed cases from RZV at the 7th analysis and 2 confirmed cases following ZVL in the historical ZVL cohort.

To date, the estimated VSD chart confirmed GBS rate in the current RZV cohort is higher than in the historical ZVL cohort, and higher than published estimates in the literature[1,2]. However, the uncertainty around the VSD estimated GBS rate following RZV is large, IR=8.2 (95% CI 1.0, 29.7), and overlapping with the background rates reported in the literature. They decided to perform a sensitivity analysis to find out what would happen if the unconfirmed case with insufficient information was assigned as a true incident case in the historical ZVL comparator for a total of 3 confirmed cases. The incidence rate became 3.6 with a confidence interval ranging from 0.7 to 10.4. That may not seem like a big difference, but following that, the RR risk decreased from 3.5 (95% CI 0.3, 47.8) to 2.3 (95% CI 0.2, 20.2) and the risk difference decreased from 5.9 per (95% CI -6.0, 17.7) to 4.7 (95% CI -7.4, 16.8). That is not a trivial change and illustrates the challenges when working with rare outcomes and small numbers of doses administered [[1]Sejvar et al. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology. 2011;36:123-33; [2]Using data from Shui et al. Guillain-Barré syndrome incidence in a large United States cohort (2000-2009). Neuroepidemiology. 2012;39:109-15].

To summarize the review of GBS cases in VAERS, there were no EB data mining or PRR findings for GBS. After review and adjudication of VAERS reports, a reporting rate of 2.4 cases per million RZV doses distributed is estimated.

Regarding the FDA assessment of the risk of GBS following RZV from Medicare data, upon detection of the statistical signal for GBS following RZV in the VSD RCA in the fall of 2018, CDC consulted with FDA on the possibility of additional analyses in other databases. Subsequently, FDA in collaboration with CDC and CMS initiated an assessment of risk of GBS following RZV in Medicare data. Interim results of an automated ICD-coded analysis are now available, and additional work to refine the analysis is in progress.

FDA focused on replicating the signaling of the VSD analysis in a cohort comparison of the post-vaccination GBS rate between a vaccinated RZV population and a historical vaccinated ZVL population. Vaccinations are identified using National Drug Codes (NDCs) in Part D. The RZV vaccination window is October 2017 through December 2018 and the ZVL vaccination window is October 2012 through September 2017. The population included individuals who aged into Medicare during those periods, so they already were 65 years of age or older. They had to have continuous enrollment in Medicare Parts A, B, and D for 365 days prior to vaccination to ensure that there was no GBS in the 365 days prior to the vaccination date. The risk window was 1 to 42 days post-vaccination. The outcome was an ICD-coded inpatient GBS diagnosis.

For the RZV vaccinated cohort, there were 15 ICD-coded GBS cases, 1.3 million eligible doses, and 514.9 total person time. That comes out to an outcome rate of 0.029/100,000 person-days. For the ZVL vaccinated cohort, there were 9 ICD-coded GBS cases, 1.8 million eligible doses, and 753.4 total person time. That is an outcome rate of 0.012/100,000 person-days. The RR is simply the GBS rate in the RZV vaccinated cohort divided by the GBS rate in the ZVL vaccinated cohort. After adjusting for age and sex, the RR was 2.34 (1.01, 5.41). Looking at outcome per million doses, the outcome rate for the RZV cohort is 11.38/million doses administered and for the ZVL cohort is 4.95/million doses administered. The RR was the same, 2.34 (1.01, 5.41), but now this is put into an attributable risk per million doses. Adjusted for age and sex, that is 6.54 (-0.11, 13.9) per million doses administered.

In summary, the interim results of the FDA cohort comparison of post-vaccination GBS rate between the vaccinated RZV population and historical ZVL population showed an elevated adjusted RR of 2.34 (95% CI 1.01, 5.41). These results should be interpreted with caution. This is an automated analysis using ICD-coded GBS diagnoses. Chart review/confirmation of cases is pending. Current versus historical comparisons are subject to potential confounding and require adjustments, which are in progress. A chart confirmed, self-controlled analysis is planned, which will control for many potential confounders of historical comparator designs.

Regarding selected secondary outcomes and secondary analyses, a descriptive analyses for lower priority outcomes in the historical comparator ZVL design shows a RR was <1 for hemorrhagic stroke (0.48) gout (0.84), pneumonia (0.65), and zoster ocular (0.63). RR was ~1 for non-hemorrhagic stroke (0.95), local reactions (0.96), uveitis/retinitis (0.89), and urgent care/emergency department visit (0.90). RR was >1 for systemic reactions (1.21), non-specific AE (1.23), and keratitis (1.15). Looking at the well-visit comparators 50+ years of age during the RZV uptake period (N=1,415,492), all high priority outcomes had a RR <1.0 except GBS, which was slightly elevated with a RR of 1.86 (5 observed versus 2.7 expected events). Looking at other non-influenza vaccine recipient comparators 50+ years of age and older during RZV uptake (N=518,115) for the high priority outcomes, RR was <1.0 except for GBS with a RR of 1.53 (5 observed versus 3.3 expected events).

In conclusion, this is still the initial uptake period for RZV and it is early in the post-licensure monitoring process considering constraints on supply. There have been 11.89 million RZV doses distributed for the US market through March 2019. There were 211,109 RZV doses included in the 7th of 18 VSD RCA analyses covering the period January through December 2018, with outcome monitored through April 2019 and 1,318,004 RZV doses included in the FDA Medicare data analysis. For the past influenza season, 5.4 million doses were administered in the VSD.

There have been no concerning patterns or findings of disproportional reporting for adverse health events in VAERS. Statistical signals detected for Bell's Palsy and GBS in VSD RCA in automated analyses. An elevated RR for GBS was detected in the FDA cohort analysis in Medicare data using automated analysis. The statistical signal for Bell's Palsy in the VSD RCA is not consistent across comparators. Currently the RR in the primary analysis is 1.31. However, the RR are <1 in the secondary concurrent comparator analysis.

The assessment of the statistical signal for GBS in VSD included chart review of all potential GBS cases identified by ICD codes in the current RZV and historical ZVL recipients. The chart confirmed RR is 3.5 (95% CI 0.3, 47.8) based on 2 RZV and 2 ZVL confirmed cases. The risk difference is 5.9 per 100,000 person years (95% CI -6.0, 17.7). The interim results of the FDA cohort comparison of post-vaccination GBS rates between the vaccinated RZV population and historical ZVL population using ICD-coded cases showed elevated rate ratio of 2.34 (1.01, 5.41) and an attributable risk of 6.54 (-0.11, 13.9) additional cases per million doses administered. Additional analysis and chart review/confirmation are pending for the FDA study.

Regarding next steps, the safety profile of RZV is generally consistent with pre-licensure clinical trial data. Two systems have detected an increased risk for GBS; however, the numbers are small in VSD and chart reviews are pending in FDA Medicare analysis. CDC will continue to monitor GBS and Bell's Palsy in VSD. FDA is in the process of accessing charts to review GBS cases in the Medicare cohort analysis, and will consider doing a chart confirmed self-controlled analysis to further assess risk of GBS following RZV. Dr. Shimabukuro emphasized that CDC believes the take-home message is that the initial safety monitoring data so far are insufficient

to conclude that a safety problem exists for GBS, but further evaluation and continued vigilance are warranted.

Discussion Points

Regarding next steps, Dr. Lee said she realized that the numbers probably would be incredibly small in the concurrent analysis (comparison groups) but wondered when data would be forthcoming from that. She also wondered about calling out seasonality of GBS as one of the potential confounders, and whether there were any odd shapes in the curve for RZV vaccination given the sudden uptick and the supply issues and whether that would be worth considering. The uptick curve looked fairly stable throughout, so probably there was not any in the VSD, but she was curious about whether there was any difference in Medicare.

Dr. Shimabukuro indicated that they plan to present the results of the primary and secondary analyses as requested by the WG and CDC. He was not aware of any seasonality for uptake of RZV in either VSD or Medicare. Uptake has been constrained by supply, so it is probably not the normal uptake that would occur if supply was meeting demand.

Given that influenza can increase GBS rates, Dr. Hunter wondered whether the cases or rates between cases and non-cases through the chart review showed more or less influenza diagnosed.

Dr. Shimabukuro replied that they have not looked for influenza disease as part of this analysis.

Dr. Moore suggested that it might be beneficial for the purposes of the discussion to hear the presentation from Dr. Dooling on the WG's interpretation of the results before engaging in a more in-depth conversation about safety.

Dr. Friedland (GSK) emphasized that GSK's top priority is patient safety and they are committed to monitoring and ensuring the safety of all of their vaccines, which includes SHINGRIX. As indicated in the presentation, the ongoing safety monitoring data to date are insufficient to conclude that a safety problem exists for GBS or Bell's Palsy. Continued vigilance and further evaluation are warranted. GSK will continue to monitor reports of GBS and Bell's Palsy following vaccination with SHINGRIX through their enhanced pharmacovigilance, and they will be evaluating any new information that becomes available. In addition, incident cases of GBS will be measured in the objectives of GSK's planned post-marketing targeted safety studies. In summary, GSK remains confident in the favorable benefit-risk ratio profile of SHINGRIX for the prevention of herpes zoster and will continue to work closely with CDC and FDA to actively monitor the safety of SHINGRIX.

Summary of HZ WG Interpretation of RZV Safety Data

Dr. Kathleen Dooling MD MPH
Herpes Zoster Work Group Liaison
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Dooling expressed the WG's gratitude to the ISO, VSD, and FDA for their contributions toward monitoring the safety of RZV. In terms of the WG's interpretation of the RZV safety data, approximately 12 million doses of RZV have been distributed in the US since the vaccine was licensed. Thus far, the most common reports have involved non-serious reactogenicity-like

symptoms consistent with findings from the RCTs. The RCA has yielded preliminary statistical signals for two conditions, Bell's Palsy and GBS. She presented a summary of the data the WG felt was key in interpreting these signals, organized in a framework of increased certainty of classification and association starting with the events reported in VAERS, followed by data from ICD-9 and ICD-10 automated sources, and finally those cases validated by vaccine safety experts and known to have occurred in the 42 days following vaccination.

In terms of Bell's Palsy following RZV, there were no signals in VAERS. With respect to administrative data cases, there was an increased risk when compared to historical ZVL in the VSD. However, there was no increased risk when concurrent comparator groups were used. Upon medical chart review of those administrative cases of Bell's Palsy, only 15 of 36 (42%) were actually validated as true incident cases. Regarding the investigation of GBS following RZV, there were no signals in VAERS. With respect to administrative cases, an increased RR was observed in both VSD and Medicare based on historical rates following VZL. However, the RR was lower when concurrent comparator groups were used in VSD. Upon medical chart review of the administrative cases of GBS, two cases were validated as true incident cases in the RZV group and two in the ZVL group. This resulted in a risk difference of between 4.7 to 5.9 cases per 100,000 person years. That represents an increased risk relative to ZVL as well as baseline rates from the literature. However, due to small numbers, the confidence intervals are very large.

In summary, GBS is rare and interpretation of elevated risk of GBS is uncertain given only 2 validated cases in the RZV and the ZVL groups. Due to wide confidence intervals that overlap baseline rates, current data are insufficient to determine if a safety problem exists. The HZ WG members agree that there is insufficient evidence at this time to support a change in policy or practice and agree with the proposed next steps to: 1) continue enhanced monitoring and clinical case review of Bell's Palsy and GBS reports following RZV in VAERS; 2) continue to track and chart validated cases of Bell's Palsy and GBS in BSD; and 3) chart validated GBS cases in Medicare and pursue self-controlled analytic options.

Discussion Points

Dr. Bernstein wondered whether there are any data regarding the use of a novel adjuvant and GBS or Bell's Palsy, or studies of just the $AS01_B$ adjuvant itself.

Dr. Shimabukuro indicated that none of the cases in the VSD had co-administration of a vaccine that had a novel adjuvant, though he would have to check the VAERS reports. In the VAERS reports, RZV was administered alone in over 90% of the Bell's Palsy and GBS cases. Based on the reports in general, RZV tends to be administered alone. There have been several reports of AEs following RZV co-administered with FLUAD™, but these were non-serious injection site reactions. In terms of the adjuvant itself, he deferred to the manufacturer.

Dr. Friedland (GSK) indicated that in the clinical trials leading to licensure of SHINGRIX, there was no increased risk of GBS or Bell's Palsy noted.

Dr. Moore commented that the WG feels that it is very important to be transparent in displaying the process of how vaccine safety evaluation works. Examining vaccine safety in an older adult population in which there are many underlying issues is more complicated than in young healthy children with very few background health issues. The WG also acknowledges that although numbers were presented that may appear quite precise, it is very difficult to study GBS given the seasonality, different rates based on age and other factors, et cetera. It is possible as

additional refinements to the studies are done, there may be a more accurate picture that has different numbers than the numbers presented during this session. She cautioned everyone to look at the trends, but not get fixated on any particular numbers because important adjustments to address confounding that has not yet been addressed might result in a different look to the final results as there is more information and better analysis. The WG wanted to share the process to let people know where they are, because it could take time before those analyses are completed.

Regarding seasonality, Dr. Dooling explained that the analysis presented during this session were based on doses given in 2018. The vaccine did not become largely available until March and April of 2018. Therefore, the doses contained in the analyses presented cover only part of a calendar year through December 23, 2018.

Dr. Lee echoed what Dr. Moore said about being grateful to ISO for the incredible vaccine safety system that has been developed and enhancing their ability to monitor any AEs that occur in near-real time. That is a major testament to the fact that they are taking a dynamic look over time. She also expressed appreciation for the transparency and willingness to think critically with ACIP about feedback and how these analyses can be made better. The analyses to date have been excellent.

Pertussis Vaccines

Henry Bernstein, MD, MHCM
Chair, ACIP Pertussis Vaccines WG
Professor of Pediatrics
Zucker School of Medicine at Hofstra/Northwell
Cohen Children's Medical Center
New Hyde Park, New York

Dr. Bernstein indicated that during this session, the Pertussis Vaccines WG wanted to address the following three questions:

1) Should the current recommendation that non-pregnant adults receive a single lifetime dose of Tdap with Td boosters every 10 years be changed to allow any Td-containing vaccine (Tdap or Td) to be used for the decennial Td booster?

2) Should any Td-containing vaccine (Tdap or Td) be allowed for tetanus prophylaxis in the setting of wound management?

3) Should the catch-up immunization schedule for Tdap/Td be changed for those ≥7 years of age?

The first two questions represent the WG's initial terms of reference, while the third arose in the midst of carrying out the first two.

In terms of what prompted these questions, the most important issue was the FDA label change to Sanofi's Tdap product Adacel®. The routine booster allows for a second dose of Adacel® to be administered ≥8 years after the first dose of Tdap. In addition, Adacel® can be used in wound management. A booster dose of Adacel® may be administered if it has been ≥5 years since the previous receipt of a tetanus toxoid-containing vaccine. There is not change to GSK's Tdap product Boostrix™. There is clear evidence that repeat Tdap vaccination is widespread.

In terms of the current ACIP Tdap recommendations for non-pregnant adolescents and adults, since 2005, ACIP has recommended a single Tdap dose in adolescents and adults ≥11 years of age. There is no minimum interval since the last Td vaccine before Tdap can be given. At this time, only pregnant women are recommended to receive more than one dose of Tdap, with a dose being given during every pregnancy. It is important to note that this is an off-label recommendation that has been in place since 2012. Part of the current guidance to maintain protection against tetanus and diphtheria in those who have received a single dose of Tdap is to receive a decennial Td booster dose. This may be indicated for wound management if it has been ≥5 years since the previous receipt of a tetanus toxoid-containing vaccine. Per the WG's terms of reference, they will be discussing whether this language should be changed to allow any Td-containing vaccine (Td or Tdap) to be used for the decennial Td booster or for wound management. Regarding the third question, the Tdap primary immunization schedule for those ≥7 years of age who have not been fully immunized is 1 dose of Tdap as part of the catch-up series that preferably should be given as the first dose. If additional doses are needed, Td is supposed to be given. It is important to recognize that the catch-up schedule includes pregnant women [Liang JL, et al. Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2018 Apr 27;67(2):1-44].

EtR Framework for the use of Tdap for Decennial Td Booster, Tetanus Wound Prophylaxis, and the Catch-Up Immunization Schedule

Fiona Havers, MD, MHS
Lead, Pertussis Vaccines Work Group
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Havers began by going over the EtR Framework for the two main policy questions that focus on the use of Tdap for the decennial Td booster and for tetanus prophylaxis, beginning with a discussion of benefits and harms. As discussed in the October ACIP meeting, the previous Pertussis Vaccines WG assessed in detail whether to preferentially recommend that Tdap replace Td. The present WG reviewed these considerations, but in general, focused on programmatic issues, including the impact that changing the recommendations would have on clinical providers. Because the WG's focus was on programmatic considerations, they did not conduct a detailed GRADE analysis of the benefits and harms of potential changes to recommendations. In addition, she reviewed the evidence for other elements of the EtR Framework (values, preferences, acceptability and feasibility, resource use), the WG's interpretation, and the catch-up immunization schedule.

In terms of benefits and harms, benefits to providers include ease and flexibility. It is often challenging to determine whether a patient has previously received Tdap, and it is cumbersome to have to stock both Td and Tdap vaccines. The WG concluded that there are benefits to giving providers the flexibility to administer either Td or Tdap.

There was considerable uncertainty about the potential benefits that result from the impact of repeat Tdap vaccination on pertussis prevention and control. There is evidence that a second dose of Tdap is immunogenic, although immunogenicity data after receipt of more than 2 doses are lacking. In addition, the duration of protection is uncertain, and may vary by population group. There is some evidence of short duration of protection in persons who were given acellular pertussis vaccines for their childhood series, but there is a lack of data on duration of protection among those primed with whole cell pertussis vaccines in childhood. In addition, Tdap vaccines have an uncertain role in the prevention of transmission and herd immunity. While several WG members felt that Tdap should be preferentially recommended to replace Td, the majority of WG members felt that there was insufficient evidence of benefits in pertussis control to recommend that Tdap replace Td for all decennial boosters.

The WG also looked at whether recommendations for healthcare personnel (HCP) should be different than for the general population. This also had been reviewed by the previous ACIP WG. While pertussis transmission has been documented in healthcare settings, there are insufficient data that HCP are at increased risk for pertussis infection. In addition, there is a lack of strong evidence that additional Tdap doses for HCP would be beneficial for pertussis control in healthcare settings. While several WG members felt that Tdap should be preferentially recommended to replace Td for HCP, the majority of WG members felt there was insufficient evidence of benefits in pertussis control to make recommendations for healthcare personnel that are different than those for the general population.

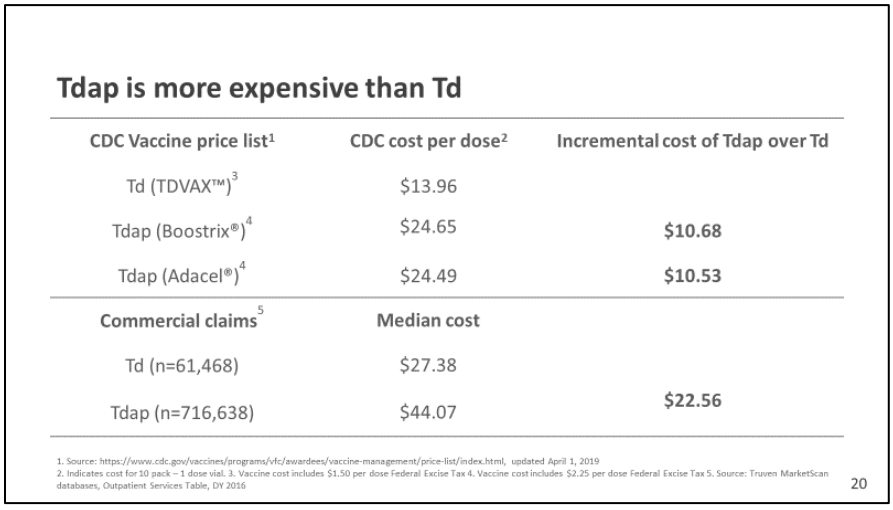
Regarding whether there are any potential harms, the safety data of a second Tdap vaccination were reviewed by the previous WG, and more recent data were presented during the October 2018 ACIP meeting. While the WG acknowledged that there were a number of studies that examined the safety of a second Tdap vaccination, there were few that looked at more than 2 doses. Nevertheless, the WG concluded that based on the evidence available, there were no substantive safety concerns in allowing Tdap to be used for the decennial booster or for tetanus prophylaxis in the setting of wound management. The WG concluded that, in general, the benefits to implementing the recommendation changes outweigh harms.

Moving on to other elements of the EtR Framework, the WG looked at evidence indicating whether patients and providers value or have a preference for repeat Tdap vaccination. There have been no studies specifically asking the preferences of stakeholders, which the WG defined as the general adult population, as well as providers and immunization programs. However, the proposed recommendation does not require any additional vaccine doses, likely making it acceptable to patients. There also is evidence indicating that repeat Tdap vaccination is already a widespread practice, indicating that providers may prefer using Tdap in place of Td.

In terms of the public sector purchases for adult doses of Td and Tdap for the 7 years from 2011-2017, in any given year Tdap purchases have been at least 10-fold more than Td purchases[1]. The WG also explored other data sources for evidence of this, including a study by the VSD that included almost 69,000 persons who had received Tdap and then later received another Td-containing vaccine. Among these patients, 89% received Tdap for their second vaccine, while only 11% received Td. This is confirmed by information from a large database of insurance claims, in which Tdap claims outnumbered Td claims by 11 to 1[2]. Given these data, it is likely that giving Tdap in place of Td is already widespread despite the fact that it is not currently recommended by ACIP and in clinical practice it is still an off-label use. The WG concluded that this likely indicates that allowing either Tdap or Td to be used would be acceptable and feasible for stakeholders and may be preferred by providers [[1]Courtesy CDC Immunization Services Division, Vaccine Supply and Assurance Branch, Data Team; [2]Jackson

ML, et al. Safety of repeated doses of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine in adults and adolescents. Pharmacoepidemiol Drug Saf 2018 Aug;27(8):921-925].

Regarding resource use, Tdap is more expensive than Td. This table shows two different sources of cost data:



Tdap is more expensive than Td

CDC Vaccine price list[1]	CDC cost per dose[2]	Incremental cost of Tdap over Td
Td (TDVAX™)[3]	$13.96	
Tdap (Boostrix®)[4]	$24.65	**$10.68**
Tdap (Adacel®)[4]	$24.49	**$10.53**
Commercial claims[5]	**Median cost**	
Td (n=61,468)	$27.38	
Tdap (n=716,638)	$44.07	**$22.56**

1. Source: https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html, updated April 1, 2019
2. Indicates cost for 10 pack – 1 dose vial. 3. Vaccine cost includes $1.50 per dose Federal Excise Tax 4. Vaccine cost includes $2.25 per dose Federal Excise Tax 5. Source: Truven MarketScan databases, Outpatient Services Table, DY 2016

20

The top half of the above table shows data from the CDC vaccine price list, with the cost per dose for the generic Td compared with the two Tdap products. The incremental cost of Tdap over Td was approximately $11 from this data source. The bottom part of the table shows claims data from commercially insured persons. In these data, the median cost for Tdap was approximately $22 more than for Td.

Regarding the question of resource use and whether allowing either Tdap or Td to be used in place of Td is a reasonable and efficient allocation of resources, the WG did reviewed pricing of the two types vaccines and also economic impact analyses, including a detailed review of an internal CDC analysis. However, the relevance of economic data to this issue is questionable if providers are already giving multiple Tdap doses. Indeed, for all economic analyses available, there is considerable uncertainty for a number of key parameters, particularly pertussis incidence estimates, which vary widely. Pertussis is underdiagnosed and likely underreported, and there is a lack of reliable estimates of disease burden, particularly in adults. Estimates are also uncertain for initial vaccine effectiveness, duration of protection, and other parameters. In addition, no analyses of the economic impact accounted for cost savings resulting from providers only carrying one vaccine instead of two and the impact on pertussis epidemiology resulting from the fact that multiple doses of Tdap were likely already being given. After evaluating the economic evidence, the WG concluded that the economic impact analyses did not drive their decision-making process for these particular programmatic questions.

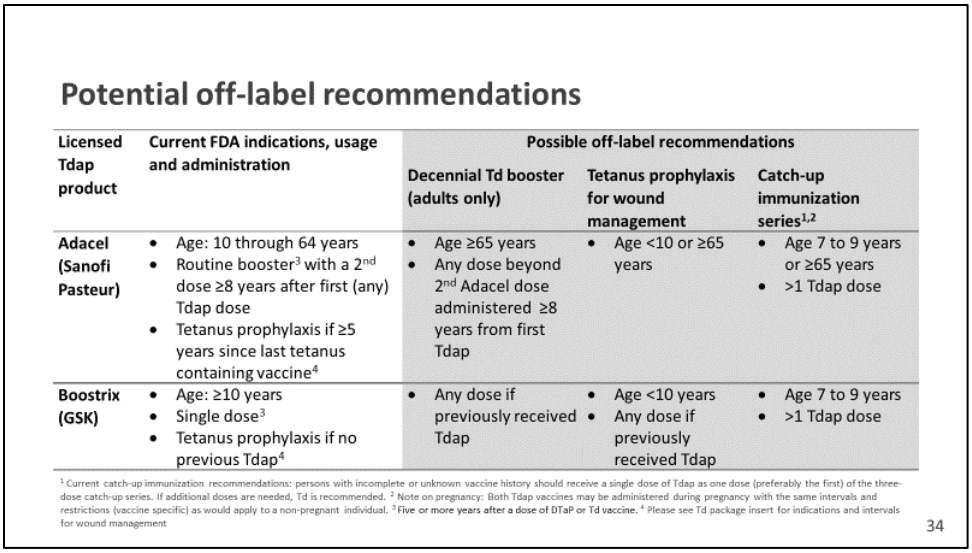
Regarding whether any Td-containing vaccine (Tdap or Td) should be allowed for use for the decennial Td booster and tetanus prophylaxis in the setting of wound management, the WG group concluded that allowing this recommendation gave increased flexibility to providers and that there may be some additional benefit for pertussis control, but that there was not enough evidence to preferentially recommend Tdap over Td. They concluded that there were no substantive safety concerns, and given this, the benefits of the recommendation change outweighs potential harms. The WG also concluded that providers value flexibility, and that

there is evidence that Tdap has largely replaced Td regardless of current recommendations, which indicates that the change would be valued by stakeholders and that it is likely acceptable and feasible. Although Tdap is more expensive than Td, economic analyses had limited utility. Given that the change has been widely implemented already, regardless of the higher cost and the uncertainty of key parameters in the various economic models, economic impact was not a major consideration for the WG group for these questions.

While the WG was discussing these questions for the decennial booster and wound management, one further question arose, "Should any Td-containing vaccine (Tdap or Td) be allowed for additional catch-up doses for those person ≥7 years old with incomplete or unknown vaccine history?" As Dr. Bernstein mentioned in his introduction, the current catch-up schedule consists of three doses, one Tdap preferably for the first dose and two subsequent Td doses. One policy option discussed was to make no change to the current catch up schedule. The WG discussed whether the catch-up immunization schedule should be a dose of Tdap followed by two doses of either Tdap or Td, which would allow providers flexibility in choosing which vaccine to give for the additional doses. They also discussed whether more than 1 dose of Tdap should be preferentially recommended over Td for either 1 or both of the additional doses. The majority of the WG agreed with a permissive change in the recommendations, which states that at least one dose of the catch-up schedule should be Tdap, but that the additional doses could be either Tdap or Td. The rationale for this was similar to that for the two main questions already addressed, in that there were benefits to providers in having more flexibility and ease of use. There also may be some additional benefit to having more than one pertussis-containing vaccine for pertussis protection in previously unimmunized persons, but there was not enough evidence to preferentially recommend Tdap over Td. In addition, particularly if the other recommendations are put into place and result in a decrease in the availability of Td, increased flexibility for providers would be helpful.

One final nuance was noted. The current catch-up schedule is the same for pregnant women as for the general population, and any changes would therefore also apply to pregnant women. Previously unimmunized pregnant women may require two doses of a tetanus-toxoid containing vaccine to prevent obstetric and neonatal tetanus. Data are lacking on the safety of multiple doses of Tdap during a single pregnancy. There are some data from pregnancy registries of patients who inadvertently received more than 1 dose during a single pregnancy, and there have been no concerning safety signals for this or for women who receive closely-spaced Tdap vaccinations in different pregnancies. Thus, the WG concluded that recommendations for catch-up immunization in pregnancy should be similar to those for the general population.

If the changes discussed in this presentation are adopted by ACIP, there are several situations in which recommendations would be off-label. This table shows the two licensed Tdap products and a summary of their FDA approved indications, usage, and administration in the second column. The last three columns indicate where use of these two products would be off-label if recommendations were changed for the decennial Td booster, tetanus prophylaxis in the setting of wound management, and the catch-up immunization series:



Potential off-label recommendations

Licensed Tdap product	Current FDA indications, usage and administration	Possible off-label recommendations		
		Decennial Td booster (adults only)	Tetanus prophylaxis for wound management	Catch-up immunization series[1,2]
Adacel (Sanofi Pasteur)	• Age: 10 through 64 years • Routine booster[3] with a 2nd dose ≥8 years after first (any) Tdap dose • Tetanus prophylaxis if ≥5 years since last tetanus containing vaccine[4]	• Age ≥65 years • Any dose beyond 2nd Adacel dose administered ≥8 years from first Tdap	• Age <10 or ≥65 years	• Age 7 to 9 years or ≥65 years • >1 Tdap dose
Boostrix (GSK)	• Age: ≥10 years • Single dose[3] • Tetanus prophylaxis if no previous Tdap[4]	• Any dose if previously received Tdap	• Age <10 years • Any dose if previously received Tdap	• Age 7 to 9 years • >1 Tdap dose

[1] Current catch-up immunization recommendations: persons with incomplete or unknown vaccine history should receive a single dose of Tdap as one dose (preferably the first) of the three-dose catch-up series. If additional doses are needed, Td is recommended. [2] Note on pregnancy: Both Tdap vaccines may be administered during pregnancy with the same intervals and restrictions (vaccine specific) as would apply to a non-pregnant individual. [3] Five or more years after a dose of DTaP or Td vaccine. [4] Please see Td package insert for indications and intervals for wound management

34

Off-label indications based on age have not changed. New off-label indications for Adacel® would include any additional routine or catch-up Td dose beyond a second dose administered ≥8 years from a first Tdap dose, if not given for wound prophylaxis within the specified guidance. For Boostrix™, any additional doses of Boostrix™ beyond the single licensed dose would be off label. The WG did not find any reason to distinguish between these two products in making their recommendations.

In summary, for the three questions of whether either Tdap or Td should be allowed to be used for the decennial Td booster, for tetanus prophylaxis in the setting of wound management, or for additional doses of the catch-up immunization schedule for persons aged 7 years or older, the work group is in favor of these interventions.

Discussion Points

Dr. Walter inquired as to how much data there are on repeat short-term administration of Tdap, particularly with regard to safety.

Dr. Havers replied that the article she included was a study conducted on Boostrix™ that examined a 0-, 1-, and 6-month catch-up schedule comparing Td and Tdap. There were no concerning safety signals in that study. Other than that, she did not think there were a lot of other data.

Referring to page 18 of the binder provided to ACIP members, the *Policy Option for Adolescent and Adult Series for Those with Incomplete or Unknown Vaccine History*, it appeared to Ms. McNally that with item 2 in the WG recommendation it would be possible that Tdap could be given 3 times. She also observed that slide 7 indicated that data are lacking on the safety of 2 or more Tdap doses. Therefore, she wondered whether safety data potentially would be forthcoming.

Dr. Havers clarified that there are a number of studies pertaining to safety data, many of which were presented during the October 2018 ACIP meeting, on 2 doses of Tdap. So, repeat Tdap vaccination has been studied. There have not been many studies on more than 2 doses, but there have not been any concerning safety signals in those studies. There is the one study

mentioned that had 3 closely spaced doses of Tdap, but there are not a lot of other studies assessing more than 2 doses.

Dr. Messonnier indicated that this could be reviewed during the next ACIP meeting in October 2019. Ms. McNally expressed appreciation for this.

Ms. Stinchfield (NAPNAP) inquired as to whether there are any data on Tdap as a primary series. When they discussed Tdap initially, effectiveness was based on a primary series of DTaP. She also observed that tetanus is state reportable to CDC, but that the Children's Hospitals and Clinics of Minnesota ED is seeing an emergence of refusal for Td or Tdap for wound care. Based on a report she read the day before, there are 3 children in Italy in the intensive care unit (ICU) with tetanus. This seems like a worrisome trend that should be tracked.

Dr. Havers indicated that there was the one study she mentioned comparing Td versus Tdap as the primary immunization series that was conducted in Germany, which assessed a cohort of adults who either had not received any vaccine for at least 20 years or who had an unknown vaccination history. Td and Tdap were immunogenically equal for the tetanus and diphtheria components and there was some antibody boost with the pertussis component.

Dr. Hariri (SME, Team Lead for the Epidemiology Team) pointed out that Tdap was licensed for adolescent use. The DTaP vaccine is the only vaccine that is licensed for use as the primary series in children.

Dr. Havers added that Tdap is used for a primary series for those ≥7 years of age who are receiving a catch-up schedule or they were un-immunized. However, there are not much data on this.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Messonnier reported that a lot of CDC attention for the past 3 months has been focused on responding to the ongoing measles outbreaks. They believe that those outbreaks are a signal that more work needs to be done to prevent vaccine-preventable diseases and vaccine-preventable disease outbreaks across the US. CDC and its partners are working to protect Americans against measles and other vaccine-preventable diseases through a larger strategy that they will be socializing and rolling out in the next couple of months. There are 3 main areas of focus. The first is vaccine access, which remains a perennial issue despite the availability through the VFC Program. Children of lower economic status or without insurance still have lower vaccination coverage, an issue which needs to be addressed. The second is the measles outbreaks occurring this year, which are primarily among pockets of under-vaccination that exist in the US. Of the cases, 90% are associated with those communities and those communities are at higher risk for spread of measles. It is necessary to do a better job of identifying those communities in advance and working with local state health departments and frontline clinicians to intercede. The third is the spread of misinformation and myths about vaccines across the US. Although overall confidence in vaccines and overall vaccine coverage remain high, the spread of misinformation continues to be a threat to undermining public confidence in vaccines. Certainly, CDC will focus on making sure that scientifically valid information is easily available and accessible to the public through all means possible. In addition, CDC is participating in

Crimson Contagion, which is an HHS exercise series focused on pandemic influenza with HHS as the lead federal agency. This is a series designed to examine information exchange, coordination of resources, and policy decisions in a pandemic influenza scenario. In addition to the series of exercises, Crimson Contagion culminates in a multi-state, multi-agency functional exercise August 13-16, 2019 to examine the local, state, and federal response to an established pandemic that is in the acceleration phase of a dynamic response. The belief continues to exist that pandemic influenza remains a high risk for the US and globally. These exercises help to refine response approaches and enhance preparedness.

Centers for Medicare and Medicaid (CMS)

Ms. Hance reported that the Center for Medicare and Medicaid had its monthly call with its Medicaid Quality Partners the previous day. CDC joined the call to share toolkits for measles and back-to-school. The primary focus of this conversation was to discuss the importance of preparing now for back-to-school immunizations with the goal of increasing immunization rates for children enrolled in Medicaid. She expressed CMS's appreciation for the coordination of their CDC colleagues in this call.

Department of Defense (DoD)

Dr. Deussing expressed the Department of Defense's (DoD's) appreciation to ACIP and CDC for its continued inclusion of the DoD in ACIP meetings and WGs. There have been significant and ongoing organizational changes throughout the military health system in relation to the National Defense Authorization Acts (NDAAs) of 2017 and 2019. Fortunately, these changes have had minimal impact on DoD immunization procurement and delivery. A specific example is the YF vaccine. The Immunization Healthcare Branch (IHB) works closely with YF vaccine manufacturer and was able to maintain vaccine availability to support worldwide DoD operations despite supply constraints. Major lines of effort supporting this success included restricted administration criteria, site ordering limitations, and active product redistribution. YF vaccine redistribution within the DoD during this national shortage from April 2016 through March 2019 totaled 6574 doses worth over $400,000. Regarding seasonal influenza vaccine, the DoD met all immunization targets during the 2018 influenza season, including mandatory vaccination of uniformed personnel and HCP. Preparations are underway for the 2019 influenza season, with final publication of the seasonal influenza vaccine policy pending. The Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAVED) study completed its first year of enrollment with the aim of assessing the clinical effectiveness of licensed influenza vaccines used by the DoD. This study group is Co-Chaired by the IHB and the Uniformed Services University (USU) Infectious Disease Clinical Research Program (IDCRP). While results are still pending, the study group was able to enroll over 1600 participants into the main study at 5 different sites and 200 of those into the immunogenicity sub-study developed in partnership with the Armed Forces Health Surveillance Branch (AFHSB), Naval Health Research Center (NHRC), US Air Force School of Aerospace Medicine (USAFSAM), and the FDA. For the upcoming season, the PAVED Study Group would like to enroll 13,500 subjects at 11 sites. Educational outreach to beneficiaries continues the IHB's public-facing webpage, online and onsite courses, and toolkits.

Department of Veterans Affairs (DVA)

Dr. Kim reported that over 1.8 million veterans enrolled in VA healthcare received free influenza vaccines in outpatient settings within VA facilities during FY2018. In addition, VA continued in a Regional Partnership Program that resulted in more than 110,000 veterans receiving vaccinations paid for by VA during the last influenza season. VA completed updates for its *Hepatitis A Immunization and Clinical Preventive Services Guidance Statement* and *Hepatitis B Immunization and Clinical Preventive Services Guidance Statement*. In those updates, VA updated indications for HepA vaccinations to include homeless individuals. In follow-up of this update, VA launched a campaign in May 2019 to ensure that homeless veterans enrolled in VA healthcare who are not immune and are unvaccinated for HepA and who had risk factors for HepB were offered vaccinations as appropriate in their next clinical encounter. As a part of this campaign, VA created a surgical dataset to identify homeless veterans who are not immune HepA and had not received HepA vaccine. This dataset could be accessed by VA medical center staff.

Food and Drug Administration (FDA)

Dr. Fink reported that there has been one vaccine approval since the last ACIP meeting. On May 1, 2019 FDA approved DENGVAXIA®, which is a live-attenuated chimeric dengue vaccine on a yellow fever (YF) backbone that is indicated for prevention of dengue disease caused by serotypes 1, 2, 3, and 4 in individuals 9 through 16 years of age with laboratory-confirmed prior dengue infection and living in endemic areas. This indication is precedent-setting for preventative vaccines in a number of ways. First, it is a vaccine indicated for secondary prevention in individuals who already have been infected at least once with dengue. This is because the safety data did not support use for primary prevention in individuals who had never previously been infected with dengue. Related to that point, the vaccine is limited for use in individuals living in dengue-endemic areas. Finally, this is the first vaccine that FDA has approved that requires a laboratory test to identify individuals for whom the vaccine is indicated. The Dengue WG will present all of the details about the data that supported the indication and the limitations of use during the discussion later in the day. ACIP will have a tough job deciding how this vaccine should be used, given that dengue epidemiology is not static and the technology available for determining prior dengue infection is evolving.

Health Resources and Services Administration (HRSA)

Dr. Nair provided an update on the National Vaccine Injury Compensation Program (VICP). HRSA continues to process an increased number of claims. In Fiscal Year (FY) 2018, there were 1248 claims. In that same FY, petitioners were awarded $226 million and attorneys were awarded $26.9 million. That includes fees to attorneys for cases that were compensated or dismissed, as well as interim fees. For this FY, 709 claims have been filed with the program as of May 2019 and petitioners and attorneys have been awarded $154 million. Because of the increased number of claims that have been filed with the program in the past three years, there is a backlog of 726 claims that are awaiting review by Medical Officers. More data about the VICP can be obtained on the HRSA website.

Indian Health Service (IHS)

Dr. Weiser reported that IHS continues to advise its clinics and hospitals to update measles vaccinations for those who need it, and to be prepared to limit the spread of measles in its facilities with careful attention to infection control practices. Since the last ACIP meeting, IHS's 2-year old MMR coverage is 87%, which is a slight increase, and its adolescent MMR coverage with 2 doses is 96%. The IHS electronic medical record (EMR) system, the Resource and Patient Management System (RPMS), is undergoing updates this month and next month. Among other things, this will include a new immunization forecaster. They are actively testing the immunization forecaster and are working to develop 2-way immunization exchange with each of the state in which there are IHS facilities. In the Northwest, there has been great support with Tribal Immunization Summits in Idaho and Oregon, and a state-led Assessment, Feedback, Incentive and eXchange of information (AFIX) program evaluations in both of those states. Dr. Weiser expressed IHS's gratitude to CDC for its support to address decreased childhood immunization rates in Indian Country, particularly in Region 10 that includes Oregon, Washington, Idaho, and Alaska through a grant addendum for the Tribal Epidemiology Centers (TECs) to focus on patient and provider education. He also expressed IHS's appreciation for the concern that ACIP and the WGs have shown for the health of AI/AN by highlighting the potential consequences from recommendations for PCV13 and the new pediatric hexavalent vaccine. IHS will continue to monitor developments related to pneumococcal disease. Regarding the pediatric hexavalent vaccine, IHS is aware that Merck is pursuing investigator-initiated studies of post-dose 1 that could provide evidence needed for a preferential recommendation for AI/AN children.

National Institutes of Health (NIH)

Dr. Beigel provided an update from vaccine-related studies and/or funding opportunities at the National Institutes of Health (NIH). Influenza is a high priority for NIH and ACIP. There are several awards ACIP should be aware of. There is a multi-center study looking at pediatric immune systems and how the initial vaccines and subsequent infections model the immune response going forward. There is an additional new universal influenza vaccine candidate that is another HA stem underway at the Vaccine Research Center (VRC) intramurally at the clinical center at NIH. In terms of STIs, the National Institute of Allergy and Infectious Diseases (NIAID) established 4 cooperative research centers with a total of $40 million over 5 years to work on STI prevention and vaccines. The expectation is that each of these will have one vaccine candidate ready for clinical trials moving forward. Hopefully, this will jump start the STI vaccines. There was a recent HepC vaccine study with an adenovirus prime and a boost. Unfortunately, that did not show any efficacy. There were some lessons learned about vaccine design in terms of clinical trials for HepC. There is a large focus on HepC vaccines moving forward, so hopefully this will not be a significant setback. Takeda had a dengue Phase III study, the development of which NIAID contributed to significantly. This was a trial of over 20,000 children and adolescents living in dengue endemic areas. The highlight is that the vaccine was shown to be efficacious. They are looking forward to the scientific community seeing the full dataset to determine whether the concerns were different from other dengue virus vaccines.

National Vaccine Program Office (NVPO) / National Vaccine Advisory Committee (NVAC)

Ms. Ann Aiken reported that on June 10, 2019, the National Vaccine Program Office (NVPO) and Office of HIV/AIDS and Infectious Disease Policy (OHAIDP) merged to become the Office of Infectious Disease Policy and HIV/AIDS (OIDP). This merger is a larger part of ReImagine HHS: Moving Towards a 21st Century Workforce to better align HHS programs, improve efficiencies, and build capacity to further the goals of the office. While the name has changed, the goals and functions of the program have not. Dr. Beckman is still the Director of OIDP. NVAC met earlier in the month during which ADM Brett Giroir delivered a new charge to the committee. There were two previous charges given to the committee. The first was helping to plan for the updated 3 to 5 year National Vaccine Plan (NVP). This plan will emphasize the importance of vaccination across the lifespan and is a merger between the previous NVP and another plan done on adult immunization. NVAC was charged with assessing goal relevance, proposing new or revised goals, and prioritizing the top three objectives within each NVP goal area or proposed goal area poised to make the greatest impact on the US immunization system in the next few years. This work was presented and voted on during the last NVAC meeting earlier in June. Those materials are available should ACIP members be interested in further details. NVAC's final task to be presented and voted on during the December 19, 2019 NVAC meeting will include identifying new stakeholders to engage during plan development and writing a report summarizing the committee's findings. NVAC also was previously charged with developing a comprehensive set of recommendations to lay the foundation for an effective national strategy for ending immunization disparities in the US to ensure that all Americans have an equal opportunity to benefit from live-saving vaccines. A WG has been established to develop a report, which will be voted on during the September 26, 2019 NVAC meeting. The third charge, which was delivered during the last meeting, called for a follow-on report to the NVAC report to the NVAC report that assessed the state of vaccine confidence in 2015. ADM Giroir charged the committee to develop a report that outlines determinants of vaccination across the lifespan; suggestions for HHS to improve confidence in recommended vaccines; and guidance on the utilization of evidence-informed best practices from scientific research fields such as anthropology, psychology, and economics; and how to successfully foster vaccine confidence through public, provider, and policy interventions. This WG is in the process of being established and has deliverables due in September 2020.

Influenza

Introduction

Emmanuel (Chip) Walter, MD, MPH
Chair, Influenza Work Group
Professor of Pediatrics, Duke University School of Medicine

Given that this was his last ACIP meeting, Dr. Walter expressed his gratitude to Dr. Grohskopf for her invaluable support during his tenure as Chair of this WG, to CDC colleagues, and to fellow WG members. He said it had been his honor to Chair this WG, and announced that Dr. Atmar would serve as Chair of the Influenza WG moving forward.

Dr. Walter reminded everyone that during the February 2019 ACIP meeting there were presentations on the 2018-2019 US influenza season surveillance and preliminary VE estimates; a presentation from Seqirus™ of results of a Phase III Randomized Observer-Blind Comparator-Controlled study of Afluria® Quadrivalent for Children 6 through 59 months of age; and a presentation of a Case-Control Study of Inactivated Influenza Vaccine (IIV) and Spontaneous Abortion (SA) in the VSD performed during the 2012-13, 2013-14 and 2014-15 influenza seasons.

Since February 2010, the WG has engaged in calls about twice a month during which members heard 2018-2019 US influenza VE updates; discussed influenza vaccine safety surveillance activities; and discussed development of the 2019-2020 influenza vaccine statement. No substantial changes in the language were proposed.

The agenda for this session included the following topics:

- ❑ 2018-2019 US Surveillance Update
- ❑ Interim Estimates of 2018-2019 Seasonal Influenza VE
- ❑ End-of-Season Update: 2018-2019 Influenza Vaccine Safety Monitoring
- ❑ WG Considerations and Proposed Recommendations for 2019-2020

Influenza Surveillance Update

Lynnette Brammer, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Ms. Brammer provided a brief update on the 2018-2019 influenza season. Based on data from public health laboratories that report their influenza positives to CDC each week, this season was remarkable because there were two roughly equal waves of influenza A viruses; first 2009 (H1N1) viruses and then influenza A(H3N2). Of the viruses reported overall, 96% were influenza A and 57% of the influenza A viruses were H1N1. Also of note was that there was very little influenza B activity during this season. The switchover from influenza A(H1N1) to A(H3N2) occurred during the last week of February.

In terms of the characterization antigenically and genetically of the viruses, the A(H1N1)pdm09 and influenza B viruses changed very little since February. All 1251 influenza A(H1N1)pdm09 viruses tested belong to the single genetic group 6B.1A, and 96.1% of those were well-inhibited by ferret antisera against the A/Michigan/45/2015 vaccine strain. All 203 B/Yamagata lineage viruses belonged to the Y3 clade, and 100% were well-inhibited by ferret antisera against the B/Phuket/3073/2013 vaccine strain. There were 3 genetically and antigenically distinct B/Victoria subclades cocirculating: V1A (14.7%), V1A.1 (50.4%), and V1A-3Del (34.9%). This was a slight increase in the V1A-3Del viruses compared to February. As a reminder, the 2018-2019 Northern Hemisphere vaccines contained a B/Colorado/6/2017-like V1A.1 virus.

There was more change among the influenza A(H3N2) viruses. Phylogenetic analysis of the HA genes of H3N2 viruses showed co-circulation of multiple clades and subclades. The proportion and geographic spread of viruses belonging to clade 3C.3a increased as the season progressed. The 3C.3a viruses are antigenically distinguishable from the 3C.2a and 3C.2a1 viruses including the A/Singapore/INFIMH-16-0019/2016 (3C.2a1), a cell-propagated reference virus representing the A(H3N2) component of 2018-2019 Northern Hemisphere influenza vaccines. This indicates that this is a drift variant, and circulation of antigenically drifted viruses

can impact VE. Looking more closely at the timeline of the 3C.3a viruses, they accounted for only 21% of the viruses in December. By the following month, they had become predominant and remained the predominant clade throughout the rest of the season.

During the February ACIP meeting, it was noted that the H1N1 and both influenza B components for the 2019-2020 influenza season had been selected but the A(H3N2) decision had been delayed until the end of March. That selection has been made, with the final selections being as follows:

- ❑ A/Brisbane/02/2018 (H1N1)pdm09-like virus
- ❑ A/Kansas/14/2017 (H3N2)-like virus belonging to the 3C.3a clade
- ❑ B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage)
- ❑ B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage) – quadrivalent only

Moving on to the activity causes by these viruses, influenza-like illness (ILI) was above baseline for the longest period that has been observed in the last 10 years. Probably due to the two waves of influenza A viruses, ILI was above baseline for 21 weeks, peaking at 5.1% during mid-February.

The overall rate of hospitalizations due to laboratory-confirmed influenza was 65.1/100,000 population. The rate was highest among persons ≥65 years of age at 221.4/100,000 population, followed by the 50 to 60 year old age group and the 0 to 4 age group. Compared to previous influenza seasons, this season was more similar to the 2014-2015 and 2016-2017 influenza seasons.

Regarding influenza-associated mortality, the percent pneumonia and influenza deaths exceeded the threshold for the first 13 weeks of the year, but only by a very small amount. The peak was 7.7% compared to a threshold of 7.3% and 7.2% during the two weeks of 7.7%. Thus, there was a very modest increase in influenza- and pneumonia-associated mortality. However, 119 influenza-associated pediatric deaths have been reported to CDC thus far. This is lower than what was observed during the 2017-2018 influenza season, but higher than what has occurred in other recent years.

CDC also calculates a severity level for each influenza season. Severity of the 2018-2019 season was classified as moderate overall and in all age categories. This is calculated using ILI, hospitalization, and pneumonia and influenza mortality data. Information on how CDC classifies severity is available at https://www.cdc.gov/flu/about/classifies-flu-severity.htm.

This year for the first time, CDC published interim estimates of influenza burden as the season progressed. There were at least 37.4 million influenza illnesses this season overall. Of those, 17.3 million were medically attended. There were at least 531,000 hospitalizations and at least 36,400 influenza-associated deaths this season. Comparing the cumulative hospitalization burden to previous seasons, this season was similar to the 2012-2013, 2014-2015, and 2016-2017 seasons.

CDC has received a lot of questions about what is occurring with influenza activity in Australia, given that Australia's influenza season began earlier than typical this year. The number of reported influenza positives this season is similar to 2017. Thus far, they have had a mix of A(H1N1)pdm09 and A(H3N2) viruses. Most recently, influenza A(H3N2) has been predominant. The number of influenza positives reported is getting close to what they saw in 2017, which was a severe season for Australia. They had a lot of activity coming into this season. Among the

A(H3N2) viruses they are seeing, the predominant clade there is 3C.2a1b viruses rather than 3C.3a. They have seen 3C.3a viruses, but these account for only about 5% of the A(H3N2) viruses.

In summary, the severity of the 2018-2019 influenza season was classified as moderate both overall and for all age groups. The season was notable for 2 waves of influenza A viruses of similar magnitude, an influenza A(H1N1)pdm09 wave followed by an H3N2 wave. The majority of H3N2 viruses belonged to the 3C.3a genetic group, which is antigenically distinct from the 3C.2a genetic group. The recommended H3N2 component for the 2019-2020 Northern Hemisphere vaccine is an A/Kansas/14/2017-like virus, which belongs to genetic group 3C.3a.

Discussion Points

Dr. Ault inquired as to whether there is a way to assess pregnant women with regard to influenza severity.

Ms. Brammer replied that the surveillance, virologic, ILI, and mortality data do not have this for pregnant women. They do assess pregnant women in the hospitalization data, but there are not enough to make a severity estimate for that individual group.

Dr. Bernstein inquired as to how the early influenza season onset in Australia predicts the US season onset or how it relates.

Ms. Brammer indicated that some years, the US has a season similar to Australia's and some years not. For example, Australia had a bad year in 2017 and so did the US. CDC was hopeful last year that because Australia had a very mild year, the US would as well. However, that did not happen. CDC watches Australia very carefully because it is important to understand what viruses they are seeing and the impact, but as far as being able to make a prediction, it does not necessarily tell them anything definitive.

Dr. Maldonado (AAP) noted that Latin America also had an early onset this season of H3N2 as well, and inquired about the genotype of those strains.

Ms. Brammer replied that Latin American also is seeing a mix among their H3N2 viruses, with a little more 3C.3a viruses.

Dr. Schaffner (NFID) called attention to Ms. Brammer's infographic showing the impact of influenza, which clearly illustrates that influenza is bad. A follow-up infographic is needed to show how the use of vaccines mitigated each of the impacts in order to promote vaccination, which he encouraged CDC to provide as quickly as possible each year.

Dr. Duchin (IDSA) inquired as to whether Ms. Brammer could characterize how well the vaccine strain antibodies performed in the context of the H3N2 virus.

Ms. Brammer indicated that 73% of the viruses this season were 3C.3a viruses, and the majority of those viruses react low using ferret antisera against that virus. Antigenically, it can be expected that roughly that proportion will be low.

Preliminary Estimates of 2018-19 Seasonal Influenza VE Against Medically Attended Influenza from Three US Networks

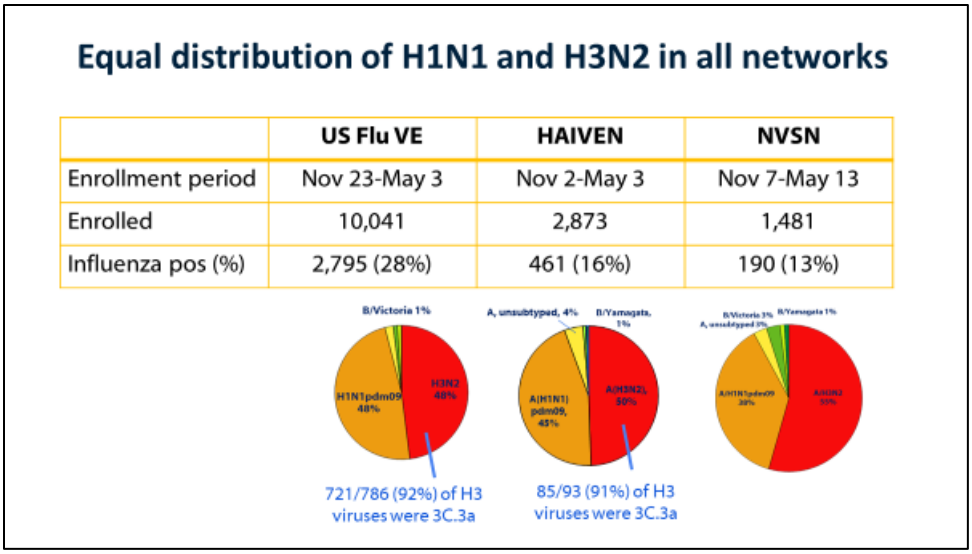
Brendan Flannery, PhD
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Flannery updated ACIP on the work that is being done with 3 networks to prove VE for the ambulatory and inpatient settings: US Flu VE Network, Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN), and New Vaccine Surveillance Network (NVSN). US Flu VE Network includes ambulatory patients 6 months of age and older and began in 2004 with studies at Marshfield Clinic Research Institute in Wisconsin. It expanded to 4 sites in 2008 and the following 5 sites in the US have been conducting the US Flu VE Network studies since 2011: Kaiser Permanente Washington, Marshfield Clinic Research Institute, University of Michigan, University of Pittsburgh, and Baylor Scott and White Health. HAIVEN is an inpatient adult network that includes 4 sites, 3 of which are also involved in the US Flue VE Network: Baylor Scott and White Health, University of Michigan, University of Pittsburgh, and Vanderbilt University. NSVN, conducted in collaboration with CDC's Division of Viral Disease (DVD), includes inpatients 6 months through 17 years of age from 7 sites: Seattle Children's, University of Rochester, Children's Mercy Hospital, Children's Hospital of Pittsburgh, Cincinnati Children's, Vanderbilt University, and Texas Children's. Both of the inpatient networks started around the 2015-2016 season for influenza VE.

This presentation of preliminary estimates for the June ACIP meeting represents a lot of work on the part of the HAIVEN and NVSN investigators for the inpatient networks to provide preliminary estimates for the 2018-2019 season. In terms of the methods, the US Flu VE network is an ambulatory network that includes patients 6 months of age and older. The acute respiratory surveillance (ARI) definition for this network is essentially cough and other respiratory illness symptoms of ≤7 days in duration for the collection of specimens for enrollment. The HAIVEN network is the inpatient adult network comprised of patients ≥18 years of age. The definition of ARI includes a variety of respiratory symptoms and the collection period is within ≤10 days for specimens for inclusion. The NVSN is the inpatient network that includes children 6 months to 17 years of age. The ARI definition includes fever and other respiratory illness symptoms, and the collection period is ≤10 for enrollment for the collection of specimens.

All three of these networks use a test-negative design that compares the odds of laboratory-confirmed influenza among vaccinated versus unvaccinated patients. Vaccination status for these analyses is done with identification of receipt of ≥1 dose for children 6 months through 8 years with of any of the 2018-2019 seasonal influenza vaccine at least 14 days prior to illness onset. The sources include medical records, immunization registries, and self-report in the ambulatory setting. The inpatient estimates are based at this time on self-report, but will be updated with final vaccination status. VE is calculated as 1 – the adjusted odds ratio (OR) x 100%. Adjustment is made for potential confounding variables including study site, age, and calendar time for the different networks.

This table shows the period of enrollment, the total number enrolled for each network, and the percent positivity. The pie charts show the distribution of virus subtypes:



There was very little influenza B in the three networks, so there are no estimates for influenza B. However, there was enough H1 and H3 for each of the networks to provide estimates for those. It is important to note that the percent positivity in inpatient networks is expected to be lower using the sensitive case definition than the percent positivity in the ambulatory network, which was about 28%. The other fact to note is that there has been a major effort to sequence a lot of the viruses. There are sequences for all of the viruses that have been identified and sent to CDC. Specifically, 92% (721/786) of the H3 viruses sequenced in US Flu VE were 3C.3a and 91% (85/93) of the H3 viruses sequenced in HAIVEN were 3C.3a. For the three networks, there is a predominance of the antigenically different 3C.3a viruses this season. That is reflected in the VE estimates.

Beginning with the ambulatory network, the VE Network data were presented through the beginning of February for the interim report. At the beginning part of the season, there was a low percentage positivity and those were predominantly H1N1 viruses in the cases. The increase in percent positivity after the interim report was associated with H3 activity at all enrollment sites and a large increase in the percentage positive overall for influenza. In terms of overall VE in the outpatient network, there were 2795 cases and 7246 controls. The percent positivity among the vaccinated was 48% and among the controls was 56%. That results in an adjusted OR in VE estimate of 29% (CI: 21% to 35%). Some difference was observed in overall effectiveness by age group. The highest VE was seen in the group 6 months through 8 years of age at 49% (38,58). There was only one other statistically significant VE, which was among those 18 through 49 years of age at 25% (10, 37). The other estimates were not statistically significant for overall VE in the outpatient setting.

The estimates are consistent with the significant antigenic drift or difference in the H3N2 viruses. These data are different from what was presented in February when some initial indication was seen of VE against H3N2 viruses. In the end of season estimate for the ambulatory network, A(H1N1)pdm09 VE is 44% (36, 51). This is consistent with the preliminary estimates for A(H1N1)pdm09. However, no VE is observed against A(H3N2) with an estimate of 9% (-4, 20). As noted earlier, a large number of the A(H3N2) viruses were sequenced. Among the 773 H3 viruses that were sequenced, there was a VE of 15% (-1, 28). That is similar to the overall effectiveness, so CDC believes that there is a good representative sample of the A(H3N2) viruses that were sequenced. Importantly, VE against A(H3N2) clade C3.3a viruses

(709/773) was 11% (-6, 26). This is very similar to the overall estimate, which would be expected. Less than 10% of the samples with the A(H3N2) clade 3C.2a1 that is similar to the vaccine virus have been sequenced. However, there is some evidence of VE against the more vaccine-like H3 clade of 45% (5, 68). Unfortunately for VE, that was not the predominant clade this season.

For HAIVEN, the inpatient adult network, overall VE was 25% (1, 41). There are some differences in the point estimates by age group. Patients 18 through 49 years of age had a VE of 1% (-58, 38). There is some evidence of VE in patients 50 to 64 years of age with a VE 47% (22, 63). There was no significant effectiveness in patient ≥65 years of age with a VE of 15% (-24, 41). However, the surprising finding in the inpatient network that differs from the finding in the ambulatory network is that the estimate against H3N2 is not zero or non-significant as found in the ambulatory network but was -43% (-102, -2). The H1N1 estimate is consistent with what was seen in ambulatory network at 60% (46, 71). There is evidence of protection in the inpatient adult network against H1N1, but no significant protection and a negative point estimate against H3N1.

Regarding the NVSN, the pediatric inpatient network for children 6 months to 17 years of age, overall VE against any laboratory-confirmed influenza was 31% (5, 51). There is some difference in the point estimate by age group, with slightly higher point estimates in patients 9 through 17 years at 53% (5, 77) than patients 6 months to 8 years of age with 26% (-6, 49). The estimates for H3N2 and H1N1 are more consistent with the ambulatory network for children. The H3N2 estimate is 13% (-13, 42) and the H1N1 estimate is 48% (14, 68).

It is notable that all three US networks identified no vaccine protection against what predominantly was an antigenically different H3N2 3C.3A clade virus this season. There is negative VE for H3N2 in the HAVIEN adult inpatient network, which is based on a small number of cases and could be related to chance or bias, especially in patients 18 through 49 years of age. CDC believes that these findings are unstable in that they are subject to changes with small alterations in case or vaccine classification. Because these are preliminary estimates with self-reported vaccination status, these estimates will be updated when final vaccination statuses become available. One of the comparison groups that has been used for VE studies in the past is people who were infected with another virus. In this case, a control group of people infected with respiratory syncytial virus (RSV) was utilized. No VE and no negative effectiveness are seen if an RSV comparison group is used in the inpatient setting. This suggests that there may be some bias in the inpatient setting compared to the outpatient setting. No similar findings of increased influenza vaccination rates are seen in the US Flu VE Network or laboratory-confirmed influenza hospitalization cases in US FluSurvNet compared to HAIVEN. The possibility that there is an alternative biological explanation cannot be excluded for negative VE in the inpatient setting.

CDC is taking several steps to look further at these estimates and finalize VE estimates for this season. As mentioned earlier, they are receiving updated data that will include vaccine verification and analysis and there will be further analyses of these VE estimates. In the review of preliminary data, especially for the inpatient adult network data, no issues were identified related to simple data miscoding or analysis. Additional data extraction is planned, especially for underlying conditions to understand the patients who were enrolled in the inpatient adult network. In addition to ongoing verification of vaccination status, estimates based on prior vaccination history and vaccine type also will be assessed. There is a unique opportunity this season to evaluate serologic specimens and virus sequencing for US Flu VE and HAIVEN network cases. There was an effort with expanded activity in the VE Network to collect acute

and convalescent sera from cases and to sequence viruses from the cases. They are hoping that this also will provide answers as to these findings for the ambulatory and inpatient network. CDC is collaborating with partners in other networks in other countries to compare findings and consider possible explanations for these findings. Finally, an update is planned for the ACIP Influenza WG in early fall 2019.

In summary, the overall VE was approximately 30% against influenza illness and hospitalizations. CDC is working to try to provide burden estimates as quickly as possible. Vaccine likely prevented between about 40,000 to 90,000 hospitalizations based on previous seasons' estimates and data from this season. Vaccine clearly reduced A(H1N1)pdm09-associated outpatient influenza illness by 44% and hospitalizations by 48% to 60%. However, no significant protection was observed against H3N2 illnesses. This is believed to be due to the emergence of the antigenically drifted/different A(H3N2) clade 3C.3a. WHO has updated the A(H3N2) component of 2019-2020 Northern Hemisphere influenza vaccines to include a virus from this 3C.3a clade. As a reminder, these VE estimates are preliminary and will be updated when final data are available.

Discussion Points

Dr. Szilagyi said it was very exciting to see the results from the three networks. He observed that there were somewhat similar VEs for the young children in the Flu VE Network and the NVSN, but they differed a lot for the children 9 through 17 years of age. Second, while the numbers might be small, he pointed out that there also is an opportunity to present results for EDs. That is a major source of healthcare and cost. Similarly, it might be possible eventually to show data for the number of ED visits and outpatient visits averted.

Dr. Flannery indicated that in the outpatient US Flu VE Network setting, the adjusted VE estimate was quite low in children 9 through 17 years of age at 6% (-22, 27) and was quite a bit lower than children 6 months through 8 years of age at 49% (38, 58). In NVSN, the estimate for children 9 through 17 years of age was 53 (5 to 77). The confidence intervals are wider on the estimates from the NVSN, so there are smaller numbers. The two estimates are consistent with some protection in the children 6 months through 8 years of age and 9 through 17 years of age when looking at both networks. However, it was a surprise with the ambulatory network that the estimate for children 9 through 17 years of age was not statistically significant and that there was not better evidence of protection in that group. CDC is examining further why the 9 through 17 year group estimates were as low as they were, especially in the ambulatory network.

Dr. Szilagyi pointed out that this may suggest that it was more protective against severe disease.

Dr. Flannery indicated that one of the reasons they set up the comparison between the ambulatory and inpatient groups was to examine the question pertaining to whether VE is higher against severe disease. In most of the estimates that CDC has presented previously that have compared adult networks for ambulatory and inpatient, there has not been a substantial difference in VE between the inpatient and outpatient groups. They will further assess this in children. There is some logistic difficulty with the two networks in having the correct comparison group for the ambulatory sites that do enroll in EDs. While there is some enrollment in EDs, it may not be enough to provide an idea of VE for ambulatory patients treated in EDs. In the inpatient networks, several of the NVSN sites are enrolling in EDs.

Dr. Fry (SME) said this is a very good point and later in the summer, they will be able to break this apart to examine it further.

Dr. Hunter asked whether there is any way to know what effect the vaccine had on the drifting of the strains during the season. That is, without the vaccine, would H1N1 have been more predominant and would the strain of H3N2 that was in the vaccine have been more predominant? Related to that, he wondered whether there is any theoretical reason that the vaccine would have created any pressure for the H3N2 strain that it is not in the vaccine to have been more predominant this season.

Dr. Flannery indicated that there is some speculation that with the high vaccination rates in the US, that may have contributed to how much of the 3C.3a antigenically different virus was seen in the US compared to other countries. There was a lot of interest in how much 3C.3a was circulating. The US seemed by far to lead in the percentage of the H3 viruses that were 3C.3a. It is not clear whether there was some selection. If the H1N1 virus had predominated the entire season or there had been more H1N1, VE may have been higher. However, it was not clear whether it would have been a lower H1N1 predominant season with lower vaccine coverage. While this is just speculation, CDC is interested in this because of the higher proportion of 3C.3a viruses seen in the US than in other countries.

Dr. Messonnier clarified that this is an intellectual exercise and she did not want their listeners to perhaps confuse the difference between an intellectually stimulation conversation versus actual fact. There are no data to suggest that high vaccination coverage in the US is in any way leading to AEs for US citizens.

Dr. Hunter said the other way to think of this was that they just saw the remainder of what is going to happen anyway, but it was less H1N1 and less H3N2 of the vaccine strain, and that was cut off with high vaccination rates and they were left with what they saw. That is another theoretical approach to the “glass half full.”

Dr. Fry (SME) emphasized that this was theoretical.

Dr. Foster (APhA) inquired as to whether there had been any evaluation of the egg-based versus cell-based component of the vaccines in terms of effectiveness.

Dr. Flannery indicated that there was a recent study by a DoD group that published 2017-2018 data from their VE network comparing FluCellVax to an egg-based vaccine that showed a small improvement for FluCellVax against the H3N2 viruses that circulated in that season. However, CDC will not have the final vaccine type information until later this year from the networks on which he just presented. When they do, they will be able to assess whether there is a difference between the various vaccine types of egg, recombinant, or cell in the networks.

Dr. Lee said she was still trying to wrap her head around the ins and outs of the test-negative design. She wondered how much information they have about chronic conditions or comorbidities associated with the patients who are in these populations. It felt to her like there was residual confounding and that once that is uncovered, that finding no longer will hold up.

Dr. Flannery replied that the inpatient network is assessing chronic conditions, previous hospitalizations, and other differences between the cases and the test-negative comparison group. There is a lot more work in the inpatient network than in the ambulatory network to assess high risk conditions. However, all three networks include high risk conditions as potential

confounders and try to compare high risk conditions among influenza cases and the influenza-negative comparison group.

Thinking about the timing of vaccination of populations with various comorbidities, Dr. Lee wondered whether a test-negative design matches by calendar week test-positive and test-negative or if it adjusts for this as a confounder.

Dr. Flannery responded that the design takes into account calendar time in different ways. In the ambulatory network, it is 2-week intervals and it is an adjustment as a confounder rather than a match design. It is part of the analysis to include calendar weeks.

Dr. Walter added that when the WG was reviewing the data, they were struck by the negative value of VE in the HAIVEN network. They were reassured with a different comparison group. There is likely some type of bias in the group selection in that particular network.

Dr. Whitley-William (NMA) asked whether there is any information in the vaccinated group regarding the timing of when they received influenza vaccination.

Dr. Flannery confirmed that CDC does have that information and will further examine the differences in the timing of vaccines among influenza positives and negatives across the different networks.

Dr. Weiser (IHS) noted that a considerable amount of time was spent the previous day talking about the indirect effects of pneumococcal vaccine, and he wondered whether Dr. Flannery could say anything about the indirect effects of influenza vaccine.

Dr. Flannery replied that they do not measure indirect effects from these networks. They measure direct effects of vaccine in these observational data. The work that has been done on the indirect effects of vaccine has been done with models.

End-of-Season Update: 2018-2019 Influenza Vaccine Safety Monitoring

Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
Centers for Disease Control and Prevention

Dr. Shimabukuro provided a safety monitoring update from VAERS, an RCA from the VSD, and an FDA assessment of GBS following influenza vaccine from Medicare data. He also described clinical research studies in progress from the Clinical Immunization Safety Assessment (CISA) Project. He shared a table defining related terms used in thinking about safety monitoring, which also are relevant for pharmacovigilance in general, as well as a table influenza vaccines abbreviations:

Vaccine safety monitoring and research terms

Term	Explanation
Adverse event	An adverse medical or health event following vaccination (a temporally associated event), which may or may not be related to vaccination (i.e., coincidental).
Adverse reaction	An adverse health event following vaccination where substantial evidence exists to suggest the event is causally related to vaccination.
MedDRA	A clinically-validated international medical terminology used by regulatory authorities to describe health outcomes and events.
ICD-10 and 9	A system used by physicians and other healthcare providers to classify and code diagnoses, symptoms and procedures associated with healthcare.
Automated analysis	Analysis on administrative or claims data or non-chart/health record confirmed data.
Chart confirmed/ medical record confirmed case	A case where review of medical charts and records by physicians or medical personnel confirms the diagnosis as valid and with accurate onset relative to timing of vaccination.
Incident case	A new case occurring for the first time ever or during a specified time period.
Prevalent or non-incident case	A case that has been diagnosed in the past prior to vaccination or prior the study period that has become part of the patient's past medical history and therefore is not new.
Biologically plausible risk interval	The time interval following vaccination where it is biologically plausible, based on the best available science, that an observed adverse event could be related to vaccination.
Statistical signal	A finding from an analysis where a calculated value (i.e., the test statistic) exceeds a specified statistical threshold; a statistical signal does not necessarily represent a vaccine safety problem and requires further assessment before conclusions can be drawn.

Influenza vaccine abbreviations[1]

Abbreviation	Vaccine
IIV3, IIV4	Trivalent and quadrivalent inactivated influenza vaccine
IIV3-HD	High-dose trivalent inactivated influenza vaccine (approved for use in individuals 65+ years old)
ccIIV4	Cell culture-based quadrivalent inactivated influenza vaccine
RIV4	Recombinant quadrivalent influenza vaccine
aIIV3	Adjuvanted trivalent inactivated influenza vaccine (approved for use in individuals 65+ years old)
LAIV4	Quadrivalent live attenuated influenza vaccine

[1]IIV is commonly used when discussing inactivated influenza vaccines as a general category

As a reminder, VAERS is a spontaneous reporting system that is co-managed by CDC and FDA. As a spontaneous reporting system, its main limitation is that generally causality cannot be assessed from VAERS reports alone. VAERS accepts all reports from all reporters without making judgments on causality, irrespective of clinical seriousness. As a hypothesis-generating system, VAERS identifies potential vaccine safety concerns that can be studied in more robust data systems.

This analysis included US influenza vaccine reports from July 2018-April 2019. They performed a clinal review of reports, including medical records when available, for all serious reports; pregnancy reports for spontaneous abortion (SA), stillbirths, congenital anomalies; and anaphylaxis reports in persons with a history of egg allergy. FDA colleagues conducted

Empirical Bayesian (EB) data mining to detect disproportional reporting for vaccine-adverse event pairings.

In terms of reports by vaccine type for the 2018-2019 influenza season, probably the most notable finding was a relatively small number of doses (n=150) for IIV3. That likely represents shifts in the market for product types. The serious and non-serious breakdown is similar to what has been observed in previous seasons and is similar across vaccine products. Relatively small numbers of reports were GBS, anaphylaxis, and febrile convulsions. There are no data mining signals for GBS, anaphylaxis, or febrile convulsion in association with IIV3, IIV4, or IIV3-HD. There were no anaphylaxis reports in persons with a history of egg allergy. Febrile convulsion reports are limited to children 6 months through 59 months of age. For ccIIV4, aIIV3, RIV4, and LAIV4, the serious and non-serious breakdown is similar to what has been seen in the past for influenza vaccines and these products and is similar across product type. There were no data mining signals for GBS, anaphylaxis, or febrile convulsion in association with ccIIV4, aIIV3, RIV4, or LAIV4. There was on ccIIV4 anaphylaxis report in a person with a history of egg allergy. There were no anaphylaxis reports in persons with a history of egg allergy for aIIV3, RIV4, or LAIV.

There were 141 total reports involving vaccination during pregnancy (IIV4=55, ccIIV4=67, IIV3=4, RIV4=6, unknown type/brand=9). The median maternal age at vaccination was 32 years. Median gestational age at vaccination when reported was 21 weeks. The breakdown of trimester in those reports was pretty evenly split at 36 (31%) in the first trimester, 44 (38%) in the second trimester, and 37 (32%) in the third trimester. In 44 (31%) of these reports, there was a pregnancy-specific AE. These included: spontaneous abortion (13), preterm delivery (9), premature labor (6), stillbirth (2), pre-eclampsia (2), oligohydramnios (2), placenta previa (2), dysmature placenta (2), premature rupture of membranes (1), gestational hypertension (1), gestational diabetes (1), placentae abruption (1), vaginal discharge (1), and nausea (1). In 18 (13%) reports, there was an infant or fetal AE. These included: low birth weight (5), large for gestational age (2), meconium in amniotic fluid (2), nuchal chord (1), hypospadias and chyothorax (1), dystocia of shoulder (1), intrauterine growth retardation (1), jaundice (1), tricuspid regurgitation and pulmonary insufficiency (1), upper respiratory tract infection, (1), cystic fibrosis carrier (1), and asymmetrical growth (1).

To summarize VAERS monitoring, no new safety concerns were detected for IIV3, IIV4, LAIV4, IIV3-HD, ccIIV4, aIIV3, or RIV4 during the 2018-2019 influenza season. Surveillance for the 2019-2020 influenza season will include enhanced safety monitoring for aIIV3 (FLUAD®), RIV4 (Flublok® Quadrivalent), pregnancy reports, and anaphylaxis reports in persons with a history of egg allergy.

Regarding the RCA in the VSD, there are 8 participating integrated healthcare organizations in the VSD collaborating with CDC: Kaiser Permanente Washington, Kaiser Permanente Northwest, Kaiser Permanente Northern California, Kaiser Permanente Southern California, Kaiser Permanent Colorado, HealthPartners, Marshfield Clinic Research Institute, and Harvard Pilgrim. The VSD has medical care and demographic data on over 12.1 million persons per year (~3.7% of U.S. population). It links vaccination data to health outcome data and is used for surveillance and research. The VSD includes data on immunizations, outpatient and clinic visits, ED visits, hospital discharge codes, procedure codes, birth and death certification information and family linkage, and enrollment and demographic information. CDC has access to EHRs and paper charts.

For influenza RCA in the VSD, CDC uses two methods: the self-controlled risk interval (SCRI) method and the current versus historical methods. In the SCRI, patients serve as their own controls and events in the risk window are compared to events in the comparison window. Risk and comparison windows vary by the actual outcome. In the current versus historical method, events in the risk window in the current season compared to events in the risk window in the historical period. For influenza vaccine, CDC performs weekly near real-time sequential monitoring to detect statistical signals for pre-specified outcomes. They focused on standard dose IIV4 and IIV3 High-Dose. Use of other influenza vaccine products was still relatively low in VSD. Just a small amount of IIV3 vaccine was used in the VSD.

In terms of background, RCA in the VSD is a powerful and sophisticated tool for near real-time vaccine-safety monitoring using sequential monitoring techniques. It employs an automated analysis that uses ICD-coded diagnoses from administrative data. It is a surveillance activity for signal detection and signal refinement, which is not the same as an epidemiologic study for signal evaluation and causality assessment. It is designed to detect statistical signals, which are values above specified statistical thresholds. When a statistical signal occurs, CDC conducts a series of evaluations using traditional epidemiologic methods. Chart-confirmation of diagnoses to confirm or exclude cases as true incident cases is a key part of statistical signal assessment. Importantly, not all statistical signals represent a true increase in risk for an AE.

RCA outcomes for the 2018-2019 influenza season include acute disseminated encephalomyelitis (ADEM), anaphylaxis, Bell's Palsy, encephalitis, GBS, seizures, and transverse myelitis. A total of 5.4 million dose 1 influenza vaccines were administered as of April 3, 2019 in VSD. Just over 70% of these were standard dose IIV4, 12% were IIV3 High-Dose, 9% were ccIIV4, 0.5% were aIIV3, and 7% were RIV4. This is a summary table of statistical signals detected during monitoring for the past influenza season:

Influenza vaccine RCA – summary of statistical signals

Pre-specified outcomes	Risk interval	Age group	Current vs. historical design			Self-controlled risk interval design		
			IIV4	ccIIV4	IIV3-HD	IIV4	ccIIV4	IIV3-HD
ADEM	1-21	≥6 mo						
Anaphylaxis	0-2	≥6 mo	Yes 10/21/18	Yes (≥4 yr) 11/11/18			Yes (≥4 yr) 12/9/18	
Bell's Palsy	1-42	<18 yr					Yes (4-17 yr) 12/9/18	
		18-49 yr						
		≥50 yr						
Encephalitis	1-21	≥6 mo						
GBS	1-42	≥6 mo						Yes (65+) 12/9/18
Seizures	0-1	6-23 mo				Yes 11/25/18		
		24-59 mo	Yes 12/9/18			Yes 11/4/18		
Transverse myelitis	1-21	≥6 mo						

[1]Doses administered through April 3, 2019; percentages subject to rounding errors

The table includes only the vaccines for which there was a statistical signal, the date, and the analysis. Dr. Shimabukuro reviewed each of these in more detail starting with anaphylaxis.

A statistical signal was detected the week of October 21, 2018 for anaphylaxis following IIV4 in the current versus historical analysis. The risk interval was 0 to 2 days and the age group was individuals ≥6 months. There were 9 observed events compared to 3.1 expected events, which is a RR of 2.88. That generated a log likelihood ration (LLR) at that time of 3.66, which exceeds the critical value of 3.0. Mathematically, this detected a statistical signal. For the end-of-season analysis, CDC chart reviewed 18 potential cases as 9 additional cases came in during the seasons. Of those, 11 had symptom onset prior to vaccination (i.e., other exposures and vaccinated in ED), 6 had onset post-vaccination but with other exposures to explain anaphylaxis like foods (3), medications (2), or exercise-induced (1); 1 case was determined to be potentially vaccine related in which the patient received IIV4 and recombinant zoster vaccine simultaneously. After chart review, there was an observed rate of 0.26 cases/1 million vaccinated, which is below the published VSD rate of 1.6 cases/1 million vaccinated.

A statistical signal was detected the week of November 11, 2018 for anaphylaxis following ccIIV4 in the current versus historical analysis. The risk interval was 0 to 2 days and the age group was individuals ≥4 years. There were 4 observed cases and 0.5 expected cases for a RR of 7.61. For the end-of-season analysis, CDC chart reviewed 7 potential cases, which included 3 additional cases that came in. After adjudication of these 7 cases, 0 cases were determined to be related to vaccine. Most had symptoms prior to vaccination and other exposures included codeine, naproxen, milk, and gentamicin.

There was a statistical signal the week of December 9, 2018 for Bell's Palsy following ccIIV4 in the self-controlled risk interval analysis. The risk interval was 1 to 42 days, the age group was 4 through 7 years of age. There were 4 events in the risk window and 1 in the comparison window for a RR of 4, which reached the threshold for a statistical signal. When the chart review was done, 1 of the 4 cases in the risk window had an initial diagnosis of Bell's Palsy. However, it was later determined that symptoms were related to acute otitis media on day 4 after vaccination. The other 3 cases were determined to be Bell's Palsy with symptom onset in the risk window. The case in the comparison window was determined to be Bell's Palsy with symptom onset 55 days prior to vaccination. For the final chart reviewed SCRI signal assessment, there were 3 cases in the risk window and 1 case in the comparison window for a RR of 3.0 (95% CI: 0.31-28.8). While there is an elevated risk, the confidence interval is very wide. In the current versus historical analysis for Bell's Palsy using automated data a statistical signal was not detected.

A statistical signal was detected the week of November 25, 2018 for seizures following IIV4 in the SCRI analysis. The risk interval was 0 to 1 day and the age group was 6 months to 23 months. There were 10 events in the risk window and 11 in the comparison window, which generated a RR of 3.18. The LLR exceeded the critical value and there was a statistical signal. There also were statistical signals for seizures following IIV4 among children 24 through 59 months of age. In the SCRI analysis, the signal occurred the week of November 4, 2018. The signal occurred the week of December 9, 2019 in the current versus historical analysis. In terms of the final SCRI analysis using chart confirmed cases of febrile seizures. The VSD RCA looks at the outcome of seizure. The records are assessed to confirm that these are incident febrile seizure cases. In the 6-23 months age group, there was an elevated IRR of 2.41 (1.12-5.18) and an attributable risk of 4.24/100,000 doses administered. For the 24-59 month age group, there was an elevated IRR of 3.50 (1.01-12.09) and an attributable risk of 1.80/100,000 doses administered. Looking at the age group in total by vaccine, there were elevated IRR for IIV4 alone, IIV4 administered with any other vaccine, and IIV administered with PCV13. These ranged from 2.33 to 2.92 and not all reached statistical significance. The attributable risks were 1.6/100,000 for IIV4 alone, 4.84/100,000 for IIV4 with any other vaccine, and 4.73/100,000 for IIV4 with PCV13.

A statistical signal was detected the week of December 9, 2018 for GBS following IIV3 high-dose in the SCRI analysis. The risk interval was 1 to 42 days and the age group was ≥65 years. There were 5 events in the risk window and no events in the comparison window for a RR of 11, which signaled. In the last SCRI analysis on April 3, 2019, there were 8 events in the risk window and 1 event in the comparison window for a RR of 8. The statistics were not generated for this because once there is a signal, there always is a signal, so there is no point in generating the LLRs. Upon chart reviews and adjudication of the 8 cases in the risk window, 1 GBS case was classified as Brighton Collaboration Level 2. The other 7 GBS cases were ruled out as prevalent/non-incident cases, had alternate diagnoses, had symptom onset prior to or on day of vaccination, and/or lacked clinical evidence to confirm that it was GBS. The 1 GBS case in the comparison window was classified as Brighton Collaboration Level 1. After case adjudication there was 1 case in the risk window and 1 case in the comparison window for a RR of 1.0. No statistical signal had been observed by April 3, 2019 for the corresponding current versus historical analysis.

The FDA, CDC, CMS conducted an SCRI analysis of GBS following influenza vaccine to further assess this within the CMS database, which contains substantially more data on individuals 65 years of age and older. The SCRI used an 8-21 day risk interval for the association between influenza vaccines and GBS. The data source was Medicare claims data for ≥65 years of age. It included more than 12 million beneficiaries in total, more than 7 million of whom received IIV3-HD. An end-of-season analysis is planned. For the results, the highest point estimate was for IIV3-HD. There were 16 cases in the 8-21 day risk interval and 26 cases in 43-84 day control interval for an odds ratio of 1.85 (95% CI 0.99, 3.44; p-value = 0.054) and attributable risk of 0.98/1 million vaccinations. The magnitude of the odds ratio is similar to what has been observed in previous seasons and the attributable risk is consistent with the labeled risk of GBS.

In summary of VSD RCA monitoring for influenza vaccine 2018-2019[1], following signal assessment and end-of-season analysis the statistical signals for anaphylaxis following IIV4 and ccIIV4 were ruled out. The finding of an elevated risk for Bell's Palsy following ccIIV4 in 4 to 17 year olds was based on a small number of cases and doses. There was an elevated RR of 3.0 but the confidence interval was very wide and included 1.0. CDC will continue to monitor and explore options for additional analyses. The 2001-2006[2] case-centered analysis with IIV3 did not find an association between Bell's Palsy and influenza vaccine. The statistical signal for GBS following IIV3-HD among individuals ≥65 years of age was ruled out. The preliminary FDA analysis of GBS following IIV3-HD in CMS data indicated that the risk, if any, is no greater than in some previous seasons and consistent with labeled risk of GBS [[1]Including FDA analysis of GBS and IIV3-HD; [2]Rowhani-Rahbar et al. Immunization and Bell's palsy in children: a case-centered analysis. Am J Epidemiol. 2012;175(9):878-85].

The final SCRI analysis of confirmed febrile seizure cases showed an elevated IRR in children aged 6-23 and 24-59 months. The risk was similar in those who received IIV4 alone and those who received IIV4 simultaneously with other vaccines, including PCV13. In some previous seasons, risk was greater with simultaneous PCV13. Attributable risk was less than that observed in some previous influenza seasons and less than the febrile seizure risk associated with MMR or PCV. This finding for febrile seizures in children in these age groups is not new. It has been observed in some previous seasons since it was first detected in 2010-2011. The magnitude of this risk does not exceed what has been observed some previous seasons.
In closing, Dr. Shimabukuro provided this table that lists some of the CISA clinical influenza vaccine studies that are in progress, which are all posted on clinicaltrials.gov:

Current CISA influenza vaccine studies

Title (ClinicalTrials.gov number)	Enrollment completed (influenza season)	CISA Study Sites
Safety and immunogenicity of simultaneous Tdap and IIV in pregnant women (NCT02783170)	Yes* (2016-17 & 2017-18)	Duke University (lead), Cincinnati Children's Hospital Medical Center
Safety of LAIV4 in children with asthma (NCT03600428 and NCT02967393)	No	Vanderbilt University (lead), Cincinnati Children's Hospital Medical Center, Duke University
Adjuvanted versus high-dose IIV in older adults (NCT03183908)	Yes (2017-18 & 2018-19)	Duke University (lead), Boston Medical Center, Cincinnati Children's Hospital Medical Center‡
Fever after simultaneous versus sequential vaccination in young children (NCT03165981)	Yes* (2017-18)	Duke University, Kaiser Permanente Northern California
Safety of quadrivalent recombinant influenza vaccine (RIV4) (Flublok® Quadrivalent) vs IIV4 (Flublok®) in pregnant women (NCT03969641)	No	Duke University (lead), Cincinnati Children's Hospital Medical Center, Boston Medical Center

*Results posted on ClinicalTrials.gov ‡Cincinnati Children's Hospital Medical Center site is supported via a sub-contract with Boston Medical Centers for this study

Discussion Points

Dr. Atmar questioned the control period for some of the neurologic outcomes -56 to -15. It seemed to him that there might be some bias about under-use of vaccine if a patient has a new diagnosis in that time interval. He wondered why that was selected or whether there is any evidence that new diagnosis in that timeframe might affect subsequent vaccination.

Dr. Shimabukuro replied that choosing comparison windows has been challenging. There have been discussions about using a pre-exposure comparison window and the bias that might be introduced for people who have that event who may be less likely to get vaccination. This certainly can be reevaluated.

Dr. Plescia (ASTHO) emphasized the importance of the safety and efficacy data, but pointed out that they are fairly difficult for the public to understand. The ASTHO membership struggles with this a great deal. While CDC and other vaccine groups do a nice job of communicating this on their websites, he wondered whether CDC could provide updates on ways they are thinking about communicating these data.

Dr. Messonnier indicated that they are in active discussions with ASTHO about this, and they are open to suggestions. This is an issue with which everyone struggles. Understanding these data requires a systematic approach to work through the data, and it is difficult to figure out how to communicate that effectively to the public.

Influenza Work Group Considerations and Proposed 2019-2020 Season Recommendations

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

Dr. Grohskopf began by thanking the CDC personnel who participate in and contribute to this WG discussions on an ongoing basis each year. She thanked Dr. Walter for his amazing leadership of the WG for the last 3 years, and welcomed Dr. Atmar as the new Chair.

During this session, Dr. Grohskopf reviewed the WG considerations and the proposed recommendations for the 2019-2020 seasons recommendations. Some of this material was discussed either earlier in the day or in previous meetings over the past year or less. No substantial changes were proposed for the coming season. The core recommendation remains unchanged, which is that:

> Annual influenza vaccination is recommended for all persons aged 6 months and older who do not have contraindications.

There are two primary updates to the vaccine compositions, the first of which is the vaccine composition. In most seasons, there is a change in the vaccine composition. For the 2019-2020 composition, there are changes in the influenza A(H1N1) and A(H3N2) components for the following compositions for trivalent and quadrivalent vaccines:

Trivalent Vaccines

- ❑ A/Brisbane/02/2018 (H1N1)pdm09-like virus—*updated*
- ❑ A/Kansas/14/2017 (H3N2)-like virus—*updated*
- ❑ B/Colorado/06/2017-like virus (Victoria lineage)

Quadrivalent Vaccines

- ❑ A/Brisbane/02/2018 (H1N1)pdm09-like virus—*updated*
- ❑ A/Kansas/14/2017 (H3N2)-like virus—*updated*
- ❑ B/Colorado/06/2017-like virus (Victoria lineage)
- ❑ B/Phuket/3073/2013-like virus (Yamagata lineage)

As Ms. Brammer mentioned earlier, this year was somewhat unusual in that there was a delay in the selection H3N2 component of the vaccine. Typically, WHO meets during the last week of February to make recommendations for all components for the following Northern Hemisphere season. This year, selection of the H3N2 component was delayed by approximately a month.

With that delay, one question that arises pertains to whether there may be a delay in the availability of vaccine. The following table was compiled by Dr. Jeannie Santoli in CDC's ISD to summarize projected supply in terms of number of doses for this seasons, as well as projected timelines as far as CDC has been made aware of them to date:

Maximum Projected Supply: 162-169 Million Doses*	
Manufacturer	**Distribution Estimated to Begin**
AstraZeneca	Early September
GSK	Mid-August
Sanofi Pasteur	Late August/Early September
Seqirus	Mid-August

*Information presented 5/16/19 at the National Adult Immunization and Influenza Summit, confirmed June 2019. The estimate aggregates information across manufacturers about potential maximum production for the season and could change based on production yield, lot release, and demand for vaccine.

The second set up updates relates to licensure changes that occurred since the publication of the 2018-2019 Statement. These were discussed during both the October 2018 and February 2019 meetings. There have been two licensure changes involving Afluria® Quadrivalent and Fluzone® Quadrivalent. The result of these changes is that for the youngest group of vaccinees, children 6 months through 35 months, it is anticipated that there will be 4 licensed IIVs for which the indicated dose volumes differ as follows:

- ❑ Fluarix® Quadrivalent (IIV4, GSK) 0.5 mL
- ❑ FluLaval® Quadrivalent (IIV4, ID Biomedical Corp/GSK) 0.5 mL
- ❑ Fluzone® Quadrivalent (IIV4, Sanofi Pasteur)* 0.25 mL or 0.5 mL
- ❑ Afluria® Quadrivalent (IIV4, Seqirus)* 0.25 mL

One of the observations discussed in the WG conversations is that this is a potential source of confusion for HCP. To that end, a very small third table has been added to the Influenza Statement that summarizes the dose volumes in this age group. Of note, for individuals over 36 months of age or ≥3 years, the dose volume is the same at 0.5 mL.

In addition, there are a few areas of minor edits to the 2019-2020 guidance language that were highlighted in the copy of the Draft Statement that was circulated to ACIP members including the following:

Timing of Vaccination
The language concerning July/August vaccination was moved to the top paragraph:

> *"For those requiring only one dose for the season, early vaccination (i.e., in July and August) is likely to be associated with suboptimal immunity before the end of the influenza season, particularly among older adults.*"

Groups That Should be the Focus of Efforts if Supply is Limited
The language describing HCP has been made consistent with "2011 ACIP Recommendations for the Immunization of Health Care Personnel."

Vaccine Doses Needed for Children Aged 6 Months Through 8 Years
The language was clarified to indicate that 8-year-olds needing two doses should receive the second dose even if they turn 9 years of age between dose 1 and dose 2, which is consistent with AAP guidance.

Concomitant Receipt of Two Vaccines Containing Novel Adjuvants
This section notes that given limited safety data, non-adjuvanted influenza vaccines may be considered when giving another vaccine containing a novel adjuvant, and that vaccination should not be delayed if a specific product is not available.

Dr. Grohskopf concluded that the proposed vote would be as follows:

> *ACIP affirms the updated statement "Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2019-20 Influenza Season."*

Discussion Points

An inquiry was posed regarding whether the information about receipt of two vaccines containing novel adjuvants would be reflected on the Vaccine Information Statement (VIS) as well.

Dr. Grohskopf said that while the WG did not discuss this, they could look into having it reflected on the VIS as well.

Dr. Messonnier added that CDC is happy to discuss the VIS separately, which involves a fairly complicated process between CDC and FDA that includes a public comment process to decide what is on the form. They have been struggling with how to make that sheet the most effective way to communicate appropriately to the public, because it has come to their attention that it is not always interpreted like it is intended. Therefore, this is perhaps part of a broader conversation about the best use of the VIS.

Dr. Walter made a motion to approve the recommendation as presented. Dr. Ault seconded the motion.

The motion was stayed until the voting session later in the day; however, the vote is included with this session for continuity.

Motion/Vote: Influenza Vaccines

Dr. Walter made a motion to affirm the updated statement "Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2019-20 Influenza Season." Dr. Ault 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, Bernstein, Ezeanolue, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
0 Opposed: N/A
0 Abstained: N/A

VFC Resolution Updates: Influenza 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 resolution was to update the table of inactivated influenza vaccines in the VFC program. Yellow highlighting was used to indicate changes to the resolution in comparison to the prior approved version. There is no change to the eligible groups, which are all children aged 6 months through 18 years. The recommended vaccination schedule also remains unchanged in that children 6 months through 8 years of age should receive 1 or 2 doses as noted in the current ACIP recommendations and children 9 through 18 years of age should receive 1 dose.

The updated table below lists the currently approved inactivated influenza vaccines in the VFC program, including the age indications for each vaccine:

Brand Name	Presentation	Age Indication
Afluria (Quadrivalent)	0.25mL pre-filled syringe	6 through 35 months
Afluria (Quadrivalent)	0.5 mL pre-filled syringe	>= 36 months
Afluria (Quadrivalent)	5.0mL multi-dose vial	>=6 months
Fluarix (Quadrivalent)	0.5 mL pre-filled syringe	>= 6 months
Flucelvax (Quadrivalent)	0.5 mL pre-filled syringe	>= 4 years
Flucelvax (Quadrivalent)	5.0mL multi-dose vial	>= 4 years
Flulaval (Quadrivalent)	0.5 mL pre-filled syringe	>= 6 months
Flulaval (Quadrivalent)	5.0 mL multi-dose vial	>= 6 months
Fluzone (Quadrivalent)	0.25mL pre-filled syringe	>= 6 through 35 months
Fluzone (Quadrivalent)	0.5mL prefilled syringe/single-dose vial	>= 6 months
Fluzone (Quadrivalent)	5.0mL multi-dose vial	>= 6 months

Note: The use of brand names is not meant to preclude the use of other comparable licensed vaccines.

Recommended Intervals/Doses, Contraindications and Precautions, and the Statement Regarding Update Based on Published Documents remain unchanged for inactivated and live attenuated influenza vaccine.

Motion/Vote: VFC Resolution for Influenza Vaccines

Dr. Walter made a motion to approve the VFC resolution for influenza vaccines. Dr. Frey 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, Bernstein, Ezeanolue, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
0 Opposed: N/A
0 Abstained: N/A

Hepatitis Vaccines

Introduction

Kelly L. Moore, MD, MPH
Chair, Hepatitis Vaccines WG
Vanderbilt University School of Medicine

Dr. Moore indicated that the term of reference for the Hepatitis WG with respect to hepatitis A (HepA) focused on updating the HepA vaccine recommendations that were published originally in 2006. Since that time, three other sets of specific recommendations were published on HepA, including the following:

- "Updated Recommendations from the ACIP for Use of Hepatitis A Vaccine in Close Contacts of Newly Arriving International Adoptees," *MMWR*, September 18, 2009, Vol 58, #36
- "Updated Recommendations from the ACIP for Use of Hepatitis A Vaccine for Postexposure Prophylaxis and for Preexposure Prophylaxis for International Travel," *MMWR*, November 2, 2018, Vol 67, #43
- "Recommendations of the Advisory Committee on Immunization Practices for Use of Hepatitis A Vaccine for Persons Experiencing Homelessness," *MMWR*, February 15, 2019, Vol 68, #6

In the period of time between May 2014 and June 2019, the WG has had 31 meetings focused on HepA topics. Between March 2019 and June 2019, they have had 5 meetings related to the proposed update of the HepA vaccine statement.

Dr. Moore indicated that during this ACIP meeting, members would hear presentations pertaining to 3 topics upon which they would vote. The first topic would be a vote on HepA routine catch-up vaccination of children through the age of 18 years, transitioning from the current wording that is more optional as a consideration for catch-up from the 2006 recommendations. In terms of background, HepA vaccines have demonstrated safety and efficacy for over 20 years. Nearly the entire cohort of children aged 13-17 years assessed in 2017, living in states where vaccination was recommended in 2006, were not yet subject to the routine recommendation for childhood vaccination. Yet as of 2017, more than 3 out of 4 teens had initiated the series and over 2/3 were fully vaccinated. A large majority of states (40%) had a daycare or school mandate, or both, for HepA vaccination in 2018, increasing over time from HepA vaccine introduction. This suggests that there is widespread acceptance and embracing of this vaccine despite the optional recommendation for catch-up in that population. Of the 30 state immunization information systems (IIS), 27 already routinely forecast HepA vaccine as being due for an 18 year old who has never been vaccinated according to the American Immunization Registry Association (AIRA). This demonstrates that for the vast majority of IISs, no changes would be necessary in order to embrace a routine catch-up recommendation.

The second topic on which there would be a vote would be on HIV as a risk group for increased HAV infection severity. As a reminder, when persons with HIV (PWHIV) are co-infected with HepA virus (HAV) infection, they experience higher peak HAV viral loads and a prolonged duration of HepA viremia than persons without HIV infection. The good news is that PWHIV usually do respond to HepA vaccination, particularly when the CD4 cell count is >200 cells/mm3 and the PWHIV has a low HIV RNA viral load. HIV co-infection outbreak data are available for a limited number of outbreak associated states, indicating excess risk of PWHIV to HAV infection in those states. Data from the Medical Monitoring Project (MMP) also indicate substantial HAV infection among PWHIV.

The third topic on which there would be a vote would be the full updated HepA vaccine statement. This includes a number of modifications, including removal of a risk group for whom the WG could no longer identify any excess risk; that is, persons with clotting-factor disorders.

The next step for the Hepatitis WG is to continue its deliberations by moving on to adult HepB vaccination topics.

Hepatitis A Vaccines

Noele Nelson, MD, PhD, MPH
CDC Lead, ACIP Hepatitis Vaccines WG
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Dr. Nelson's presentation included an overview of HAV epidemiology and Hep A vaccines; a presentation of the EtR Framework for catch-up HepA vaccination; a review of the EtR Framework that was presented during the February 2019 ACIP meeting for persons with HIV as a recommended risk group for HepA vaccination; updates for pregnancy and clotting-factor disorders; and presentation of the proposed HepA recommendations and updates deliberated on by the WG.

Data collection for HepA started in 1966. The highest number of HepA cases reported was in 1971 when approximately 60,000 cases were reported at a rate of 30 cases/100,000 population. Vaccine was recommended in 1996. From 1996-2011, there was a 95.5% decrease in reported

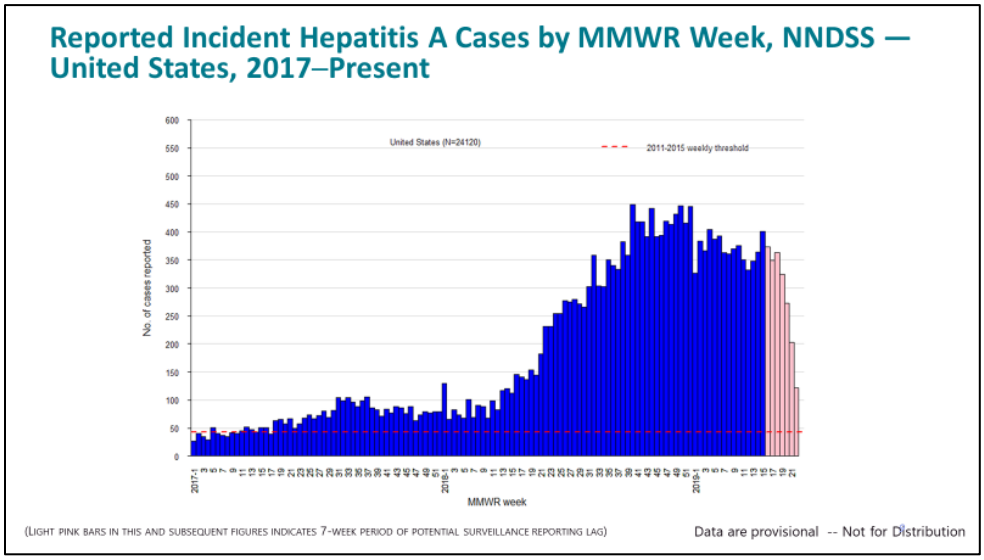
cases. The number of reported cases fluctuated slightly from 2011-2015 due to outbreaks, but has started to increase sharply since then. In 2017, there were 3365 reported cases [CDC, National Notifiable Diseases Surveillance System (NNDSS); Armstrong GL. *Pediatrics* 2007;119:e22-9].

The rate of reported cases was 1.0 case/100,000 population in 2017 nationally, the highest rate since 2007. Looking at the rates of reported cases by age group, in 2017, persons aged 30-39 years had the highest rate at 2.07 cases/100,000 population, followed by persons aged 40-49 years at 1.53 cases/100,000 population and persons aged 20-29 years at 1.45 cases/100,000 population [CDC, National Notifiable Diseases Surveillance System; Pre-Decisional; for federal use only; not for distribution].

Widespread outbreaks of HepA have occurred across the US since 2016. Since the outbreaks were first identified, 24 states have publicly reported the following as of June 21, 2019: 20,512 cases; 11,776 hospitalizations (57% of cases); and 194 deaths. The number of deaths due to HAV infection had been very low historically, though disease severity is known to increase with age. The high number of deaths in the current outbreaks is likely due to co-morbidities and underlying health conditions of the HepA cases, something that requires further investigation [https://www.cdc.gov/hepatitis/outbreaks/2017March-HepatitisA.htm].

Data from the National Notifiable Diseases Surveillance (NNDSS) system show that HepA incidence rates have increased dramatically in the wake of the outbreaks. In 2015, during a non-outbreak year, the national HepA incidence rate was 0.4 cases/100,000 population. Based on preliminary data, the national HepA incidence rate increased to 3.8 cases/100,000 population during 2018. The increased incidence rates are even more dramatic when compared at the state level. In 2018, state HepA incidence rates ranged between 0 cases/100,000 population in Alabama, Montana, and North Dakota to 111.92 cases/100,000 population in West Virginia [National Notifiable Diseases Surveillance (NNDSS), US Census Bureau; 2018 data are preliminary].

This latest National Epi curve also was created with NNDSS data. Due to reporting lag and the relatively long incubation period of the virus, the far right side of the curve is subject to change:



To summarize the changing epidemiology, asymptomatic children were associated with HAV transmission in past outbreaks in the pre-vaccine era. Now, recent outbreaks are occurring primarily among adults. Among states with publicly available case information by age group, the median age of HepA cases is in the 30-39 year age range, with a substantial percentage of cases aged in the 20-29 and 40-49 year age range. In the current outbreaks, disease severity is thought to be due to comorbidities and the poor underlying health of many HAV associated cases, including persons co-infected with HepB and HepC. Many cases have occurred among persons who use drugs and persons experiencing homelessness. Person-to-person contact, crowding, and poor hygiene are thought to contribute to virus transmission among these groups. Increases of HAV infections also have occurred among MSM. These outbreaks are estimated to cost tens of millions of dollars in healthcare expenditures. Though person-to-person spread is now the predominant mode of HepA virus transmission, sporadic foodborne outbreaks also continue to occur.

Two inactivated single-antigen HepA vaccines are licensed in the US. HAVRIX® was licensed in 1995 and VAQTA® in 1996. A combined HepA/HepB vaccine, TWINRIX®, also is available in the US for adults aged ≥18 years. In a clinical trial, VAQTA®'s efficacy in protecting against clinical HepA was 100% among over 1000 New York children aged 2 to 16 years who received one dose while living in a community with a high HepA disease rate[1]. HAVRIX®'s efficacy in protecting against clinical HepA was 94% among more than 38,000 Thai children aged 1 through 16 years who received two doses 1 month apart while living in villages with high HAV disease rates[2]. After 3 doses of TWINRIX®, antibody responses are equivalent to responses seen after the single antigen vaccines administered separately on standard schedules [[1] Werzberger, A et al. New Engl J Medicine. 1992;327:453–7; [2]Innis BL, et al. JAMA 1994;271:1328–34].

All licensed vaccines are highly immunogenic when administered to children and adolescents. Of persons aged 2-18 years, 97% to 100% had protective levels of antibody 1 month after receiving the first dose and 100% had protective levels 1 month after the second dose, with high GMTs. All licensed vaccines are highly immunogenic in persons aged >18 years when administered according to the recommended schedules. Protective antibody levels were identified in 94% to 100% of immunocompetent adults 1 month after the first dose. After the second dose, all persons had protective levels of antibody with high GMTs [[1]Clemens R et al. J Infect Dis 1995;171(Suppl 1):S44–9; [2]Nalin DR. VAQTA™, Drugs of the Future 1995;20:24–9; [3]McMahon BJ, et al. J Infect Dis 1995;171:676–9; [4]Sharapov et al. Hepatology, 2012; 56: 516–522; [5]Van Herck et al. Expert Review of Vaccines 2005; 4(4): 459-471].

Anti-HAV has been shown to persist in vaccine recipients for at least 22 years in adults administered inactivated vaccine as children with a 3-dose schedule, which has been shown to be equivalent to the current 2-dose schedule. At least 20 year anti-HAV persistence was demonstrated among adults vaccinated with a 2-dose schedule as adults. Detectable antibodies are estimated to persist for 40 years or longer based on mathematical modeling and anti-HAV kinetic studies. Protection following natural infection is lifelong and may also be following vaccination [[1]Mosites, E, et al. J Med Virol. 2018; 90: 1418–1422.; [2]Theeten H, et al. *Vaccine*. 2015 Oct 13;33(42):5723-7; [3]Hens N, et al. *Vaccine*. 2014;32(13):1507-1513].

In pre-licensure trials, adverse reactions to HAVRIX®, VAQTA®, and TWINRIX® were mostly injection site reactions and mild systemic reactions. Post-marketing surveillance for AEs following receipt of HepA vaccines has been performed primarily by VAERS and VSD. No unusual or unexpected safety patterns were observed for any of the HepA vaccines licensed in the US. Additional detailed safety data was presented in GRADE presentations at the February

2018, October 2018, and February 2019 ACIP meetings, with additional information on vaccine safety in pregnancy to be shown later in this presentation [Vaccine Information Statement (VIS) https://www.cdc.gov/vaccines/hcp/vis/vis-statements/hep-a.html; MMWR 2006;55(RR-7); Unpublished CDC].

HepA vaccination was introduced incrementally in the US from 1996-1999. In 1996, vaccine was recommended for children at age 2 years in communities with high rates of disease and children at age 2 years and older children in outbreaks. In 1999, vaccine was recommended for children at age 2 years in 11 states (Washington, Oregon, Idaho, California, Nevada, Utah, Arizona, New Mexico, Oklahoma, South Dakota, Alaska) with average annual HepA rates of 2 times the national average or ≥20 cases/100,000 population. Vaccine was considered in 6 states (Montana, Wyoming, Colorado, Texas, Missouri, and Arkansas) with rates above the national average or ≥10 cases/100,000 population. Routine vaccination was recommended in 2006. Universal early childhood vaccination was recommended for use at age 12-23 months in all states. Existing vaccination programs for children ages 2-18 years were recommended to continue. Catch-up vaccination in outbreaks and areas with increasing disease rates could be considered. Any person wishing to obtain immunity is recommended for HepA vaccine [*MMWR* 1996;45(RR-15); MMWR 1999;48(RR-12); MMWR 2006;55(RR-7)].

In addition, groups at increased risk of HAV infection or severe HAV disease are recommended to receive HepA vaccine. These groups include:

- ❑ Travelers
- ❑ Men who have sex with men
- ❑ Users of injection and non-injection drugs
- ❑ ~~Persons with clotting-factor disorders~~ [proposed for removal]
- ❑ Persons with occupational risk for infection
- ❑ Persons who anticipate close personal contact with an international adoptee
- ❑ Persons experiencing homelessness
- ❑ Persons with chronic liver disease
- ❑ Persons with HIV [proposed for addition]

Dr. Nelson noted that during this session, the WG deliberations regarding adding persons with HIV as an indication for vaccination would be discussed.

In terms of HepA vaccine coverage in 2017, [1]for children aged 19-35 months, ≥2 dose coverage was 59.7% and ≥1 dose coverage was 86.0%. The ≥2 dose coverage is likely underestimated since the first dose can be given up to age 23 months, with the second dose administered at least 6 months after the first. [2]For adolescents age 13-17 years, ≥2 dose coverage was 68.4% and 1 dose coverage was 77.2%. [3]For adults ≥19 years, ≥2 dose coverage was 10.9%; 17.7% for travelers and 20.8% for persons with chronic liver disease (CLD). These rates are slightly higher when considering adults in the limited range of 19 through 49 years [[1]Hill HA, et al. MMWR 2018;66:1171–1177; [2]Unpublished data from Assessment Branch/ISD/NCIRD/CDC – Not for Distribution; [3]Vaccination Coverage Among Adults in the United States, National Health Interview Survey, 2017; https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/NHIS-2017.html#box2].

Regarding estimated HepA vaccine coverage in 2017 in relation to other selected vaccines among adolescents aged 13-17 years, Tdap ≥1 dose coverage was 88.7%. Coverage with ≥1 dose of quadrivalent meningococcal conjugate vaccine was 85.1%. Coverage for ≥1 and ≥2 HepA vaccine coverage follows at 77.2% and 68.4%, respectively. Coverage with ≥1 dose of

HPV vaccine, which was introduced in 2011, was 65.5%. Coverage with ≥2 doses of quadrivalent meningococcal conjugate vaccine and ≥3 doses HPV coverage are lower. Thus, coverage for HepA vaccine among adolescents aged 13-17 years is comparable to other vaccines administered to adolescents for which a routine catch-up vaccination recommendation exists [Estimated Vaccination Coverage with Selected Vaccines and Doses* among Adolescents Aged 13-17 Years, by Survey Year — National Immunization Survey-Teen, United States, 2008-2017; Includes unpublished data from Assessment Branch/ISD/NCIRD/CDC–Not for Distribution].

As of October 2018, approximately 44% of states have introduced mandates for daycare or daycare plus school or school alone compared to 28% of states in 2011. The increase in mandates is likely partially responsible for the increase in adolescent HepA vaccine coverage [Immunization Action Coalition: http://www.immunize.org/pdfs/hepa.pdf].

Currently, ACIP recommends HepA vaccination for all children aged 12-23 months, with a shared clinical decision-making recommendation for catch-up vaccination. The WG proposes strengthening this recommendation to include routine catch-up. The proposed recommendation is as follows, “ACIP recommends that all children and adolescents aged 2 through 18 years who have not previously received HepA vaccine be vaccinated at any age (i.e., children and adolescents are recommended for catch-up vaccination).” This language aligns with the HepB vaccine statement language.

The policy question and PICO for catch-up vaccination are as follows, “Should HepA catch-up vaccination be recommended for children aged 2-18 years?” The population is children aged 2-18 years and the intervention is HepA vaccination (HepA vaccine series). The comparison is HepA vaccination based on shared clinical-decision making, and the outcomes of interest include HepA infection and AEs. With that in mind, Dr. Nelson presented the EtR Framework for catch-up vaccination.

In terms of Criterion 1 pertaining to whether the problem is of public health importance, the WG judged “Yes.” The rate of reported acute HepA cases in 2017 was 1.0 case/100,000 population. There were 1.45 cases/100,000 population among young adults aged 20-30 years compared to 0.87 cases/100,000 population in 2016. The incidence was 2.07 cases/100,000 population among adults aged 30-39 years compared to 0.92 cases/100,000 population in 2016, representing the highest rate of HepA cases and more than double the 2016 rate for this age group.

In 2017, national HepA vaccine ≥2-dose coverage was 68.4% for adolescents age 13-17 years and 1-dose coverage was 77.2%. Children living in states where routine vaccination at 12-23 months was first recommended in 2006 who were 1 year of age in 2006, were 12-13 years old in 2017 when these coverage data were collected, and thus were not subject to the universal recommendation for children aged 12-23 months. However, coverage among these children is only slightly lower than the total cohort, at 61% for ≥2 doses and 71% with ≥1 dose. Despite catch-up vaccination being based on shared clinical decision-making, the overall coverage in the 13-17 year old age cohort demonstrates that catch-up vaccination is occurring.

As previously stated, the ongoing HAV outbreaks have caused a substantial number of cases, hospitalizations, and deaths. Among states with publicly available case information by age group, the median age of HAV cases is in the 30 age range, with a substantial percentage of cases aged in their 20s and 40s. Vaccinating adolescents who could be at risk for HAV infection

at present or in the future (e.g., persons who use drugs, persons experiencing homelessness, travelers) can have an impact on improving coverage among young adults.

In terms of Criterion 2 pertaining to how substantial the desirable anticipated effects are, the WG judged "Large." HAVRIX® and VAQTA® are highly immunogenic when administered to children and adolescents according to multiple schedules. The immunogenicity and long-term protection data were mentioned earlier in this presentation. Catch-up vaccination is a way to increase herd immunity and ensure that the percentage of children and adolescents who miss vaccination as scheduled or who were born outside of the routine vaccination cohort are protected. Since the implementation of risk-based vaccination in adults has been poor, catch-up vaccination will more rapidly increase the proportion of adults with risk factors who are protected. HepA vaccination in childhood has demonstrated long-term protection.

With respect to Criterion 3 regarding how substantial the undesirable anticipated effects are, the WG judged "Minimal." Rates of AEs following HAVRIX®, VAQTA®, and TWINRIX® vaccination were similar to those seen with separately administered vaccines. No unusual or unexpected safety patterns were observed in VAERS for any HepA vaccines. Limited data from studies conducted among adults indicate that simultaneous administration of HepA vaccine with diphtheria, poliovirus, tetanus, typhoid, cholera, Japanese encephalitis (JE), rabies, or yellow fever (YF) vaccines does not decrease the immune response to either vaccine or increase the frequency of reported AEs.

In terms of Criterion 4 pertaining to whether the desirable effects outweigh the undesirable effects, the WG judged that the intervention is favored. HepA vaccination affords long-term protection against HAV infection. Disease severity increases in older persons and persons who are immunocompromised or have CLD or other underlying health conditions. Over 20 years of safety monitoring have shown no known safety concerns. Earlier HepA vaccination among healthy children and adolescents provides protection against HAV infection before persons develop increased risk for HAV infection or HAV-associated complications.

Regarding Criterion 5 concerning the overall certainty of this evidence for the critical outcomes, there were no included studies for the effectiveness of the intervention or the safety of the intervention. GRADE was not used to evaluate the evidence for several reasons. HepA vaccine has been recommended for administration to children since 1996. HepA vaccine has been recommended for catch-up vaccination based on shared clinical decision-making since 2006. The efficacy and safety of HepA vaccines has been evaluated and well-documented. There are no known safety concerns with HepA vaccines based on over 20 years of use.

With respect to Criterion 6 relating to whether the target population feels that the desirable effects are large relative to undesirable effects, the WG judged "Probably Yes." In 2017, HepA coverage among adolescents was as previously stated, and was substantially higher than 2008 coverage of 25.3% (≥2 doses) and 36.2% (1-dose). This demonstrates substantial catch-up implementation and acceptance despite a recommendation based on shared clinical decision-making. Although specific studies of desirability among older children or parents for HepA vaccine have not been conducted, the fact that almost 80% of adolescents had initiated the HepA vaccine series by 2017 demonstrates the demand and preference for protection against HepA. The HepA vaccine adolescent 2-dose coverage is comparable or greater than other vaccines with a routine catch-up schedule, which provides further evidence of acceptability by the target population.

For Criterion 7 regarding whether there is important uncertainty about or variability in how much people value the main outcomes, the WG judged “Probably no important uncertainty or variability.” The high coverage rate, despite this recommendation being based on shared clinical decision-making, provides strong and consistent evidence that most parents and patients believe that it is as important as some routinely recommended vaccines.

Regarding Criterion 8 pertaining to whether the intervention is acceptable to key stakeholders, the WG judged “Probably Yes.” As previously stated, the number of states with mandates increased from 28% in 2011 to 44% in 2018. These states choose to achieve higher rates of vaccine coverage for children, even though CDC has not strongly recommended HepA vaccine catch-up. During the HAV multistate outbreaks, educational communications and two Health Alert Network (HAN) advisories have been disseminated, increasing the level of awareness among all clinicians and states and the general public about the threat of person-to-person spread of HepA and the value of a vaccine that provides lifelong protection. The HepA adolescent 2-dose coverage is comparable or greater than other vaccines with a routine catch-up schedule which provides evidence of acceptability by key stakeholders.

With respect to Criterion 9 regarding whether the intervention is a reasonable and efficient allocation of resources, the WG judged “Probably Yes.” A cost-effectiveness model used to assess nationwide routine HepA vaccination was adapted to assess the cost-effectiveness of catch-up HepA vaccination and was presented during the June 2017 ACIP meeting. The findings of the study were that over the lifetime of the cohort, catch-up vaccination would reduce the total number of infections relative to the baseline by 741 while increasing doses of vaccine by 556,989. Across the age-cohorts, the cost-effectiveness of catch-up vaccination was most favorable at age 12 years due to splitting administration costs with other vaccines, resulting in an incremental cost-effectiveness ratio (ICER) of $189,000 per QALY gained. Catch-up was more effective when it was assumed to replace more adult vaccination and was targeted to children in late adolescence, because there is lower vaccine coverage and a higher probability of symptomatic disease among older children, less discounting of future costs of disease, and less delay in averting adult vaccination costs. The impact of vaccination on the ICER was most sensitive to the discount rate (3%), followed by the rate of adult vaccination.

The model had some limitations. The model was based on HepA incidence from 2008 through 2012. The conclusions are strongly tied to factors such as vaccine uptake and disease transmission patterns, which may change over time and alter future cost. The model also excluded herd immunity effects of vaccination. The incremental costs of catch-up now would be more favorable, because the adolescent vaccination coverage rates are much higher than when this study was conducted. In 2009, 1-dose coverage was 42% and 2-dose coverage was 29.5% compared to 2017 coverage. Achieving 80% to 90% coverage among teens would require a much smaller number of additional vaccines given. In addition, the HAV incidence overall is higher due to the ongoing multistate outbreaks. There were 0.5 cases/100,000 population in 2012 versus 1.0 case/100,000 population in 2017. Rates are known to be much higher in 2018 and 2019 based on preliminary outbreak data.

Though a formal updated cost analysis was not done, a cost example is as follows for a target HepA vaccine series completion percentage of 80% and a target HepA vaccine series initiation of 90%. The example assumes that 2017 coverage rates apply to all younger adolescents who have higher coverage, that 100% of 1-dose recipients complete the series when calculating the cost of 80% completion, and that 50% of the vaccination cost is at the private price of $32.89 and 50% at the CDC price of $20.52. To achieve 90% HepA vaccine series initiation, 3.2 million persons would need to be vaccinated with 1 dose of HepA vaccine at a cost of $52.8 million

(private) and $32.9 million (CDC). To achieve 80% HepA vaccine series completion, 2.2 million additional persons would need to be vaccinated with one dose and 701,747 persons would need to be vaccinated with 2 doses, at a cost of $59.3M (private) and $37M (CDC).

In terms of Criterion 10 pertaining to whether the intervention is feasible to implement, the WG judged "Yes." Of the 30 registries that the AIRA was able to query to test forecasting algorithms, 27 (90%) already routinely forecast HepA vaccine as being due for an 18 year old who has never been vaccinated. All 30 algorithms forecast the second dose in any 18 year old who has had one dose. Therefore, 27 of 30 tested registries would not have to change to implement routine catch-up. Routine HepA catch-up already exists in states with school mandates. The NYC Bureau of Health recommends that all children and adolescents not previously vaccinated should receive the two-dose HepA vaccine series by their 19th birthday for lifetime protection. There are opportunities to administer HepA vaccine to adolescents concurrently with vaccines protecting against other infections, such as HPV and Meningitis.
A 2014 survey found that if ACIP made a recommendation for catch-up HepA vaccination at health maintenance visits for all children 2 to 18 years of age, 96% of pediatricians and 79% of family medicine physicians reported it would be very feasible to routinely assess HepA vaccination status and vaccinate children and adolescents who were not fully vaccinated. An additional 4% and 19%, respectively, indicated that it would be moderately feasible. Since then, increased education and awareness among providers and the public due to the ongoing HAV outbreaks have likely decreased barriers to vaccination.

In terms of the balance of consequences, the WG judged that the "Desirable consequences probably outweigh undesirable consequences in most settings." Regarding whether there is sufficient information to move forward with a recommendation, the WG judged "Yes." With regard to Policy Options for ACIP consideration, the WG proposed that "ACIP recommend the intervention."

The proposed routine recommendation for children is:

- ❑ ACIP recommends hepatitis A vaccination for all children aged 12-23 months [Current]

- ❑ ACIP recommends that all children and adolescents aged 2 through 18 years who have not previously received hepatitis A vaccine be vaccinated at any age (i.e., children and adolescents are recommended for catch-up vaccination) [Proposed]

Turning to the potential addition of PWHIV to the list of groups at increased risk of HAV or severe HAV disease, the following policy question and PICO were presented to ACIP in February 2019 and are as follows, "Should routine two-dose* vaccination to prevent HepA virus infection be given to HIV-positive persons? *Or three-dose when combination vaccine is used?" The population was adult HIV-positive persons regardless of another indication for vaccination. The intervention was routine two-dose HepA vaccination. The comparison was no routine two-dose HepA vaccination. The outcomes of interest were HepA infection, mild AEs, and SAEs.

In terms of background, at the end of 2016, an estimated 1.1 million people aged 13 years and older had HIV infection in the US[1]. When PWHIV are co-infected with HepA virus infection, they experience higher HAV viral loads and a prolonged duration of HepA viremia than persons without HIV infection[2,3]. In addition, HAV infection has the potential to increase HIV viral loads and HIV transmission. PWHIV respond to HepA vaccine with a seroconversion rate of 48.5% to 93.9% following a 2-dose monovalent vaccine schedule, and factors associated with a protective antibody response in PWHIV include a CD4 cell count greater than 200 cells/mm^3

and a low HIV RNA viral load[4,5] [[1]CDC. HIV Surveillance Supplemental Report 2019;24(1); [2]Puoti, M., et al. Semin Liver Dis (2012) 32(02): 103-113; [3]Gallego, M., et al. Journal of the International Association of Physicians in AIDS Care, vol. 10, no. 1, Jan. 2011, pp. 40–42; [4]Weissman, S. , Feucht, C. and Moore, B. A. (2006), Journal of Viral Hepatitis, 13: 81-86; and [5]Mena, G et al. Human vaccines & immunotherapeutics vol. 11,11 (2015): 2582-98].

In 2017, the number of new HIV diagnoses was 38,739 and these were mostly among adults. The highest numbers were among adults ages 20-39 years. CDC classifies HIV diagnoses into transmission categories to which transmission may be attributed. Based on this classification, approximately 76% of persons living with HIV already have another risk group for which HepA vaccination is recommended. The MMP, which looks at a nationally representative sample of persons living with HIV, was used to answer the question, "What percentage of PWHIV do not have an existing risk factor for which HepA vaccine is recommended?" The percentage of persons living with HIV without a recommended risk group for HepA vaccination is higher when looking at more specific risk factor data. MMP estimates that 59.9% (95% CI: 57.3 - 62.4) of PWHIV had a risk factor of MSM, injection or non-infection drug use, CLD, clotting-factor disorder, or homelessness in the past 12 months. Data were not available for proportions of PWHIV with occupational risk, travel, or close contact with an international adoptee. Excluding these groups, 40.1% (95% CI : 37.6-42.7%) of PWHIV in the US do not have an ACIP recommended indication for HepA vaccine.

GRADE and the EtR Framework were presented during the February ACIP meeting. The GRADE summary is as follows. The benefit outcome, HepA infection, for RCTs was graded as an Evidence Type 2. This was downgraded for indirectness due to variability of HepA antibody seroconversion thresholds used. The benefit outcome, HepA infection, for observational studies was graded as an Evidence Type 4. This was downgraded for indirectness due to variability of HepA antibody seroconversion thresholds used and for risk of bias due to limited studies comparing a 2-dose standard intervention to no vaccine. The harm outcome, mild AEs, for RCTs was graded as an Evidence Type 1. The harm outcome, mild AE, for observational studies was graded as an Evidence Type 3. The harm outcome, SAEs, for RCTs was graded as an Evidence Type 3. This was downgraded for imprecision due to small study population size. The harm outcome, SAEs, for observational studies was graded as an Evidence Type 4. This was downgraded for imprecision due to small study population size. The WG judged that the "Desirable consequences *probably outweigh* undesirable consequences in most settings." For Policy Options for ACIP Consideration, the WG proposed that "ACIP recommends the intervention."

In terms of additional information regarding HAV infection among PWHIV, among people with a diagnosis of HIV who received outpatient HIV medical care during 2014-2017, the prevalence of a diagnosis of HepA recorded in the medical record at the primary HIV care site during a 2-year period was 0.48% (95% CI=0.26-0.70). Regarding additional information pertaining to HAV outbreaks and PWHIV, HIV co-infection outbreak data are available for a limited number of states. Among 249 reported cases of HAV in Tennessee, 11 (4%) patients were PWHIV. Among 359 reported cases of HAV in Massachusetts, 14 (4%) were PWHIV. Among 85 reported cases of HAV in Illinois, 7 (8.2%) were PWHIV. This shows a clear excess of HAV infection risk among PWHIV. The US population estimate is 327 million, with PWHIV comprising less than 0.34% of the general US population.

Several questions were asked by ACIP during the February 2019 meeting. Dr. Nelson provided explanations for the following selected questions:

- Is there value in knowing laboratory criteria before administering the vaccine? Should anti-HAV titers be checked periodically after vaccine administration? Will CD4 count thresholds be utilized for the recommendation of HepA vaccination among PWHIV?

- What are the costs of vaccinating PWHIV?

Since response to vaccine might be reduced in PWHIV who are immunosuppressed (lower CD4 counts), post-vaccination testing is proposed to be recommended for all PWHIV at least 1 month after vaccination. Although patients with lower CD4 counts may not respond as well to the vaccine, in order to avoid missed opportunities to immunize, immunization against HepA should not be delayed until the CD4 count exceeds a particular threshold. PWHIV who do not respond to vaccine should be considered susceptible to HAV infection and counseled about precautions to prevent HAV infection and the need to obtain IG post-exposure prophylaxis (PEP) for any known or likely exposure to an HAV infected person.

The cost of adult vaccines are approximately $30 CDC cost and $68 private cost. Vaccine administration fees range from a few dollars up to $20 based on the best available information. Regarding how much it would cost to vaccinate PWHIV, a formal cost-effectiveness analysis was not done for PWHIV as a risk group for HepA vaccination. Considering that about 400,000 PWHIV are potentially unvaccinated against HepA vaccine, a very basic calculation, assuming 50% vaccine uptake, is as follows: 200,000 X $68 (1 dose) = $13.6 million; 200,000 X $136 (2 doses) = $27.2 million, in addition to a small administration fee. There are a number of other considerations as well. Not all PWHIV will be vaccinated at the same time and the cost would be spread out over time. Vaccination in this high risk population would help disrupt outbreaks by providing increased herd protection. In an outbreak response, the associated costs, including health care expenses and deferred activities, are substantial.

The proposed recommendation for PWHIV is as follows:

- ACIP recommends that all persons with HIV aged ≥1 year be vaccinated with HepA vaccine.

Moving to the pregnancy update, pregnancy has been on the *Recommended Adult Immunization Schedule by Medical Condition and Other Indications* since 2005-2006 if another risk factor is present. A review of the published data on HepA during pregnancy[1] found that HepA infection during pregnancy is associated with gestational complications (e.g., preterm labor, placental abruption, premature rupture of membranes)[2]. Generally, infants born to mothers with HAV infection are healthy, but there are rare exceptions. There is no increased risk of maternal or infant mortality after HepA vaccination in pregnancy [[1]Chaudhry SA, Koren G. Hepatitis A infection during pregnancy. Can Fam Physician 2015;61:963-964; [2]Elinav E, Ben-Dov IZ, Shapira Y, Daudi N, Adler R, Shouval D, Ackerman Z. Acute hepatitis A infection in pregnancy is associated with high rates of gestational complications and preterm labor. Gastroenterology. 2006 Apr;130(4):1129-34].

A VAERS study by Moro et al in 2014 based on VAERs reports of AEs in pregnant women who received HepA or HepAB vaccine from January 1, 1996 to April 5, 2013 found no unusual clustering of birth defects. VAERS received 139 reports of AEs in pregnant women. Of those, 7 (5.0%) were classified as serious, 65 (46.8%) did not describe any AEs, and no maternal or

infant deaths were identified. The review of VAERS reports concluded that no concerning pattern of AEs in pregnant women or their infants following maternal HepA or HepAB immunizations during pregnancy was identified [Moro PL, Museru OI, Niu M, et al. Reports to the Vaccine Adverse Event Reporting System after hepatitis A and hepatitis AB vaccines in pregnant women. *Am J Obstet Gynecol* 2014;210:561.e1-6].

Preliminary results of a large, ongoing retrospective cohort study in the VSD were presented to the WG. Among pregnancies ending in live births, HepA vaccine was not associated with common maternal and infant AEs, but a potential signal for small for gestational age (SGA) births was identified. The observed effect size for SGA was an absolute difference of 4%, or 12.3% in vaccine exposed versus 8.3% in vaccine unexposed. General US prevalence estimates for SGA are approximately 10% and up to 14% among women of Asian race, who comprised 30% of the vaccine exposed group in the study. The investigators and the WG considered that this SGA finding was likely due to unmeasured confounding, and was unlikely to be clinically meaningful. This study is expected to be published later this year [Unpublished VSD data].

The 2006 Hepatitis Vaccine Statement indicated that data on pregnancy were lacking and as such, no recommendation was made. The proposed HepA recommendation for pregnant women, which is consistent with the vaccine schedule and is parallel to the HepB vaccine recommendations, follows:

- ACIP recommends that:
  - Pregnant women who are identified as being at risk for HAV infection during pregnancy or for having a severe outcome from HAV infection (e.g., travelers, persons who use injection and non-injection drugs, persons who have occupational risk for infection, persons who anticipate close personal contact with an international adoptee, persons experiencing homelessness, persons with chronic liver disease, PWHIV) should be vaccinated during pregnancy if not previously vaccinated [Proposed]
  - Pregnant women who are not vaccinated against HAV infection during pregnancy should be counseled concerning other methods to prevent HAV infection [Proposed]

Regarding clotting-factor disorders proposed for removal as a recommendation, persons who have clotting-factor disorders have been recommended to receive the HepA vaccine since 1996[1]. However, the risk of HAV infection has decreased over time, and the risk for viral transmission for persons with clotting-factor disorders is considered the same as that for the general population[2]. In the US, >80% of persons with hemophilia are treated with recombinant clotting-factor concentrates, which are sterilized (e.g., pasteurization, heat inactivation, filtration) enabling these factors to be safe[2]. Previously, some processes focused only on treatment with solvents/detergents which inactivated lipid-enveloped viruses[3], but not non-enveloped viruses, such as HAV, resulting in a risk for HAV infection[4]. Secondary virus reduction steps are now common[2,5,6] [[1]Fiore AE, Wasley A, Bell BP. MMWR Recomm Rep 2006;55:1-23; [2]Klamroth, R., Gröner, A. and Simon, T. L. (2014), Transfusion, 54: 1406-1417; [3]Tabor, E. (1999), Transfusion, 39: 1160-1168; [4]Mannucci PM, Gdovin S, Gringeri A, et al. Ann Intern Med 1994;120:1–7; [5]GRÖNER, A. (2008), Haemophilia, 14: 54-71; and [6]US Food and Drug Administration. Guide to inspections of viral clearance process for plasma derivatives. 2009. [cited 2013 Jan 25]. Available from: https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail /PB98137144.xhtml].

During 1992-1993, several outbreaks of HepA were reported in Europe among persons who had clotting-factor disorders who had been administered solvent detergent-treated factor VIII concentrates that presumably had been contaminated from plasma donors incubating HAV[1]. In the US, data from one serologic study published in 1994 suggested that hemophilic patients may be at increased risk for HAV infection[2]. During 1995-1996, several patients who had clotting-factor disorders reportedly developed HepA after having been administered solvent-detergent-treated factor VIII and factor IX concentrates[3] [[1]Mannucci PM, Gdovin S, Gringeri A, et al. Ann Intern Med 1994;120:1–7; [2]Mah MW, Royce RA, Rathouz PJ, et al. Vox Sang 1994;67(suppl 1): 21–2; and [3]CDC. MMWR 1996;45:29–32].

The clotting-factor recommendations from the 2006 ACIP Hepatitis A Vaccine Statement kept part of the 1996 recommendations, "Susceptible persons who are administered clotting-factor concentrates, especially solvent-detergent-treated preparations, should receive hepatitis A vaccine." The 2006 recommendation added that, "Changes in clotting-factor preparation practices and donor screening have greatly reduced the risk for hepatitis A for recipients of clotting-factors."

The ACIP Hepatitis Vaccines WG received input from the FDA and reviewed the literature on HAV infection among persons with clotting factor disorders. No case studies of HepA infections among US persons with clotting-factor disorders were found in the literature in the last 20 years [Soucie JM, Robertson BH, Bell BP, et al. Hepatitis A virus infections associated with clotting factor concentrate in the United States. Transfusion 1998;38:573-9].

The WG considerations are as follows. Persons who have clotting-factor disorders has been a risk group for HepA vaccination since 1996. The risk of HAV infection has decreased over time, and persons with clotting factors are currently at an extremely low risk for infection with HAV. No case study has been reported for any person in the US infected with HAV after exposure to clotting factors in 20 years[1]. Secondary virus reduction steps are now common instead of solvent-detergent treated. Many of the clotting factors now in use are recombinant factors. Source plasma is now screened for HAV[2]. There is no longer a specific risk of HepA virus infection associated with clotting-factor disorders; therefore, this group may be removed from consideration as part of a high risk population for whom HepA vaccination is specifically recommended [[1]Soucie JM, Robertson BH, Bell BP, et al. Transfusion 1998;38:573-9; [2]Gröner, A. (2008). Haemophilia, 14: 54-71].

In closing, Dr. Nelson recapped the proposed recommendations:

Recommendation #1: Proposed Routine Recommendation for Children
ACIP recommends hepatitis A vaccination for all children aged 12-23 months [Current; Revise]

ACIP recommends that all children and adolescents aged 2 through 18 years who have not previously received hepatitis A vaccine be vaccinated at any age (i.e., children and adolescents are recommended for catch-up vaccination) [Proposed].

Discussion Points

Regarding the balance of consequences and the WG's "Probably Yes," Dr. Atmar inquired as to what detracted from a definitive "Yes" and what the concerns were of the WG that weighed in as a "Probably Yes."

Dr. Nelson indicated that the WG deliberation was about being more conservative and saying "Probably Yes" instead of "Yes" due to the past cost-effectiveness analysis that was presented. The WG was unanimous in agreeing that the catch-up vaccination should be proposed to be recommended.

Dr. Moore added that there was no hesitation about this whatsoever on the WG. Everyone was unanimously and strongly in favor of a routine recommendation for catch-up. In fact, they had a conversation about which box to tick. The thought on the WG was that if they were so definitive, they would probably get questions from the full committee about why they were so definitive. In fact, no concerns were expressed. They felt that the economic analysis conducted in 2014 no longer reflects the current conditions. While no formal economic analysis was done, the WG knew that things would be much more favorable currently than they appeared in 2014.

Dr. Messonnier pointed out that typically when they get to this point, the evidence framework simplifies it though they have talked about it so much. Since the last time they assessed this, there has been an increase in large HepA outbreaks. In the cases, 40% of the patients do not have an identifiable risk factor. Even though the current intervention for the current outbreaks is more targeted toward adults because that is where the risk groups are and likely will be controlled with the intervention, there is an upcoming cohort of children and HepA is cyclical. As they approach adulthood, another cycle of outbreaks would be expected. The goal is to catch them up on vaccination at a time when it is known they are more likely to seek medical care, with the expectation that the vaccine will last long enough that when they reach their risk period, they will then be protected.

Dr. Moore added that the WG's great concern was that the longstanding risk-based recommendations for adults have been poorly implemented for many reasons. Many of the adults who find themselves at risk later on are often those with poor access to healthcare and utilization of health services. This vaccine can provide long-term, possibly lifelong, protection. There is now an opportunity to have the entire cohort cared for before they become adults and acquire or express risk factors. That was the strong motivation of the group.

Dr. Hunter emphasized that this was another example, along with HPV and pneumococcal conjugate vaccine, of the importance of vaccinating children to protect adults. He wanted to make sure that they were clear that this catch-up recommendation would not detract in any way from the young childhood routine vaccination recommendation.

Dr. Moore responded that close to 80% of teens already have initiated the series, and there are many opportunities now for immunization during adolescence when catch-up can occur. The WG had the conversation and discussed whether there should just have a blanket HepA vaccination sometime before becoming 18. There was a strong feeling that the routine recommendation that children should be vaccinated at the earliest opportunity to protect them should be maintained, which as 12 months to 23 month of age. The proposed recommendation would be only for children who missed out on that opportunity. In fact, the current cohort were not subject to that routine recommendation in early childhood. They were caught up over time in many cases, but were not subject to the original recommendation.

Dr. Maldonado (AAP) indicated that she is a pediatrician who went through some of those early days, especially in California where they had the risk-based vaccination. It was extremely confusing for pediatricians to determine which children were actually high risk and should be vaccinated. She thought it had to do with the incidence in the county, so it was very complicated. She thought this was a great opportunity to stem a fatal disease that is easily preventable, and that the recommendation would be helpful for adult internists and pediatricians.

Noting that it had been a long time since ACIP had reviewed the economic models, Dr. Lee thought that the ICERs looked much better if herd immunity was accounted for. This is a holistic program that is actually capturing adolescents and avoiding the need to track down high risk adults. At least in terms of the economic analysis, she was confident that this would be a very cost-effective recommendation.

Dr. Szilagyi also wondered why the WG did not select a definitive "Yes," because it seemed definitive to him. He also was impressed with the feasibility data that Dr. Nelson presented. He asked why a formal economic analysis was not performed.

Dr. Nelson indicated that the cost-effectiveness analysis was presented in June 2017; however, it was not updated to represent the changing epidemiology.

Dr. Walter said that as a general pediatrician who has administered catch-up vaccination for a number of years, he was glad to see that they were moving forward with a full recommendation to administer catch-up vaccination. One thing that was curious to him was the disparity between second dose coverage in teens versus younger children, with a much narrower gap in the older adolescents.

Dr. Nelson indicated that they believe it is due to under-estimation of 2-dose coverage in the younger group 19 months through 35 months of age. If children are vaccinated close to 23 months and they can be vaccinated up to 18 months for the second dose, they might be missed in that survey.

Dr. Moore moved to accept the proposed recommendation for routine catch-up vaccination for children as written. Dr. Walter seconded the motion. There was no further discussion.

Recommendation #2: Proposed Recommendation of HepA Vaccine for Persons with HIV

The full risk-based recommendations are shown here. It is proposed to remove "persons with clotting-factor disorders" as a recommendation, add PWHIV as being at increased risk, and update persons with CLD.

Persons At Increased Risk for HAV Infection

- Persons traveling to or working in countries that have high or intermediate endemicity of Infection.
- Men who have sex with men (MSM)
- Persons who use injection or non-injection drugs
- Persons who have occupational risk for infection
- Persons who anticipate close contact with an international adoptee
- Persons experiencing homelessness
- ~~Persons with clotting factor disorders (remove)~~

Persons At Increased Risk For HAV Associated Complications
- Persons with HIV [Vote 2]
- Persons with chronic liver disease [update]

Any person wishing to obtain immunity

The language for Vote #2 is:

ACIP recommends that all persons with HIV aged ≥1 year be vaccinated with hepatitis A vaccine.

Discussion Points

Related to the proposal to perform post-vaccination serologic testing at least 1 month after vaccination, Dr. Atmar wondered what would be done with that information should a person be seronegative and whether there would be a proposal to boost. Conversely, there already is a prevalence of seropositivity in persons with HIV who presumably would not be at risk and would not require vaccination. In that case, he wondered whether there was consideration for screening for seropositivity and only vaccinating those who are seronegative, or if that was not thought to be worthwhile from a cost-benefit perspective.

Dr. Nelson indicated that for post-vaccination testing of those who are not positive, the proposal is to counsel that person about risk of exposure and inform them that they would need IG in case they were exposed or concerned about exposure and the potential for revaccination. However, the WG was just giving clinical guidance on that versus proposing to recommend that there would be continued revaccination. Regarding pre-exposure testing, that should not deter or preclude vaccination in those who could not be tested.

Dr. Walter requested clarification regarding whether testing would be done after series completion, which Dr. Nelson confirmed.

Dr. Romero asked how much additional cost testing would add to the figures for cost of vaccination.

Dr. Nelson indicated that the cost of antibody testing is approximately $30, though she said she would have to verify that.

Dr. Atmar thought it was probably $30 to $50, but the point was that if there is high seroprevalence, this would be cost-saving because they would not be vaccinating. If there was low seroprevalence, there would be added costs. However, averting unnecessary vaccination potentially could be cost-saving.

Dr. Moore indicated that the WG had conversations about this, but did not feel that it could be provided as clinical guidance rather than having the ACIP weigh in on it. It will depend upon the patient population. There is not a uniform answer for everyone who has HIV. In certain clinical settings, it may be convenient and easy to screen in advance and they may do that. However, the WG did not want this to be perceived as any kind of barrier to immunization if routine immunization already was going to be done. The other thing about post-vaccine serologic testing is that it was intended to harmonize with the HepB post-vaccine serologic testing that is already recommended for these individuals after they receive the HepB series. The idea was

that this could be tagged on at the same time. The WG did not have data to recommend booster doses, so they did not address this.

Dr. Messonnier pointed out that perhaps there was a language issue on Slide 59 in the first bullet stating, ". . . proposed to be recommended for all PWHIV at least 1 month after vaccination" in that it sounded like a recommendation rather than clinical guidance.

Dr. Nelson indicated that this was addressed with the statement language on Slide 85 in the first bullet stating, "Testing for the presence of anti-HAV antibody after vaccination is recommended for the persons whose subsequent clinical management depends on knowledge of their immune status: PWHIV, and other immunocompromised persons (e.g., hematopoietic stem-cell transplant recipients, persons receiving chemotherapy)," the second bullet stating, "Testing should be performed at least one month after administration of the final dose of the vaccine series with total anti-HAV or IgG anti-HAV assays," and the third bullet stating, "Persons who do not respond immunogenically to vaccination should be considered susceptible to HAV infection and counseled about precautions to prevent HAV infection and the need to obtain IG post-exposure prophylaxis for any known or likely exposure to a HAV infection."

Dr. Messonnier did not feel that the language was correct, given that it was clinical guidance versus recommended. While ACIP was not being asked to vote on this language, she thought there was a way to articulate the language to more clearly indicate that it was clinical consideration versus a recommendation.

Dr. Cohn added that ACIP members were sent a draft of this document, but there was still plenty of time to incorporate some of these comments and address those even if they voted to approve the statement during this meeting.

Dr. Lee was fully in favor of thinking about this population as one that they should be targeting. With that said, she thought modeling would have been helpful in this instance to have given them more insight into the questions that Dr. Atmar raised and because it was incorporating clinical guidance pertaining to testing and clarifying what the benefit would be. This is a small population that has been involved in outbreaks, so from an outbreak perspective this is very important. However, she did not feel that this would affect her voting decision.

Dr. Stephens indicated that he too had concerns about the post-vaccination language to some degree. However, his question regarded what would occur with revaccination in those individuals. The lack of data on revaccination seemed like an opportunity.

Dr. Moore made a motion to accept the second recommendation that all persons with HIV aged ≥1 year be vaccinated with HepA vaccine as proposed. Dr. Ault second the motion.

Dr. Talbot noted that the proportion of the HIV population who do not respond may not respond because they have not had reconstitution of their immune system. To her, it would seem reasonable once they have return of immune function to try vaccination again. In anticipation of receiving this question a lot from HIV providers, she suggested including something in the clinical guidance section to that effect. Providers also are likely to ask how many times they should try, so she suggested including guidance about that as well.

Recommendation #3: ACIP Affirmation of the Updated Statement "Prevention of Hepatitis A Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices" with respect to the following:

PWHIV Clinical Guidance

- Since response to vaccine might be reduced in PWHIV who are immunosuppressed, post-vaccination testing is recommended for all PWHIV at least 1 month after vaccination
- Although PWHIV with lower CD4 cell counts or percentages may have reduced response to the vaccine, in order to avoid missed opportunities to immunize, immunization against hepatitis A should not be delayed until the CD4 cell count exceeds a particular threshold
- PWHIV who do not respond to vaccine should be considered susceptible to HAV infection and counseled about precautions to prevent HAV infection and the need to obtain IG post-exposure prophylaxis for any known or likely exposure to HAV
- PWHIV who received hepatitis A vaccine should be counseled that the vaccination against hepatitis A infection may not provide long term protection and they may need to obtain IG after a high risk HAV exposure (e.g., sexual or household contact)

Persons with Chronic Liver Disease [Update]

ACIP recommends that:

- Persons with chronic liver disease (including, but not limited to, persons with hepatitis B virus infection, hepatitis C virus infection, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and an alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice the upper limit of normal) should be routinely immunized against hepatitis A. [Proposed]

Hepatitis A Vaccine Recommendation for Pregnant Women

ACIP recommends that:

- Pregnant women who are identified as being at risk for HAV infection during pregnancy or for having a severe outcome from HAV infection (e.g., travelers, persons who use injection and non-injection drugs, persons who have occupational risk for infection, persons who anticipate close personal contact with an international adoptee, persons experiencing homelessness, persons with chronic liver disease, PWHIV) should be vaccinated during pregnancy if not previously vaccinated [Proposed]

- Pregnant women who are not vaccinated against HAV infection during pregnancy should be counseled concerning other methods to prevent HAV infection [Proposed]

Implementation Strategies

Settings Providing Services to Adults (NEW)

- Settings in which a high proportion of persons have risk factors for HAV infection (e.g., health care settings targeting services to people who use injection or non-injection drugs, group homes and nonresidential day care facilities for developmentally disabled persons). A health care provider (HCP) may assume that unvaccinated adults age ≥19 years are at risk for HAV infection and offer hepatitis A vaccination without individual risk-factor screening if they have not previously completed vaccination
- Hepatitis A vaccination may be offered in outreach and other settings in which services are provided to persons at risk for HAV infection (e.g., homeless shelters, syringe service programs)

- HCP should consider implementing standing orders to identify adults recommended for hepatitis A vaccination and administer vaccination as part of routine services
- Vaccination of staff should be considered in facilities where hygiene is difficult to maintain (e.g., group homes for developmentally disabled)

Hepatitis A Vaccination During an Outbreak [Update]

ACIP recommends that:

- All unvaccinated children aged ≥1 year and adults age ≥19 years who are at risk for HAV infection (e.g., persons who use injection or non-injection drugs, persons experiencing homelessness) should receive one dose of hepatitis A vaccine during a hepatitis A outbreak [Proposed]
- In the event of a community outbreak propagated by person-to-person transmission, public health officials should consider recommending administration of pre-exposure hepatitis A vaccination in close congregate settings providing services to high risk persons in the vicinity of the outbreak (e.g., persons incarcerated in correctional facilities, health care settings targeting services to people who use injection or non-injection drugs, homeless shelters, syringe service programs) due to the risk of an outbreak in these settings and increased risk of HAV infection among persons in these settings [Proposed]

Prevaccination Serologic Testing [Update]

- Prevaccination serologic testing for hepatitis A immunity prior to vaccination is not recommended, but may be considered in specific settings as a way to reduce costs by not vaccinating persons who are already immune [Update]
- Prevaccination serologic testing should not be a barrier to vaccination of susceptible persons, especially in populations that are difficult to access [Update]
- If prevaccination serologic testing is performed, commercially available tests for total anti-HAV or IgG anti-HAV should be used [Update]
- Antibody production in response to HAV infection results in lifelong immunity to hepatitis A and, presumably, to HAV infection
- Prevaccination serologic testing of children is not indicated because of their expected low prevalence of infection
- Persons for whom prevaccination testing will likely be most cost-effective include adults who were either born in or lived for extensive periods in geographic areas that have a high or intermediate endemicity of HAV; and adults in certain population groups; American Indians, Alaska Natives, and Hispanics
- In populations that are expected to have high rates of previous HAV infection, vaccination history should be obtained where feasible prior to testing or vaccination [Update]
- Vaccinations should not be postponed if vaccination history cannot be obtained, if records are unavailable or if prevaccination testing is not feasible [Update]
- Vaccination of a person who is immune because of previous infection does not increase the risk for adverse events from vaccination

Postvaccination Serologic Testing [Update]

- Testing for the presence of anti-HAV antibody after vaccination is recommended for the persons whose subsequent clinical management depends on knowledge of their immune status: PWHIV, and other immunocompromised persons (e.g., hematopoietic stem-cell transplant recipients, persons receiving chemotherapy) [Update]
- Testing should be performed at least one month after administration of the final dose of the vaccine series with total anti-HAV or IgG anti-HAV assays [Update]

- Postvaccination testing is not indicated for other persons because of the high rate of hepatitis A vaccine response among children and adults
- Persons who do not respond immunogenically to vaccination should be considered susceptible to HAV infection and counseled about precautions to prevent HAV infection and the need to obtain IG post-exposure prophylaxis for any known or likely exposure to a HAV infection [Update]

Revaccination [New]
- Revaccination (i.e., booster dose, challenge dose, or revaccination with a complete series) is not generally recommended for persons with a normal immune status who were vaccinated as infants, children or adults (Theeten 2015, Spradling 2016, Mosites 2018)
- Anti-HAV long-term persistence studies do not indicate a need for additional hepatitis A vaccine doses beyond the 2-dose primary vaccine series or 3-dose series if combination Hepatitis A-Hepatitis B vaccine was administered
- For other immunocompromised persons (e.g., PWHIV, hematopoietic stem-cell transplant recipients, persons receiving chemotherapy), the ACIP has no specific guidance because limited data are available to determine the need for booster doses or revaccination with a complete series

Other Guidance
- Interrupted Schedules and Minimum Dosing Intervals
- Other Immunization Management Issues and Considerations

The language in these two sections is consistent with previously published recommendations and in best practices guidance at ACIP.

Discussion Points

Dr. Ault asked whether there was a registry study about pregnancy in the HepA vaccine a couple of decades ago when it was new.

Dr. Nelson indicated in 1998, FDA published a general population two-year review of HepA vaccine using VAERS data that found few unexpected HAV vaccine–associated SAEs after the use of at least 6 million vaccine doses in the US. She did not present these data during this session because it was used as evidence for the 2006 recommendations. GSK has a TWINRIX® pregnancy registry.

Dr. Cohn requested that when the pregnancy language is updated, language be included about the catch-up recommendation for adolescents younger than 18 who are pregnant.

Dr. Hahn (CSTE) pointed out that every case of HepA in the US in theory is investigated by local health departments and is reported to CDC. She wondered whether state health departments were queried to determine whether they had reported any cases of clotting-factor disorder since not every case gets published.

Dr. Nelson replied that while they did not query state health departments, they did work closely with the FDA to determine whether there had been any reports.

Related to the EtR framework for HIV that was included in the background documents, Dr. Lee asked whether the criteria for resource use could be updated and marked as “Uncertain” as she felt that it would more accurately reflect the information currently available. She was thinking about the consistency by which they apply these criteria across recommendations, and that perhaps they should identify that a revised version of the cost-effectiveness model was not done to answer that specific question. While she felt comfortable that it would be cost-effective, she still thought that this should be changed to “Uncertain” versus “Probably Yes.”

Dr. Moore indicated that the WG would be happy to consider that and thanked Dr. Lee for the feedback, pointing out that this is a learning process for all of them as they navigate how to use this framework consistently. With respect to Dr. Hahn’s point, she thought the primary issue in conversations the WG had with FDA was that it was understood that the problem with clotting-factors themselves have been addressed and that, therefore, the risk of exposure from having a clotting-factor disorder no longer exists. It was not just that the WG did not find anything.

Dr. Hahn (CSTE) pointed out that the data showed greater than 80%, so it does not sound like 100% are using recombinant material. She also reminded everyone that the state health department is a great data source that CDC may not always think to check. These cases are investigated, there are great data, and they do not often hear it even mentioned that they looked at their own data.

Dr. Moore made a motion to affirm the updated statement “Prevention of Hepatitis A Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices.” Dr. Frey seconded the motion.

Dr. Hunter commended the WG on trying to harmonize as much as possible, particularly with HepB, and for harmonizing medical condition definitions between different recommendations for different vaccines as much as possible. He believes that practicing clinicians will be appreciative of that.

Dr. Bernstein noted that there was language about recommendations for HepA vaccine during an outbreak that mentioned children aged ≥1 year of age. Now that ACIP is recommending HepA vaccine for 6 months through 11 months for those traveling outside of the US to certain areas, he wondered whether they should be making the same recommendation in an outbreak situation.

Dr. Moore indicated that the WG did not consider a recommendation for vaccination below the licensed age for children who are in communities where outbreaks occur. They recommended it for travel because MMR vaccine also is given at 6 months to 11 months of age prior to international travel. Normally, HepA IG would be given because it is not a licensed product below a year of age. In that case, they recommended the vaccine instead if protection against HepA was necessary because HepA IG cannot be given with MMR vaccine at the same time because it interferes with measles protection. For a number of reasons, ACIP did not recommend the vaccine for ages for whom it is not licensed in outbreak settings in the US.

Dr. Messonnier added that the other part of that regarded whether children ≥1 year of age are at risk of HepA in the ongoing outbreaks.

Dr. Moore said that the outbreaks that are spreading from person-to-person are occurring among adults. Symptomatic HepA is extremely rare in an infant. They may become a passive transmitter or may be infected, but they do not get sick. Since there is not a health threat to those infants, protection of the adults is the focus.

Dr. Romero said that he has been on ACIP for 5 years and thanked Dr. Nelson for shepherding numerous changes to HepA and updating it.

Dr. Quach (NACI) asked whether in the CLD component they were talking about including people with an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level greater than twice the upper limit of normal, which seemed low to her in clinical day-to-day work.

Dr. Nelson indicated that the language paralleled the HepB vaccine statement and was deliberated on by the sitting WG a number of times.

Dr. Atmar said that they see a lot of patients who have an acute illness whose ALT is more than twice normal, so that language gave him pause as well. It seemed to him that there should be some chronicity associated with an elevated ALT and not in the setting of an adverse drug reaction or acute illness. Perhaps that could be included as a consideration, but it should not prompt a clinician to think they have to give the vaccine.

Dr. Moore indicated that the WG would be glad to take that into consideration. It was not intended for a temporary blip because of an acute illness. It is for an ongoing condition in the same way it was meant for a HepB vaccination.

Motion/Vote #1: Hepatitis A Vaccine Catch-Up

Dr. Moore made a motion to approve the recommendation that all children and adolescents aged 2 through 18 years who have not previously received hepatitis A vaccine be vaccinated at any age (i.e., children and adolescents are recommended for catch-up vaccination). Dr. Walter 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, Bernstein, Ezeanolue, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
0 Opposed:	N/A
0 Abstained:	N/A

Motion/Vote #2: Hepatitis A Vaccine for Persons with HIV

Dr. Moore made a motion to approve the recommendation that all persons with HIV aged ≥1 year be vaccinated with hepatitis A vaccine. Dr. Ault 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, Bernstein, Ezeanolue, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
0 Opposed: N/A
0 Abstained: N/A

Motion/Vote #3: Updated Statement

Dr. Moore made a motion to affirm the updated statement "Prevention of Hepatitis A Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices". Dr. Frey 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, Bernstein, Ezeanolue, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
0 Opposed: N/A
0 Abstained: N/A

VFC Resolution Updates: Hepatitis A 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 resolution was to streamline the Recommended Vaccination Schedule and Intervals section, update the language related to catch-up vaccination, add information about the accelerated Twinrix® schedule, clarify the timing of vaccine and immunoglobulin receipt, and remove pregnancy as a precaution. Yellow highlighting is used to indicate changes to the resolution in comparison to the prior approved version.

Eligible groups remain unchanged, which includes infants 6-11 months of age traveling to countries outside of the US for which protection against hepatitis A is recommended and all children aged 1 through 18 years of age.

For the Recommended Vaccine Schedule, the primary change is in the catch-up language. In addition, there is an accelerated schedule for Twinrix®, which previously was included in the HepB resolution that has now been added to this resolution for HepA:

- ❑ All children should receive hepatitis A vaccine at 1 year of age (i.e., 12-23 months). Vaccination should be completed according to the licensed schedules below.
- ❑ Catch up is recommended for all unvaccinated children and adolescents aged 2-18 years. Children and adolescents who have not previously received HepA vaccine should be vaccinated routinely at any age.

Vaccine[1]	Age	# of Doses	Schedule[2]
Havrix (pediatric formulation)	1 year	2 doses	0, 6-12 months
Vaqta (pediatric formulation)	1 year	2 doses	0, 6-18 months
Twinrix (adult formulation)[3]	18 years	3 or 4 doses	• 0, 1, 6 months; • 0, 7 days, 21-30 days, 12 months (accelerated schedule)

1. Use of brand names is not meant to preclude the use of other hepatitis A vaccines where appropriate.
2. 0 months represents timing of the initial dose; subsequent numbers represent months after the initial dose.
3. Only persons 18 years of age are eligible to receive Twinrix through the VFC program.

The Recommendation for Use of Hepatitis A Vaccine for Post-Exposure Prophylaxis remains unchanged:

> Healthy persons aged 12 months through 18 years, who have been exposed to HAV within the prior 14 days and have not received hepatitis A vaccine previously should receive a single dose of hepatitis A vaccine as soon as possible. The hepatitis A vaccine series can be completed with the second dose at least 6 months after the first dose.

For the Selected Special Categories section, clarifying language has been added related to the use of vaccine and IG that will be part of the HepA recommendation update that ACIP has been discussing:

- ❑ A single dose of hepatitis A vaccine should be administered to infants age 6-11 months of age traveling to countries outside the United States for which protection against hepatitis A is recommended on CDC's Traveler's health website (https://wwwnc.cdc.gov/travel/). Infants should then receive the full 2-dose hepatitis A vaccine series at ≥12 months of age as recommended.

- ❑ Persons administered IG for whom hepatitis A vaccine is also recommended should receive a dose of vaccine simultaneously with IG. If only IG or only vaccine is available, either available product should be administered as soon as possible. For persons who receive vaccine, the second dose should be administered according to the licensed schedule to complete the series. The efficacy of IG or vaccine when administered >2 weeks after exposure has not been established.

Recommended Intervals/Doses remains unchanged. Pregnancy was previously listed under Contraindications and Precautions and has now been removed. There are no changes to the Statement Regarding Update Based on Published Documents.

Motion/Vote: VFC Resolution for Hepatitis A Vaccine

Dr. Moore made a motion to approve the VFC resolution for hepatitis A vaccines. Dr. Walter 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, Bernstein, Ezeanolue, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
0 Opposed: N/A
0 Abstained: N/A

Meningococcal Vaccines

Introduction

David S. Stephens, MD
Chair, Meningococcal WG
Advisory Committee on Immunization Practices
Emory University

Dr. Stephens began by thanking ACIP, the WG members, and CDC for his last 4 years of service on the Meningococcal WG. He then introduced the Meningococcal Vaccine WG session. This session focused on Serogroup B meningococcal (MenB) booster doses in persons at increased risk for serogroup B meningococcal disease. ACIP recommends a MenB primary series for persons at increased risk for serogroup B meningococcal disease. Booster doses are not currently recommended for persons who remain at increased risk. During the February 2019 meeting, data were presented to ACIP on:

- ❑ Persistence of the immune response following MenB primary vaccination
- ❑ Immunogenicity, safety, and persistence of a MenB booster dose
- ❑ GRADE and EtR Framework for MenB booster doses
- ❑ WG's interpretation and policy options for MenB booster doses

In terms of activities subsequent to the February 2019 meeting, the WG has: 1) reviewed ACIP feedback received during the February 2019 meeting; 2) discussed potential programmatic challenges of MenB booster doses, with specific updates proposed to CDC's outbreak guidance related to booster dose implementation during outbreaks; and 3) developed an updated ACIP statement to harmonize existing meningococcal vaccine recommendations and potential MenB booster recommendations into a single document.

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

- ❑ Summary of immunogenicity and safety data, GRADE, EtR, and policy options for MenB booster doses in persons at increased risk for serogroup B meningococcal disease
- ❑ Updated the ACIP Statement for Meningococcal Vaccination in the US
- ❑ Votes on the MenB booster doses for persons at increased risk and on the updated ACIP Meningococcal Vaccine Statement

Serogroup B Meningococcal Vaccine Booster Doses

Sarah Mbaeyi, MD, MPH
CDC Lead, ACIP Meningococcal Vaccines WG
National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Mbaeyi sincerely thanked Dr. Stephens for his leadership of this WG over the last couple of years, and emphasized that they had enjoyed having him as their Chair. During this session, she summarized data evaluated by the WG to inform policy options for serogroup B meningococcal vaccine booster doses in persons at increased risk for serogroup B meningococcal disease. She summarized information previously presented to ACIP at the February 2019 meeting. This included reviewing the rationale for MenB booster doses in persons at increased risk for serogroup B meningococcal disease; summarizing the WG's interpretation of the persistence of the immune response following a MenB primary series and immunogenicity and persistence of a MenB booster dose; summarizing the GRADE and EtR for MenB booster doses in persons at increased risk; and reviewing the WG's considerations for policy proposals related to MenB booster doses.

Meningococcal disease is a serious infection that can progress rapidly, and 1 in 10 patients die despite antibiotic treatment. Among survivors, 1 in 5 have long-term sequelae. The incidence of meningococcal disease continues to decline in the US, with an incidence of 0.11 cases/100,000 population in 2017. Serogroup B now accounts for approximately 40% of all cases. While incidence is low in the US, certain individuals are at increased risk for serogroup B meningococcal disease. These include persons with complement deficiency, complement inhibitor use, anatomic or functional asplenia, and microbiologists routinely exposed to *Neisseria meningitidis* isolates. The magnitude of increased risk in these individuals can be up to 10,000-fold. Based on the population estimates for each group, these individuals comprise less than 0.1% of the US population aged at least 10 years. In addition, persons may be at increased risk due to a serogroup B meningococcal disease outbreak. During a college outbreak, the magnitude of increased risk is approximately 165-fold, and is even higher in freshmen, on-campus residents, and Greek-life students. Approximately 35,000 college students are at increased risk annually due to an outbreak.

In February 2015, ACIP recommended that persons aged 10 years or older at increased risk for serogroup B meningococcal disease receive a MenB primary series. These groups also are recommended to receive quadrivalent meningococcal conjugate (MenACWY) vaccination, with booster doses every 5 years thereafter for as long as risk remains. In addition, in June 2015, ACIP recommended that adolescents aged 16-23 years may be vaccinated with a MenB primary series based on individual clinical decision-making, with a preferred age of 16-18 years.

College students are at increased risk for serogroup B meningococcal disease and outbreaks compared to similarly aged young adults who do not attend college[1]. Thirteen serogroup B outbreaks have been reported since 2013. In all of these outbreaks, a MenB primary series was implemented as part of outbreak response[2]. Two of these outbreaks occurred at a New Jersey university during a 3-year period. During the first outbreak in 2016, MenB-FHbp vaccination was recommended for all undergraduates[3]. In the most recent outbreak reported in February 2019, MenB vaccination was again recommended to all undergraduates. For the first time, booster vaccination also was recommended for students who completed a primary series at least 1 year previously. Thus, college students are the primary group at increased risk for serogroup B outbreaks who may have received a MenB primary series as healthy adolescents. Current MenB vaccination coverage among adolescents is low, with approximately 15% of 17 year olds receiving at least 1 dose in 2017, though coverage has steadily increased since licensure[4,5] [[1]Mbaeyi, et al. Pediatrics. 2019; [2]Soeters, et al. Congress of the European Meningococcal and Haemophilus Society. 2019; [3]Soeters, et al. Emerging Infectious Diseases. 2016; [4]Walker, et al. MMWR. 2018; [5]Jones-Jack, presented at the National Immunization Conference (2018)].

Additionally, several serogroup B cases have been reported in patients who received MenB vaccination. Of the 5 reported cases to-date who received any MenB vaccine, 3 were fully vaccinated with MenB-4C, 1 was partially vaccinated with MenB-4C, and 1 was partially vaccinated with MenB-FHbp. Among those fully vaccinated with MenB-4C, 2 had known underlying conditions that may have increased their risk for meningococcal disease and 1 was a young adult with no known conditions. The interval from last MenB dose to disease onset ranged from 5 to 26 months. Preliminary analysis on the strains showed that potential protection is dependent on just 1 of the 4 antigens, NHBA, and human serum bactericidal activity (hSBA) results suggest that MenB-4C likely confers limited protection against these strains. No isolate was available for the patient who was partially vaccinated with MenB-FHbp, and thus the strain could not be analyzed further. Information on these patients is not sufficient to evaluate or compare effectiveness of MenB vaccine products.

In summary, although incidence of serogroup B meningococcal disease is low in the US, a small group of individuals are at substantially elevated risk. ACIP recommended a MenB primary series for persons at increased risk over 4 years ago. Evidence presented to ACIP during the February 2019 meeting suggests that waning of immunity occurs within 1-2 years following primary vaccination and thus, some vaccinated people may no longer be protected. Serogroup B outbreaks among college students continue to occur. One university to-date has implemented off-label and ACIP recommendations for a booster dose. Finally, no further data on persistence following a primary series or booster dose are expected from the manufacturers. Additional data on MenB effectiveness and duration of protection in adolescents and adults in US populations may take years to generate.

Turning to a review of the WG's interpretation of the persistence of the immune response following a MenB primary series, clinical trial data for both 3-dose and 2-dose MenB-FHbp primary series data from baseline (or pre-vaccination) through 48 months post-primary series for each of the four test strains showed that antibodies wane by 12 months following completion of a MenB-FHbp primary series and then remain stable for up to 4 years in healthy adolescents[1]. For MenB-4C, four clinical trials have been conducted to assess immunogenicity and persistence to each of the 4 vaccine antigens through 7.5 years post-primary series. Persistence following a MenB-4C primary series was difficult to generalize due to the elevated baseline titers in two studies, heterogeneous results by vaccine antigens, different time points assessed in different studies, and more limited persistence data for NHBA, which contributes most to strain coverage in the US[2]. In light of this, the WG's interpretation was that antibodies

wane by 2 years following the primary series in healthy adolescents and adults, though they may wane earlier [[1]Adapted from Marshall H, Lancet Infectious Diseases 2017 and Vesikari, Vaccine 2019; [2]Adapted from Read RC, Vaccine 2017; Block SL, Vaccine 2015; Szenborn L, Pediatr Infect Dis J. 2018; Perrett KP, Vaccine 2015; Nolan T, Vaccine 2019; Santolaya ME, Lancet 2012; Watson PS, Expert Review of Vaccines 2019, and results on clinicaltrials.gov; * hSBA titer of 1:5 used in US/Poland study].

In addition, persistence of MenB primary vaccination against diverse serogroup B strains, including from college outbreaks, has been assessed in several observational studies. Variable patterns of short-term persistence were observed when measured up to 12 months post-vaccination[1-4]. In another recent study to assess seroprevalence at Princeton University following the 2013 outbreak, suboptimal short-term immunogenicity followed by substantial antibody waning to the outbreak strain was observed in students vaccinated with MenB-4C. At 2 months post-vaccination, 61% of students had an hSBA titer of ≥1:4, which declined to 24% by 20 months post-vaccination[5] [[1]Lujan, et al. Clin Vaccine Immunol. 2017; [2]Lujan, et al. Clin Infect Dis. 2017; [3]Giuntini et al, Clin Vaccine Immunol. 2017; [4]Basta, et al International Pathogenic *Neisseria* Conference (2018); [5] Basta, et al. Congress of the European Meningococcal and Haemophilus Disease Society (2019)].

In summary, given the variable rate of waning between vaccine types and between studies, antibody persistence following a MenB primary series was difficult to generalize across the two vaccine products. It must also be noted that the two vaccines are completely different, and evaluations of immunogenicity and persistence were conducted using different strains and immunologic endpoints, and thus cannot be directly compared. However, the WG felt that by 1 to 2 years following a MenB primary series, booster vaccination is indicated for persons who remain at increased risk.

Dr. Mbaeyi next reviewed the immunogenicity and persistence of a MenB booster dose. Immunogenicity and persistence of a MenB-FHbp booster dose administered 4 years after completion of either a 2 or 3 dose primary series demonstrates a robust immune response at 1 month with gradual waning and evidence of persistence through 26 months post-booster dose. Thus, the WG's assessment was that the immune response to a MenB-FHbp booster dose persists for at least 2 years in healthy adolescents, and given the gradual antibody decay pattern, may last longer [Adapted from Pfizer data presented to ACIP Meningococcal WG].

For MenB-4C, regardless of timing since completion of the primary series (whether 2, 4, or 7.5 years), a robust immune response was demonstrated 1 month following either a MenB-4C or investigational MenABCWY booster dose. No studies assessed persistence of a MenB-4C booster dose. However, following a booster dose with the investigational MenABCWY vaccine with the same MenB component as MenB-4C, antibody persistence was observed through 12 months post-booster for most antigens. While there are no data on immune persistence following a MenB-4C booster dose to inform the WG interpretation, the WG took into account the demonstration of persistence of an investigational MenABCWY booster dose through 12 months, as well as modelled data presented by the manufacturer during the February 2019 meeting suggesting that persistence is likely several years [Adapted from Szenborn L, Pediatr Infect Dis J. 2018; Nolan T, Vaccine 2019; Watson PS, Expert Review of Vaccines 2019; * hSBA titer of 1:5 used in US/Poland study].

To summarize, a MenB booster dose elicits a strong immune response, and the persistence appears to exceed that of a MenB primary series. Thus, the WG's interpretation was that antibody persistence of a MenB booster dose is likely at least 2-3 years, and may be longer, in healthy adolescents and adults.

Dr. Mbaeyi next summarized the GRADE and EtR for MenB booster doses in persons at increased risk for serogroup B meningococcal disease. The over-arching policy question was, "Should persons vaccinated with a MenB primary series who remain at increased risk for serogroup B meningococcal disease receive a MenB booster dose?" The population was persons aged 10 years or older at increased risk due to specific underlying conditions and microbiologists, and persons exposed during a serogroup B meningococcal disease outbreak. The intervention was either a MenB-FHbp or MenB-4C booster dose, and the comparison was no booster dose. Outcomes of interest related to MenB booster doses were identified by the WG, though only data on short-term immunogenicity, persistence of the immune response, and SAEs were available. For GRADE, there were four PICO questions, two for each group at increased risk and two for each MenB vaccine. Beginning with persons at increased risk due to underlying conditions or microbiologists, for both MenB-FHbp and MenB-4C, the evidence type across outcomes was a 4, indicating that the overall certainty of evidence in this population is very low.

The WG also reviewed additional considerations as part of the EtR Framework. Persons at increased risk due to certain underlying medical conditions and microbiologists comprise a small group at substantially increased risk. Thus, in this group, prevention of serogroup B meningococcal disease is an important concern. However, immunogenicity to MenB-4C is reduced in persons with complement deficiency or complement inhibitor use compared to healthy controls, and these persons may be at increased risk for meningococcal disease even if they develop antibodies following MenB vaccination. Thus, in these persons, the desirable effects of vaccination may be more limited compared to others in the target group. The undesirable effects of booster vaccination are expected to be minimal. Safety of the MenB primary series has been demonstrated in several large evaluations in healthy persons, though no data on booster doses (including repeated doses) are available in persons with underlying conditions. In a survey, the majority of pediatricians and family physicians stated that they would recommend a MenB primary series for children at increased risk, demonstrating acceptance of MenB vaccination, though there is a disparity by provider type which may reflect levels of awareness or feasibility. There are no data on cost-effectiveness in this population.

Thus, the WG's interpretation was that for this population at increased risk, serogroup B meningococcal disease is a problem of public health importance. The desirable effects of a MenB booster dose may vary in persons with underlying conditions. The undesirable effects are likely minimal. The intervention of a MenB booster dose is favored, but there is very low certainty of the evidence. The target population may feel uncertain that the desirable effects are large relative to undesirable effects, though there is important uncertainty in how much these persons value the main outcomes. A MenB booster dose is probably acceptable to key stakeholders, though it is uncertain whether the intervention is a reasonable and efficient allocation of resources or is feasible to implement. Thus, the majority of WG members were in favor of proposing a recommendation for MenB booster doses in this population.

Next, Dr. Mbaeyi reviewed GRADE and EtR for persons at increased risk due to a serogroup B meningococcal disease outbreak. For MenB-FHbp, the evidence type across outcomes was a 4, indicating that the overall certainty of evidence is very low. For MenB-4C, the evidence type was a 3 or 4 across outcomes depending on study design, indicating that the overall certainty of evidence is low.

The WG also reviewed other considerations as part of the EtR Framework for this population. Of the serogroup B cases in the US, 7% are outbreak-related and college students are disproportionately affected[1]. Limited data are available on effectiveness and duration of protection in adolescents and adults, and no data are available in US populations. Following mass vaccination with MenB-4C in a region of Quebec, Canada that is experiencing increased rates of disease, the vaccine was estimated to be 79% effective in persons under the age of 20 years up to 4 years post-vaccination, but the confidence intervals were very wide[2]. However, an additional factor is that the evidence to-date suggests no impact of MenB vaccines on meningococcal carriage; thus, herd immunity is unlikely[3,4]. As the safety of a MenB primary series has been demonstrated through multiple evaluations following mass vaccination during outbreaks[5-8], the harms are likely minimal for a booster dose.

The WG also reviewed factors specific to college outbreaks. All 13 universities that experienced outbreaks since MenB vaccines became available implemented a MenB primary series, indicating acceptance of MenB vaccines to stakeholders, though first-dose coverage varied widely[1]. This may reflect values, feasibility, or other factors. Additionally, 1 university to-date has implemented a booster dose even in the absence of an ACIP recommendation, reflecting acceptance of this intervention. MenB mass vaccination during college outbreaks is resource-intensive, though is estimated to be more cost-effective than universal vaccination of all students at college entry[2,3]. Outbreaks require intensive coordination, significant human resources, and action among multiple stakeholders to efficiently respond within a short time[4-7]. MenB booster doses may create additional complexities, though colleges have already demonstrated the feasibility of conducting mass vaccination under very challenging circumstances. Indeed, additional challenges related to booster dose implementation were noted at the New Jersey University, including additional communication and logistical challenges related in part to the lack of an ACIP recommendation as well as challenges in determining booster eligibility (e.g., if a primary series was completed and which product was used) [[1]Soeters, et al. Congress of the European Meningococcal and Haemophilus Society. 2019; [2]Fisher, et al. J Adol Health, 2018; [3]Leeds et al., Am J Prev Med, 2018; [4]Capitano et al., Hum Vacc and Imm, 2018; [5]Ritscher et al., J Am Coll Health, 2018; [6]Fiorito et al., J Am Coll Health, 2017; [7]Fisher et al., J Adol Health, 2018].

Thus, the WG's interpretation was that for this population at risk during an outbreak, serogroup B meningococcal disease is a problem of public health importance. The desirable effects of a MenB booster dose may be large, with minimal undesirable effects. The intervention of a MenB booster dose is favored, but there is very low certainty of the evidence. The target population may feel that the desirable effects are large relative to undesirable effects, and there is probably variability in how much these persons value the main outcomes. The WG considered that the intervention of a MenB booster dose is acceptable to key stakeholders, a reasonable and efficient allocation of resources, and feasible to implement. Therefore, the WG favored recommending a MenB booster dose for persons at increased risk during a serogroup B outbreak.

To summarize the WG's deliberations for MenB booster dose policy options in persons at increased risk, the WG reviewed the data just presented on the persistence of the immune response following a MenB primary series, immunogenicity, persistence, and safety of a MenB booster dose, and results from the GRADE and EtR evaluations. The majority of WG members agreed upon the need for and timing of MenB booster doses. A small minority felt there was insufficient evidence on the safety and efficacy of MenB booster doses to inform policy options. The following represents the views of the majority of WG members.

The WG felt that MenB booster vaccination is necessary to sustain protection in persons who remain at increased risk. The WG suggested that a MenB booster dose is indicated at 1 year following completion of the primary series. Greater persistence is expected after the booster dose, and thus, a longer interval for repeat booster doses may be considered. Given the serious nature of meningococcal disease, the WG felt that the potential benefits of MenB booster vaccination outweigh potential risks in this population. As with MenB primary vaccination, challenges in the implementation of MenB booster doses are anticipated, but the WG felt the potential benefits of booster vaccination justify the additional implementation efforts that will be needed. Thus, the WG proposed that ACIP recommend MenB booster vaccination in persons aged 10 years or older at increased risk for serogroup B meningococcal disease who previously completed a MenB primary series. This recommendation does not apply to persons who previously completed a MenB primary series as an adolescent based on individual clinical decision-making and who are not at increased risk for serogroup B meningococcal disease. For persons with complement deficiency, complement inhibitor use, asplenia or microbiologists, a MenB booster dose is recommended 1 year following completion of a MenB primary series, followed by booster doses every 2-3 years thereafter, for as long as increased risk remains. For persons determined by public health officials to be at increased risk during an outbreak, a one-time MenB booster dose is recommended if it has been ≥1 year since completion of a MenB primary series. A booster dose interval of ≥6 months may be considered by public health officials depending on the specific outbreak, vaccination strategy, and projected duration of elevated risk.

Dr. Mbaeyi concluded that ACIP would be asked to vote on the policy proposal for MenB booster doses in persons at increased risk for serogroup B meningococcal disease. In advance of the afternoon's vote, ACIP members were asked to provide any additional feedback on the WG's policy proposal for MenB booster doses. She indicated that Vote #1 for this meeting would be for ACIP to recommend MenB booster vaccination in persons aged ≥10 years at increased risk for serogroup B meningococcal disease who previously completed a MenB primary series.

Discussion Points

Dr. Atmar requested a reminder about the basis for the original recommendation approval in terms of MenB vaccines and whether it was based on safety and immunogenicity. He also wondered about the rationale for not conducting a formal cost analysis, though he understood the cost-effectiveness assessment done for the original recommendation and what the extra cost and benefit would be for a booster recommendation

Dr. Mbaeyi indicated that immunogenicity data were reviewed for both vaccines when making the recommendation for persons at increased risk, as well as for adolescents who are not at increased risk. They do not have any VE or duration of protection estimates that informed that policy. The WG did not conduct a formal cost-effectiveness evaluation because these recommendations are for a very small group of individuals at increased risk. They are not

considering booster recommendations for adolescents who are not at increased risk, which is a much broader population. They attempted to look at some of this, but found that there was a wide variety in the assumptions that would have to be made and the NNV based on the uncertainty around the level of increased risk, population size, et cetera. The numbers were not very meaningful, which was why she did not present them.

Dr. Cohn requested a reminder of the total estimated size of the population for both increased risk and the average number of college students who are vaccinated during an outbreak.

Dr. Mbaeyi replied that the population at risk would be a little under 300,000 and the college students would be about 35,000. These are estimates. For example, the majority of people with complement component deficiency are not aware of their deficiency. Often people find out after their first episode of meningococcal disease or another infection, or if they have family members with the deficiency.

Dr. Maldonado (AAP) pointed out that since this is a booster recommendation and pediatricians are somewhat concerned about how to counsel families given the very low risk of disease, she suggested stating actual numbers of cases in addition to incidence and prevalence. For example, there is a total of 134 cases of MenB disease in all ages in the US based on the 2017 surveillance data from CDC.

To respond to Dr. Atmar's question, Dr. Stephens indicated that the license of MenB vaccine is based on immunogenicity and the correlate of protection is the serum bactericidal assay (SBA). That has been a standard for a number of years for most meningococcal vaccines. In terms of the complement inhibitor, even though they are recommending vaccination and booster vaccination in this group, this problem has not been solved in terms of the seriousness and data have been presented on this in the past. As pointed out, this is a small group for whom boosters are being recommended at this time.

Dr. Hunter wondered whether the ACHA, NACCHO, and ASTHO liaisons could comment on the issue that if there is an outbreak on a college campus how much the booster recommendation would help in the implementation of a response to that in terms of vaccine history.

Dr. Even (ACHA) responded that in an outbreak situation, students are unlikely to know whether they have received MenB previously. This depends upon the recordkeeping and ease of recordkeeping. If all students' immunization records are quickly available in an electronic record, that is beneficial. However, that is not a general practice. Her assumption is that a campus would use the vaccine that was most readily available and administer that as widely as possible. In a situation in which a student was aware of the vaccines they had before, every attempt would be made to use that same vaccine. The speed of the response seems to be more important in an outbreak situation.

Dr. Zahn (NACCHO) replied that it depends upon the size of the target population. If 30 people potentially could be exposed, this is very different from the potential for 3000 people to be exposed. Either way, there is a potential for missing people. Even if there is no recommendation, extra doses are still going to be given because some people who have been vaccinated may not realize it. It is known that after a couple of years, immunity wanes. To him, it is an obvious question and concern and there is potential utility to it. There is an issue in terms of getting everyone's vaccine status right and over-vaccinating. There is a better chance that someone might know what they had in the previous 6 months. On balance, he thought the

recommendation would be helpful, clarified the question, and would be welcomed by public health.

Dr. Messonnier expressed appreciation for the systematic way the WG worked through the issue and the desire to fill a gap in the recommendations, which she thought tried to provide helpful guidance to clinicians. The groups at risk have a more lifetime risk. While she understood the limitations of the available data and the desire to provide recommendations beyond a single booster, she wondered whether the WG could comment separately on reassurance that they did not have concerns about safety, recognizing that the effectiveness of repeat vaccination is not known after even a first booster.

Dr. Stephens said that the WG reviewed the data from a safety standpoint and did not have a major concern with regard to the safety of repeated booster doses. This is a memory-inducing vaccine. Therefore, a booster dose should provide significantly longer protection than the original priming series. There are no data to support that, but that is the message from the limited data that are available.

Dr. Atmar pointed out that if this recommendation were to go forward, it would be important for those at lifetime risk to generate those data because it may well be that the interval could be longer as more doses have been delivered.

Dr. Ezeanolue expressed concern about the foundation upon which they would make a recommendation that people with sickle cell disease risk should be immunized with the primary series and receive a booster dose every 2 to 3 years for life.

Dr. Stephens replied that it is known that this vaccine works and does prevent disease in high risk groups. In those individuals with functional asplenia, the risk is significant. Prophylactic penicillin is used with some individuals for other increased risk for lengthy periods of time. Thus, his response was that he would believe that a booster could help protect these individuals. The question regarded how often the booster should be given and how long the recommendation should continue for this particular group. He agreed with Dr. Atmar that more data are needed on repeated boosters.

Dr. Mbaeyi added that a major reason persons with sickle cell disease are considered a risk group for meningococcal disease in general is that if they do get it, they have an extremely high case fatality rate. Approximately 60% to 70% of people can get an overwhelming post-splenectomy infection. Therefore, it is important to consider them in this population.

Dr. Ezeanolue stressed that while he understood why this needed to be done, he was wondering how they were going to explain that this recommendation is being made with limited available data. He suggested that ACIP should commit to collecting these data in the future and reviewing the information again in 5 years.

Dr. Quach (NACI) thought it would be interesting to look at this vaccination strategy as an added value above and beyond chemoprophylaxis. There have been thoughts about giving prophylaxis to people on eculizumab, because the meningococcal disease was non-vaccine type. She wondered how much more would be added by boosting with MenB. As a microbiologist, it was not clear to her whether she would want the vaccine every 2 to 3 years. The study was from 2005 but the process in the laboratory is now safer working with Biosafety Level 2 (BSL-2) and above such that the risk may no longer be the same. She found the recommendation to be very heavy in terms of boosting.

Dr. Mbaeyi said that the WG tried to better understand these issues and they recognized that every 2 to 3 years is a pretty short interval. The WG presented every 5 years as an option to ACIP, but ACIP had concerns that the data did not support this interval. She agreed that there are gaps in the data. They do not have more refined estimates among microbiologists since that 2005 paper. As Dr. Stephens mentioned, there are still a lot of issues to be worked out with people taking complement inhibitors and how much vaccination actually protects them. However, the WG felt that they know that they are at exceptionally high risk and there is a possibility of benefit in these groups, so they should continue recommending a primary series and booster doses in this group.

Dr. Messonnier pointed out that there is a routine review of recommendations every 5 years. ACIP is certainly welcomed to include language in their statement directing CDC to try to find ways to evaluate this. It would be difficult to have a standalone study, so they would be looking for existing studies among these groups in which blood is being drawn from patients with sickle cell, for example. CDC will look for collaborators who have clinical care of these patient populations to determine whether there is a way to answer some of the questions. Perhaps someone in the larger community knows of a researcher who is working on sickle cell disease who could connect CDC with someone to help answer these questions.

Dr. Bernstein said that since the two vaccines are not interchangeable, he struggled with calling it a “booster” in the population of students during an outbreak for whom vaccine status and product type may not be known. It was not clear whether they would be doing these individuals a service by giving them a single dose of vaccine since one of the two products is a 0, 1 month schedule. Perhaps the recommendation should be extended for those who have not received MenB vaccine in college or for whom vaccination status and product are unknown.

Dr. Mbaeyi indicated that the WG discussed this in-depth and it is a major feasibility concern. The ACIP recommendation would be to use the same product and that the vaccine products are not interchangeable, just as it is for the primary series. The WG recognizes that this is a challenge during an outbreak, and CDC attempted to review with the WG potential guidance for CDC’s outbreak guidance document, understanding that they are not always going to get it right but do feel that these students should be offered the chance to get a booster vaccination. The New Jersey University presented to the WG about their experience. While it sounded like it was a challenge, they felt overall that it was something they could work with.

Dr. Hunter’s perception was that the booster recommendation would offer more flexibility rather than limiting the direction of an outbreak response. At least if it was determined later that someone was vaccinated a second time, it would not be against the recommendation.

Dr. Fryhofer (AMA) said that as a practicing physician, she has had difficulty figuring out which other vaccines her patients have received. It is not indicated on the Georgia Registry of Immunization Transactions and Services (GRITS). Oftentimes, she has to call a pharmacy or pediatrician, which can be quite cumbersome. It is important to include the specifics on registries and in notes.

Dr. Even (ACHA) added that with the general lack of a broad recommendation for all entering college students to receive the MenB vaccine and having it be a clinical decision-making recommendation, uptake is low. Colleges would understand that they have some students who have previous doses, but would be looking at it as an initial outbreak dose such that the booster

might be the flexibility for those who already had vaccine at some point in the past, but that this is the outbreak dose they are under recommendation to give.

Dr. Stephens made a motion to approve the language reading, "ACIP recommends MenB booster vaccination in persons aged ≥10 years at increased risk for serogroup B meningococcal disease who previously completed a MenB primary series."

Dr. Lee indicated that she had a counter motion. She recognized that there still was a great deal of uncertainty, but acknowledged that they still had to make a decision in the face of that uncertainty. She strongly felt that there should be the equivalent of a post-marketing requirement specific to this area, because additional safety and effectiveness are needed, including with the interchange of the different products if that happens in outbreak settings. The counter motion would be to, "Consider shared clinical decision-making for populations who remain at increased risk, which is a heterogeneous population" because of Dr. Quach's comments about whether a blanket recommendation was being made in the face of uncertainty versus a recommendation that would allow people to use their judgment. While there were some populations for which she felt more strongly about it, there were others where she felt that it was less clear what the right answer would be and they were mixing them all together.

Dr. Ezeanolue agreed that while they did not have all of the data needed, they had enough data to make a recommendation if it also committed to collecting additional data. Attached to that is that there are 100,000 people with sickle cell, for example. He clarified that he supported Dr. Stephens' motion with this amendment to collect additional data.

Dr. Romero noted that with two motions on the table, they should go with Dr. Stephens' motion as Chair of the WG. Dr. Ezeanolue's supported Dr. Stephens' motion with the amendment regarding data and seconded the motion to move forward.

Dr. Messonnier pointed out that recommendations usually do not have the language that Dr. Ezeanolue suggested as part of the paragraph. That could be included regardless of the recommendation language.

Dr. Atmar requested that a counter proposal reflecting Dr. Lee's recommendation be drawn up during lunch so that in the event that the first motion by Drs. Stephens and Ezeanolue was voted down, they could review it before voting. Dr. Romero confirmed that this could be done.

Dr. Talbot pointed out that this recommendation did not state when or how often to do this after the primary series.

Dr. Cohn clarified from a procedural perspective that Dr. Ezeanolue had put an amendment on the table. Technically, if that amendment was seconded, they would have to vote on the amendment and then vote after the public comment on the proposed amendment. She thought Dr. Messonnier's comment that this language could be incorporated but not included in the policy would be an option as well.

Dr. Romero requested further clarification from Dr. Messonnier.

Dr. Messonnier clarified that they have worked hard, especially in the last 5 years, to make the recommendations clearly pertain just to vaccination and not other language. Many years ago, the recommendation language was so complicated, people felt that it was difficult to understand. The language Dr. Ezeanolue suggested could be part of the paragraph leading up to the actual

recommendation and it could be in the statement rather than actually be included in the language ACIP votes on.

An inquiry was posed regarding whether the shared decision-making would be just for persons at increased risk for meningococcal disease. There are concerns about shared decision-making in an outbreak setting, given how challenging this would be for those who deal with outbreaks.

Dr. Moore supported the original recommendation in that the reason a routine recommendation is important for boosters for individuals at increased risk is that there is no question that they need boosting in order to be protected against MenB disease. There is no question that if they wish to be protected and they are at increased risk, they need to be boosted. The best evidence available suggests that this should be done 2 to 3 years later. It is important to collect ongoing information to understand whether this needs to be done lifelong or if the timeframe can be lengthened. This needs to be a clear guidance that if someone is in one of these increased risk categories, it is a recommendation versus a requirement. People choose all of the time not to get vaccines that are recommended for them, but for protection, they need the booster.

Dr. Lee clarified that she was not talking about outbreaks. She was talking about the at risk population.

Dr. Stephens commented that shared decision-making would be very difficult in this setting where there are obvious risks. Interpretation potentially could be different among people at risk for whom ongoing risk is not necessarily going to change. To be soft in terms of this recommendation would be a mistake.
Dr. Ezeanolue wanted to put on record that he did not believe shared decision-making would help guide what they do. If they were going to make this recommendation based on recognizing the limitations of the data, they should make a recommendation that would help them collect the data that would guide them in further review.

Dr. Fryhofer (AMA) said that speaking as a practicing physician, they must think about who is giving these vaccines (private offices, public health, et cetera). They do not have the expertise that ACIP does. When ACIP makes a recommendation, it is not a law. Shared decision-making does occur with the patient and the person offering and providing the immunization. Specific guidance is needed, and she thought that the shared decision-making was somewhat of a copout.

Dr. Hunter said that he was not against the shared decision-making possibility for the high risk groups, but the initial recommendation for vaccinating the high risk groups is a routine recommendation. He requested confirmation that if they recommended shared decision-making for the booster, that would be routine for the initial series and shared decision-making for the booster.

Dr. Lee withdrew her motion, but requested clarification. The reason she was thinking about this was because if it became a recommendation, it might become a requirement for microbiologists to receive the vaccine and if they opt out, there could be a potential consequence. In thinking about Dr. Quash's comment about whether risk has changed for microbiologists, what an isolate is may be unknown when it is received. Therefore, enhanced protection might make sense. In a known setting, this would be different. Specific to the asplenia population and the balance of prophylaxis and vaccination, prophylaxis would not be stopped in those patients with ongoing asplenia for multiple reasons, some of which could be sickle cell, but could be due to a variety of reasons. She just wanted to ensure that they think of the ongoing safety and benefit/risk

balance for that population. She had no challenge at all for people on eculizumab who are at extremely high risk for MenB or meningococcal disease in general or the other groups at increased risk.

Dr. Romero pointed out that the scenario Dr. Lee described of an unknown isolate coming in occurred at their hospital recently.

Dr. Stephens said he thought the Sejvar study conducted in 2005 probably needed to be updated. Some cultures are still done without the type of protection needed, so the unknowns are of concern. To all of the points, more data are needed to further assess risk.

Dr. Messonnier added that the Sejvar study was conducted during a time when meningococcal rates were higher and they were able to demonstrate an increased risk. The absolute risk now is so much lower that it will be much more difficult to identify whether there is still substantive risk associated with laboratory exposures. The problem is that it is an occupational health hazard. It would be difficult unless there are concrete data showing that they are not at risk to remove the recommendation because of exactly these types of incidents such as the tragic incident at Emory University that was preventable because there was a vaccine.

Dr. Maldonado (AAP) said that her understanding was that the MenB vaccine is a shared decision-making vaccine, not a routine vaccine.

Dr. Romero said that was correct, but they were talking about high risk individuals.

Dr. Cohn added that there is a routine recommendation for persons who are at increased risk.

Dr. Maldonado (AAP) said she requested clarity because she has received many emails from AAP members who are concerned, because they wondered whether this meant they had to start vaccinating everyone because they might be at risk. She stressed that they need to make it really clear that the vaccine itself is not routinely recommended, but that a booster would be routinely recommended for people who already have been vaccinated.

Dr. Kimberlin (AAP) requested clarity regarding whether Vote #1 included college students.

Dr. Mbaeyi clarified that Vote #1 was only for people who are identified as being at increased risk for meningococcal disease.

Dr. Maldonado (AAP) pointed out that the table talks about outbreaks, which is college students.

Dr. Messonnier said she thought the language that was put up for a proposed vote may have been simplified too much. She suggested that over lunch, they revise the wording. She asked the CDC leads to write language that included as background the information Dr. Ezeanolue requested that clearly would be part of what they would be saying, so that they could see that as well as the recommendation language.

Dr. Romero pointed out that they would need to make new motions upon returning from the lunch break since the wording would be revised during that time. He asked whether Drs. Stephens and Ezeanolue would be willing to withdraw their motions and reconsider them after the lunch break.

Dr. Stephens withdrew his motion and Dr. Ezeanolue withdrew his second with an amendment.

During the lunch break, Vote #1 was amended to read as follows:

For persons aged ≥10 years with complement deficiency, complement inhibitor use, asplenia, or microbiologists:

- ACIP recommends a MenB booster dose 1 year following completion of a MenB primary series followed by MenB booster doses every 2-3 years thereafter, for as long as increased risk remains.

For persons aged ≥10 years determined by public health officials to be at increased risk during an outbreak:

- ACIP recommends a one-time booster dose if it has been ≥1 year since completion of a MenB primary series.
- A booster dose interval of ≥6 months may be considered by public health officials depending on the specific outbreak, vaccination strategy, and projected duration of elevated risk.

The following additional guidance will be included based on the feedback received:

- These recommendations do not apply to persons who previously completed a MenB primary series as an adolescent based on individual clinical decision-making and who are not at increased risk for serogroup B meningococcal disease.
- MenB vaccines are not interchangeable. The same product must be used for all doses.
- Collection of safety and effectiveness data for repeated booster doses of MenB vaccine in persons at increased risk for serogroup B meningococcal disease is needed for the ongoing evaluation of these recommendations by the ACIP.

Dr. Stephens made a motion to approve Vote #1 as amended. Dr. Lee seconded the motion.

Updated ACIP Statement for Meningococcal Vaccination in the US

Sarah Mbaeyi, MD, MPH
CDC Lead, ACIP Meningococcal Vaccines WG
National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Mbaeyi reviewed the updated ACIP statement for meningococcal vaccination in the US. In terms of background, the last statement was published in 2013 and included ACIP recommendations for MenACWY vaccination. Since that time, 5 Policy Notes related to MenACWY and recently-licensed MenB vaccines have been published. In 2019, an updated statement was developed to consolidate all existing ACIP recommendations for MenACWY and MenB vaccines in a single document. In addition, if ACIP voted during this meeting to recommend MenB booster doses in persons at increased risk, these recommendations would be included in the document. The objectives of the updated statement are to: 1) describe the background on meningococcal disease, epidemiology, and risk groups; 2) provide updated information on currently licensed and available vaccines; 3) describe the process undertaken and rationale used in support of ACIP recommendations; and 4) provide ACIP recommendations and guidance for use of meningococcal vaccines.

A systemic review of the literature was conducted related to safety, immunogenicity, and effectiveness of MenACWY and MenB vaccines in the age groups in whom the vaccines are licensed. Existing MenACWY and MenB recommendations were consolidated and clarified, and preliminary MenB booster recommendations were drafted. The draft statement was shared with WG group members and ACIP voting members to provide an opportunity for feedback prior to this meeting.

Information was included on the 4 vaccines that are currently licensed and available in the US, 2 MenACWY and 2 MenB vaccines. Additionally, two vaccine products included in the previous ACIP statement are no longer available in the US, polysaccharide meningococcal vaccine and a combined Hib and meningococcal serogroups C and Y vaccine. Thus, detailed information and recommendations related to these two vaccines were not included in the updated statement.

All recommendations for the currently licensed MenACWY and MenB vaccines were included, starting from MenACWY introduction in 2005 through preliminary MenB booster dose recommendations in 2019 as shown on this table:

Year	Licensures and Recommendations
2005	MenACWY-D licensed and routinely recommended for adolescents and persons aged 11–55 at increased risk .
2006	Children entering high school and persons at increased risk years prioritized due to initial limited vaccine supply.
2007	MenACWY-D recommended for all adolescents aged 11–18 years as well as children aged 2–10 years at increased risk.
2009	MenACWY-D booster dose recommended for persons who remain at increased risk.
2010	MenACWY-CRM licensed. Booster dose recommended for adolescents aged 16 years, and 2-dose primary series recommended for persons with certain underlying medical conditions.
2011	MenACWY-D primary series recommended for children aged 9–23 months at increased risk for meningococcal disease.
2012	Hib-MenCY-TT licensed and primary series recommended for children aged 2–18 months at increased risk.
2013	MenACWY-CRM licensed and primary series recommended for children aged 2–23 months at increased risk for meningococcal disease.
2014	MenB-FHbp licensed.
2015	MenB-4C licensed. MenB primary series recommended routinely for persons at increased risk; adolescents aged 16–23 years may be vaccinated with MenB vaccine based on individual clinical decision-making.
2016	MenACWY primary series recommended for persons living with HIV.
2017	MenB-FHbp recommendations updated to allow 2-or 3-dose series, depending on indication, following updated licensure. Distribution of MPSV4 and Hib-MenCY-TT discontinued in the United States.
2019	*MenB booster dose recommendations to be included here if voted upon by ACIP.*

6

Key changes in the updated statement include a compilation of all existing MenACWY and MenB recommendations, as well as the proposed new recommendation for MenB booster doses, in a single document. The previous “Category B” language for MenB primary vaccination in adolescents will be updated to, “ACIP recommends a MenB primary series for individuals aged 16-23 years based on shared clinical decision-making.” In addition, the appendices with guidance for chemoprophylaxis of close contacts and management of outbreaks are no longer part of the ACIP statement. Guidance for these aspects of public health management are included in CDC guidance documents.

Dr. Mbaeyi indicated that Vote #2 for this meeting would be to affirm the updated statement titled, “Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices.”

Discussion Points

Dr. Stephens made a motion to affirm the updated statement "Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices." Dr. Frey seconded the motion. There was no further discussion.

Motion/Vote #1: Meningococcal Vaccine Booster Doses

Dr. Stephens made a motion to approve the following language pertaining to booster doses of meningococcal vaccines:

For persons aged ≥10 years with complement deficiency, complement inhibitor use, asplenia, or microbiologists:

- ACIP recommends a MenB booster dose 1 year following completion of a MenB primary series followed by MenB booster doses every 2-3 years thereafter, for as long as increased risk remains.

For persons aged ≥10 years determined by public health officials to be at increased risk during an outbreak:

- ACIP recommends a one-time booster dose if it has been ≥1 year since completion of a MenB primary series.
- A booster dose interval of ≥6 months may be considered by public health officials depending on the specific outbreak, vaccination strategy, and projected duration of elevated risk.

The following additional guidance will be included based on the feedback received:

- These recommendations do not apply to persons who previously completed a MenB primary series as an adolescent based on individual clinical decision-making and who are not at increased risk for serogroup B meningococcal disease.
- MenB vaccines are not interchangeable. The same product must be used for all doses.
- Collection of safety and effectiveness data for repeated booster doses of MenB vaccine in persons at increased risk for serogroup B meningococcal disease is needed for the ongoing evaluation of these recommendations by the ACIP.

Dr. Lee 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, Bernstein, Ezeanolue, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
0 Opposed: N/A
0 Abstained: N/A

Discussion Points

Dr. Atmar said he was somewhat bothered by a booster recommendation with the limited information available. However, based on the rationale for the initial approval and the risk groups being at definite risk, he was persuaded by the earlier discussion to vote for approval.

Dr. Hunter said that he was reassured that there will be follow-up by CDC.

Motion/Vote #2: Meningococcal Statement

Dr. Stephens made a motion to affirm the updated statement "Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices." Dr. Frey 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, Bernstein, Ezeanolue, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
0 Opposed:	N/A
0 Abstained:	N/A

VFC Resolution Updates: 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 resolution was to update the resolution to reflect (a) currently available meningococcal conjugate vaccines; and (b) new recommendations for booster doses for serogroup B meningococcal vaccines. In addition, the language regarding the intervals for one of the serogroup B vaccines covered by the resolution has been updated to more closely reflect the current ACIP recommendation language. Yellow highlighting in the presentation is used to indicate changes to the resolution in comparison to the prior approved version.

The only change to the Meningococcal Conjugate Vaccines (MenACWY) section will be removal of reference to HibMenCY since the vaccine is no longer available in the VFC program. There are no changes to the Recommended Vaccination Schedule and Intervals, Recommended Dosages, or Contraindications and Precautions components of this section.

For the Serogroup B Meningococcal Vaccines (MenB) section, there are no changes to Eligible Groups. The Recommended Vaccination Schedule and Intervals table has a column added for the booster dose for Serogroup B meningococcal vaccine and the second table note has been updated to more closely reflect the current ACIP recommendation language:

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. **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.
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)	

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.

Recommended Intervals/Doses, Contraindications and Precautions, and the Statement Regarding Update Based on Published Documents remain unchanged for serogroup B meningococcal vaccine.

Motion/Vote: VFC Resolution for Meningococcal Vaccines

Dr. Stephens made a motion to approve the VFC resolution for meningococcal vaccines. Dr. Ault 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, Bernstein, Ezeanolue, Frey, Hunter, Lee, McNally, Moore, Romero, Stephens, Szilagyi, Talbot, Walter
0 Opposed: N/A
0 Abstained: N/A

Dengue Virus Vaccine

Introduction

Robert Atmar, MD
Chair, Dengue Vaccines WG
Advisory Committee on Immunization Practices

Dr. Atmar reminded everyone that the new Dengue Virus WG was convened in October 2018 in response to the Sanofi resubmission of the BLA to the FDA for DENGVAXIA®. There were previous dengue vaccine discussions in 2016-2017 as part of the ACIP Flavivirus Vaccines WG, with ACIP presentations on dengue and dengue vaccines in February and June 2017. Dengue vaccine discussions were put on hold in early 2018 while Sanofi Pasteur reanalyzed long-term vaccine trial data and reworked the BLA. There was an FDA Vaccine and Related Blood Products Advisory Committee (VRBPAC) review in March 2019 and the vaccine received approval in May 2019.

Regarding the Dengue Virus Vaccine WG's terms of reference, the objective of the WG is to develop recommendations for the use of safe and effective dengue vaccines in the US and US Territories among children and adults, including those living in dengue-endemic areas and for persons traveling from non-endemic to endemic areas. The WG's goals with regard to dengue vaccines are to:

- ❑ Review safety, immunogenicity, and efficacy data from clinical trials and long-term follow-up studies for dengue vaccines submitted for licensure in the US
- ❑ Develop evidence-based recommendations for implementation of vaccination in the public and private sectors with dengue vaccines licensed for US use
- ❑ Identify areas where additional data are needed (i.e., future directions) to improve control of dengue through safe and cost-effective vaccination

Dr. Atmar indicated that presentations would be provided on the following topics during this session:

- ❑ Dengue Epidemiology in the US
- ❑ DENGVAXIA® Phase III Clinical Trials and Long-Term Follow-Up
- ❑ Dengue Vaccines WG Considerations and Next Steps

Future WG plans are to present a GRADE analysis and preliminary DENGVAXIA® recommendations during the October 2019 ACIP meeting, and present final recommendations for a vote during the February 2020 ACIP meeting.

Epidemiology of Dengue

Gabriela Paz-Bailey, MD, PhD, MSc
Dengue Branch
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

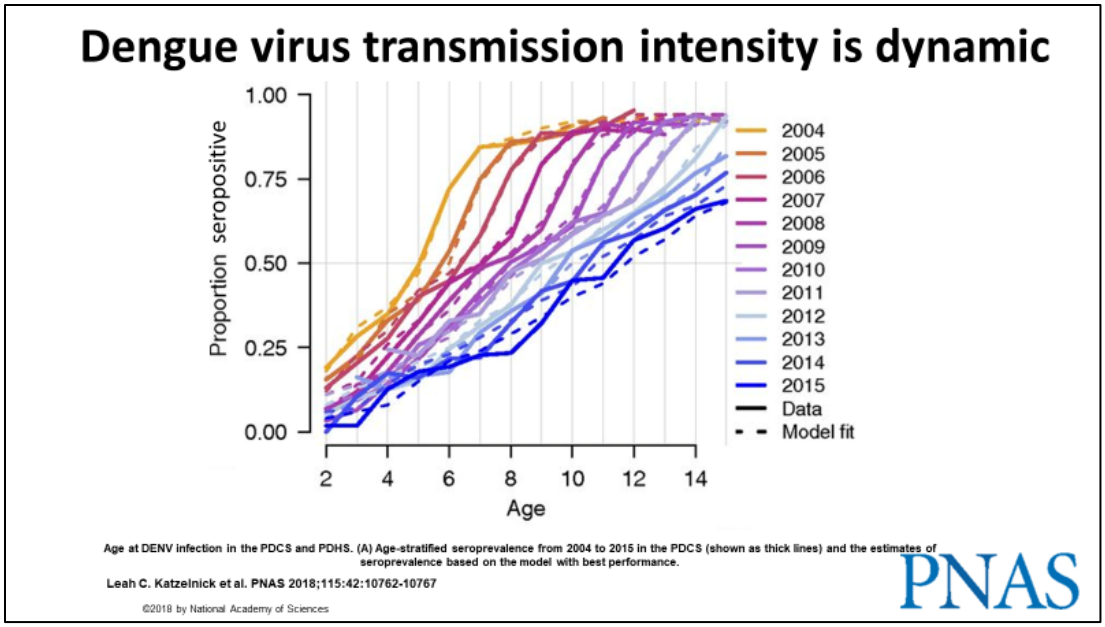
Dr. Paz-Bailey presented on the global epidemiology of dengue, considerations pertaining to dengue testing as the vaccine requires pre-vaccination serostatus screening, and dengue epidemiology in the US and its territories to consider where a dengue vaccine may be beneficial.

Regarding the global dengue burden of disease and where it is a public health problem, dengue is the most important virus transmitted by mosquitoes worldwide. Dengue virus (DENV) is transmitted by *Aedes* species mosquitoes, primarily by *Aedes Aegypti* and *Aedes Albopictus*. It is arguably the most important arbovirus in terms of worldwide morbidity and mortality with an estimated 390 million infections; approximately 100 million of which are associated with clinical manifestations; 500,000 hospitalizations; and 20,000 deaths estimated in 2010. Epidemics typically have a cyclical pattern over years and with seasonal incidence correlated with higher temperatures and rainfall months. Dengue virus is a public health problem throughout the tropics and subtropics in 128 countries and is endemic in Asia and Latin America including the Caribbean, Africa, and the Pacific. With increasing travel and connectivity and rising world temperatures, more areas are becoming at risk [S Bhatt *et al. Nature* 000, 1-4 (2013) doi:10.1038/nature12060].

Infections can occur with any of four distinct dengue virus serotypes. Natural infection results in lifelong protection for that serotype. In theory, a person can be infected with dengue 4 times in her or his lifetime. About 25% to 35% of infections are symptomatic. Typical classic symptoms include abrupt onset of fever, headache, retro-orbital pain, muscle and bone pain (hence the term “breakbone” fever), and often rash. Of those who are symptomatic, between 10% to 20% are hospitalized and 1% to 5% of clinical cases result in severe dengue. Hospitalization rates vary regionally based on early recognition, appropriate management, and local clinical practices [Flasche et al, Plos Med 2016; 13(11):e1002181; Wilder-Smith A. et al, Lancet 2019;393:350-63; Salje H. et al, Nature 2018; 557:719-728].

The detection of all virus serotypes has expanded worldwide together with growing hyperendemicity, which means that more than one serotype is circulating. Diagnostic capability has changed over time. Until the 1980s, the majority of areas had reported only 1 or 2 dengue virus serotypes. More recently, all 4 virus serotypes frequently co-circulate.[1] An example of this is Puerto Rico, which has monitored serotype distribution for over three decades. In addition to co-circulation of multiple virus serotypes, the proportion of each of the 4 serotypes circulating varies over time, with 1 or 2 serotypes predominating in any given year[2] [[1]Messina JP et al. Trends in Microbiology 2014:22;3:138-146; [2]Arbonet, National Arbovirus Surveillance System].

This graph emphasizes that dengue transmission is dynamic, constantly changes, and seroprevalence measured 10 years ago does not necessarily reflect seroprevalence today. This data comes from a cohort study in a particular Managua district in Nicaragua. The data show how seroprevalence by age group changed substantially between 2004 and 2015. The y-axis shows the proportion seropositive and the x axis shows age. Highlighting the difference between the yellow line that is 2004 and the dark blue line that is 2015, 50% of children were seropositive by age 4.5 in 2004, but 50% seroprevalence was reached by age 11 years in 2015:



Of the $8.9 billion estimated global financial burden of dengue, most ($5.1 billion) results from patients who are hospitalized or die from dengue. Age, co-morbidities, host genetics, and virus strain are risk factors for severe dengue. Heterotypic secondary infections is the greatest risk factor for dengue hemorrhagic fever and dengue shock syndrome [Shepard DS et al. Lancet ID 2016; 18(8):935-41; Wilder-Smith A. et al, Lancet 2019;393:350-63].

The way in which secondary dengue infections increase the risk of severe dengue is thought to be explained by the phenomenon of antibody-dependent enhancement (ADE). The mechanism is that at a specific concentration, heterotypic antibodies bind but do not neutralize virions of the subsequent infecting dengue type, leading to higher viremias and non-structural antigenemia and imbalanced inflammatory responses that result in vascular leak and severe dengue disease or shock. Only recently has it been demonstrated that mid-range specific dengue antibody titers are associated with risk of severe dengue disease. Data from a longitudinal analyses of the risk or hazard of severe dengue disease by pre-existing DENV-Ab titer for the pediatric dengue cohort in Nicaragua illustrated that dengue hemorrhagic fever and dengue shock syndrome showed a cumulative hazard of 11% for intermediate antibody titer compared to 1.6% among dengue naïve children and 1.5% for children with high titers. That is, having no antibody titers or having high antibody titers is better than just having some antibody titers [Leah C. Katzelnick et al. Science 2017;358:929-932].

Thus, there is a question about what percentage of primary, secondary, or post-secondary infections result in hospitalizations and severe disease. Sam Clifford and Stefan Flasche of the London School of Hygiene kindly shared modeling results fit to the most recent DENGVAXIA® Phase III trial data to present during this meeting. The data show what proportion of first and second infections progresses to the given disease outcome (symptomatic VCD, hospitalization, and severe dengue) in a follow up period of 2 years for symptomatic VCD and 5 years for hospitalization and severe dengue. The model estimates that 19% (14.8-23.2) of primary infections result in symptomatic dengue, 3% (1.9, 4.4) are hospitalized, and less than half a percent (0, 0.7) progress to severe dengue. The uncertainty is clear based on the confidence intervals for each of these estimates. The estimate for secondary infections is that 35% (31.4-38.7) result in symptomatic dengue, 11% (9.4, 11.8) in hospitalizations, and 2% (1.8, 2.9) in

severe disease. This shows that the majority but not all hospitalizations occur after secondary infections in this model [Sam Clifford and Stefan Flasche LSHTM, personal communication; Sridhar, NEJM 2018;379:327-40, Flasche et al, Plos Med 2016; 13(11):e1002181].

The current dengue vaccine requires screening for dengue serostatus before vaccination. Likely IgG testing will be used to determine previous serostatus. No IgG test is currently FDA-approved in the US, and there are limited data regarding cross-reactivity with other flaviviruses after the Zika epidemic. When thinking about test performance, sensitivity and specificity are not the only target metrics for assay development. Tests with a given sensitivity and specificity are more likely to misclassify truly seronegative individuals in low transmission settings than in high transmission settings, because the pretest probabilities of testing positive are lower. In an example of a 20% seroprevalence, with a test specificity of 90% and sensitivity of 70%, 36% of persons testing positive would be false-positives or actually negative for past dengue infection. In a higher prevalence setting of 80% seroprevalence, the positive predictive value (PPV) is higher at 97% and only 3% of persons testing positive would be false positives. The problem here would be imperfect sensitivity, since more than half of those testing negative would be true seropositive who could benefit from the vaccine.

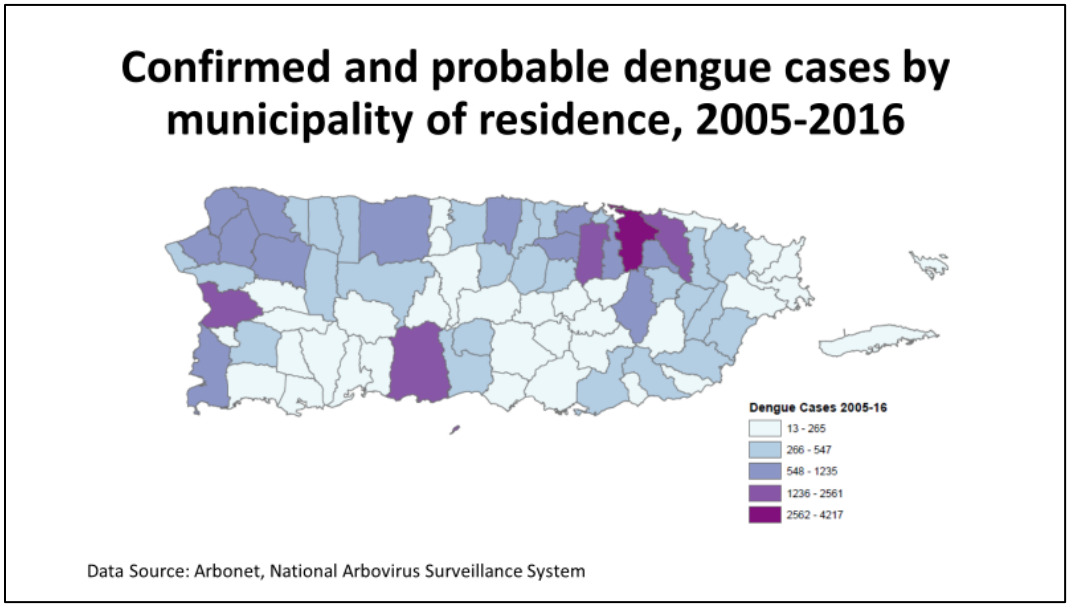
Turning to a review of dengue epidemiology in the US and its territories in consideration of which areas may benefit from a dengue vaccine, economist and modelers in collaboration with WHO have proposed levels of risk based on seroprevalence to identify areas that would benefit from vaccination and where the risk of false negatives would be low. Areas with 10% seroprevalence at the target age group to start vaccination are considered very low risk, 30% low risk, 50% moderate risk, 70% high risk and 90% very high risk [Flasche et al, Plos Med 2016; 13(11):e1002181].

Ideally, it would be beneficial to have seroprevalence data available to assess risk. But as for the rest of the world, limited seroprevalence data are available in the US and its territories. A proposal has been made to use the dengue risk definition in the *CDC Yellow Book* that provides health information advice for travelers. Since dengue epidemics in many regions typically occur every 3 to 5 years, the *Yellow Book* assumes that endemic areas would be the most likely to report more than 10 dengue cases in at least 3 distinct years over the most recent 10-year period. These areas are classified as frequent/continuous risk. For areas that did not meet the frequent/continuous definition, the *Yellow Book* classifies areas with at least some or sporadic risk defined as any area with at least one reported, locally acquired case in the previous 10 years. Areas with no reports of DENV transmission were classified as no evidence of risk. These criteria then define endemic areas as including the US territories of American Samoa, Puerto Rico, US Virgin Islands, and the US-affiliated Federated States of Micronesia and Palau.

In terms of the US territories that would fall into frequent continuous risk and the epidemiology of dengue in Puerto Rico, data comparing dengue incidence rates in Puerto Rico to countries in Latin America show that rates are similar to several countries. For Brazil, rates are 10 times higher than for all other countries, and the scale is different. It is important to note that reporting practices and under-reporting vary by country [Source: Talia Quandelacy and Mike Johansson, personal communication; Data from dengue passive surveillance from Ministries of Health and latest population census].

Regarding suspected cases for the most recent years in Puerto Rico, passive surveillance data show that the highest number of cases occurred in 2010 and 2013. In 2013, there was a large Chikungunya virus (CHIKV) outbreak, and in 2016 a large Zika virus (ZIKV) outbreak. There has been some, but little, circulation of dengue since 2014.

This map shows the number of cases by Puerto Rico municipality. Dengue transmission occurs through the island, but with local heterogeneity. Areas with higher population density have more cases, such as San Juan in the Northeast and Ponce on the South Coast:



For each of the territories, Dr. Paz-Bailey presented the number of cases and rates for the most recent years when there was transmission. Passive surveillance data from Puerto Rico for 2010-2013 show that the highest numbers and rates of confirmed and probable cases are in the 10-14 age group and the 15-19 years of age group. Hospitalized cases and severe illness cases are also highest in these age groups. The number of cases in older age groups drops likely because most people have probably had 2 infections by age 20. However, almost 50% of cases occurred among adults. A high degree of under-reporting has been documented in Puerto Rico. A recent published study estimated that for every 1 reported case, there are about 100 cases not reported. For every hospitalized case reported, there are 5 to 9 cases not reported [Arbonet, National Arbovirus Surveillance System].

With regard to dengue-associated deaths, the case fatality rate has varied by outbreak year. Data on fatal dengue cases by age in Puerto Rico (n=64) from 2010–2013 show that in contrast to the higher number of cases in children and adolescents, only 6 of the 64 laboratory-confirmed deaths in this period were in children and only 1 was in the 15 to 19 year old age group. Death occurred in adults 20 to 88 years of age. Thus, 90% of lab positive deaths were in adults from 2010 through 2013 [Arbonet, National Arbovirus Surveillance System].

One of the few seroprevalence surveys available for Puerto Rico was done in 2007 in Patillas in the Southeast of the island. The seroprevalence among 10-11 year olds was 43%, and by 16-18 years of age, 60% were seropositive [Argüello DF et al. Incidence of dengue virus infection in school-aged children in Puerto Rico: a prospective seroepidemiologic study. Am J Trop Med Hyg. 2015 Mar;92(3):486-91. doi: 10.4269/ajtmh.14-0231. Epub 2015 Feb 2].

With regard to how dengue test results are processed in Puerto Rico, persons who are symptomatic and seek care will visit their private provider's office or go to an emergency department (ED). If the provider suspects dengue, a dengue test is ordered. Testing is centralized at the Public Health Laboratory, where polymerase chain reaction (PCR) and immunoglobulin M (IgM) tests are done. These results are sent back to the name in the form that appears as the provider, which could be the clinical laboratory, hospital, or physician that ordered the test. It is not clear how many of these make it back to the patient's record, but anecdotally it is reported that many do not. Dengue is a notifiable disease and all results are kept in the Arbovirus Surveillance System that is managed by the Puerto Rico Department of Health (PRDH).

There is an immunization registry in Puerto Rico. There are 220 providers for the VFC Program that cover about 60% of the vaccines administered. There are also 300 private providers, including vaccination centers. Those provide about 40% of the vaccines that are administered in Puerto Rico. The immunization registry covers both children and adults and it is pretty complete. They have 70% coverage of private providers and 100% of providers in VFC [Personal communication, Angel Rivera and Iris Cardona, PRDH].

The past 25 years have seen several periods of increased dengue virus transmission in the US Virgin Islands, with the most recent in 2012-2013. During the last outbreak, a seroincidence study was conducted in schools in St. Croix in 2012. Of the school-aged children and adolescent, 20% were recently infected with dengue virus and 17% of teachers were recently infected. In 2012 and 2013, 310 cases were reported. In terms of the age distribution and incidence rate, the highest number and rate were in the 10-14 year age group, while 69% of reported cases were in adults [Arbonet, National Arbovirus Surveillance System, CDC. MMWR 2013;62 (9): 171-172].

The US Pacific territories and affiliated independent states include American Samoa, Guam, the Northern Mariana Islands, Palau, the Marshall Islands, and the Federated States of Micronesia. Periodic dengue outbreaks have been detected among the Pacific Islands since 1958, usually with only one dengue serotype at a time[1]. Whether continuous endemic transmission occurs in any of the islands is unclear. However, a 2010 serosurvey in American Samoa among adults found that 96% percent of the sampled population had dengue IgG antibody[2]. In 2016-2018, there was a large dengue outbreak in American Samoa with over 1000 laboratory-confirmed cases[3]. Data from passive surveillance show that the highest numbers and rates of cases and hospitalizations are among 10-14 and 15-19 year olds in American Samoa in 2017-2018[4] [[1]Hammon et al., *Am J Trop Med Hyg*, 1958; [2]Lau, EID, 2013; [3]Cotter et al. MMWR 2018:67(47);1319–13222; [4]Arbonet, National Arbovirus Surveillance System].

In terms of sporadic and uncertain transmission, there have been large dengue outbreaks historically in Hawaii. More recently in 2015-2016, there were 264 cases reported due to DENV 1 on the big island of Hawaii. The outbreak strain was a DENV 1, that was different from the 2001 Hawaii outbreak strain. A serosurvey in a small rural community in 2001 on the island of Maui showed that 14% had evidence of recent infection and 17% had evidence of past infection[1] [[1]Hayes JM et al. TRSTMH 2006; 100 (6):559-566].

Several counties in Southern and Central Florida have reported locally acquired cases. In 2009 and 2010, nearly 90 cases were reported. In 2013, a locally acquired dengue outbreak took place and 21 cases were reported. A survey in Martin County showed that 2% had evidence of recent infection, while a separate survey in Key West showed that 4% has evidence of a recent infection and 7% had evidence of past infection [Moody-Geissler S et al. CSTE 2014; Messenger AM et al. VBZD 2012;14(11):783-787].

Since 1980, Texas has detected a number of outbreaks with a few locally acquired dengue cases in border cities that are associated with large outbreaks in neighboring Mexico cities. In 2013, there were 24 locally-acquired cases reported[1]. A serosurvey conducted in 2005 at the end of a DENV 2 outbreak showed large differences in seropositivity on the Mexico side of the border compared to the US side. Overall, IgM positivity measuring recent infections was 32% in Matamoros, Mexico and only 4% in Brownsville, Cameron County on the US side. IgG seroprevalence was high in Matamoros at 77% for all age groups and 39% overall in Cameron County in the US side[2] [[1]Arbonet, National Arbovirus Surveillance System; [2]Ramos et al Am J Trop Med Hyg 2008;78(3):364-369].

About 800 dengue cases a year are reported among US travelers on average. The most common travel destination overall has been the Caribbean, but this varies year to year. About 800 dengue cases a year are reported among US travelers. ACIP's Dengue Vaccines WG will likely review available data for foreign-born or territory-born travelers and consider that data in making any dengue vaccine recommendations [Arbonet, National Arbovirus Surveillance System].

In summary, dengue is a public health problem throughout the tropics and subtropics including the Americas. Unfortunately, seroprevalence data are limited. Seroprevalence affects assay performance. US territories with frequent or continuous risk include Puerto Rico, US Virgin Islands, American Samoa, and some US-affiliated Pacific Islands. Cases and incidence rates in Puerto Rico, US Virgin Islands, and American Samoa are highest in the 10-19 age group, but many cases occur in adults as well.

Discussion Points

Dr. Romero asked what the average turnaround time is for the test in Puerto Rico once it reaches the center. He also wondered how much disruption had occurred in the Puerto Rico immunization registry due to the recent climate challenges they have faced, and whether they is an estimate of when it will be back to its previous state.

Dr. Paz-Bailey indicated that the average turnaround time depends upon the volume of testing that is occurring, but it is about 2 weeks. While the vaccine immunization registry probably was disrupted in the immediate days after Hurricane Maria, CDC has learned through conversations with the health department that it is now fully operational.

DENGVAXIA® Phase III Clinical Trials and Long-Term Follow-Up

Gustavo Dayan, MD
Global Clinical Sciences
Sanofi Pasteur

Dr. Dayan discussed Sanofi Pasteur's Phase III clinical trials for DENGVAXIA® in terms of efficacy, safety, and long-term follow-up. DENGVAXIA® which is a tetravalent live-attenuated viral vaccine. The development of this vaccine has taken more than 20 years of research. DENGVAXIA® combines two different viruses, YF 17D virus where the capsid and non-structural proteins act as the backbone of the vaccine and also the dengue viruses. The precursor membrane and envelope genes were isolated from each of the 4 dengue serotypes and were inserted into that backbone. The result was a chimeric vaccine, which is a combination of the 2 viruses that produces protection against the 4 dengue serotypes.
The DENGVAXIA® development program began in 2002. It comprises 26 clinical studies that have been completed that involved 41,000 subjects enrolled in 16 countries. Over 28,000 subjects received DENGVAXIA® in clinical trials and most of them (N=21,000) were 9 to 45 years of age. DENGVAXIA® is now licensed in 20 countries, including the US and the EU. The indication in the US is for seropositive individuals 9 to 16 years of age.

Regarding the efficacy results, the program included two Phase III clinical trials, both of which were randomized, observer-blind, placebo-controlled studies. Study CYD14 was conducted in children 2-14 years of age in 11 centers across 5 countries in Asia Pacific (Malaysia, Philippines, Thailand, Vietnam, Indonesia). Study CYD14 enrolled 10,275 children who were randomized 2:1 to receive either DENGVAXIA® (N=6841) or placebo (N=3424). Study CYD15 was conducted in children and adolescents 9-16 years of age in 22 centers across Latin America in 4 countries (Brazil, Colombia, Honduras, Mexico) and the US territory of Puerto Rico. Study CYD15 enrolled 20,869 children and adolescents who were randomized 2:1 to DENGVAXIA® (N=13,920) or placebo (N=6949). Each study also included baseline samples in a subset of 2000 subjects for immunogenicity and reactogenicity, in accordance with the WHO-recommendations for the development of dengue vaccines.

Both studies were identical in design. They included 3 doses separated by 6 months each (0,6, 12 months) and a long-term follow-up period of 5 years after the last injection. The study was divided into two phases, the Active Phase and the Hospital Phase. The Active Phase began with the first injection and ended at Month 25. The main purpose of this phase was to assess efficacy. There was an active surveillance system to be able to detect any suspected dengue cases. Efficacy was assessed 1 month after the third injection, which was the primary endpoint of the study, and also from the moment of the first injection until Month 25. The studies also had a Hospital Phase that began at Month 25 and finished at the end of the studies. In this phase, the surveillance system was detecting only hospitalized cases and the primary purpose was long-term safety follow-up. In summary, safety for hospitalized and severe dengue was started from the beginning of the studies and was continued until the end of both studies.

Regarding the results, both studies met their primary endpoints. Efficacy was approximately 55% (46.8, 61.7) in CDY14 and approximately 65% (58.7, 69.9) CYD15. They also were able to show efficacy against hospitalized dengue and in severe dengue cases. During the long-term follow-up, the investigators began to see an increased risk of hospitalized dengue in approximately Year 3 in Study CYD14, which was the study conducted in the younger children.

The protocols included some pre-specified analyses by International Conference on Harmonisation (ICH) age groups, and they were able to see that this was particularly focused in children 2 to 5 years of age. This safety signal detection prompted the investigators to conduct some additional analyses using different age groups. They were able to show that the relative risk for hospitalization and severe dengue was lower in subjects who were more than 9 years of age, which prompted them to used 9 years of age as the cutoff for the initial indication in endemic countries. However, they knew that the age was closely related to the baseline studies of prior dengue infection. The problem was that they did not have baseline specimens from all of the subjects, because these were collected only in a subset of patients. By design of the studies, they had 1 sample in almost all subjects in Month 13. That was 1 month after the third injection. Then they faced another problem. They had the blood samples, but not the assay. The assay they used was a plaque reduction neutralization test (PRNT) assay, which cannot distinguish vaccination from prior infection. It was specifically designed to assess the response to the vaccine. Therefore, they had to leverage the NS1 antibody assay to infer baseline serostatus from the Month 13 samples.

In terms of the results of the NS1 Supplemental Analysis, a very different response was seen in those who were seropositive in which all of the estimates were to the left of the null value indicating protection compared to the seronegative subjects where the estimates were to the right of the null value indicating an increased risk. Regarding risk reduction against hospitalized dengue in seropositives by serotype among children and adolescent 9 to 16 years of age, the US indication, the risk was decreased for all 4 serotypes. Importantly, the upper bound of the 95% confidence intervals spared the null value.

They also looked at the time to dengue hospitalization in seropositive subject 9 to 6 years of age. Looking at the cumulative cases for DENGVAXIA® and the control group, there was a clear separation of both curves from the moment of the first injection until the end of the surveillance period. They performed a similar exercise for the severe dengue cases among seropositive subjects 9 to 16 years of age. The pattern was the same, with separation of the curves for the DENGVAXIA® and control group from the first dose until the end of the surveillance period.

Traditional VE was assessed against any symptomatic dengue disease in seropositive subjects 9 to 16 years of age during the Active Phase. Efficacy was consistent in both studies at approximately 75% in Study CYD14 and 76% in Study CYD15. They also assessed the efficacy among seropositive subjects 9 to 16 years of age by serotype. There was efficacy for each of the 4 types and the lower bound of the confidence interval was spared the null value.

The investigators also assessed the population level effects, for which they looked at the attributable risk and cumulative incidence over a 5-year period. Basically, they looked at the differences in the attributable risk, which is the difference in the incidence in vaccinated and non-vaccinated children. They observed that the attributable risk for hospitalized dengue cases was -15% and severe dengue was -4%.

In summary of the efficacy data, the investigators observed a different profile by serostatus that was favorable for seropositive subjects and unfavorable for seronegative subjects. In seropositive subjects 9 to 16 years of age, there was protection against symptomatic, hospitalized, and severe dengue. The evidence of vaccine efficacy was consistent across both Phase III clinical trials and there was protection against the 4 serotypes. In terms of population effects, vaccination of 1000 seropositive subjects would prevent 15 hospitalized cases and 4 severe dengue cases in the conditions of these clinical trials.

Regarding the overall safety profile after any injection in the DENGVAXIA® and saline placebo control group in Study CYD15, the percentages in the reactogenicity subset were somewhat higher in the vaccine compared to the placebo. This was particularly true for the injection site reactions. In terms of the safety analysis set, SAEs were similar in the vaccine compared to the control group at ≤ 28 days post any dose and >28 days to 6 months post any dose. The investigators also assessed viscerotropic and neurotropic disease because this vaccine has the backbone of the YF vaccine virus, so there was a concern that vaccination with DENGVAXIA® could cause viscerotropic or neurotropic disease. However, no cases were identified. No vaccine-related deaths occurred during the study.

In terms of the solicited systemic reactions that were assessed in both trials (pain, erythema, swelling), the percentage of pain and swelling were somewhat higher in subjects receiving the vaccine compared to those receiving placebo in Study CYD15. Most of the injection site reactions were Grade 1 or Grade 2, short in duration, and began within 3 days after vaccination. Solicited systemic reactions (fever, headache, malaise, myalgia, asthenia) also were assessed. The percentages were fairly similar between the vaccine and placebo recipients, with no clinically significant differences. Most reactions were mild or moderate in intensity and of short duration. Unsolicited AEs and ARs also were similar between the vaccine and placebo recipients, most were mild or moderate.

There are also post-marketing data because the vaccine has been used. Approximately 3 million doses have been distributed primarily in Brazil (300,000 doses) and the Philippines (830,000 doses) where vaccination campaigns were organized. There were approximately 3000 spontaneous case reports, including 553 serious AEs. The most frequently reported AEs were consistent with the clinical development program. Though some allergic and anaphylactic reactions were detected in the post-licensure experience that had not been detected in the pre-licensure process, these were rare with a reporting frequency of <0.01%. Approximately 134 potential allergic reactions occurred in the first 7 days following vaccine and 69 occurred within 24 hours, and there were 3 cases of anaphylactic reactions. Allergic and anaphylactic reactions have been included in the prescribing information.

To summarize the safety results, rates of some solicited reactions were higher in the DENGVAXIA® versus the placebo recipients. There were low rates of Grade 3 events overall, with the majority of reactions being mild to moderate in intensity and transient. Rates of SAEs among DENGVAXIA® recipients were low and were similar to the control group, and no cluster of events was identified. There were no viscerotropic or neurotropic cases and no related deaths were reported. Allergic and anaphylactic reactions were detected in post-marketing surveillance.

Regarding the indication and dosing summary, DENGVAXIA® was approved for use in the US to prevent dengue disease caused by dengue virus serotypes 1, 2, 3, and 4 in individuals 9 through 16 years of age with evidence of laboratory-confirmed previous dengue infection and also living in endemic areas. Previous dengue infection can be assessed through medical record of a previous laboratory-confirmed infection or current serotesting prior to vaccination. DENGVAXIA® is administered subcutaneously on a 3-dose schedule at 0, 6, and 12 months.

Given that the vaccine is linked to serotesting, Sanofi Pasteur started to explore different possibilities to execute serotesting globally and particularly in Puerto Rico. There are two CLIA-approved tests available in Puerto Rico, which are the SciMedx Dengue IgG Serum Microwell ELISA and the Biocan RDT - Tell Me Fast Dengue IgG/IgM. The specificity of these tests is very

high at 100% for SciMedx and 99.1% for Biocan. This is very important in terms of avoiding the possibility of obtaining false positive results.

In conclusion, through multiple studies among more than 25,000 subjects, DENGVAXIA® has demonstrated that in seropositive individuals 9 through 16 years of age, the safety profile is favorable and there is efficacy against symptomatic, hospitalized, and severe dengue against each of the 4 dengue serotypes.

Discussion Points

Dr. Moore noted that Dr. Dayan mentioned the rates of viscerotropic and neurotropic disease in reference to the clinical trials, but she wondered whether this was assessed in the post-marketing surveillance as well.

Dr. Dayan indicated that viscerotropic and neurotropic disease were assessed in both the clinical trials and post-licensure experience, with none identified. There was a specific protocol to assess this in the clinical trial because it was considered to be an AE of special interest.

Dr. Ezeanolue requested further information about deaths since everyone was tested for seropositivity before vaccination, as well as the cost for testing.

Dr. Dayan clarified that when the vaccine was used in the field campaigns, everybody was vaccinated because they did not have the information about seropositivity yet. Therefore, vaccine use started without the restriction on the seropositive subjects. Once they learned this information, they began to incorporate the new recommendation in seropositive subjects. This recommendation was incorporated into the FDA submission, and was part of the approval for use in the US. He did not know the exact cost of the testing, but did not think it was very expensive.

Dr. Maldonado (AAP) said that there is a table with the available tests and costs for them. Regarding the earlier studies of DENGVAXIA®, the WHO website still has data from 2017 and they have not updated it. There is no citation for those data, so she assumed it was not published. However, their pooled data efficacy was much different. Their efficacy against serotype 3 was 71.6%, serotype 4 was 76.9%, serotypes 1 was 54.7%, and serotype 2 was 43.0%. Regarding use of the vaccine in the Philippines, she noted that Dr. Dayan did not mention the 14 deaths that supposedly were associated with the vaccine and whether those data were ever confirmed.

Dr. Dayan explained that those data combined studies but did not take into account seropositivity or serostatus at baseline. The Sanofi Pasteur NS1 Supplemental Study analysis was published last year in the *New England Journal of Medicine* (*NEJM*) by serostatus. Regarding the 14 deaths in the Philippines, the vaccine was approved for use in the Philippines in 2015. They followed the WHO recommendations and the recommendations of their own regulatory agencies. They conducted various vaccination campaigns with approximately 800,000 subjects. It took some time for Sanofi Pasteur to make information public because they had to develop the assay and produce the analysis. The license was suspended for a while, and then it was withdrawn completely. The issue was that the Philippines reported some deaths that they said were associated with the vaccine. But it was very difficult to get a clear association with the vaccine, and most of the deaths were not biologically confirmed dengue. They reported the cases but did not have virologic confirmation sometimes. There are not sufficient data to assess the cases completely.

Dr. Maldonado indicated that she worked with the Philippine Pediatric Society (PPS) on this issue, and they had a huge antivaccine response because of this. Whether it is true or not, each of the children had a code number and were being followed by the government. These children clearly received vaccine or placebo. When she talked to the Ministry of Health and WHO, they all had different stories about how they were investigating the deaths. She wondered how Sanofi Pasteur handled this.

Dr. Dayan responded that these children received the vaccine, because they were vaccinated during the campaign. The problem was to identify whether the deaths were or were not related to the vaccine. A special WHO Advisory Committee on Safety looked into the cases, but could not draw a finite conclusion. Of course, any death is a problem and Sanofi Pasteur feels very sad about that.

Dr. Maldonado emphasized that he did not mention them at all during his presentation. She apologized for belaboring this, but 14 deaths is a big deal. Those children received the vaccine and he could have calculated a comparison with children who did not receive the vaccine. Dr. Messonnier said she thought Dr. Maldonado was recommending that the ACIP WG review those original data.

Dr. Maldonado indicated that there are two good papers and additional information about what happened can be found on the WHO website.

Dr. Stephens asked whether Dr. Dayan could provide the immunological thinking about why this vaccine is protective in those who have had prior disease versus the younger group.

Dr. Dayan indicated that secondary infections are related to more severe disease. This is based on different theories, but is not entirely clear. It is thought to be due mainly to ADE. There is an increase of antibody titers after the first infection that are protective to that serotype. There also is cross-reactive protection against other serotypes, but in short duration. When the heterotypic response starts to decrease, the risk of more severe disease increases through different mechanisms that triggers an immune response that produces plasma leakage. This is the immunological pathogenesis. It is thought that when the vaccine is given to seronegative subjects, they are being infected for the first time and creating a primary infection. Therefore, they will be at risk of more severe disease when they have a secondary infection. For a person who has been infected previously, vaccination would be a secondary infection and would decrease the risk of hospitalization and induce efficacy to protect against future infections.

Dr. Cohn inquired as to what number of the approximately 25,000 children in the pooled data were from Puerto Rico versus other countries and how generalizable these data actually would be to children living in Puerto Rico.

Dr. Dayan indicated that approximately 1300 subjects were recruited in Puerto Rico. There were two sites, one in San Juan and one in the Southern part of the island in Guayama. The demographic characteristics were fairly similar. The efficacy of the vaccine was about 94%. The confidence intervals were wide because there were not many cases, but it is very comparable. There were not enough hospitalized cases to assess.

Dr. Messonnier requested confirmation that while the vaccine is licensed in other countries, no country is currently routinely using it and that no country has implemented vaccination specifically the way that the FDA recommended it for use in the US. Therefore, ACIP would

have to make its recommendations based on the available data as no additional data will be forthcoming.

Dr. Dayan indicated that different countries had different indications. In the beginning, there was an indication for the entire population. When Sanofi Pasteur realized that there was a safety signal and the problem with those who were seronegative, they informed all of the regulatory authorities and they began to update their recommendations. Most of the updated recommendations included the clause of having seropositivity to be eligible for vaccination. The vaccine is now available in the private market where the vaccine is recommended. At this point, there are no ongoing vaccination campaigns. If the vaccination indication has been updated in a country, they have to follow the new indication.

It sounded to Dr. Hunter that ACIP would be asked to vote on a scenario such as operationalization in Puerto Rico, with a test that's sensitivity produces false negatives and false positives with a turnaround time of two weeks, and which has never been done anywhere else. He did not find this very reassuring as a voting member and thought it would be more reassuring to have additional evidence before ACIP votes on this.

Dr. Dayan said that at this point, they were trying to discuss what would be the potential ways to use the vaccine in a setting such as Puerto Rico. They have been in discussions with the ACIP WG and the regulatory authorities in Puerto Rico to determine how this could be implemented because they have some laboratory testing that could be used with the system that Dr. Paz-Bailey explained. Sanofi Pasteur acknowledges that this is difficult to implement. They also have some materials, HCP guidelines, and an online training program that potentially could be used by HCP, because they want this to be very clear to the HCP who would be administering the vaccine. The plan is to make the new information available to everyone as soon as possible. They are analyzing additional data from the NS1 analysis.

Dr. Atmar pointed out that the WG already had begun to struggle with this key issue and would continue to assess it over the coming months. The WG will present to the full committee the results of its struggle with this question. Ultimately, he thought it would strongly influence the assessments that ACIP has on the potential utility of the vaccine.

Dr. Hunter pointed out that he was coming at this from the perspective of working at a local or state health department where the CDC cannot help them unless invited to do so. If Puerto Ricans in some fashion were strongly demanding this and were willing to take the risks because they felt that it would benefit them, that would change his opinion.

Dr. Romero emphasized the importance of the voting members airing their questions now, because this will be very difficult.

Dr. Ezeanolue requested clarification regarding whether administering the vaccine to a seronegative individual would place them at increased risk for infection or at increased risk for side effects.

Dr. Dayan said that Sanofi Pasteur asserts that when seronegative subjects receive the vaccine, they have an increased risk of hospitalization and to have more severe disease. "Severe disease" was classified by an Independent Data Monitoring Committee (IDMC) as increased risk of hospitalization and severe dengue.

Dr. Ezeanolue emphasized that he would consider increased risk of hospitalization to be a side effect, and that if a seronegative person gets the disease after having the vaccination, it would be more severe.

Dr. Dayan indicated that VE also was not good for those who were seronegative. For example, VE was about 38% to 39% among seronegative subjects who were more than 9 years of age. However, the confidence intervals were very wide. VE in those less than 9 years of age was lower and the vaccine was not very efficacious in that particular group of seronegatives. On top of that, there was increased risk of severe disease.

Dr. Moore requested further information about the allergic reactions that were observed in the post-marketing surveillance.

Dr. Dayan replied that the reaction were typically associated with associated with the standardized MedDRA query that they used to group all of the reactions. While he did not have the complete list, he recalled that they were related to rash, skin reactions, et cetera. They have a protocol to follow these subjects. These were considered potential allergic reactions, but none of them were anaphylactic reactions. This was done during the pre-clinical and clinical studies, and also was detected in the post-marketing experience. The anaphylactic reactions did not occur in the clinical studies, but were observed during the post-marketing experience. That is why they were included in the indication.

Dr. Ault asked whether VAERS is friendly to Spanish-speakers.

Dr. Shimabukuro indicated that the website, guidance, instructions, and 1-800 number for reporting are available in Spanish. The report form itself is in English for multiple reasons, such as difficulties with MedDRA coding. There are plenty of opportunities to take a report from someone who speaks Spanish as their first language.

Dengue Virus Vaccines

Steve Waterman, MD, MPH
Chief, Dengue Branch
Centers for Disease Control and Prevention
San Juan, Puerto Rico

Dr. Waterman summarized the Dengue Vaccines WG's considerations to date and next steps for ACIP toward making a recommendation regarding DENGVAXIA®. The FDA approved indication recommended by the VRBPAC and announced in May 2019 for DENGVAXIA® is for children 9-16 years of age who have a laboratory-confirmed previous dengue infection and live in an endemic area such as the US territories of American Samoa, Guam, Puerto Rico, and the US Virgin Islands.

The Dengue Vaccines WG drafted the following policy question to guide the EtR Framework and the GRADE assessment, "Should 3-doses of CYD-TDV be administered routinely to persons 9-16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas to prevent virologically-confirmed dengue, hospitalizations, and severe dengue?"

As reported by Dr. Paz Bailey, dengue viruses have caused steadily increasing morbidity and mortality worldwide over the last 60 years. In the US territories of Puerto Rico, the US Virgin Islands, and American Samoa, dengue viruses circulate at endemic or virtually endemic levels,

a situation that also applies to two US-affiliated Pacific nations, Palau and the Federated States of Micronesia. Age-specific seroprevalence data are scarce in most of the world, including the US. Higher population prevalence of dengue antibody reduces the likelihood of false positive pre-vaccination screening tests. Based on modeling of DENGVAXIA® impact with Sanofi trial data, the WHO SAGE recommends that countries could consider vaccinating without screening at seroprevalence levels in 9 year olds of at least 80%.

Severe dengue can occur in infants, children, and adults. In the Sanofi trials, severe dengue occurred in about 4% of unvaccinated children with virologically confirmed clinical dengue overall. Severe dengue often manifests as a leaky capillary syndrome, which can lead to shock and death if untreated. Shock from dengue almost always can be successfully managed if monitored for and treated appropriately with fluid replacement. Severe illness can sometimes manifest with GI hemorrhage, liver failure, or meningoencephalitis. Higher risk of leaky capillary syndrome is associated with secondary dengue infections. The proposed pathogenetic mechanism is known as antibody dependent enhancement or ADE. Prospective studies in Nicaraguan children have demonstrated higher risk of this syndrome when heterotypic or cross-reactive dengue antibody levels fall to moderate levels, consistent with the ADE mechanism.

As Dr. Dayan summarized with regard to the long-term Phase III trial data for DENGVAXIA®, in seropositive children 9-16 years, the vaccine is about 75% efficacious against virologically-confirmed symptomatic dengue with higher levels of protection for hospitalization and severe illness. The vaccine is effective against all four serotypes in seropositives. The highest efficacy is for the dengue 4 virus serotype. Depletion antibody studies by Dr. DeSilva at the University of North Carolina showed that DENGVAXIA® produces high levels of homotypic antibody for dengue 4 compared to the other serotypes.

However, in seronegatives the risk of hospitalization is higher in vaccinated children with a hazard ratio of 1.41 and a hazard ratio for severe disease of 2.44. Apart from this risk in seronegatives, the clinical trial safety profile data are comparable in vaccinees and controls.

The WG's view is that the quality of these clinical trials is that they are first-rate and the efficacy analyses were conducted to the highest standards. As mentioned by Dr. Atmar earlier, the Dengue Vaccines WG convened last October after over a year's hiatus in dengue vaccine-related discussions as part of the Flavivirus WG. The topics covered during WG meetings over the last 8 months have included the following:

- ❑ CYD-TDV Phase III trials including long-term follow-up and imputed pre-vaccination serostatus analysis
- ❑ Epidemiology of endemic dengue in the US
- ❑ Published dengue vaccine cost-effectiveness studies
- ❑ Clinical dengue and disease severity
- ❑ Review of the EtR and GRADE frameworks
- ❑ Dengue diagnostics and available IgG screening tests and target product profile, with 3 WG meetings on IgG tests that might be used for pre-vaccination screening.
- ❑ CYD-TDV safety and pharmacovigilance

Dr. Robert Luo presented to the WG on a systematic review of 10 published evaluations of 4 rapid diagnostic tests. These tests are not FDA cleared tests, but are available in various parts of the world and could be performed in the US under Clinical Laboratory Improvement Amendments (CLIA) regulations. The sensitivities ranged between 30% and 60%. The specificities ranged between 65% and 100%, with wide confidence intervals. The CDC Dengue

Branch also conducted a preliminary landscape analysis of over 30 rapid diagnostic tests (RDTs) and IgG enzyme-linked immunosorbent assay (ELISA) tests. Both the Luo paper for WHO and the CDC assessment point out that these tests were designed for detecting acute infection, not past infection. The composition of the panels to evaluate these tests does not have information on infections with other flaviviruses or flavivirus vaccinations. Such samples are needed to evaluate cross-reactivity and specificity. Sanofi has identified 3 tests, 2 RDTs and 1 IgG ELISA, that are available in Puerto Rico and American Samoa. One of the RDTs was included in the Luo study. Sanofi evaluated the sensitivity and specificity of these tests with a well-characterized set of 400 samples including YF and JE neutralization test-positives. This evaluation found specificities of >99% for all three tests. When the 3 tests were evaluated with Zika microneutralization test-positive samples, the cross-reactivity was 3% to 13%. The initial 99% did not involve Zika-positive samples. A manuscript on these results is in preparation. Sanofi is co-developing with a biotech company in San Diego an RDT IgG test that could be used for pre-vaccination screening, which they plan to submit for FDA clearance.

WHO also is working on a Target Product Profile (TPP) project. The optimal pre-vaccination screening test would be a low-cost RDT that could be performed on whole blood from a fingerstick sample. The minimum sensitivity and specificity would be >90%. The optimal reference panel would include curated specimens that are positive for dengue, other flavivirus, and dengue plus previous flavivirus samples at varying time points after infection, as well as a variety of flavivirus vaccine recipients.

The WG will be completing the EtR framework and GRADE analyses over the next few months in order to make recommendations to ACIP. The topics covered will include CYD-TDV cost-effectiveness studies, acceptability, implementation issues, and an update of any information available on laboratory tests. In formulating recommendations, the WG will need to consider overall cost-effectiveness given the unusual requirement for pre-vaccination screening, and best information on the sensitive and specificity of available tests. Hopefully, an independent evaluation of available IgG laboratory tests using close to optimum serum panels can be conducted in the near future. The confidence in cost-effectiveness and predictive value estimates will improve with updated population representative seroprevalence data. CYD will clearly need to be explained to the population through immunization program outreach and implemented with carefully vetted informed consent language. It will be necessary to determine what the feasible logistics are of pre-vaccination screening in the US territories, and whether there is a strong territorial program for vaccinating school age children. With better seroprevalence data, the optimal age for vaccination might need to be adjusted. It also seems worth considering identifying subpopulations living in the US from endemic areas who frequently return to endemic areas to visit friends and relatives (e.g., Puerto Ricans in Florida and New York or Latino populations living on the highly mobile US Mexico border).

Discussion Questions

Dr. Hunter said that Dr. Waterman's summary of what the WG is addressing and thinks that the important issues are was very reassuring to him. The goal of achieving >90% sensitivity and specificity is key, though it will likely be quite a challenge. It would be nice to have some hard data on whether that works in an implementable way.

Dr. Romero asked whether a higher level of informed consent would be required and if so, what the impact of this would be on patient/physician interaction.

Dr. Messonnier asked whether the local AAP chapter was involved in these discussions. Clearly, a major issue regarded the feasibility of implementation in Puerto Rico. Using all of the appropriate channels to answer that question seems quite important.

Dr. Kimberlin (AAP) responded that they had not begun those conversations yet, but this presentation would give them the opportunity to do so during AAP's Fall Committee on Infectious Diseases (COID) meeting. They also have a liaison representative on the Sociedad Latinoamericana de Infectologia Pediatrica (SLIPE), which is the Latin American Society of Pediatric Infectious Diseases. The SLIPE representative is Puerto Rican. He thought the recommendation to obtain more input from people who live in the areas that would be impacted by the recommendations was a fantastic suggestion.

Dr. Talbot thought it would be helpful for ACIP for someone other than Sanofi Pasteur to review what occurred in the Philippines in order to answer the pending questions and put some of the concerns to rest.

Certification

Upon reviewing the foregoing version of the June 26-27, 2019 ACIP meeting minutes, Dr. José Romero, ACIP Chair, certified that to the best of his knowledge, they are accurate and complete. His original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

ACIP Membership Roster

Department of Health and Human Services
Centers for Disease Control and Prevention
Advisory Committee on Immunization Practices
November 2018 – June 30, 2019

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

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

EZEANOLUE, Echezona, MD, MPH
Professor of Pediatrics and Public Health
Department of Epidemiology and Biostatistics
Director, Global Health and Implementation Research Initiatives
University of Nevada
Las Vegas, NV
Term: 07/01/2015-06/30/2019

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

GRAVENSTEIN, Stefan, MD, MPH
Professor of Medicine and Health Services Policy and Practice
Brown University
Associate Director, Center of Innovation for Long-Term Care Services and Supports
Providence Veterans Administration Hospital
Providence, RI
Term: 10/26/18 - 6/30/2022

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

MOORE, Kelly, MD, MPH,
Assistant Clinical Professor, Department of Health Policy
Vanderbilt University School of Medicine
Nashville, TN
Term: 07/01/2015-06/30/2019

STEPHENS, David, MD
Professor of Medicine, Division of Infectious Diseases
Chair, Department of Medicine
Emory University School of Medicine
Emory University
Atlanta, GA
Term: 07/01/2015-06/30/2019

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

WALTER, Emmanuel (Chip), Jr., MD, MPH
Professor of Pediatrics
Duke University School of Medicine
Durham, NC
Term: 07/01/2015-06/30/2019

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)
DEUSSING, ERIC, MD, MPH
Commander, Medical Corps, United States Navy
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)
NAIR, Narayan, MD
CAPT, USPHS
Division Director/Chief Medical Officer
Division of Injury Compensation Programs
Healthcare Systems Bureau
Rockville, MD

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

National Vaccine Program Office (NVPO)
BECKHAM, Tammy
Acting Director

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

LIAISON REPRESENTATIVES

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

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

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

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

American College Health Association (ACHA)
EVEN, Susan, MD
Executive Director
Student Health Center
University of Missouri
Columbia, MO

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)
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)
NETOSKIE, Mark J., MD, MBA
Market Medical Executive, CIGNA
Houston, TX

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

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

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

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

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

Association of Immunization Managers (AIM)
FINLEY, Christine, RN, MPH
Immunization Program Manager
Vermont Department of Health
Burlington, VT

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)
SMITH, Nathaniel, MD, MPH
Director and State Health Officer
Arkansas Department of Health
Little Rock, AR

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

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

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

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

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

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

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

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

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

National Immunization Council and Child Health Program, Mexico
DURAN, Luis, MD
Director, Center for Children and Adolescent Health (CeNSIA)
Ministry of Health / Secretaría de Salud
Mexico

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

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

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

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

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

Society for Healthcare Epidemiology of America (SHEA)
WEBER, David, MD, MPH
Professor of Medicine, Pediatrics, and Epidemiology
University of North Carolina Schools of Medicine and Public Health
Medical Director, Hospital Epidemiology and Occupational Health, UNC Health Care
University of North Carolina
Chapel Hill, NC