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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
June 20-21, 2018
Atlanta, Georgia

Table of Contents	Page
Agenda	4-5
Acronyms	6-10
Wednesday: June 20, 2018	
Welcome and Introductions	11-17
Influenza • Introduction • VE Update • 2017-2018 Influenza Season Vaccine Safety Update • Narcolepsy following Adjuvanted Monovalent Pandemic H1N1 Influenza Vaccine: Results of the SOMNIA Study • Study Results of an Adjuvanted Quadrivalent Influenza Vaccine in Young Children • 2018-2019 Recommendations • Public Comment • Vote	18-42
Anthrax Vaccines • Introduction • GRADE • Summary of Work Group Considerations and Proposed Policy Options • Public Comment • Vote	42-57
HPV Vaccines • Introduction • Current Issues and Background • HPV Vaccine in Mid-Adults: Results from Clinical Studies • Considerations and Work Group Plans	57-73
Update on NITAGS • Introduction • Global NITAG Activities and the GNN	73-78
Mumps Vaccine • Introduction • Current US Mumps Epidemiology and CDC Guidance for Implementation of the ACIP Recommendation for a 3rd Dose of MMR Vaccine During Outbreaks	78-84
Zoster Vaccine • Introduction • Herpes Zoster Vaccination Evaluation Update	84-87
Public Comment	87-91

Thursday: June 21, 2018	
Agency Updates • Centers for Disease Control and Prevention (CDC) • Department of Defense (DoD) • Department of Veteran's Affairs (DVA) • Food and Drug Administration (FDA) • Heath Resources and Services Administration (HRSA) • Indian Health Services (I HS) • National Institutes of Health (NIH) • National Vaccine Advisory Committee (NVAC) • National Vaccine Program Office (NVPO)	91-96
Japanese Encephalitis Vaccine • Introduction • JE-VC GRADE • Comparative Analysis Background • Comparative Analysis of JE Vaccination Strategies • Summary and Conclusions	96-112
Pneumococcal Vaccines • Introduction • Safety of PCV13 in Adults Ages >65 Years Old • Pneumonia Incidence in the US • Pneumococcal Carriage, Invasive Disease, and Hospitalizations Following Community-Acquired Pneumonia (CAP) among Native American Populations • Racial disparities in Invasive Pneumococcal Disease and PCV13 Impact • Overview of the Evidence to Recommendations Framework (EtR) for the Ongoing Review of the PCV13 Recommendation for Adults ≥65 Years Old	112-134
Vaccine Supply	134-135
Public Comment	135-139
Certification	140
Membership Roster	141-149
Attachment A: Public Comment Letters Submitted	150-155

Final - June 13, 2018

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 20-21, 2018

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
Wednesday, June 20			
8:00	**Welcome & Introductions**		Dr. Nancy Bennett (ACIP Chair) Dr. Amanda Cohn (ACIP Executive Secretary; CDC)
8:30	**Influenza Vaccines**		
	Introduction		Dr. Chip Walter (ACIP, WG Chair)
	VE update		Dr. Brendan Flannery (CDC/NCIRD), Dr. Yun Lu (FDA)
	2017-2018 influenza season vaccine safety update	Information & Discussion	Dr. Tom Shimabukuro (CDC/NCEZID)
	Narcolepsy following adjuvanted monovalent pandemic H1N1 influenza vaccines: Results of the SOMNIA study		Dr. Tom Shimabukuro (CDC/NCEZID)
	Study results of an adjuvanted Quadravalent Influenza vaccine in young children		Dr. Gregg Sylvester (Seqirus)
	2018-19 recommendations		Dr. Lisa Grohskopf (CDC/NCIRD)
	Public Comment		
	Vote	**Vote**	Dr. Lisa Grohskopf (CDC/NCIRD)
10:40	***Break***		
11:00	**Anthrax Vaccines**		
	Introduction		Dr. David Stephens (ACIP, WG Chair)
	GRADE	Information & Discussion	Dr. William Bower (CDC/NCEZID)
	Summary of Work Group considerations and proposed policy options		Dr. William Bower (CDC/NCEZID)
	Public comment		
	Vote	**Vote**	Dr. William Bower (CDC/NCEZID)
12:15	***Lunch***		
1:30	**HPV Vaccines**		
	Introduction	Information & Discussion	Dr. Peter Szilagyi (ACIP, WG Chair)
	Current issues and background		Dr. Lauri Markowitz (CDC/NCIRD)
	HPV vaccine in mid-adults: results from clinical studies		Dr. Alain Luxembourg (Merck)
	Considerations and Work Group plans		ACIP HPV Vaccines Workgroup
2:40	**Update on NITAGS**		
	Introduction	Information	Dr. Abigail Shefer (CDC/GID)
	Global NITAG activities and the GNN		Dr. Joachim Hombach (Executive Secretary SAGE, WHO IVB)
3:10	***Break***		
3:40	**Mumps Vaccine**		
	Introduction	Information & Discussion	Dr. Kelly Moore (ACIP, WG Chair)
	Current US mumps epidemiology and CDC guidance for implementation of the ACIP recommendation for a 3rd dose of MMR vaccine during outbreaks		Dr. Mariel Marlow (CDC/NCIRD)
4:10	**Zoster Vaccine**		
	Introduction	Information	Dr. Edward Belongia (ACIP, WG Chair)
	Herpes Zoster vaccination: evaluation update		Dr. Kathleen Dooling (CDC/NCIRD)
4:35	**Public Comment**		
4:50	**Adjourn**		

page 1 of 2

Final - June 13, 2018

Thursday, June 21

8:00	**Agency Updates & Unfinished Business**		
	CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NIH, NVPO	Information	Dr. Nancy Messonnier (CDC/NCIRD); *Ex Officio* Members
8:30	**Japanese Encephalitis Vaccine**		
	Introduction	Information & Discussion	Dr. Chip Walter (ACIP, WG Chair)
	JE-VC GRADE		Dr. Susan Hills (CDC/NCEZID)
	Comparative analysis background		Dr. Marc Fischer (CDC/NCEZID)
	Comparative analysis of JE vaccination strategies		Dr. Martin Meltzer (CDC)
	Summary and conclusions		Dr. Susan Hills (CDC/NCEZID)
10:30	***Break***		
11:00	**Pneumococcal Vaccines**		
	Introduction	Information & Discussion	Dr. Grace Lee (ACIP, WG Chair)
	Safety of PCV13 in adults aged >65 years old		Dr. Tom Shimabukuro (CDC/NCEZID)
	Pneumonia Incidence in the US		Dr. David Swerdlow (Pfizer)
	Pneumococcal carriage, invasive disease, and hospitalizations following community acquired pneumonia (CAP) among Native American populations		Dr. Laura Hammitt, Director, Infectious Disease Prevention Program, Center for American Indian Health
	Racial disparities in invasive pneumococcal disease and PCV13 impact		Dr. Almea Matanock (CDC/NCIRD)
	Overview of the Evidence to Recommendations Framework for the ongoing review of the PCV13 recommendation for adults ≥65 years old		Dr. Almea Matanock (CDC/NCIRD)
12:30	**Vaccine Supply**	Information	Dr. Jeanne Santoli (CDC/NCIRD)
12:35	**Public Comment**		
12:45	**Adjourn**		

Acronyms

CDC	Centers for Disease Control & Prevention
CMS	Centers for Medicare and Medicaid Services
DoD	Department of Defense
DVA	Department of Veterans Affairs
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRSA	Health Resources and Services Administration
IHS	Indian Health Service
JE-VC	Vero cell culture-derived Japanese encephalitis
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]
NCI	National Cancer Institute
NIH	National Institutes of Health
NITAG	National Immunization Technical Advisory Groups
NVPO	National Vaccine Program Office
PCV13	13-valent pneumococcal conjugate vaccine
VFC	Vaccines for Children
WG	Work Group
WHO IVB	World Health Organization, Immunization, Vaccines and Biologicals

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core Surveillance
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American Congress of Obstetricians and Gynecologists
ACP	American College of Physicians
ADEM	Acute Disseminated Encephalomyelitis
AE	Adverse Events
AESI	Adverse Events of Special Interest
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
AIM	Association of Immunization Managers
AIP	Arctic Investigations Program
Anti-HBsAg	Hepatitis B Surface Antigen
Anti-PA IgG	Anti-Protective Antigen Immunoglobulin G
AOA	American Osteopathic Association
APhA	American Pharmacists Association
aQIV	Adjuvanted Quadrivalent Influenza vaccine
ARI	Acute Respiratory Illness
ASTHO	Association of State and Territorial Health Officers
ATS	American Thoracic Society
AVA	Anthrax Vaccine Adsorbed
B. anthracis	*Bacillus anthracis*
BARDA	Biomedical Advanced Research and Development Authority
BLA	Biologics License Application
CAIH	Center for American Indian Health
CAP	Community-Acquired Pneumonia
CAPiTA	Community-Acquired Pneumonia Immunization Trial in Adults
CBER	Center for Biologics Evaluation and Research
ccIIV4	Cell-Culture Quadrivalent Vaccine
CDC	Centers for Disease Control and Prevention
CICP	Countermeasures Injury Compensation Program
CIN2+	Cervical Intraepithelial Neoplasia Grade 2 or Worse
CISA	Clinical Immunization Safety Assessment
CLD	Chronic Liver Disease
CME	Continuing Medical Education
CMS	Center for Medicare and Medicaid Services
CNS	Central Nervous System
COI	Conflict of Interest
COID	Committee on Infectious Diseases (AAP)
COPD	Chronic Obstructive Pulmonary Disease
CSELS	Center for Surveillance, Epidemiology, and Laboratory Science
CSF	Cerebrospinal Fluid Leak
CSTE	Council of State and Territorial Epidemiologists
CVD	Cardiovascular Disease
CWF	Common Working File

CXR	Chest X-Ray
DICP	Division of Injury Compensation Programs
DMSS	Defense Medical Surveillance System
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DPEI	Division of Preparedness and Emerging Infections
D-QIV	Fluarix® Quadrivalent
DSMB	Data Safety Monitoring Board
DTaP	Diphtheria and Tetanus Toxoid and Pertussis
DVA	Department of Veterans Affairs
ED	Emergency Department
EDS	Excessive Daytime Sleepiness
EGL	External Genital Lesions
EHR	Electronic Health Record
EMA	European Medicines Agency
EMR	Electronic Medical Record
EPI	Expanded Programme on Immunization
EPIC	Etiology of Pneumonia in the Community
EtR	Evidence to Recommendation
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FFS	Medicare Fee-For-Service
FQHC	Federally Qualified Health Center
FUTURE	Females United to Unilaterally Reduce Endo/Ectocervical Disease Study
GAVI Alliance	Global Alliance for Vaccines and Immunisation
GBS	Guillain-Barré Syndrome
GCC	(Tom Harkin) Global Communications Center
GID	Global Immunization Division
GMT	Geometric Mean Titers
GNN	Global NITAG Network
GPRA	Government Performance Results Act
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
GVAP	Global Vaccine Action Plan
HAIVEN	Hospitalized Influenza Vaccine Effectiveness Network
HCAP	Healthcare-Associated Pneumonia
HCP	Healthcare Personnel / Providers
HCW	Healthcare Workers
HEMU	Health Economics Modeling Unit
HELLP	Hemolysis, Elevated Liver Enzymes, and Low Platelet Count
HepA	Hepatitis A
HepB	Hepatitis B
HHS	(Department of) Health and Human Services
HI	Hemagglutinin Inhibition
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HQ	Headquarters
HRSA	Health Resources and Services Administration
HZ	Herpes Zoster

IAC	Immunization Action Coalition
ICD	International Classification of Diseases
ICAN	Informed Consent Action Network
ICER	Incremental Cost-Effectiveness Ratio
IDSA	Infectious Disease Society of America
Ig	Immunoglobulin
IHS	Indian Health Service
IIS	Immunization Information Systems
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
ILINet	Influenza-like Illness Surveillance Network
IM	Intramuscular
IND	Investigational New Drug
IPD	Invasive Pneumococcal Disease
IPTW	Inverse Probability of Treatment Weighting
IPV	Inactivated Polio Vaccine
ISD	Immunization Services Division
ISO	Immunization Safety Office
IPTW	Inverse Probability of Treatment Weighting
JE	Japanese Encephalitis
JE-MB	Inactivated Mouse Brain-Derived JE Vaccine
JE-VC	Inactivated Vero Cell Culture-Derived JE Vaccine
JID	*Journal of Infectious Diseases*
LAIV	Live Attenuated Influenza Vaccine
LD_{50}	Median Lethal Dose
LLR	Log Likelihood Ratio
LTFU	Long-Term Follow-Up
MAE	Medically Attended Adverse Event
MAM	Mid-Adult Men Study
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Measles, Mumps and Rubella
MMWR	*Morbidity and Mortality Weekly Report*
NMNH	National Museum of National History
MPA	(Swedish) Medical Products Agency
MSLT	Multiple Sleep Latency Test
MSM	Men Who Have Sex With Men
NACCHO	National Association of County and City Health Officials
NAIIS	National Adult and Influenza Immunization Summit
NAP	National Action Plan
NAPNAP	National Association of Pediatric Nurse Practitioners
NAS	National Academy of Sciences
NCCPE	National Certification Committee for Polio Eradication
NBPP	Non-Bacteremic Pneumococcal Pneumonia
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHS	National Center of Health Statistics
NCI	National Cancer Institute
NCIRD	National Center for Immunization and Respiratory Diseases
NDD	Neurodevelopmental Disorder
NFID	National Foundation for Infectious Diseases

NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHP	Non-Human Primate
NIAC	National Immunization Advisory Committee (China)
NIAID	National Institute of Allergy and Infectious Diseases
NIC	National Immunization Conference
NIH	National Institutes of Health
NIPH	National Institute of Public Health (Poland)
NITAGs	National Immunization Technical Advisory Groups
NNDSS	National Notifiable Diseases Surveillance System
NNV	Number Needed to Vaccinate
NOCD	New Onset Chronic Diseases
NP	Nasopharyngeal
NRC	NITAG Resource Center
NTTO	National Travel and Tourism Office
NVAC	National Vaccine Advisory Committee
NVC	National Verification Committee for Measles and Rubella
NVPO	National Vaccine Program Office
NVT	Non-Vaccine Types
OBE	Office of Biostatistics and Epidemiology
OB-GYNs	Obstetrician-Gynecologists
OID	Office of Infectious Disease
OM	Otitis Media
OP	Oropharyngeal
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PEP	Post-Exposure Prophylaxis
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
PIVI	Partnership for Influenza Vaccine Introduction
PrEP	Pre-Exposure Prophylaxis
PRNT	Plaque Reduction Neutralization Test
PT	Preferred Terms (MedDRA)
QALY	Quality-Adjusted Life-Year
QIV	Quadrivalent Influenza Vaccine
Q-QIV	FluLaval® Quadrivalent
RA	Rheumatoid Arthritis
RAVIN	Rotavirus Accelerated Vaccine Introduction Network
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
REM	Rapid Eye Movement
RITAG	Regional Immunization Technical Advisory Group
RIV	Recombinant Influenza Vaccine
ROA	Route of Administration
RR	Relative Risk
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
RZV	Recombinant Zoster Vaccine
RVE	Relative Vaccine Effectiveness

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
sBLA	Supplemental Biologics License Application
SC	Subcutaneous
SCRI	Self-Controlled Risk Interval
SEED	Study to Explore Early Development
SES	Socioeconomic Status
SFHR	Small Fragment Homologous Replacement
SLE	Systemic Lupus Erythematosus
SMD	Standardized Mean Difference
SME	Subject Matter Experts
SOMNIA	Systematic Observational Method for Narcolepsy and Influenza Immunization Assessment
SQ	Subcutaneous
SSD	Shared Systems Data
SSUAD	Serotype-Specific Urinary Antigen Detection
STI	Sexually Transmitted Infection
TA	Technical Assistance
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis
TIV	Trivalent Influenza Vaccine
UAD	Urinary Antigen Detection
UAT	Urinary Antigen Test
UK	United Kingdom
UNICEF	United Nations Children's Fund
US	United States
USPHS	US Public Health Service
USPRT	Updating Sequential Probability Ratio Test
US Flu VE	US Influenza Vaccine Effectiveness Network
USUHS	Uniformed Services University of the Health Sciences
VA	(US Department of) Veteran's Affairs
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VFC	Vaccines For Children
VICP	Vaccine Injury Compensation Program
VLP	Virus-Like Particles
VRBPAC	Vaccine and Related Blood Products Advisory Committee
VSD	Vaccine Safety Datalink
VT	Vaccine Type
VT-CAP	Vaccine-Type Community-Acquired Pneumonia
VTEUs	Vaccine and Treatment Evaluation Units
WG	Work Group
WHO	World Health Organization
VIS	Vaccine Information Sheet
ZVL	Zoster Vaccine Live

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

Nancy Bennett, MD, MS
ACIP Chair

Amanda Cohn, MD
Executive Secretary, ACIP / CDC

Dr. Bennett called to order the June 2018 Advisory Committee on Immunization Practices (ACIP) and welcomed those present, noting that it was her great honor to use the Stanley Plotkin gavel to open the meeting.

Dr. Cohn welcomed everyone to the June 2018 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 then recognized others in the room who were to be present throughout the duration of the meeting to assist with various meeting functions: Ms. Stephanie Thomas and Ms. Natalie Greene.

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. Slides presented during this meeting will be posted on the ACIP website approximately two weeks after the meeting concludes after being made visually accessible to all viewers, including the visually disabled. The live webcast will be posted within four weeks following the meeting, and the meeting minutes will be available on the website within approximately 90 days following the meeting.

The next ACIP meeting will be convened at the Centers for Disease Control and Prevention (CDC) on Wednesday and Thursday, October 24-25, 2018. Registration for all meeting attendees is required and may be completed online at www.cdc.gov/acip. The registration deadline for Non-United States (US) citizens is September 26, 2018 and for US citizens registration closes October 10, 2018. Registration is not required for webcast viewing. As a reminder for non-US citizens attending ACIP meetings, completion of several forms is required for each meeting at the time of registration. It is important that these forms are submitted within the required time frame. Stephanie Thomas, the ACIP Committee Management Specialist, will be able to assist with any questions about the process.

The following guests, members, Liaisons, and *Ex-Officio* representatives were identified:

Guests

- ❑ Dr. Joachim Hombach, Executive Secretariat, World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE)

- ❑ Iwona Paradowska-Stankiewicz, Deputy Head of Epidemiology Department, Head of the Vaccine Preventable Disease Unit, Poland National Institute of Public Health (NIPH)

Liaison Representatives

- James Campbell, MD, FAAP representing the American Academy of Pediatrics (AAP) Committee on Infectious Diseases (COID)

Ex-Officio Members

- Dr. John Beigel, Associate Director for Clinical Research, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), is a new member representing the National Institutes of Health (NIH)
- Dr. Mary Rubin, is a substitute member representing the Health Resources and Services Administration (HRSA)
- Dr. Tom Weiser, Medical Epidemiologist, Northwest Tribal Epidemiology Center, is a new member representing the Indian Health Service (IHS)

Regarding public comments, Dr. Cohn indicated that topics presented during ACIP meetings include open discussion with time reserved for public comment. She explained that time for public comment pertaining to topics on the agenda was scheduled following the end of the day's sessions, and that time for public comments also would be provided prior to each vote by ACIP to enable these comments to be considered before a vote. People who planned to make public comments were instructed to visit the registration table at the rear of the auditorium where Ms. Stephanie Thomas would record their name and provide information on the process. People making public comments were instructed to provide three pieces of information: name, organization if applicable, and any conflicts of interest (COI). Registration for public comment also was solicited in advance of this meeting through the *Federal Register*. Given time constraints, individuals were asked to limit their public comments to 3 minutes total. Participants unable to present comments during this meeting were invited to submit their comments in writing for inclusion in the meeting minutes.

To summarize COI provisions applicable to the ACIP, 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 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. It is important to note that at the beginning of each meeting, ACIP members state any COIs.

Detailed instructions for submission of names of potential candidates to serve as ACIP members may be found on the ACIP website and inquiries may be emailed to acip@cdc.gov The deadline for consideration of ACIP applications for the Term of July 1, 2019-June 30, 2023 is August 1, 2018. The membership process begins about a year in advance of each new term.

Dr. Bennett conducted a roll call to determine whether any ACIP members had COIs. The following COIs were declared:

- Dr. Belongia declared a conflict with regard to influenza due to research support from Seqirus™.

The Liaison and *Ex Officio* members introduced themselves. A list of Members, *Ex Officio* Members, and Liaisons is included in the appendixes at the end of this document.

Dr. Bennett recognized the following departing ACIP members:

Dr. Ed Belongia

Dr. Belongia has been a stalwart member of the Influenza Workgroup (WG), Chair of the Zoster WG, and an incredible ACIP member. He has been a critical member of the committee, is amazingly insightful, and takes very complex problems and breaks them down into relatively simple but important and critical questions. He also served as one of the leads on two extremely controversial topics in recent meetings.

Dr. Laura Riley

Dr. Riley has served on the Human Papillomavirus (HPV), Cholera, and Respiratory Syncytial Virus (RSV) WGs and as Chair of the Adult Schedule WG. She also has the distinction of being the Chair of a WG that was never created, the Maternal WG. She has brought incredible expertise to ACIP with respect to maternal vaccination, and has clearly articulated what it is like for obstetrician-gynecologists (OB-GYNs) in practice to help ACIP better understand how to implement maternal vaccination in the US. Dr. Riley became “Ms. Zika” a few years ago.

Ms. Cynthia Pellegrini

Ms. Pellegrini has been an incredible consumer representative. She has served on and contributed enormously to the Mumps, Flavivirus, Child/Adolescent Schedule, General Recommendations, and HPV WGs. Most importantly, what Ms. Pellegrini did that has been so critical to ACIP and will stay with them going forward is that she defined this position. There has been a lot of uncertainty over the years about how exactly a consumer representative can help

ACIP, which Ms. Pellegrini made very clear. She was never afraid to ask the hardest questions or “swim against the tide” when necessary.

Departing members offered the following responses on the second day of the meeting, which were incorporated here for continuity:

Ms. Pellegrini: This is hard, right? This is a hard group to leave, not only because you feel like you are doing important and valuable work, but because the people are so amazing. The members of this committee are like a family. We all care so much about each other. I think that shows in the meetings and it shows in the work as well, because it has been an incredible privilege to work with such a group of committed, passionate, brilliant people who care so much about this work and who are doing their level best day in and day out to do the right thing, who want to prevent suffering, who want to help people of all ages, and keep them healthy, and keep them happy, and keep them able to do the things that they want to do in their lives. I think this will always end up being one of the great highlights of my career. The CDC staff is, of course, without parallel. Again, a group of incredibly brilliant, committed, passionate but also compassionate people. It has been an amazing experience. It has been a learning experience. I will never be able to go to the General Muir without looking around and going, “Where is everybody?” Thank you all for your wisdom, for teaching me, for everything you do every day, and for your friendship and your caring.

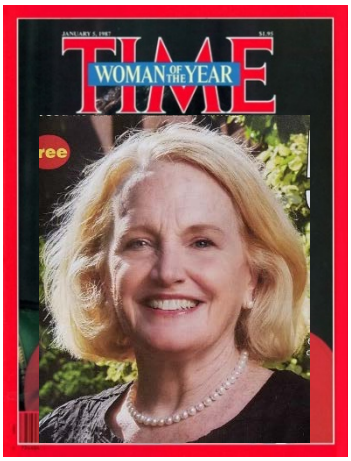
Dr. Riley: Cindy always has been a very hard act to follow, so I won’t even try. But, I too would like to thank everybody on the committee and everybody in this room for the privilege of having this job for 4 years. Prior to this, I spent 4 years on the outer circle and I always was dying to get into the inner circle. Then it’s one of those things where once you get in, you’re like, “What have I been wishing for all along?” One thing that has been really special to me is that I think I have been impressed by how much energy and attention has been paid to pregnancy in the last 10 years, because I think before 2009 I felt like it was a constant fight to bring any pregnancy issues to the forefront. Then after 2009, people woke up. Since then, there’s really been a lot of attention and interested paid to a very special group that has very different physiology. So, for that, I am very, very thankful. It has been a pleasure to be part of that. The other thing that has been an eye-opener to me is that I really didn’t understand the power of public health until I was on the inner circle. I have so much respect for the people at CDC and what they do. It’s incredible that you can manage to make such huge decisions for an entire country, and so that’s been another really important thing to me. When I think about evidence-based medicine and how to apply it, the funny thing is that at the end of the day, I’m sitting in this chair as a mom and as a black woman, and so it has a different picture for me, but it’s incredibly hard to think about the entire population. Thank you for that opportunity.

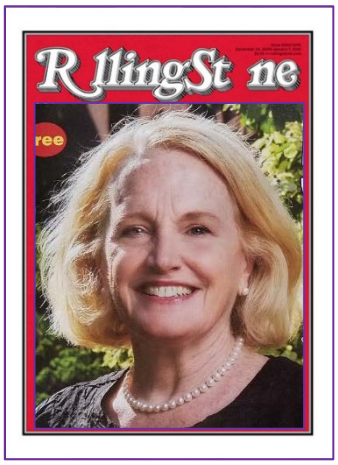
Dr. Belongia: It’s hard to follow two eloquent presentations. I would just say that I echo all of those feelings. What I said yesterday with regard to the WG also applies to my experience more generally as an ACIP member. It has been a tremendous privilege to be working with friends and colleagues, both the members and the CDC staff. I have been incredibly impressed. It’s the highlight of my professional career. I leave knowing that vaccine policy decisions are in really good hands. This is a highly functional federal advisory committee. I don’t think it gets any better than this. Not everybody agrees with the decisions, but I don’t think anybody can make a credible claim that it’s not done clearly, transparently, and openly which is how it should, in fact, work. I have been humbled by the challenge of turning science into policy and making tough decisions with incomplete data. I know that tradition will continue after I leave. I also think we need an ACIP Alumni Association. Thank you.

Dr. Bennett: I completely agree and we're going to make you President. Thank you all so much again and thank you for your service.

Dr. Cohn indicated that in addition to losing three ACIP members, they also would be losing Dr. Bennett after serving 7 years on ACIP. She called upon Drs. Romero and Messonnier to deliver an appreciation presentation for Dr. Bennett. Dr. Romero indicated that Dr. Bennett was an ACIP member from July 2011-June 2015 and ACIP Chair from July 2015-June 2018. As with all high-pressure, high-intensity positions that have the potential to change the applicant, the Chairmanship of ACIP is no exception. However, Dr. Bennett learned the art of leadership and herding cats early in her career as Chief Resident in 1984-1985 in the Department of Medicine, Bellevue Hospital/New York University Medical Center, New York, New York (NY). The skills she developed there contributed to her success as ACIP Chair. In 2006, Dr. Bennett was appointed Director of the Center for Rochester's Health and Prevention. Her many accomplishments over the last 14 years earned her the respect and admiration of a wide audience. Yet, many people cried "foul" when she was asked to grace the cover of *55 Plus Magazine* many years before she met the minimum age requirement:

Dr. Romero said he would venture a guess that this is a high-impact journal based on the article title, "You've Made It: Welcome to Age 66! Big question now: Should you apply for full retirement with the Social Security or wait? See Financial Health column inside." He said he was certain that Dr. Bennett's contributions in public health would continue for years after leaving the ACIP. They will miss her and those who have come to know her well will not be surprised in the very least to see her image on the covers of such notable publications as *Time* and joining such icons as Mick Jagger, Elton John, and Lady Gaga on the cover of the *Rolling Stone*:





Dr. Romero expressed gratitude for all that she has done for ACIP and for keeping them in line.

Dr. Messonnier then recalled that Dr. Bennett started her term as Chair during a time of a lot of change at CDC. Dr. Larry Pickering, who was the Executive Secretary of ACIP for many years, retired. Dr. Anne Schuchat moved into her current role as Principal Deputy Director of the agency, which she held for several months during which multiple individuals served in several acting roles. Through that time, Dr. Bennett's steadying leadership of ACIP was incredibly important. During Dr. Bennett's tenure on ACIP, 60 votes were taken, 19 GRADE presentations were listened to, 44 nights were stayed at the Emory Conference Center, 9 meetings ended on time, 1 luggage mishap occurred, and half of a meeting was cancelled for fear of a "Snowpocalypse."

Throughout this time, ACIP grappled with some incredibly challenging and complex decisions. For example, there was the recommendation for a live attenuated influenza vaccine (LAIV) preference and then new data that led to an unprecedented change in ACIP recommendations over several years. During that time, ACIP also recommended pneumococcal conjugate vaccine for older adults with the caveat that this would be reassessed in 2018, and recommended for the first time a recombinant zoster vaccine with a preference as the first vote. Through all of these decisions, Dr. Bennett pushed ACIP to focus on the data and for ACIP members to listen to each other's perspectives and public comments surrounding these decisions. Dr. Bennett's time at ACIP will be remembered for her intelligence, savvy, and the grace with which she led. Dr. Messonnier expressed gratitude to Dr. Bennett and her husband for giving CDC/ACIP her time and service:

Dr. Cohn presented Dr. Bennett with a bell that came from China. Dr. Bennett was supposed to take a trip there to share her experience as the ACIP Chair with colleagues in China, but was unable to travel due to a family illness. Dr. Cohn also presented Dr. Bennett with a traditional gift for departing ACIP chairs, a framed poster from the childhood immunization campaign using Dr. Seuss, reading, "Healthy birds fly high. Healthy children smile and play. Protect kids from disease. Get them baby shots today. Immunization schedules have changed. Have you got a

clue? Do you know each and every time a baby shot is due? You may have questions. Your doc or nurse will explain. Though the names and timing have changed, the importance is still the same. For protection against serious disease, it's wise to immunize. Complete the full schedule on time and your kids will lead healthier lives."

Dr. Bennett thanked everyone and said she could not begin to tell them all how much this meant and how sad she was to be finishing her term. However, she noted that it was time for "new blood" and that Dr. Romero would do a fantastic job leading them forward. She shared a picture of the Temple of Vaccinia in England at the home of Edward Jenner, who gave cowpox vaccine:

She visited there about six months before she took over as Chair. The people she was visiting in Bristol had no idea she served on the ACIP or was becoming Chair. They coincidentally took her to Jenner's house, which was a wonderful event. Dr. Bennett said the reason she was showing this photograph was because she wanted to reflect for a moment on the work that ACIP does and the fact that it has such a long and amazing history, of which they are all a part. One reason this position has meant so much to her is because she felt like she could play a tiny role in the progression of vaccine science and immunization in this country. It is an incredible history, one that means so much to her, and one in which all members play a critical role.

She emphasized what a huge honor it had been to serve on the ACIP and participate in the decision-making they engage in every time they meet. She thanked the members, liaisons, *Ex Officios,* and especially CDC staff for how much she has learned from them. The other part of this position that was amazing to her was "standing on the shoulder of giants" like Dr. Carol Baker and others before her, from whom she learned every day. She expressed her deep gratitude for being given this opportunity.

Influenza Vaccines

Introduction

Emmanuel (Chip) Walter, MD, MPH
Chair, Influenza Work Group

Dr. Walter reminded everyone that during the February 2018 ACIP meeting there was a presentation from GlaxoSmithKline (GSK) on the results of a randomized controlled trial (RCT) on Fluarix® Quadrivalent for children 6 through 35 months of age, and an update on US influenza surveillance and vaccine effectiveness. In addition, LAIV topics included a presentation from MedImmune on a study of shedding and immunogenicity of LAIV4 containing a new H1N1pdm09-like virus; a presentation of combined US individual-patient level analysis and systematic review of LAIV effectiveness; and a vote for recommendation of use of LAIV4 for the 2018-2019 influenza season.

Since the February 2018 ACIP meeting, the WG has engaged in calls twice a month during which members previewed and discussed the following:

- ❑ US vaccine effectiveness (VE) estimates from CDC on the US Influenza Vaccine Effectiveness (US Flu VE) Network and the US Hospitalized Influenza Vaccine Effectiveness Network (HAIVEN)
- ❑ Food and Drug Administration (FDA) study of relative effectiveness of cell-culture based versus egg-based vaccines
- ❑ 2017-18 influenza vaccine safety surveillance update
- ❑ Seqirus™ study of quadrivalent adjuvanted inactivated influenza vaccine for young children
- ❑ Review and drafting of ACIP recommendations documents for the 2018-19 season

In addition, a Maternal Influenza Immunization Sub-Working group was formed. The purpose of this WG is to provide advice on a study of spontaneous abortion (SAB) following inactivated influenza vaccine (IIV). The WG met for the first time in April to review the protocol for the Vaccine Safety Database (VSD)-SAB study and provided recommendations for secondary and sensitivity analyses. This sub-WG is ongoing.

The agenda for this session included the following topics:

- ❑ VE Update: US Flu VE Network and HAIVEN
- ❑ Relative Effectiveness of Cull-Cultures versus Egg-Based Influenza Vaccines, 2017-2018
- ❑ Influenza End-of-Season Update: 2017-2018 Influenza Vaccine Safety Monitoring
- ❑ Narcolepsy Following Adjuvanted Monovalent Pandemic H1N1 Influenza Vaccines: Results of the Systematic Observational Method for Narcolepsy and Influenza Immunization Assessment (SOMNIA) Study
- ❑ Adjuvanted Quadrivalent Influenza vaccine (aQIV) in young children
- ❑ WG Considerations; 2018-2019 recommendations

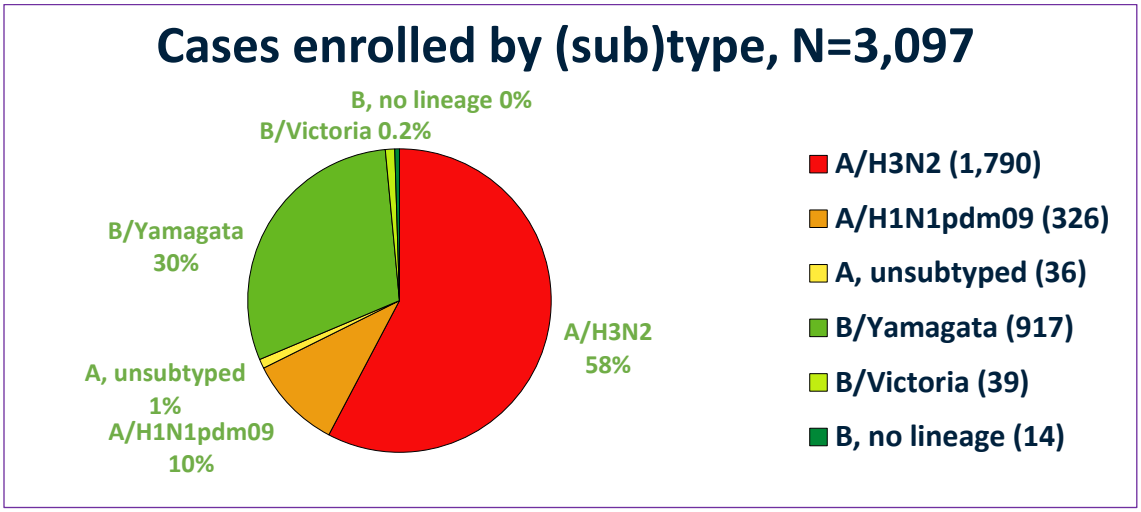
Preliminary Estimates of 2017-2018 Seasonal Influenza Vaccine Effectiveness against Laboratory-Confirmed Influenza from the US Flu VE and HAIVEN Networks

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

Dr. Flannery pointed out that the work on the US Flu VE data analysis was performed by Ms. Jessie Chung, while Jill Ferdinands and Elif Alyanak provided the HAIVEN Network numbers. He then reviewed the preliminary estimates for this season, noting that there would not be a surveillance presentation as there was in February 2018 but emphasizing that 2017-2018 was a high severity season for all age groups based on outpatient visits, hospitalizations, and deaths. The 2009-2010 season reached very high severity for the indicator in children, but other than that there have been several seasons since the 2009 pandemic that reached high severity for the composite indicator. The 2017-2018 season reached high severity for the composite indicator for each age group and all age groups together [Biggerstaff, et al Am J Epi 2018].

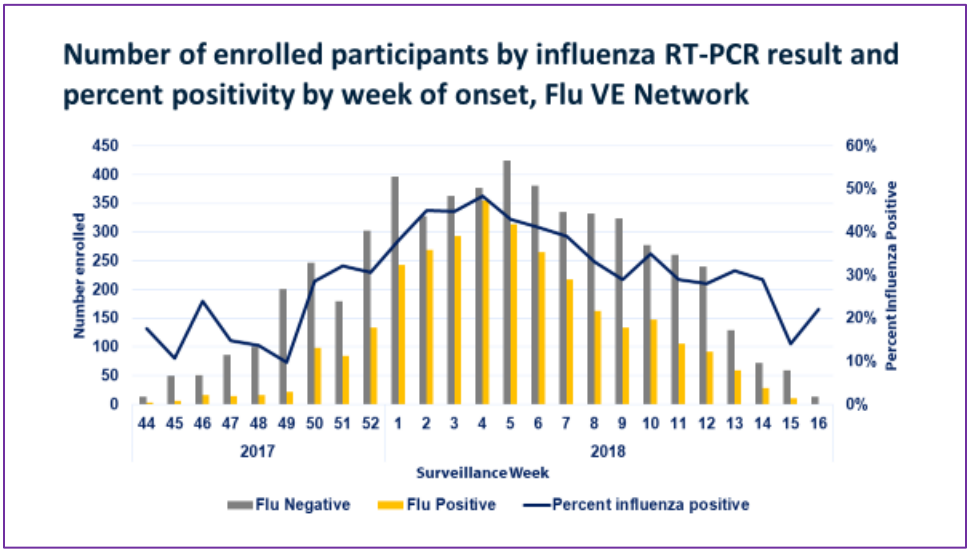
There are 5 collaborating institutions in the US Flu VE Network: Baylor Scott and White Health, Kaiser Permanente Washington, Marshfield Clinic Research Institute, University of Michigan, and University of Pittsburgh. In terms of the Flu VE Network methods, enrollees include outpatients 6 months of age and older with acute respiratory illness (ARI) defined essentially as cough ≤7 days duration. The dates of enrollment for these data are November 2, 2017 through February 3, 2018. This analysis uses a test-negative design that compares vaccination odds among influenza reverse transcriptase polymerase chain reaction (RT-PCR)- positive cases and RT-PCR negative controls. Vaccination status for the interim estimate is defined as receipt of at least one dose of any 2017-2018 seasonal influenza vaccine according to medical records, immunization registries, and/or self-report. VE is calculated as 1 – adjusted odds ratio x 100%. Several variables are included in adjusted estimates: study site, age, self-rated general health status, race/Hispanic ethnicity, interval from onset to enrollment, and calendar time.

From November 2, 2017 through April 20, 2018 there were 8635 total subjects enrolled from the 5 sites who are included in this analysis. Of these, 3097 (36%) were influenza RT-PCR positive and 5538 (64%) were influenza RT-PCR negative. The following pie chart shows cases enrolled by subtype:



There was enough A/H1N1pdm09 (N=326) to have estimates for H1N1 VE, which is notable because this is the first season with the A/Michigan/45/2015 (H1N1)pdm09-like virus strain. Though not as relevant for this presentation, the B/Victoria lineage was the trivalent vaccine lineage for this season.

This graphic shows the enrollment by week. During the middle part of the season, essentially from Week 1 to Week 9, a large number of influenza positives were enrolled:

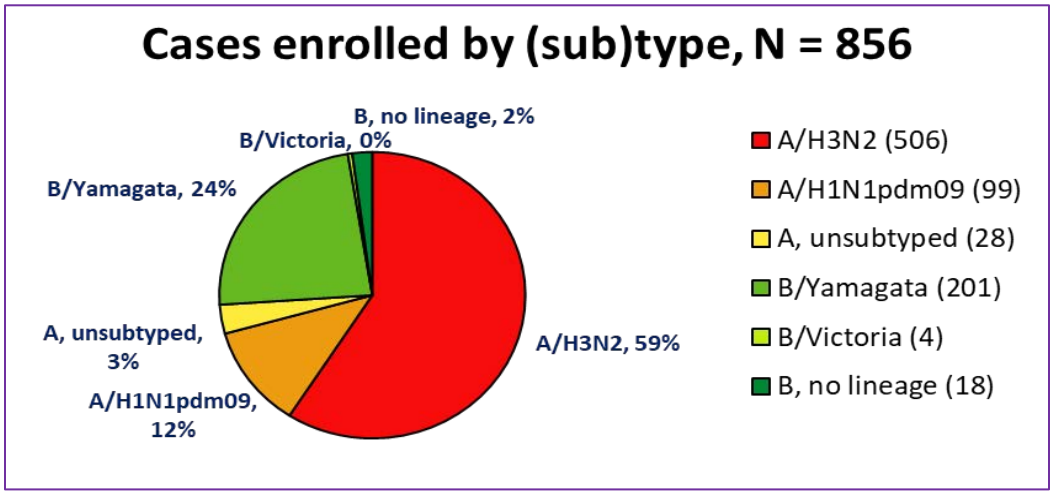


In terms of preliminary VE against medically attended influenza, the number vaccinated among the influenza positive patients was 42% overall for all ages, while the percent vaccinated among the influenza negative patients was about 54%. The unadjusted overall VE was 38% (CI: 32% to 43%) and the adjusted overall influenza VE was 40% (CI: 34% to 46%). The only age group that had a slightly higher VE was 6 months to 8 years of age at 53% (CI: 42% to 62%). All of the other age groups were statistically significant, with the exception of 65 and older for which the estimate was 20% (CI: -9% to 41%). Regarding the subtype-specific estimates, the adjusted VE estimate for A(H3N2) was 24% (CI: 15% to 33%) for any age group. It was higher in the 6 months to 8 years of age group at 37% (CI: 17% to 52%), and was not statistically significant in any of the other age groups from 9 through 17-year olds to 65 years of age and older. For A(H1N1)pdm09, the overall VE was 65% (CI: 55% to 73%). The estimates were higher for all age groups, with the exception of those 65 years of age and older that had an estimate that was not statistically significant. For influenza B/Yamagata, the overall estimate for all ages was 49% (CI: 40% to 56%). Again, the VE for those 65 years of age and older was not statistically significant. While there is not an adjusted estimated for influenza B/Victoria, the crude estimate does not suggest that there is very large difference between B/Yamagata and B/Victoria this season.

Turning to the HAIVEN Network, the 4 sites include: Baylor Scott and White Health, University of Michigan, University of Pittsburgh, and Vanderbilt University Hospital. Enrollees include inpatients 18 years of age and older with ARI with new or worsening cough or sputum production ≤10 days duration. The dates of enrollment are from October 6, 2017 through April 28, 2018, slightly wider than the dates for the Flu VE Network. This analysis uses a test-negative design that compares vaccination odds of influenza among vaccinated and unvaccinated enrollees. Vaccination status for the interim estimate is defined as receipt of at

least one dose of any 2017-2018 seasonal influenza vaccine according to self-report. VE is calculated as 1 – adjusted odds ratio x 100%. Several variables are included in adjusted estimates: age, site, days from illness onset to specimen collection, timing of illness onset, home oxygen use, and number of self-reported hospitalizations in the prior year.

Included in this analysis were 3597 subjects enrolled from October 6, 2017 through April 28, 2018 at 4 sites (10 hospitals). Of those enrolled, 856 (24%) tested positive for influenza by RT-PCR and 2741 (76%) test negative by RT-PCR. This pie graph is similar to what was seen in the Flu VE network, with a very similar distribution of the positives by subtype and lineage:



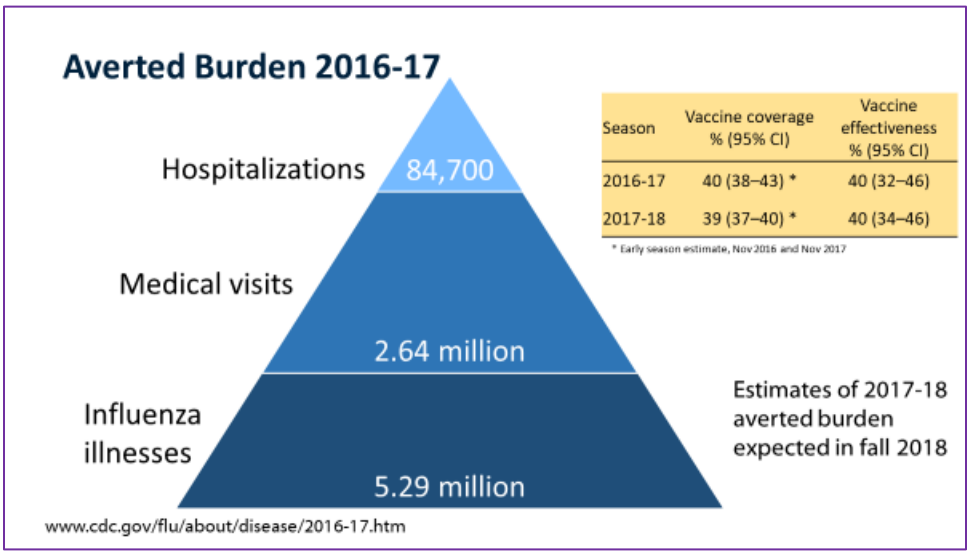
The percentage of all positives for B/Yamagata was slightly lower than for the outpatient setting, while A/H1N1 was very similar to the outpatient setting. The distribution of positives and negatives enrolled by week also was very similar to the outpatient setting, except that the percentage positive reached only 35% at the peak. This is actually very high for inpatients with this sensitive definition of ARI. There also was some positivity for influenza B.

In terms of VE against influenza hospitalization, the overall VE against any influenza in adults was 22% (CI: 8% to 35%). This was statistically significant only in those 50 to 64 years of age at 32% (CI: 9% to 49%), but all of the estimates were quite similar. For influenza A(H3N2), the overall VE estimate was not statistically significant at 16% (CI: -5% to 32%). Again, the VE estimate was statistically significant only for those 50 to 64 years of age at 33% (CI: 2% to 54%). All of these estimates are quite low. For influenza A(H1N1)pdm09, the overall VE estimate was 58% (CI: 36% to 73%). The overall VE estimate for those 65 years of age and older was 69% (CI: 34% to 85%). Recalling the ≥65 age group in the US Flu VE ambulatory data, the estimates were disappointing in the outpatient setting. For some reason that is not yet understood, this actually looks very good in the ≥65 age group in the in-patient setting. For influenza B/Yamagata in the inpatient setting, the overall VE estimate was 35% (CI: 11% to 52%) with very similar estimates by age group, though none were statistically significant.

By having preliminary end-of-season estimates in June for outpatient and inpatient VE networks, it is now possible to compare the results for adults. The VE estimates among inpatients and outpatients were very similar. The take-home message is that the vaccine provides protection not only against outpatient influenza illness, but also against more severe inpatient disease in adults. The estimates for inpatients for those 18 to 49 and ≥65 years of age were not significant, but the point estimates and confidence intervals suggest that these

estimates are very similar for inpatients and outpatients. Vaccine provided very similar protection against inpatient and outpatient disease in adults against A(H3N2), although disappointing, but was much higher in A(H1N1)pdm09 and B/Yamagata for all adult age groups.

In summary, 2017-2018 was an influenza season with high severity. A(H3N2) viruses were the predominant circulating virus. Influenza vaccination reduced outpatient visits for influenza-associated ARI by 40% (CI: 34% to 46%) among persons aged 6 months and older. Among adults, VE estimates were similar for outpatients and inpatients. Vaccination reduced influenza-associated hospitalization among adults by 22% (CI: 8% to 35%). VE estimates against A(H1N1)pdm09 (65%) and B/Yamagata (49%) viruses were higher than VE against A(H3N2) viruses (24%), similar to previous seasons. Final VE results will include VE by vaccine type (standard dose versus high dose IIVs for patients aged ≥65 years) and effects of prior season vaccination. Averted burden estimates will be available in the Fall for the 2017-2018 season and are expected to be greater than what was observed in 2016-2017. The comparative estimates for vaccine coverage and VE for 2016-2017 and 2017-2018 seasons are shown in the upper right of the following graphic. Based on models that CDC has developed, the estimates are very similar and it is known that the actual burden of influenza was much higher in the 2017-2018 season, so higher numbers are expected for averted burden than were observed in the 2016-2017 season:



CDC continues to try to enhance work towards better vaccines and to expand the evidence base, especially for the low VE for the H3N2 virus. Some of the ongoing work includes investigation into the immunologic basis of influenza vaccine failures, including the initiation of collection of acute and convalescent sera from a subset of influenza cases in US VE Network and HAIVEN. One gap in knowledge is the response to natural infections as well as the acute phase response in vaccinated people, which will help to understand vaccine failures. The second activity is increased funding to expand enrollment for US Flu VE and HAIVEN Networks. This will allow for collection of more data, especially by vaccine type, in the 2017-2018 season. That is related to the next activity to expand the evidence base for the contribution of antigen dose, especially in 65 and older, and adjuvants. CDC also hopes to better understand the effects of egg-adaptive changes on VE, which has received a lot of attention from ACIP and the media this year, and determining the differences between egg-based and non-egg vaccines. There are currently too few non-egg vaccines being used in the Flu VE Networks to be able to

provide estimates at this time. Finally, a much larger effort at CDC is ongoing to engineer optimal vaccine viruses that have fewer disruptive egg-adaptive changes.

Relative Effectiveness of Cell-Cultured versus Egg-Based Influenza Vaccines, 2017-2018

Yun Lu, PhD on behalf of the FDA, CMS, and Acumen Team
Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research
Food and Drug Administration

Dr. Lu presented results from a study on the relative effectiveness of cell-cultured versus egg-based influenza vaccines for the 2017-2018 season. This was the joint work of the FDA, Center for Medicare and Medicaid (CMS), and Acumen. A CDC-sponsored interim analysis of the A(H3N2)-dominated 2017-2018 influenza season showed a low VE of 18% among individuals ages ≥65 years in the US. Because most of the influenza vaccines were prepared in chicken eggs, one hypothesis is that egg-adaptation led to lower VE during 2017-2018.

Therefore, the FDA/CMS/Acumen study examined the relative effectiveness of inactivated influenza vaccines prepared in mammalian cells (cell-cultured) versus embryonated chicken eggs (egg-based) among Medicare beneficiaries ages ≥65 years. The observation period was from August 6, 2017 to April 20, 2018. The exposures included 5 types of influenza vaccines: cell-cultured quadrivalent, egg-based quadrivalent, egg-based high-dose trivalent, egg-based adjuvanted, and egg-based standard-dose trivalent. The study population included Medicare fee-for-service (FFS) beneficiaries who received the cell-cultured or any of four egg-based influenza vaccinations. The primary outcome was influenza hospital encounters (inpatient + emergency department (ED)), while the secondary outcome was influenza-related office visits, with related influenza diagnostic testing plus a prescription of antiviral treatment. The post-hoc outcome was influenza inpatient hospitalizations only. All outcomes were monitored during high influenza circulation periods.

In terms of the selection process for beneficiaries included in the study, inclusion and exclusion criteria were applied to a base population of beneficiaries who received any of the five types of influenza vaccines within the specified time period for the season from August 6, 2017 to January 31, 2018. Beneficiaries had to be at least 65 years of age with continuous Medicare Part A/B enrollment for the 6 months prior to their vaccination date, had to have received only one influenza vaccine type on the index day, were not in a nursing home facility on vaccination day, did not receive any influenza vaccine prior to index date in the season, and had to reside in one of the 10 Department of Health and Human Services (HHS) regions. This selection process resulted in the following final study populations:

- ❑ Cell-Cultured Quadrivalent (ccIIV4): N= 653,099
- ❑ Egg-Based Quadrivalent (IIV4): N= 1,844,745
- ❑ Egg-Based High-Dose Trivalent (IIV3-HD): N= 8,449,508
- ❑ Egg-Based Adjuvanted (aIIV3): N= 1,465,747
- ❑ Egg-Based Standard-Dose Trivalent (IIV3): N= 1,007,082

To make sure that the 5 vaccine cohorts were comparable, standardized mean differences (SMDs) were used to determine the cohort balance for 62 covariates. Approximately half of the 62 demographics and health utilization covariates were initially imbalanced. Stabilized inverse probability of treatment weighting (IPTW) was used to address imbalance in all measured covariates. Following IPTW, cohort balance was achieved with SMDs <0.05 for all covariates. This table shows selected covariates that initially were imbalanced before weighting, with those having the largest imbalance shown in red:

Covariates	ccIIV4	IIV4	IIV3-HD	aIIV3	IIV3	*Pre-Weight Max SMD*	*Post-Weight Max SMD*
Vaccinated at Pharmacy	19.2%	**9.2%**	44.4%	67.5%	11.7%	1.39	0.03
Dual Eligible	13.3%	11.3%	**6.9%**	**6.8%**	16.3%	0.22	0.05
Month of Vaccination: August & September	27.4%	26.1%	33.6%	30.9%	22.6%	0.25	0.03
No Prior Outpatient Non-ER Visits	43.5%	**32.2%**	36.9%	40.4%	37.5%	0.14	0.02

To address potential sources of bias, IPTW was used to address imbalance in all measured covariates. IPTW did not necessarily address imbalance for unmeasured potential confounders, an issue often found when real-world data are used. IPTW adjusted relative vaccine effectiveness (RVE) was obtained using univariate Poisson regression.

Regarding the study results, IPTW adjusted Poisson regression RVE was used for both the 2- and 5-vaccine comparisons. The egg-based quadrivalent vaccine cohort was used as the reference group. Cell-cultured quadrivalent vaccine had about 10% RVE for both primary and secondary outcomes. For the 2-vaccine comparison sensitivity analysis, all outcomes had similar results. For the 5-vaccine comparison sensitivity analysis, the primary outcome had similar results. Both the cell-cultured and egg-based high-dose cohorts had better VE compared with the egg-based quadrivalent cohort. The results were not very sensitive to the two sensitivity analyses for the hospital encounters. However, the results were inconsistent for the office visit outcomes. There are possible differences with regard to different health-seeking behaviors, so analyses are currently being performed to investigate the office-based outcome and to compare pharmacy with a non-pharmacy cohort.

Regarding the strengths of the analyses, these real-world data include nearly all of the actual vaccine recipients ages ≥65 nationally. Data reflect the exposure and outcome experiences during routine clinical practice. Unlike clinical trials, Medicare beneficiaries have a wider range of health conditions. The large dataset provides power to detect small but clinically relevant differences and analyze rare serious outcomes. However, there also are limitations. Real-world data are not collected or organized with the goal of supporting research, nor have they typically been optimized for such purposes[1]. There is a potential for exposure and outcome misclassification, as well as unmeasured confounding even after adjusting for measured covariates. Influenza-related office visit results were inconsistent. There was no virologic case confirmation, and it is not possible to differentiate between A(H3N2), A(H1N1), or B infections.

There were processing delays for exposure and outcome codes [N Engl J Med 2016; 375:2293-2297 DOI: 10.1056/NEJMsb1609216].

To summarize, in this analysis, the cell-cultured and high-dose vaccines were marginally more effective than the egg-based quadrivalent vaccines for hospital outcomes among US people ≥65 years during the 2017-2018 season. Cell-cultured vaccines were 10.7% (95% CI 7.5, 13.7) more effective. High-dose vaccines were 8.4% (95% CI 6.6, 10.1) more effective. These findings contribute to a growing evidence base about new and enhanced vaccines compared to traditional vaccines. This is the first comparison of several new and enhanced vaccines to both egg-based traditional vaccines and to each other. RVE will continue to be monitored for additional seasons. Findings from this single observational study should be considered as part of the entire body of evidence. While cell-cultured and high-dose influenza vaccines appear to offer some additional benefit to older adults, further efforts are needed to improve influenza vaccine effectiveness. RVE could vary from season-to-season, so data from more seasons are needed. The results from similar studies conducted in different settings or health systems would provide important context for these results. Investigators continue to investigate ways to minimize and quantify potential sources of bias in real-world evidence studies.

Discussion Points

In response to an inquiry from Dr. Riley regarding whether it was known who in the various cohorts was pregnant, Dr. Flannery replied that they do not collect pregnancy status routinely from all of the sites.

Dr. Riley requested that they begin collecting pregnancy data. She emphasized that it is very difficult to convince patients to receive vaccine when they are never able to say that it is beneficial to them in any way. She pointed out that having some sense of the degree of disease in children less than 6 months of age also would be a reflection of whether maternal immunization is helping.

Dr. Flannery indicated that they have considered collecting information on pregnancy in these networks, including in a pandemic setting, for children less than 6 months of age to examine the effects of maternal vaccination. These may not be the best platforms to be able to do that, because there are not many pregnant women enrolled in the Flu VE Network. This may require a special approach to enroll women from places they would seek care with ARI during pregnancy, and then for special recruitment of young infants.

Fry (SME) agreed that this is difficult in CDC's routine platforms, but they do have some special studies. They have some data with an estimate of VE against hospitalization among pregnant women. This will be presented to the WG during the summer.

In terms of HAIVEN vaccination data all being self-report, Dr. Bennett asked whether there were any plans to change that to have better data on the types of vaccine people receive.

Dr. Flannery indicated that the only reason they present the self-report data now is because self-report is complete for all of the sites. Once they have the final vaccination histories and documentation for this season, the HAIVEN Network will present VE data by vaccine type to the WG.

Dr. Baker (IDSA) requested clarity regarding analysis of the data by high influenza intervals in terms of whether this was all during the dates shown for which influenza was measured. She also asked how the diagnosis of influenza is made in inpatients and outpatients.

Dr. Lu responded that all outcomes were from the high circulation period. They used a 15% cutoff for the percent of tests positive. If they had higher than 15%, this was considered to be a high period and that outcome was recorded. In terms of the diagnosis, international classification of diseases (ICD)-10 codes were used for hospitalization. For the office visits, a different code was used. One thing they looked for was oseltamivir within two days of the test. More inclusion criteria also were applied to the secondary office visit outcomes, because the beneficiary had to have Part D benefits as well.

Dr. Hunter wondered how much they wanted to compare VE between different influenza vaccines, given that from a practical point of view this would change so much from season-to-season. The relative difference between the cell-culture versus egg-based culture vaccine of 10% is pretty small, especially in terms of the absolute difference in order to calculate, from a clinician's point of view, what the number needed to vaccinate (NNV) is. For vaccinated versus not vaccinated, he calculated the NNV to be about 10 to 20 based on the absolute differences that he quickly looked at of 5% to 10% between vaccinated and not vaccinated in the different age groups. It is not clear how they could make a decision in advance of a season if they did not know what the relative difference would be.

Dr. Messonnier pointed out that CDC values ACIP's opinion about how to interpret these data and would be interested in knowing what relevant questions would drive an ACIP decision. Policy-makers throughout this and other countries are interested in knowing what can be done to incrementally improve vaccines given the current technology. CDC counts on ACIP to help CDC hone its thinking. The question regarding NNV is a great way to consider these data.

Dr. Hunter said that while he really wanted to see these data, he did not know whether it would change what he thinks regarding what to do about it.

Regarding the outpatient surveillance definition requiring rapid influenza testing, Dr. Atmar said his health system has removed the ability for outpatient physicians to perform influenza testing because of the poor sensitivity, particularly among adults. He inquired as to whether there was any information about how many individuals had a diagnostic code but did not have a rapid influenza test to support it. Many guidelines recommend that the decision to treat or not to treat be made based on the clinical presentation, not on the diagnostic test because of poor sensitivity.

Dr. Lu responded that they are conducting analyses looking at this, and they have seen some differences regarding the percentage of testing across regions. The results are not ready to present at this time, but they are looking into this.

Regarding the approximately 60 covariates assessed, Dr. Stephens asked whether medications and underlying disease were examined from the perspective of the impact on influenza.

Dr. Lu responded that they did examine underlying health conditions and some medications.

Dr. Lee asked whether the potential impact of the distribution in the vaccines given was being examined. She noticed that the distribution looked very different for the dual eligibles when given in the pharmacy, and wondered whether that led to potential disparities in patient outcomes as a consequence.

Dr. Lu replied that they are currently investigating the pharmacy versus non-pharmacy setting to determine whether there is potential bias.

Dr. Belongia pointed out that over the next year or two, there should be a lot more data in terms of the relative performance of non-egg-based versus egg-based vaccines using laboratory-confirmed outcomes.

End-of-Season Update: 2017-2018 Influenza Vaccine Safety Monitoring

Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Shimabukuro presented an end-of-season update on 2017-2018 influenza vaccine safety. As a reminder, Vaccine Adverse Event Reporting System (VAERS) is a spontaneous reporting system that is co-managed by CDC and FDA. The strengths of this system are that it is comprised of national data, accepts reports from anyone, can detect safety signals rapidly, can detect rare adverse events (AEs) subject to the limitations of spontaneous reporting, and the data are available to the public. The weaknesses of the system include the potential for reporting bias, inconsistent data quality and completeness, lack of an unvaccinated comparison group, and the inability to assess causality from these data alone. As a hypothesis generating system, VAERS identifies potential vaccine safety concerns that can be studied in more robust data systems.

US influenza vaccine reports received through May 11, 2018 on those who were vaccinated July 1, 2017 through April 30, 2018 were included in this end-of-season analysis. Signs, symptoms, and diagnoses were coded using the Medical Dictionary for Regulatory Activities (MedDRA) terms. A clinical review was performed of reports, which includes medical records when available for all serious reports; pregnancy reports for spontaneous abortion, stillbirth, congenital anomalies, and pregnancy reports; and anaphylaxis reports in persons with a history of egg allergy. FDA colleagues conducted Empirical Bayesian data mining to detect disproportional reporting for vaccine-adverse event pairings.

Of the total US reports to VAERS following IIV3, IIV4, and IIV3-HD in the 2017-2018 season, 94% to 96% were classified as non-serious. That is consistent with what has been observed in previous seasons with these products. Serious reports ranged from 4% to 6%. It is important to keep in mind that these are spontaneously submitted reports to VAERS that meet the regulatory definition of “serious.” This does not mean that 4% to 6% of individuals who receive an influenza vaccine experience a serious AE (SAE). There were no data mining signals for Guillain-Barré syndrome (GBS) or anaphylaxis in association with IIV3, IIV4, or IIV3-HD. Non-serious reports following ccIIV4, aIIV3, RIV3, RIV4, and IIV4-ID ranged from 94% to 98%. This is consistent with the other vaccine products and with what has been observed in previous seasons with these vaccine products. There were no data mining signals for GBS or anaphylaxis in association with ccIIV4, aIIV3, RIV3, RIV4, or IIV4-ID.

There were 59 total reports following vaccination during pregnancy (IIV4=23, ccIIV4=17, IIV3=9, RIV4=2, aIIV3=1, unknown brand=7). The median maternal age at vaccination was 31 years, while median gestational age was 16 weeks. Of the reports, 43 had the trimester documented: 20 (44%) in the first trimester, 12 (26%) in the second, and 14 (30%) in the third. Of the 59 reports, 13 (22%) were pregnancy-specific AE reports: spontaneous abortion (8); morning sickness (2); uterine inversion (1); preterm delivery (1); and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome (1). There were 19 (32%) non-pregnancy specific AE reports, and 27 (46%) reports with no AE documented.

In summary, no new safety concerns were detected for trivalent inactivated influenza vaccine (IIV3), quadrivalent inactivated influenza vaccine (IIV4), high-dose trivalent inactivated influenza vaccine (IIV3-HD), cell culture-based trivalent and quadrivalent inactivated influenza vaccine (ccIIV4), adjuvanted trivalent inactivated influenza vaccine (aIIV3), recombinant trivalent influenza vaccine (RIV3), recombinant quadrivalent influenza vaccine (RIV4), or intradermal quadrivalent inactivated influenza vaccines (IIV4-ID) during the 2017-2018 influenza season. Surveillance for the 2018-2019 influenza season will include enhanced safety monitoring for aIIV3 (FLUAD®), RIV4 (Flublok® Quadrivalent), pregnancy reports, and anaphylaxis reports in persons with history of egg allergy.

Turning to the Vaccine Safety Datalink (VSD) Rapid Cycle Analysis (RCA) for the 2017-2018 influenza season, the VSD was established in 1990 as a collaboration between CDC and several integrated healthcare plans. This system is comprised of data on over 10 million persons per year, which represents approximately 3% of the US population. The VSD links vaccination data to health outcome data (hospital, ED, outpatient) by unique identifiers (IDs). The data are linked and kept at each site, not at CDC. RCA in the VSD is weekly near real-time sequential monitoring to detect statistical signals for pre-specified outcomes. This includes methods to adjust for sequential testing and is focused on standard dose IIV3 and IIV4 and IIV3-HD. This presentation focused on specific results for standard dose IIV3 and IIV4. Uptake of other influenza vaccine products is still relatively low in VSD. Two designs are used for RCA. One is self-control in which each patient serves as his/her own control, looking for a clustering of events in a biologically plausible risk window compared to a comparison window. The second is current versus historical, looking at incidence of events in the current seasons compared to incidence in the historical period.

These are the pre-specified outcomes, which have not changed from the previous season:

Pre-specified outcome	Age group	Risk window (days)	Control window[1] (days)
Acute disseminated encephalomyelitis (ADEM)	≥6 mon	1-21	Historical only
Anaphylaxis	≥6 mos	0-2	7-9
Bell's palsy	≥6 mos to <18 yrs 18-49 yrs ≥50 yrs	1-42	-56 to -15
Encephalitis	≥6 mos	1-21	-56 to -15
Guillain-Barré syndrome (GBS)	≥6 mos	1-42	43-84
Seizures	6-23 mos 24-59 mos	0-1	14-20
Transverse myelitis	≥6 mos	1-21	-56 to -15

In terms of dose 1 influenzas vaccine doses administered in the VSD through April 11, 2018, standard dose IIV3 and IIV4 comprise about 83% of total doses and there was a substantial amount of IIV3-HD as well (8%). The total number of doses was 5.3 million during the analytic period for this report.

With regard to the RCA results for the IIV3 and IIV4 self-controlled risk interval (SCRI) design, the log likelihood ratio (LLR) did not exceed the critical value for any of the pre-specified outcomes, so there were no statistical signals. Regarding the results for standard dose IIV3 for the current versus historical design, again the LLR did not exceed the critical value for any of the pre-specified outcomes. In terms of the results for standard dose IIV4 for the current versus historical design, anaphylaxis with a risk interval of 0 to 2 days, there were 11 observed cases, 4.20 expected cases, and a relative risk (RR) of 2.62. The LLR was 3.8, which exceeds the critical value of 3.67 and meets the threshold for a statistical signal that needs to be further analyzed.

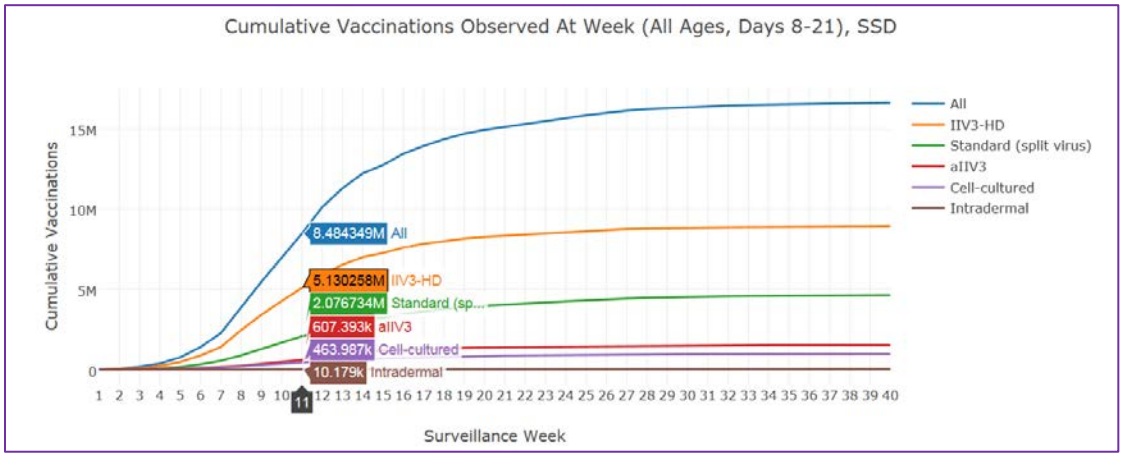
This statistical signal was detected the week starting October 15, 2017. There were 9 anaphylaxis cases observed, with 1.13 cases expected for a RR of 8.00. By the week starting November 5, 2017, there were 10 cases observed and 2.06 cases expected for a RR of 4.84. Upon chart review of these 10 anaphylaxis cases, 9 cases had symptom onset prior to vaccination. Of these, 5 had possible or probable environmental triggers and 1 probable case with onset at approximately 12 hours had no other suspected triggers. The signal was not confirmed after chart review. There was 1 additional anaphylaxis case detected in the week starting January 7, 2018. This case was not reviewed, given that it would not have changed the final results.

In summary, there were no confirmed RCA signals in either the SCRI or current versus historical designs. Data for IIV3-HD, ccIIV3/ccIIV4, aIIV3, RIV3/RIV4, and IIV4-ID are limited due to low use, but were generally reassuring. In VSD influenza vaccine safety monitoring and research for the 2018-2019 influenza season, SCRI and current versus historical RCA will be conducted using the same pre-specified conditions and risk intervals. For next season, standard dose IIV3 and IIV4 will be combined into a single vaccine category for monitoring, but if statistical signals are detected, these vaccine types will be analyzed separately.

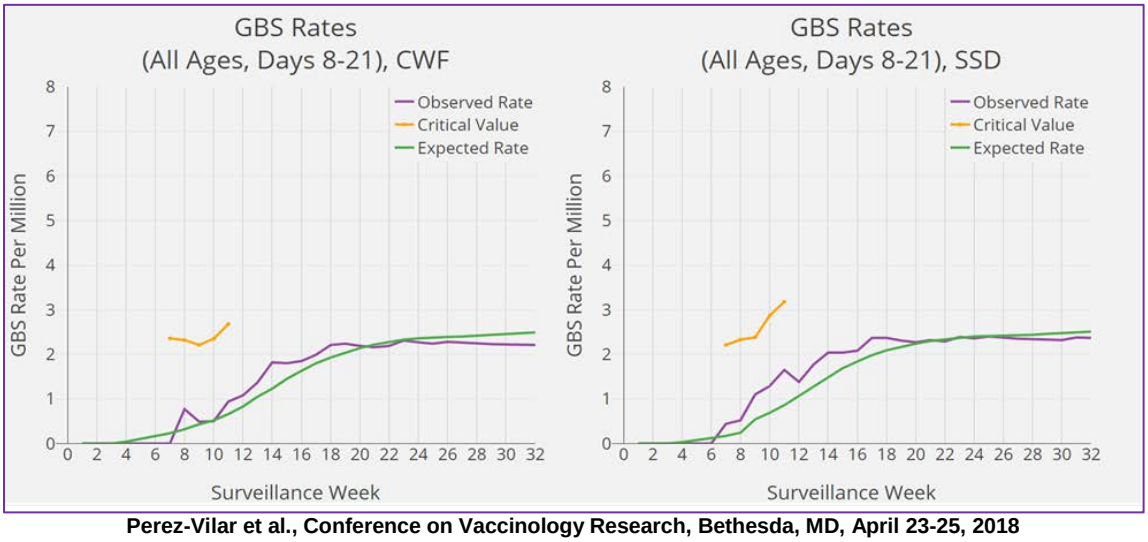
Moving to the FDA's monitoring of GBS following influenza vaccination among Medicare beneficiaries, the approach is to conduct near real-time surveillance Updating Sequential Probability Ratio Test (USPRT)[1] during Weeks 7 through 11 of the influenza vaccination season. They also provide descriptive statistics for the entire season, and perform an SCRI end-of season analysis. Claims are extracted for the population enrolled in FFS Medicare, wherein beneficiaries enrolled in FFS are enrolled in Medicare Parts A and B, and not Part C. They are looking for influenza vaccination and GBS diagnosis as the primary discharge diagnosis. This information comes from the weekly Common Working File (CWF) and the Shared Systems Data (SSD), which both contain information about Medicare patient services and diagnoses.

The FDA uses a 5-year historical cohort as the comparison group. The primary risk window for GBS is 8 to 21 days and they also use a secondary risk window of 1 to 42 days post-vaccination. The null hypothesis is that the observed rate should not be higher than 2.5 times the expected rate based on historical data[2]. In addition to the overall analyses for all ages and all influenza vaccines, they perform subgroup analyses in those ≥65 years for all vaccines, ≥ 65 years for IIV3-HD, ≥ 65 years for standard dose IIV3/IIV4 [[1] MaCurdy, 2012; Burwen, 2012; Franks, 2014; [2] Manuscript under preparation].

This figure shows cumulative vaccination uptake for 2017-2018 observed at week 11 for all vaccines and all ages for days 8-21, which is the primary risk window:



These figures show the results from the two different Medicate datasets, neither of which showed a signal for a potential 2.5-fold increased risk of GBS compared with the five prior historical seasons used as controls:



Perez-Vilar et al., Conference on Vaccinology Research, Bethesda, MD, April 23-25, 2018

In the SCRI approach, the primary risk window is Day 8 to 21 and the secondary risk window is 1 to 42 days. This is similar to the way CDC conducts self-controlled risk interval as well. This analysis used vaccination data up to January 5, 2018 and GBS cases up to May 18, 2018. There is substantial use of high-dose in this population as would be expected, with a little over 8 million doses of high-dose administered during this timeframe. No statistically significant increased risks were identified using the SCRI end-of-season analysis.

In conclusion, FDA's near real-time surveillance did not show a risk of GBS higher than the pre-specified testing threshold of a ≥ 2.5-fold increased risk of GBS compared with the five prior historical seasons used as controls. The SCRI end-of-season analyses using all seasonal influenza vaccines did not show any statistically significant GBS risk in the 8-21 and 1-42 days post-vaccination windows, with or without seasonality adjustments.

Dr. Shimabukuro then briefly discussed two Clinical Immunization Safety Assessment (CISA) Project studies. The first is titled *Safety and immunogenicity of FLUAD® versus Fluzone® High-Dose in Older Adults* (ClinicalTrials.gov: NCT03183908), which is an observer blinded randomized clinical trial (RCT) among adults aged ≥65 years randomized 1:1 to receive FLUAD® (adjuvanted) or Fluzone® High-Dose trivalent inactivated influenza vaccine. In this study, safety outcomes are collected for 42 days after vaccination and blood is collected at baseline and 28 days after vaccination for immunogenicity. Participants will be enrolled from 3 sites during the 2017-2018 and 2018-2019 influenza seasons, with a goal of 880 participants. During the first season, 279 participants were enrolled and randomized. A safety panel of three vaccine safety experts who are not study investigators reviewed interim safety data on June 6, 2018. Each panel member concluded that no substantial safety concerns were observed [Duke University (Lead), Boston Medical Center, Cincinnati Children's Hospital Medical Center (to be added via sub-contract with Boston for 2018-19 season)].

The second CISA study is titled *Fever after Simultaneous versus Sequential Vaccination in Young Children* (ClinicalTrials.gov: NCT03165981), an open label RCT among children 12 through 16 months of age randomized 1:1 to receive a simultaneous or sequential schedule as follows:

Schedule	Visit 1	Visit 2 (2 weeks later)
Simultaneous	PCV13, DTaP, and IIV4	Health education (dental care)
Sequential	PCV13 and DTaP	IIV4 and health education

The primary outcome is any fever on day 1 and/or day 2 following Visit 1 and/or Visit 2. The study enrolled and randomized 221 children out of a goal of 280 during the 2017-2018 season. Enrollment was paused early due to widespread influenza activity. This analysis is in progress [Duke University (Lead), Kaiser Permanente Northern California].

SOMNIA: Study to Assess the Risk of Narcolepsy Following Adjuvanted 2009 H1N1 Influenza Vaccines

Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

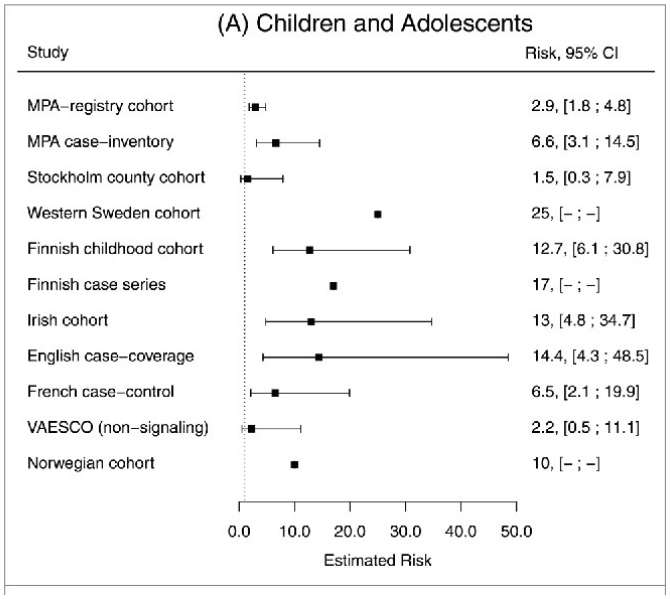
Dr. Shimabukuro explained that the purpose of the SOMNIA study is to assess the risk of narcolepsy following adjuvanted pH1N1 vaccines. This is a large multi-site, multi-country international study involving a lot of coordination. It is led by Steve Black, Miriam Sturkenboom, and Daniel Weibel. He pointed out that this presentation would be somewhat odd, given that most of it would be spent talking about the background and rationale, with only a brief discussion of the high-level main findings. A posting from the Swedish Medical Products Agency (MPA) dated August 18, 2010 announced that the agency would be investigating reports of narcolepsy in patients vaccinated with Pandemrix®. Pandemrix® is a monovalent AS03-adjuvanted influenza A(H1N1) vaccine manufactured by GSK that was used widely in Europe during the 2009 H1N1 influenza pandemic. It was widely used in Scandinavian countries.

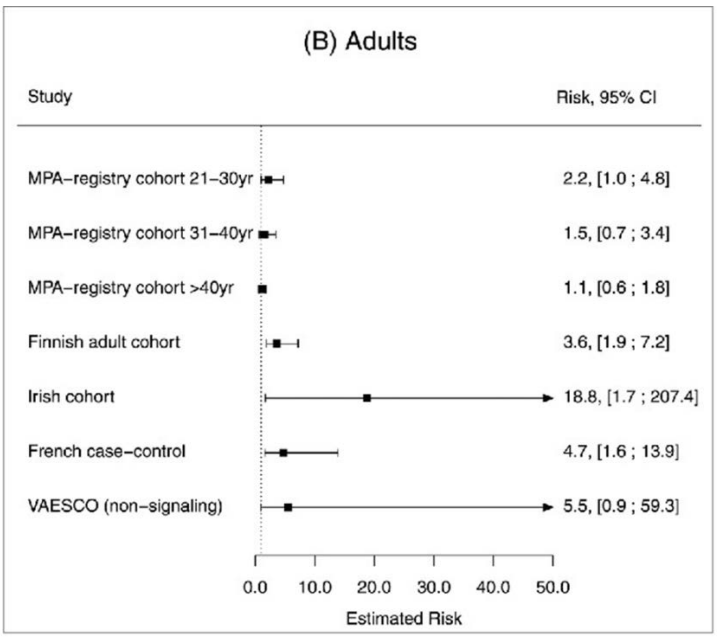
Narcolepsy is a central nervous system (CNS) disorder characterized by excessive daytime sleepiness (EDS) and abnormal manifestations of rapid eye movement (REM) sleep. It includes sleep attacks, disrupted nocturnal sleep, sleep paralysis, hypnagogic hallucinations, and cataplexy. It is a chronic disease that can be treated with medication and behavior modification, but there is no cure. There are two diagnostic entities: narcolepsy with cataplexy and narcolepsy without cataplexy. The Brighton Collaboration case definition is primarily based on the presence of symptoms and an abnormal multiple sleep latency test (MSLT) characteristic of narcolepsy.[1] Narcolepsy with cataplexy is thought to be caused by damage to hypocretin secreting neurons in the hypothalamus. It is strongly associated with the HLA DQB1*0602 allele and is present in 5% to 38% of people. It is thought to be an autoimmune and multi-event process. Suspected infectious triggers include febrile illness, influenza infections, and β-hemolytic streptococcal infections. Narcolepsy onset can occur at any age, but peaks during the teenage years. It is very rare in individuals under 5 years of age and over 40 years of age. Prevalence estimates vary widely (Israel: 0.23/100,000; US: 30-56/100,000; and Japan: 160/100,000). There is often a long delay from symptom onset to diagnosis, which can be many years[2] [[1]Poli et al. Narcolepsy as an adverse event following immunization: case definition and guidelines for data collection, analysis and presentation. Vaccine. 2013;31(6):994-1007; [2]Silber et al. The epidemiology of narcolepsy in Olmsted County, Minnesota: a population-based study. Sleep 2002;25:197-202; Longstreth et al. Prevalence of narcolepsy in King County, Washington, USA. Sleep Med 2009;10:422-426; Partinen et al. Narcolepsy as an autoimmune disease: the role of H1N1 infection and vaccination. Lancet neurology 2014;13:600-613].

Regarding the Pandemrix® narcolepsy timeline, largescale vaccination programs were implemented in many European countries in October and November 2009. In February 2010, a Finnish narcolepsy expert discussed this association of narcolepsy following Pandemrix® with some of his colleagues. By August 2010, there was extensive media and regulatory attention around an association in children and adolescents. About this time, studies were undertaken in Europe to further assess this potential association. The SOMNIA study planning started in earnest in 2012. The problem with studying narcolepsy is the potential impact of heightened awareness. The initial symptom is onset of EDS and other issues that go along with it such as problems concentrating, poor school performance, behavioral problems, employment issues such as problems holding a job, et cetera. This can occur for a long time before an individual is referred to a specialist for a work-up, a MSLT, and ultimately receives a narcolepsy diagnosis. The lag time to diagnosis can be years to decades. In terms of what will happen upon awareness (media, public, provider) as occurred in 2010 in Europe, this can be likened to shaking an apple tree. The analogy is that the apples would have ripened and fallen during the normal course of apples ripening and falling, as would narcolepsy cases being diagnosed during the normal course of diagnosing narcolepsy based on epidemiology and how the health system functions. However, awareness can cause the apples/cases to fall out. Looking at a short time window could give the impression that there is a cluster of narcolepsy and temporal association with vaccination. In the case of Pandemrix® and narcolepsy, the impact of the change in the lifetime among vaccinated cases appears most prominent early after the signal and may subside later [Wijnans et al. The incidence of narcolepsy in Europe: before, during, and after the influenza A(H1N1)pdm09 pandemic and vaccination campaigns. Vaccine. 2013 Feb 6;31(8):1246-54].

The following two figures summarize data from a paper looking at on Pandemrix® and narcolepsy:

Figure 1.





The overall trend among children is for an increased risk of narcolepsy associated with Pandemrix® vaccination. However, that is not the case in every study. The point estimates vary widely and the confidence intervals are quite wide as well. There might be some evidence of an increased risk among adults; however, it is not nearly as striking as among children. Many of the adult studies did not show an increased risk of narcolepsy following Pandemrix® [Verstraeten T et al. Pandemrix™ and narcolepsy: A critical appraisal of the observational studies. Hum Vaccin Immunother. 2016;12(1):187-93].

Regarding the understanding of Pandemrix® and narcolepsy prior to the SOMNIA study, many studies were conducted in Europe, some with variable results within the study and limited power to produce definitive results. Media and regulatory awareness might have impacted diagnosis patterns in European countries. This is challenging to control or account for because of the short time period between vaccination and awareness.

There is no clear biologic mechanism to explain the findings. The rationale for the CDC-sponsored SOMNIA study was to inform pandemic preparedness for influenza vaccines, further evaluate AS03-adjuvanted pH1N1 vaccines, and address the lack of data on MF59®-adjuvanted pH1N1 vaccines. The scope of the study was to assess the risk of narcolepsy following both AS03- and MF59®-adjuvanted monovalent 2009 pH1N1 vaccines. The study objectives were to evaluate any trends in incidence rates over time of narcolepsy diagnoses, and evaluate a possible association between vaccination, infections and narcolepsy.

Moving to the incidence rate study, the following table lists the study sites and vaccines used in each:

Country/Province	Adjuvanted pH1N1 vaccine used
Canada Manitoba Alberta British Columbia	Arepanrix (AS03)* Arepanrix (AS03) Arepanrix (AS03)
Denmark	Pandemrix (AS03)
The Netherlands	Pandemrix (AS03), Focetria (MF59)
Spain Valencia Catalonia	Focetria (MF59), Pandemrix (AS03) Focetria (MF59), Pandemrix (AS03)
Sweden	Pandemrix (AS03)
Taiwan	Focetria (MF59)
United Kingdom	Pandemrix (AS03)

Some of these study sites also used unadjuvanted vaccines as well, though only adjuvanted vaccines are listed in the above table. Arepanrix™ is a monovalent AS03-adjuvanted influenza A (H1N1) vaccine manufactured by GSK/ID Biomedical Corporation in Canada and was used in Canada during the 2009 H1N1 influenza pandemic. Focetria® is Novartis's MF59® adjuvanted vaccine that was used worldwide.

This was a dynamic retrospective cohort study. The trends and incidence rate ratios were assessed between the periods before the H1N1 pandemic, during the H1N1 pandemic but pre-vaccination, and during/post-H1N1 pandemic and pH1N1 vaccination. Sweden was an *a priori* identified signaling country, which was used as a comparator for the other countries. There was a dramatic increase in the incidence rate, particularly in the 5 to 19-year-old age group in 2009 in Sweden, and maybe less so in the 20 to 59-year-old age group, which began to decrease in 2011. No change was found in incidence rates over time in any of the countries or age groups

beyond Sweden post-vaccination and in Taiwan during circulation of wild-type pH1N1 virus. Looking more closely at Taiwan, the incidence rate increased during pH1N1 wild-type virus circulation before vaccination and decreased after vaccination. Most of the vaccine used in Taiwan was non-adjuvanted. Unique to Taiwan is that they had a short diagnosis lag time of 2 months, compared to other countries, between the onset of EDS and narcolepsy diagnosis. There are some data from a study in China, as well, showing evidence of an association with wild-type disease and narcolepsy.

Moving to the case-control study, the study sites and adjuvanted vaccines used are shown in the following table:

Country/Province	Adjuvanted pH1N1 vaccine used
Argentina	Focetria (MF59)
Canada Ontario	Arepanrix (AS03)
The Netherlands*	Pandemrix (AS03), Focetria (MF59)
Spain Valencia Catalonia	Focetria (MF59), Pandemrix (AS03) Focetria (MF59), Pandemrix (AS03)
Switzerland	Pandemrix (AS03), Focetria (MF59)
Taiwan	Focetria (MF59)

This was a retrospective case-control study for which the primary index date was MSLT referral and the secondary index date was EDS or cataplexy onset. MSLT referral had to be used as the index date because it is quite difficult to determine when EDS begins. In some cases, it cannot be determined. A sensitivity analysis using EDS or cataplexy onset yielded similar results. The two main analyses performed were a restrictive period and a total period. One way to address detection bias based on media awareness is to censor the data when it is believed that media awareness might be impacting detection of cases. The total period analysis was out to 2015 for most countries, excluding those cases that might have been artificially clustering. The restricted and total period analyses had similar results. Dr. Shimabukuro pointed out that he was presenting the total period analysis because CDC thinks that this is a more robust analysis.

In terms of the case-control total period analysis, the data from Arepanrix-AS03 came from Ontario, Canada. Arepanrix-AS03 was used only in Canada and the only study site in the case-control study was Ontario, so this is really a non-pooled single-site study. There was no increased risk of narcolepsy in either children or adults following receipt of Arepanrix-AS03. Focetria- MF59® was a two-stage random effects meta-analysis of data from Taiwan; Argentina; the Netherlands; and Valencia and Catalonia, Spain. There was no increased risk of narcolepsy following receipt of Focetria- MF59® in children or adults. For Pandemrix-AS03, the case-control study data came from Valencia, Spain. There was no increased risk in adults following receipt of Pandemrix-AS03.

In the Netherlands, cases born from 2004 through 2009 were analyzed using a case-coverage design. Pandemrix® exposure in cases was obtained through a national database. Exposure prevalence was then obtained in the population for children born in the same year by calendar

week and year of birth. This case-coverage analysis was a post-hoc, off-protocol analysis in children in the Netherlands. The design allowed investigators to include information from the Netherlands, where individual exposure data were not available. In this analysis, there was no increased risk for narcolepsy following receipt of Pandemrix® in children.

In conclusion, the incidence rate study data did not show a rise in the rate of narcolepsy following vaccination except in the one signaling country included, Sweden, which used Pandemrix®. The case-control analyses for the AS03-adjuvanted pH1N1 vaccines, Arepanrix™ and Pandemrix®, did not show evidence of an increased risk of narcolepsy, though data were limited for Pandemrix®. The case-coverage analysis for Pandemrix® in children in the Netherlands did not show evidence of an increased risk of narcolepsy, but the number of exposed cases was small (N=7). The case-control analysis for the MF59®-adjuvanted vaccine Focetria® did not show evidence of an increased risk of narcolepsy.

Discussion Points

Regarding the fact that the HLA type associated with narcolepsy varies a lot in populations and that it is unusually prevalent in Scandinavia compared to other parts of the world, Dr. Moore noted that only one Scandinavian country was involved and it did show a signal with Pandemrix®. She wondered how the SOMNIA study addressed the prevalence of the HLA type in question if it varies so much in populations.

Dr. Shimabukuro replied that there were several European studies in the Scandinavian countries (Finland, Sweden, Norway), which did show an increased risk. They were not able to incorporate the HLA type frequency into the study. The HLA type prevalence ranges from 15% to 25% of the population, but appears to be quite low in Taiwan at 3.4%. The HLA type is quite common and is probably about 25% or maybe a little higher in the Scandinavian countries. This did not really factor into the analysis.

Dr. Atmar noted that if a shortened lag time was a possible explanation for increased public awareness, with continued surveillance the rates of diagnosis might be expected to decrease. He wondered if something like that had been observed.

Dr. Shimabukuro responded that if the incidence is not changing the longer the observation period is extended, a temporary increase in incidence followed by a decrease below baseline may be observed. More work needs to be done to further analyze the incidence trends looking at more follow-up time.

Adjuvanted Quadrivalent Influenza vaccine (aQIV) in Young Children

Gregg C. Sylvester, MD, MPH
Head of Medical Affairs
Seqirus™: A CSL Company

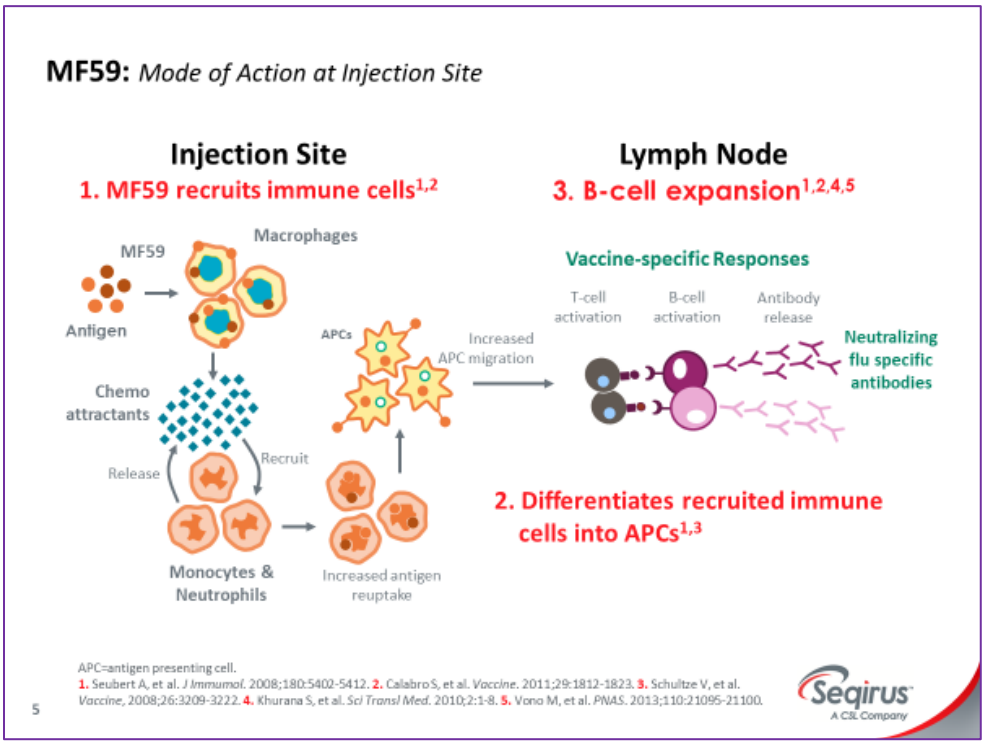
Dr. Sylvester presented the Phase 3 results for Seqirus's™ (aQIV) in young children ages 6 months to 72 months, including an immunogenicity analysis of a subset of the entire population studied in this Phase 3 trial.

Regarding the burden of disease, influenza and related complications pose a public health threat to young children, especially those under 2 years of age. Influenza is an important cause of respiratory illness in children. Depending upon the age, more than 20% of those hospitalized

with ARI is caused by influenza. Based on data for two influenza seasons from 2002–2004, 48% of hospitalizations of children under 5 years of age presenting with an ARI or fever were among children ≤6 months of age, 30% were among children 6 to 23 months of age, and 22% were among children 24 to 59 months of age [Poehling KA, et al. N Engl J Med. 2006;355:31–40].

It is also known that traditional influenza vaccines have been less effective in children; thus, the need for more improved vaccines in this age group. Therefore, Seqirus™ added an adjuvant, MF59®, to its quadrivalent influenza vaccine to improve the immune response in children. MF59® is an oil-in-water emulsion composed of squalene and polysorbate 80. Squalene is a biodegradable and biocompatible oil found in plants and animals. It is an intermediate metabolite in the synthesis of cholesterol. Humans synthesize it in the liver (>1 g/day) and it is derived from dietary sources and ingested in various dietary sources[1]. Polysorbate 80 is a non-ionic surfactant and emulsifier forming a homogeneous solution [[1]O'Hagan DT, et al. *Expert Rev Vaccines.* 2013;12:13-30].

Seqirus™ believes that MF59® enhances the immune systems in several important ways as depicted in the following illustration:



In the top left-hand side, it recruits macrophages to the injection site. It differentiates and recruits monocytes and neutrophils into antigen-presenting cells and increases the migration of these cells into lymph nodes where T-cell and B-cell activation expands the B-cell repertoire, creating higher antibody levels, broader antibody coverage, and longer antibody responses.

Fluad™, which is the trade name, is Seqirus's™ adjuvanted influenza vaccine. It has been licensed elsewhere for the last 20 years. It was first licensed in 1997 in Europe for adults ≥ 65 years of age, focusing on those who have waning immune systems or immunosenescence. It has been licensed in Canada for older adults as well as children 6 to 24 years of age, and was

licensed in 2016 in the US for adults ≥ 65 years of age. The United Kingdom (UK) and Australia added Fluad™ to this year's influenza season for enhanced protection.

In children 6 months to 72 months of age, Seqirus™ performed a multi-center RCT double-blinded Phase 3 trial that evaluated the safety, efficacy, and immunogenicity of pediatric Fluad™ compared with a US licensed influenza vaccine in the same age group. Safety was assessed throughout the entire study. Active surveillance was conducted, which meant that parents were called during the 6 months following receipt of the vaccine or until the end of the season. If a child met the definition of influenza-like illness (ILI) of a temperature of ≥100°F / ≥37.8°C along with any of several symptoms (cough, sore throat, nasal congestion, or runny nose), they were brought in for a laboratory-confirmed influenza test via PCR assay. The study was comprised of 10,644 children, who were split nearly equally between the aQIV arm (N=5300) and the trivalent influenza vaccine/quadrivalent influenza vaccine (TIV/QIV) arm (N=5193). They began with the trivalent because it was the only licensed product in that age group at that time. The following year, QIV was licensed so they moved to that product. About a third of the children participated in the immunogenicity study.

In terms of the baseline demographics, the mean age was slightly over 3 years. Children enrolled in the study received either 1 or 2 doses, depending upon their previous influenza vaccination history reported by a parent and their age. If a parent stated that the child had not received a previous influenza vaccine, they were given 0.25 mL on Day 1 and then returned at Day 30 for a second dose. If the parent stated that the older child already had received a previous vaccine, they were considered no longer naïve and received a 0.5 mL dose. During the first of the two study seasons, less than 15% of the total subjects were enrolled. It turns out that there were only 10 cases in that season, so 98% or higher occurred in the second season when 85% and higher were enrolled. Therefore, this really is a one-season study. In the first season, the vaccine matched fairly well to the predominant circulating strains. However, in the second season (2014-2015) all vaccines had influenza A(H3N2)/Texas, but the predominant circulating strain was A(H3N2)/Hong Kong.

Regarding PCR-confirmed influenza among subjects 6 months to 72 months, Fluad™ worked as well as the US licensed competitor for any strain for the entire age range. The primary endpoint success criterion was defined as a lower 95% CI of rVE >0%. However, the rVE was -0.67 (-19.81, 15.41) which missed that agreed upon criterion for success set by the FDA and the company. This was driven predominantly by the A/H3N2 strain with 400 of the 500 cases coming from that strain group. In the younger age group of 6 months to 24 months, there was a benefit with the adjuvanted product with 55 cases among Fluad™ recipients versus 79 cases of TIV/QIV for an rVE that was 31.37 (3.14, 51.38) better among the Fluad™ recipients than the comparator recipients. Once again, this was driven by the A/H3N2 group where there were 44 cases among Fluad™ recipients compared to 66 TIV/QIV recipients.

The immunogenicity study in a subset of the subjects 6 months through 23 months and 2 through 5 years of age looked at both geometric mean titers (GMTs) and GMT ratios. For the entire age range of 6 months through 72 months, as well as 6 months through 23 months and 2 through 5 years, Fluad™ showed superior immunogenicity by GMTs and the GMT ratios and also demonstrated superior seroconversion.

Regarding safety data, local AE reporting was solicited for the first 7 days after any vaccination. If a child received two vaccinations, it was checked twice during that time. The aQIV group had a slightly higher local AEs compared to the comparator group. However, very few severe local AEs were reported. Systemic AEs also were assessed. Of the enrollees receiving aQIV, 20%

experienced one or more systemic AEs, including irritability, sleeplessness, change in eating habits, and diarrhea. Most people have been asking about fever rates. In the younger group, 20% of the Fluad™ recipients had noted fever compared to 14% among the comparator recipients. Across the entire age group, it was 19% compared to 9%. Once again, the vast majority of the fever rates in both vaccine groups were <39°C. During the treatment period, febrile convulsions were observed in 2 aQIV subjects versus 1 subject in the comparator group. When Dr. Sylvester presented these data to the ACIP WG and the American Academy of Pediatrics (AAP) Committee on Infectious Diseases (COID), they really wanted to know about co-administration. Among the more than 10,500 children in the study, only 55 may have received an influenza and other pediatric vaccines within a 7-day window. This suggests that the numbers are just too small to make any type of meaningful conclusion. This clearly shows that there are very few fevers, but it is not necessarily the same day or different arms when they were receiving the vaccine. Among the 6 through 24 month and 24 to 72 month age groups, the proportion of children with any unsolicited AEs were similar for aQIV and the comparator vaccine groups. The same pattern also was observed with serious AEs, new onset chronic diseases (NOCD), and AEs of special interest (AESI). Of the new onset chronic disease, no clustering has been observed. However, those children have been followed closely.

In conclusion, an increased incidence of local and systemic reactogenicity was seen after vaccination with aQIV. This is consistent with past pediatric aTIV trials. The majority of local and systemic AEs occurred within the first 3 days after vaccination, were mild to moderate in severity, and were observed up to a total of 2 to 3 days. There was an increased incidence of fever compared to the comparator vaccine, but there was no increase in febrile convulsions. The incidences of unsolicited AEs, AESIs, and NOCDs were comparable. Among subjects 6 through 72 months of age, aQIV efficacy was comparable to the comparator for PCR-confirmed influenza, and aQIV elicited a superior immune response as reflected by GMT ratios relative to the comparator vaccine against all 4 strains. Among subjects 6 through 24 months, aQIV efficacy was significantly greater for PCR-confirmed influenza and aQIV elicited a superior immune response as reflected by GMT ratios relative to the comparator vaccine against all 4 strains.

Discussion Points

Dr. Szilagyi inquired as to whether prior seizures or febrile seizures were exclusion criteria for the RCT.

Dr. Sylvester indicated that children who had a neurologic seizure or epilepsy were excluded. None of them had febrile seizures upon enrollment into the study. It is known that there is an increased risk of febrile seizures after the first one.

Dr. Belongia asked whether for the superior immunogenicity against the 4 vaccine strains there were titers against egg-adapted vaccine viruses and if so, whether they had assessed titers against cell-grown viruses.

Dr. Sylvester responded that the PCR assays used were similar to what was in the vaccine, so they have not assessed these compared to cell-based viruses at this point. However, this is something that they can and should do.

Based on the analysis of children 6 through 24 months for Fluad™ versus TIV/QIV, Dr. Hunter calculated that the NNV would be 60 in order to prevent, relatively speaking, one case of laboratory-detected influenza in that age group. Dr. Sylvester confirmed that this number would be accurate.

Dr Walter asked whether there are any plans to conduct studies of co-administration with other vaccines, particularly with regard to fever rates.

Dr. Sylvester replied that they have a Phase 4 trial in its third year with Professor Mark Loeb at McMaster University in Canada. What is done in this study is that it is typically done on a vaccine day in a religious community. This is not a licensed product in this age range, but Seqirus™ is in negotiations with the FDA. If the FDA moves toward approval of this age group, one of the post-marketing commitments is likely to be examination of that.

Dr. Belongia pointed out that one of the concerns with adjuvanted vaccines, particularly in children, is the fact that if this is started at 6 months to 1 year, the child will receive an adjuvanted vaccine potentially every year for a long time. He wondered whether there was any existing information on, or plans to examine, the effects of being repeatedly vaccinated with an adjuvanted vaccine.

Dr. Sylvester indicated that from the first to second year in this study, 600 children received a second vaccine. They could have had 2 in the first year and then 1 in the third year, or 1 in the first year and 1 in the second. In the second year, they followed an additional 1600 children and did a crossover. If they received aQIV, 400 received aQIV for the second or just standard and then in the same standard they could have had aQIV or standard. The Canada trial has a data monitoring oversight committee that is looking at AEs and whether there is any potentiation with the adjuvant. Again, this is only 3 years of study that concludes at the end of 2018. However, Seqirus™ has every intention of continuing the study for at least 3 more years in order to have multiple years of data for the adjuvanted product.

Dr. Bennett requested that Dr. Sylvester comment on the diversity of the population of children in the study.

Dr. Sylvester indicated that the first year that enrolled about 15% was predominantly done in Europe and the US. During the second year, they went to the Philippines. About 45% of the study population are Asian, about 40% are Caucasian, a little less than 15% are Black, and the remainder are other.

WG Considerations: Updates to the 2018-2019 Recommendations

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

Dr. Grohskopf reported on the WG considerations and ongoing discussion, as well as the 2018-2019 recommendations draft in terms of what is new.

With regard to considerations, the WG heard previews of all of the information presented during this session. In general, the thinking is that the 2017-2018 season safety data are reassuring. There was discussion regarding the quadrivalent adjuvanted vaccine for young children, which centered primarily around reactogenicity and the very limited data on coadministration with other

vaccines. The WG is engaged in a number of ongoing discussions. Regular vaccine efficacy and effectiveness updates are presented to the WG and during ACIP meetings, which continues to be a topic of major interest, particularly with regard to trying to make assessments of VE of certain types of vaccines versus others. For example, there are ongoing discussions regarding the efficacy and effectiveness of LAIV4, which was recommended for use again for 2018-2019 during the February 2018 ACIP meeting; egg-based versus non-egg-based vaccines; and vaccines for persons 65 years of age and older. The WG also continues to hear surveillance, safety, and vaccine coverage updates.

As a reminder, ACIP generally has a vote on the core recommendation language each year in either February or June. Given that this was not done in February, it was raised during this meeting. The ACIP members were provided with copies of the recommendations documents. The recommendations were to be published in the same format as last year, on their own with some limited explanatory references. The bulk of the literature review was published in another larger document. Because that was well-received last year, the decision was made to do the same this year.

First, the document re-iterates the core recommendation that annual influenza vaccination is recommended for all persons aged 6 months and older who do not have contraindications. In terms of updates, the US influenza vaccine composition for 2018-2019 for trivalent vaccines includes A/Michigan/45/2015 (H1N1)pdm09-like virus, A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus—updated, and B/Colorado/06/2017-like virus (Victoria lineage)—updated. Quadrivalent vaccines include the same three strains as the trivalent vaccines, plus B/Phuket/3073/2013-like virus (Yamagata lineage).

New language was approved by ACIP in February 2018 for FluMist® Quadrivalent (LAIV4) and is summarized in the new recommendations document. It also was the subject of a recent *Morbidity and Mortality Weekly Report* (*MMWR*) Policy Note published on June 8, 2018 that summarizes the data and discussion. For the 2018-2019 season, providers may choose to administer any licensed, age-appropriate influenza vaccine (IIV, RIV4, or LAIV4). LAIV4 is an option for those for whom it is otherwise appropriate. VE updates for LAIV4 will be presented to ACIP as they become available. Contraindications and precautions for LAIV4 remain the same as previously. LAIV4 is acceptable for persons with a history of egg allergy, which was approved by ACIP in February 2016, prior to the decision to not recommend use of LAIV4 for 2016-2017. That is incorporated into the document for the 2018-2019 season. Essentially, individuals with a history of egg allergy may receive any licensed, recommended, age-appropriate vaccine.

As is typical when the guidance is updated, some new products or licensure changes occur. One licensure change is discussed in the guidance for the coming seasons, which is for Fluarix® Quadrivalent (IIV4, GSK) that was discussed during the last ACIP meeting. A 0.5mL dose was licensed for children aged ≥6 months (previously licensed for ≥3 years) in January 2018. These data were presented to ACIP in February 2018. This brings IIV licensed for 6- through 35-month-olds to a total of 3, including: Fluarix® Quadrivalent (IIV4, GSK) at a 0.5mL dose, FluLaval® Quadrivalent (IIV4, GSK) at a 0.5mL dose, and Fluzone® Quadrivalent (IIV4, Sanofi Pasteur) at a 0.25mL dose.

With the guidance and updates in mind, the WG proposed to reaffirm the seasonal influenza recommendations for the 2018-2019 season.

Discussion Points

Dr. Grogg (AOA) requested that the AAP representative comment on why they suggested LAIV as a last resort.

Dr. Campbell (AAP) responded that the AAP/COID also reviewed the same data reviewed by ACIP. The AAP/COID's vote was to recommend LAIV, but to recommend it after recommending IIV as the first choice.

Dr. Baker (IDSA) requested further clarification from Dr. Campbell, given that it sounded as though they were recommending giving IIV and then LAIV.

Dr. Campbell (AAP) clarified that the intent was not to recommend giving both vaccinations, but rather to offer IIV as the first choice and to offer LAIV to those who do not want to take IIV who would not otherwise be vaccinated if age-appropriate and not contraindicated.

Public Comment

No public comments were provided during this session.

Motion/Vote: 2018-2019 Recommendations

Dr. Romero made a motion to approve and Dr. Moore seconded the proposed recommendation language as presented to reaffirm the seasonal influenza recommendations for the 2018-2019 season.

The motion carried with 13 affirmative votes, 0 negative votes, and 1 abstention. The disposition of the vote was as follows:

13 Favored:	Atmar, Bennett, Bernstein, Frey, Hunter, Lee, Moore, Pellegrini, Riley, Romero, Stephens, Szilagyi, Walter
0 Opposed:	N/A
1 Abstained:	Belongia

Anthrax Vaccine

Introduction

David S. Stephens, MD, FIDSA
ACIP Anthrax Vaccine WG

Dr. Stephens reminded everyone that the Anthrax Vaccine WG was reconvened in March 2017 to discuss new data published since the last review in 2010. Anthrax vaccine is unique compared to the vaccines usually reviewed by ACIP. One of the uses of anthrax vaccine is for post-exposure prophylaxis (PEP) in the event that *Bacillus anthracis* (*B. anthracis*) is used as a bioweapon. The US government stockpiles anthrax vaccine for use in the event of wide-area release of *B. anthracis* spores over a densely populated area. To provide vaccine effectively in

this situation, decisions on how to provide the vaccine and to whom would have to be made quickly. For this reason, decisions on how best to use the vaccine should be well-vetted prior to an event. Therefore, CDC asks ACIP for advice on policies that could be implemented to improve the efficiency of a mass vaccination campaign in the event of a wide-area release of *B. anthracis* spores.

The following topics were the focus of this session:

- Grading of Recommendation Assessment, Development and Evaluation (GRADE) evaluation of the evidence
- Policy questions under consideration:
  - Route of Administration: May the intramuscular (IM) route of administration (ROA) be used if the subcutaneous (SC) ROA presents clinical, operational, or logistical challenges that may delay or prevent effective vaccination?
  - Dose-Sparing Schedules: Should there be an inadequate supply of anthrax vaccine available for PEP, may either 2 full doses or 3 half doses of anthrax vaccine adsorbed (AVA) be used to expand vaccine coverage?
  - Antimicrobial Duration: Can the duration of the antimicrobial component of PEP be decreased to less than 60 days when given in conjunction with AVA?

GRADE Evaluation of the Evidence

William Bower, MD, FIDSA
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Before going into the GRADEing of the evidence reviewed by the Anthrax Vaccine WG, Dr. Bower first explained how the data were used to support the policy changes to be presented to ACIP during this session. Inhalation anthrax is very rare, so the effectiveness of AVA for PEP in humans cannot be directly assessed. For this situation, the Food and Drug Administration (FDA) has recommended using the “Animal Rule” where data from animal studies are used to generate a correlate of protection model based on immune response measured in animals following vaccination. Then the data from human studies on immune response can be used to estimate human survival based on antibody concentrations generated by the vaccine in humans. The predicted human survival data are all indirect measures since it is derived from a comparison of human to animal data. Therefore, the supporting evidence was downgraded in the GRADE evaluation.

The animal survival data came from a study in non-human primates (NHP) given serial dilutions of AVA to generate a range of anti-protective antigen immunoglobulin G (anti-PA IgG) concentrations and then challenged with *B. anthracis* spores. The antibody concentrations and survival data were placed in a model to generate a survival curve. Two other non-human primate studies using slightly different vaccine dilutions and dosing schedules supported the findings in this model.

The human immunogenicity data came from two main sources. The Wright study directly compared the IM to SC route of administration for immunogenicity and AEs when given on a pre-exposure prophylaxis (PrEP) dosing schedule. The human immunogenicity data for the dose-sparing schedule came from the Bernstein study that directly compared the antibody concentrations generated by the dose-sparing schedules under consideration to the antibody concentrations generated by the licensed dosing schedule. The data to support a decrease in antimicrobial PEP duration came from these studies plus others that looked at immunogenicity of AVA when given on the licensed dosing schedule.

The following policy questions were posed to ACIP, all of which related to the use of AVA as PEP. The first two questions pertain to optimizing the use of vaccine during a large mass vaccination event, while the third question pertains to the use of antimicrobials in conjunction with vaccine:

1) May the IM ROA be used if the SC ROA presents clinical, operational, or logistical challenges that may delay or prevent effective vaccination?

2) Should there be an inadequate supply of anthrax vaccine available for PEP, may either 2 full doses or 3 half doses of AVA be used to expand vaccine coverage?

3) In immunocompetent individuals who are being vaccinated with anthrax vaccine, do antimicrobials provide adequate protection when given for: a) at least 42 days after the first vaccine dose, or b) 2 weeks after the last vaccine dose, whichever comes later?

As noted earlier, it is not possible to directly assess the effectiveness of AVA for PEP in humans so the correlates of protection model must be used to estimate human survival at the anti-PA IgG antibody concentrations generated by the vaccine. The animal antibody concentration and survival data came from the Sivko study in which NHP were given three-fold serial dilutions of AVA at 0 and 14 days to generate a range of anti-PA IgG concentrations. The animals were then challenged with an average of 205 the median lethal dose (LD_{50}) *B. anthracis* spores on day 28. The antibody concentrations and survival data were placed in a logistic regression model to generate a survival curve. Two other non-human primate studies which used slightly different vaccine dilutions and dosing schedules supported the findings in the Sivko paper.

As stated before, the human data came from two main sources. The Wright paper directly compared the IM to SC ROA for immunogenicity and AEs when given on a PrEP dosing schedule. From this study, a subset of the data was assessed where vaccine recipients received AVA at 0, 14, and 28 days, which is the PEP vaccine schedule. The human immunogenicity data for the dose-sparing schedule came from one study, the Bernstein paper, that looked at AVA given as 2 full doses at either 0 and 14 days or 0 and 28 days, or 3 half doses given at 0, 14 and 28 days. Other studies supported the finding of the Wright study that looked at immune response and AEs with vaccine given by either the IM or SC route. Several other papers also support the findings in the Bernstein paper (Hopkins, 2014; Rynkiewicz, 2011; King, 2015; Zhang, 2008; Ionin, 2013; and Minang, 2014). All of these studies and the Wright and Bernstein studies were used to inform the consideration on decreasing the antimicrobial duration when given in conjunction with AVA.

Regarding the GRADE evaluation of the evidence on the first policy question, *May the IM ROA be used if the SC ROA presents clinical, operational, or logistical challenges that may delay or prevent effective vaccination?*, a systematic review of the literature was conducted with the following parameters: Healthy adults 18 to 65 years of age who received 3 doses of AVA administered IM at 0, 2, and 4 weeks compared to AVA administered SC at 0, 2, and 4 weeks, which is the currently licensed route of administration. The outcomes of interest were immunogenicity and AEs.

The Wright study is the only paper that directly compared IM and SC ROA for immune response and AEs and received a GRADE of 1. In addition, there were 3 other RCTs and 3 observational studies that looked at IM or SC ROA separately and supported the finding in the Wright study. These papers all were downgraded for benefit because they were not a direct comparison between the IM and SC ROA and the survival benefit was derived from an indirect comparison of human to animal data. The overall evidence GRADE for benefit of immune response for IM compared to SC ROA was 2 and for AEs was 1.

In terms of the GRADE evaluation of the evidence for the second policy question, *Should there be an inadequate supply of anthrax vaccine available for PEP, may either 2 full doses or 3 half doses of AVA be used to expand vaccine coverage?*, a systematic review of the literature was preformed to look for papers where health adults 18 to 65 years of age received dose-sparing schedules of AVA and anti-PA IgG concentrations were measured at time points prior to 60 days after first dose of vaccine. There was one paper that met these criteria. Once the immunogenicity data were identified, the correlates of protection model described earlier could be used to predict survival for the dose-sparing schedules compared to the current licensed schedule.

The data on the different dose-sparing strategies all came from the same sources. The Bernstein paper that looked at the dose-sparing schedules in healthy adults was downgraded because of indirectness as the data is compared to non-human primate antibody concentration and survival data. However, it was upgraded due to strength of association and the dose response gradient. The final evidence GRADE for the human immunogenicity data is 1. The Sivko paper used to generate the non-human primate antibody concentration and survival curves was downgraded by 2 for indirectness because the data were used to estimate human response and placed into a model to predict survival. However, the evidence was upgraded due to strength of association and dose response gradient. The overall GRADE for the non-human primate immune response data is 1. However, given the overall indirectness of comparing human and non-human primate data, the overall evidence GRADE is 2 for the benefit of dose-sparing strategies. Harm was not a factor for this question.

In regard to the third policy question, "*In immunocompetent individuals who are being vaccinated with anthrax vaccine, do antimicrobials provide adequate protection when given for at least 42 days after the first vaccine dose, or 2 weeks after the last vaccine dose, whichever comes later?,* the systematic review of the literature for this question was similar to the prior review. Papers were identified in which humans received AVA on a PEP dose-sparing schedule or AVA on the licensed PEP dosing schedule where anti-PA IgG concentrations were measured at time points prior to 60 days after the last dose of vaccine.

Since the systematic review of the literature for this question was similar to the prior review, the GRADE was also similar. The data for the dose-sparing strategies immune response was GRADE 1 and the non-human primate immune response and survival data was GRADE 1. However, again given the indirectness of comparing the human and non-human data in the correlates of protection model, the overall evidence GRADE is 2 for the benefit of decrease the duration of antimicrobials when given in conjunction with dose-sparing schedules. Again, harm was not a factor for this question.

There were 6 additional studies, 4 RCT and 2 observational, that supported the data on the immune response in humans for the licensed PEP dosing schedule at time points prior to 60 days, so the WG felt better about the evidence for decreasing the antimicrobial duration when using the licensed schedule. However, again given the indirectness of the comparison of the human and non-human data, the overall GRADE for the benefit of decreasing the antimicrobial duration in conjunction with the licensed PEP schedule is 2.

To recap the GRADE summary, for the question regarding whether the IM ROA can be used as an alternative during a mass vaccination campaign, the overall GRADE was a 2 for benefit and 1 for harm. For the questions on dose-sparing strategies and antimicrobials duration for PEP when used in conjunction with vaccine, the overall grade was a 2 for benefit and harm was not assessed.

Summary of WG Considerations and Proposed Policy Options

William Bower, MD, FIDSA
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Bower presented the Anthrax Vaccine WG's deliberations on potential policy changes to AVA use for PEP, first reviewing the current indications for AVA. The following recommended uses of AVA came out of the last ACIP review in 2010. First, AVA was recommended for preventing infection in persons before exposure to *B. anthracis* by giving a 5-dose series administered by the IM route at 0, 1, 6, 12, and 18 months, followed by annual boosters. This is called PrEP. Second, AVA was recommended to prevent infection after exposure to aerosolized *B. anthracis* spores by administering a 3-dose series by the SC route at 0, 2, and 4 weeks in conjunction with a 60-day course of antimicrobials. This use is called PEP. As of 2010, the FDA had not approved the PEP indication for AVA, so it was to be used under an Investigational New Drug (IND) or possibly an Emergency Use Authorization (EUA) provision for this indication.

Since the last ACIP review of AVA, there have been slight modifications to the licensed indications. In 2012, FDA approved a change in the PrEP priming series from 5 doses over 18 months to 3 doses over 6 months followed by boosters at 12 and 18 months and annually thereafter. This was based on data that showed protective antibody concentrations were obtained by 6 months. This allowed for work in environments with potential exposures to *B. anthracis* to begin sooner. In 2015, AVA was licensed for PEP in person who have been potentially exposed to aerosolized *B. anthracis* spores. For this indication, it is given in a 3-dose series administered SC at 0, 2, and 4 weeks. Antimicrobials are to be co-administered for 60 days. These changes will be added to the updated policy recommendations to align them with the licensed indications.

AVA currently is licensed for persons 18 through 65 years of age. There are little to no data on the use of AVA in children, pregnant women, or geriatric populations. However, the benefit of preventing anthrax in persons potentially exposed to aerosolized *B. anthracis* spores is believed to outweigh the potential unknown AEs from receipt of the vaccine. AAP and American Congress of Obstetricians and Gynecologists (ACOG) both recommend using the vaccine as recommended for the general adult population under the appropriate emergency use protocols. These policy changes will apply to all populations, except where explicitly stated otherwise.

The WG reviewed new AVA safety data published since the last ACIP review. All but one of the studies listed here showed no association between receipt of AVA and the measured adverse outcome:

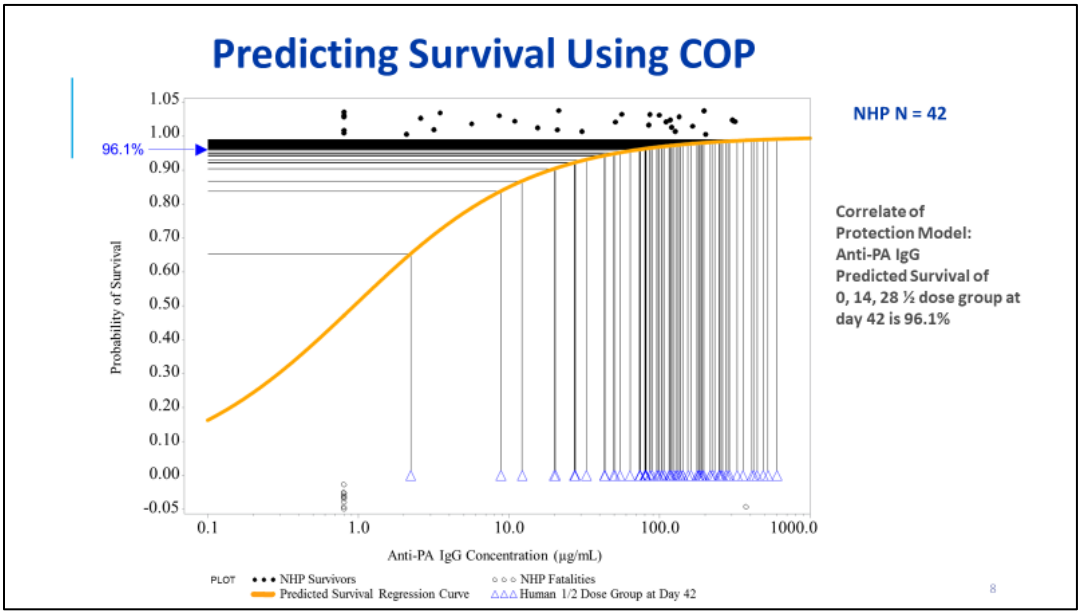
Study	Study Design (# Participants)	Measure(s)	Outcome
Phillips CJ. *Vaccine.* 2009	Cohort study (1497)	Develop Squalene Antibodies	No association between squalene antibody status and chronic multi-symptom illness
Sulsky SI. *Vaccine.* 2011	Cohort study (1,001,546)	Disability Risk	AVA not associated with differences in risk of disability
Sulsky SI. *Vaccine.* 2011	Case-control study (154,780)	Disability	No association between receipt of AVA and long-term disability
Stewart B. *Vaccine.* 2012.	Randomized controlled trial (1562)	Health-Related Quality of Life	No association between receipt of AVA and quality of life over a 42-month period
Duderstadt, SK. *Vaccine.* 2012	Retrospective population-based cohort (2.3 million)	Type 1 Diabetes	No increased risk for AVA and type 1 diabetes
Conlin AM. *Vaccine.* 2015	Retrospective cohort (126,839)	Birth Defects	No associations between AVA vaccination during pregnancy and birth defect risk
Bardenheier BH. *Military Medicine.* 2016	Matched case-control (463)	Rheumatoid Arthritis (RA) Systemic Lupus Erythematosus (SLE)	AVA associated with recent onset but not long-term RA No association with SLE

The one study, listed at the bottom, that showed a potential AE suggested an association between onset of rheumatoid arthritis (RA) and recent receipt of AVA. The authors felt that since there was no association with long-term onset of RA, that AVA might have triggered earlier onset in persons who would have eventually developed RA.

The WG felt that were no new safety concerns based on VAERS review or data published since AVA was last reviewed. These data continue to support the safety of AVA for use as PrEP and PEP given the high mortality associated with anthrax. The WG felt that more data are needed to evaluate the safety of AVA in pediatric populations.

As discussed earlier, inhalation anthrax is rare so it is not possible to assess the effectiveness of AVA directly for PEP in humans. Because of this, the FDA has recommended using the "Animal Rule." This allows bridging of data from animal and human studies to determine correlates of protection and subsequently to estimate human survival based on post-vaccination antibody concentrations. The Sivko study was used to generate a range of anti-PA IgG concentrations and survival data to produce the survival curve for the correlates of protection model. Two other animal studies supported the data derived in the Sivko study. The Wright paper provided a direct comparison between the immunologic response and AE for AVA given by the IM and SC ROA. These data inform the decision on the alternative route of administration. The human immunogenicity data for the dose-sparing schedule came from the Bernstein paper that compared the dose-sparing schedules being considered during this session. The data to support a decrease in antimicrobial PEP duration came from these studies plus others that looked at immunogenicity of AVA when given on the licensed schedule.

For an example of how this works, this is the Kohberger Method for bridging animal and human data to determine correlates of protection and the model the FDA recommends for predicting human survival based on antibody concentrations generated in animal models:



The NHP were given AVA at 0 and 14 days. On the above graph, the x-axis shows concentration of anti-PA antibodies levels at the time just prior to challenge with around 205 LD_{50} *B. anthracis* spores on day 28. The NHP survivors are represented by the black circles at the top of the graph and the non-survivors are represented by the white circles at the bottom. A logistic regression curve of estimate survival is then plotted. The probability of survival is on the y-axis based on the NHP anti-PA IgG concentrations. The blue triangles are the human anti-PA IgG concentrations at 42 days after receiving half-dose AVA at 0, 14, and 28 days. Plotting the individual probabilities of survival and taking the average results in the mean survival for the population. In this example, the probability of survival at 42 days after receiving half dose AVA at 0, 14 , and 28 days is 96.1%.

As a reminder, the policy questions for ACIP to consider during this session all focused on the use of AVA as PEP. The first two questions for ACIP to consider pertained to ways to optimize vaccination in a mass vaccination event, while the third question related to duration of antimicrobial use in conjunction with vaccine.

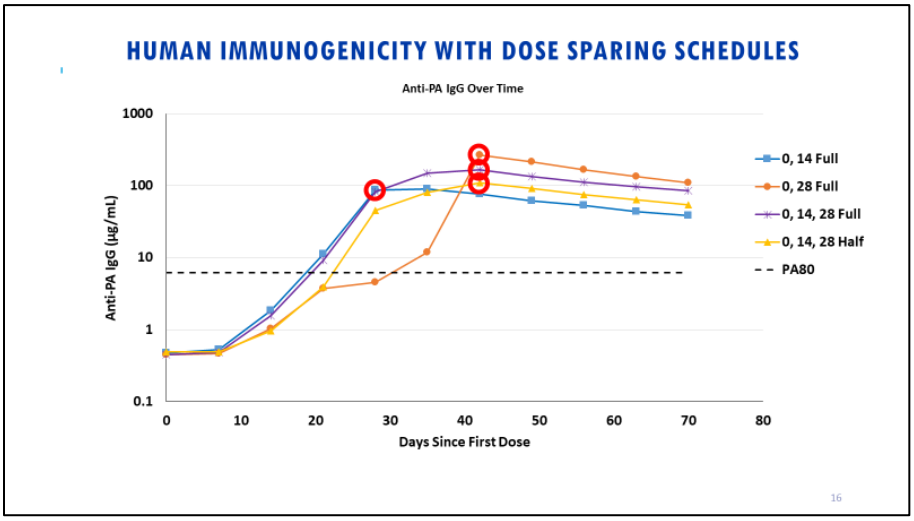
Regarding the WG's deliberations on the first policy question, the antibody concentrations were significantly lower at day 28 following receipt of AVA given by the IM route compared to the SC route. However, using the correlates of protection model discussed earlier, the estimated human survival is very high at this time point and only 3.8% points different from the SC route. In addition, at this time point, as long as they are adherent with recommendations, vaccine recipients should still be protected by the antimicrobials that are given in conjunction with vaccine. By day 56, the antibody concentration and predicted survival for AVA given by the IM and SC routes are no longer significantly different. The SC ROA produced significantly more frequent localized AEs in most of the parameters evaluated. For systemic AEs, the IM ROA had a higher occurrence of generalized muscle aches compared to the SC route. Otherwise, there were no other statistical differences for systemic AEs.

There are some operational concerns related to a mass anthrax vaccination campaign. Data from an anthrax event in 2001 suggest that adherence to the antimicrobial component of anthrax PEP wanes over time and could be as low as 50% by day 30 of the 60-day antimicrobial PEP recommendation. Higher antibody concentrations achieved by the SC ROA could protect persons who are not adherent to the antimicrobial component of PEP. However, these studies on adherence were done in a unique situation and may not be generalizable to a mass exposure event if it occurred today. The higher rates of localized AEs for the subcutaneous compared to intramuscular route of administration raises concerns that individuals might not return for subsequent vaccine doses.

In order to administer vaccine to a large number of people during a mass casualty event, the most efficient method available is needed. Most routine vaccines are given by the IM route and healthcare personnel/providers (HCP) are more accustomed to giving IM injections. Because there is more experience in the healthcare community giving IM injections, this route might be more efficient for quickly vaccinating large numbers of individuals. In addition, many state and local jurisdictions plan to use just-in-time training for persons to administer AVA during a mass vaccination event. When surveyed, they stated that the IM route is easier to teach and thus may be more efficient.

The WG preferred the SC route of administration over the IM route due to the higher antibody concentrations at 4 weeks that would provide higher levels of protection to individuals who were not adherent to the antimicrobial portion of PEP. Thus, this route of administration should be used whenever possible. However, when balancing the operational concern of administering vaccine to a large number of people over a short period of time, the WG agreed that AVA for PEP may be administered using an IM route if the SC ROA poses significant materiel, personnel, or clinical challenges that might delay or preclude vaccination. The WG also thought it was acceptable for individuals to receive the vaccine by the IM route if they had experienced significant AEs from AVA administered by the SC route.

Regarding the WG's deliberations on the second policy question, this graph shows the human anti-PA IgG concentrations over time with the various dose-sparing schedules reviewed by the WG:

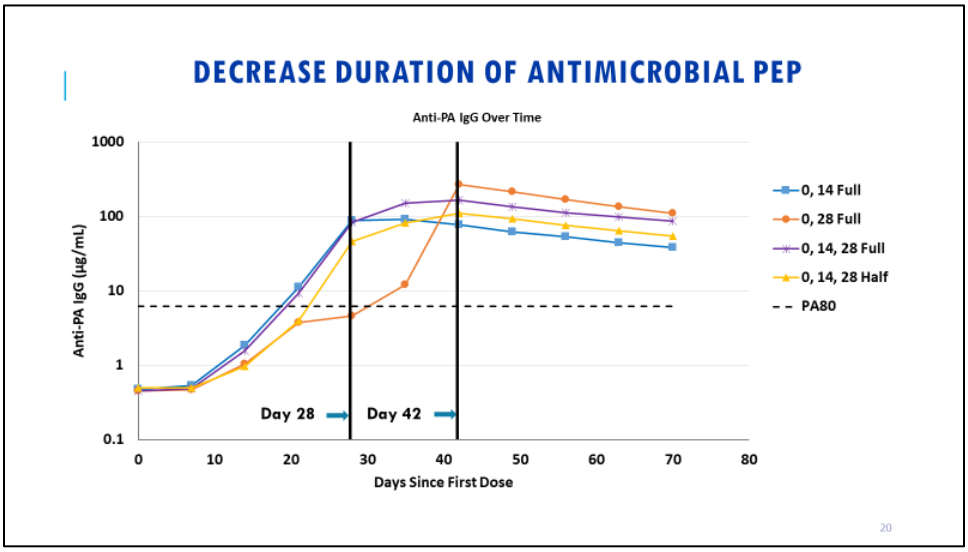


AVA given as 2 full doses at 0 and 14 days is represented by the blue line; AVA given as 2 full doses at 0 and 28 days by the orange line; and AVA given as three half doses at 0, 14, and 28 days by the yellow line. The licensed schedule, 3 full doses at 0, 14 and 28 days is represented by the purple line. The dashed line represents the antibody concentration that provides an estimated 80% level of protection as determined from the correlates of protection model. This graph shows that the three groups that received a dose at day 14 have higher antibody concentrations at day 28 than the one group that did not. The 2 full doses 28 days apart produced the highest antibody concentrations from day 42 onward. The 3 full doses produced higher antibody concentrations than the 3 half doses. Peak response is 2 weeks after the last dose for all the schedules and the peak response is estimated by the correlates of protection model to be highly protective.

The predicted survival at day 28 was high for the groups who received 2 doses, but was lower for the 0, 28 full-dose group who had only received 1 dose at that time point. The predicted survival was very high at day 42 for all dosing schedules and continued at a high level of predicted survival through day 63.

The WG agreed that all dose-sparing schedules provide high levels of estimated protection 2 weeks after the last dose and that the protection was only slightly less than the estimated protection provided by the licensed schedule. Thus, it seems reasonable that in an actual or impending vaccine shortage, the benefits of providing protection to a larger number of individuals outweigh the risk of slightly lower protective levels. The selection of the dose-sparing strategy to implement depends upon the anticipated shortage. The 2 full-dose strategy will expand the vaccine supply by 50%, and the 3 half-dose strategy will expand it by 100%.

With regard to the WG's deliberations on the third policy question, this is the same graph as previously shown but with lines at days 28 and 42:



These are the two time points the WG evaluated when considering shortening the antimicrobial duration. Again, this graph shows the human anti-PA IgG concentration over time with the various dose-sparing schedules and the currently licensed schedule. The dashed line represents the antibody concentration that provides an estimated 80% level of protection determined from the correlates of protection model. The vertical line at day 28 is when

individuals received the last dose if using the licensed schedule or the proposed dose-sparing schedules, except for the day 0 and 14 dose-sparing schedule. The line at day 42 is 2 weeks after the last dose of all the schedules that end on day 28, and is 4 weeks after the end of the day 0 and 14 dose-sparing schedule.

Estimated protection at days 28, 42, and 63 for the dose-sparing schedules was reviewed by the WG. The estimated peak protection for all schedules occurred 2 weeks after the last dose, is estimated to be highly protective, and is maintained through day 60 when the antimicrobial component of PEP is currently recommended to end. It is important to note that the animal studies used to develop the estimated levels of protection used a high-dose challenge at day 28 with no antibiotics; whereas, humans in an exposure scenario would have only residual spores 4 to 6 weeks after an initial exposure, so this is considered to be an extremely conservative worst-case estimate.

For most of the dose-sparing schedules as well as the licensed schedule, day 42 is 2 weeks after the last dose. For the 0- and 14-day dose-sparing schedule, day 28 is 2 weeks after the last dose. The peak response occurs around 2 weeks after the last dose for the currently licensed schedule and for all dose-sparing schedules. The peak response in all the schedules is estimated to be highly protective. However, even though the peak response is at day 28 for the 0- and 14-day dose-sparing schedule, the WG advised continuing antimicrobials for 42 days to allow for additional clearance of residual spores from the lungs. Discontinuation of the antimicrobial component of PEP once peak immune response is reached would shorten the antimicrobial requirement and potentially reduce AEs related to continued antimicrobial use. Shortening the duration of the antimicrobial component of PEP might improve adherence.

The WG felt that the antimicrobial component of PEP could be discontinued at 42 days after initiation of vaccine if given on schedule for both the licensed and dose-sparing schedules. However, it is important to note that the second dose of vaccine is critical to producing high antibody concentrations, so to take that into consideration that in an emergency situation the vaccine may not be given exactly on schedule, the WG advised that in immunocompetent individuals, antimicrobials should be continued for at least 42 days after the first dose or 2 weeks after the last dose of the vaccine series, whichever comes last. Since there is no reason to suggest that giving vaccine should lengthen the need for antimicrobial PEP, the WG saw no need to continue antimicrobials past 60 days, which is the recommended length for antimicrobial PEP when not given in conjunction with vaccine.

The above recommendation is for otherwise healthy individuals 18 through 65 years of age. Persons with an immunocompromising condition that might interfere with their ability to develop an adequate immune response or populations where there are no data on immune response, such as those 65 years of age and older, should continue to receive antimicrobials for 60 days concurrently with vaccine. Some of the WG members felt that despite the lack of data, there is also no evidence to suggest children would not have a robust immune response to AVA. A minority of WG members felt that decreasing the duration of antimicrobials as described above could be extended to otherwise healthy children 2 through 17 years of age.

The WG's deliberations and forthcoming recommendations will be used by CDC to inform state and local health departments to better prepare for an emergency response to wide-area release of *B. anthracis* spores. As a reminder, when considering this evidence, the human data were derived from studies in healthy adults 18 to 65 years of age. Thus, the evidence is less supportive in age groups outside this range or in special populations.

The WG proposed the following policy language for an ACIP vote:

- ❑ The IM ROA may be used if the SC ROA presents clinical, operational, or logistical challenges that may delay or prevent effective vaccination
- ❑ Should there be an inadequate supply of anthrax vaccine available for PEP, either 2 full doses or 3 half doses of AVA may be used to expand vaccine coverage
- ❑ In immunocompetent individuals 18-65 years of age, antimicrobials given in conjunction with vaccine may be discontinued at 42 days after the first vaccine dose or 2 weeks after the last vaccine dose, whichever comes later

Discussion Points

Recognizing that vaccine is licensed only for those 18 years of age and older and that the evidence and recommendations align with that, Ms. Pellegrini inquired as to whether the WG meant for the first two questions also to apply to children in addition to the question about antibiotics. She also wondered whether there was any intent to obtain animal data to address that age group.

Dr. Bower responded that the WG believes that in a mass event, vaccinating everybody in the same way would be important for operational issues and that the immune response in children should be robust. While there are no plans to obtain animal data, if there is an event, data will be collected on immunogenicity and side effects in children and older adults.

Dr. Walter asked what defines a large mass vaccination event in which a switch would be made to a dose-sparing strategy.

Dr. Bower replied that there is not a specified trigger. This decision would be left up to the operational capacity of the jurisdiction in which an event was occurring. This would be an exceedingly rare event that hopefully would never occur, but they have to anticipate that such a situation could occur. Different jurisdictions will be able to handle such a situation differently, so it would have to be decided at the time. That is why it is so important to have these types of discussions ahead of time.

Dr. Messonnier added that in the event of a mass event, guidance will be provided by HHS. It really will be a question of whether the exposed population exceeds the vaccine supply, so it will not be left completely to the jurisdictions to make those decisions. This would be an anxious and hectic time and those jurisdictions will be looking to CDC. The idea of this policy is to help CDC and HHS assess local capacity if there is an event. The intention is also for pregnant women to be vaccinated in the assumption that the exposure risk is there, with the idea that pregnant women also would be studied in the event setting.

Dr. Bernstein asked whether there is a lower age with regard to the inclusion of the pediatric population.

Dr. Bower relayed that the WG felt that 2 years of age would be the lower end. There are no data on anyone less than 18 years of age.

Dr. Cohn clarified that this pertained to antimicrobial administration versus vaccination, so she asked where children 0 to 2 years of age would go in terms of antimicrobial duration.

Dr. Bower responded that for children 2 through 17 years of age, the WG was requesting further information about whether ACIP was agreeable with decreasing the antimicrobial duration for those 18 through 65 years of age and those 2 through 17 years of age.

Henry Walker (SME) clarified that the current plan is to give 60 days of antimicrobials for those under 18 years of age. The question for ACIP regards whether this could be reduced to 42 days for children 2 through 17 years of age. A minority of WG members felt that decreasing the duration of antimicrobials to 42 days could be extended to otherwise healthy children 2 through 17 years of age.

Dr. Stephens emphasized that there are no data and only a minority of the WG members thought that a reduction to 42 days would be acceptable specifically in children 2 through 17 years of age.

Dr. Atmar added that the majority of the WG members felt that in the absence of data and regardless of the risk group (children, pregnant women, persons over 65 years of age, immunocompromised persons), the 60-day duration of PEP should be the default used. The majority of WG members felt that where there are data, among otherwise healthy individuals 18 through 65 years of age, the shorter PEP period of 42 days would be acceptable.

Dr. Bennett asked whether the WG considered what would happen if dose-sparing was used in addition to using an IM route and how that would play out in terms of immunogenicity.
Dr. Stephens replied that there was considerable concern and discussion about the IM ROA, particularly given the difference at 28 days in particular in terms of the immunogenicity. The WG revisited this issue on a number of occasions and there was concern regarding whether a dose-sparing regimen in addition to IM ROA would be a consideration. The dose-sparing data do look pretty good at least 2 weeks after that dose.

Dr. Atmar thought there were two questions, one of which regarded the antibiotic prophylaxis duration. There was a lot of discussion about whether it could be even shorter than 42 days depending upon the regimen. Based on the graphs that were shown, 42 days looked to be a good point at which everyone who had received at least 2 doses should have high levels of antibody. SC versus IM was based on the logistic regression model shown on slide 8 showing that only one NHP with a high level of detectable (LOD) antibody died after challenge. All of the other ones who died were at or below the LOD threshold. Essentially, with that one exception that is not understood, the NHP that had detectable antibody were protected. Most of the WG members felt that going by the logistic regression model was appropriate, but some wondered whether there should be a threshold of detectable antibody. The consensus was that higher antibody levels are better in SC at 28 days versus IM, which was the reason for the preference of SC over IM.

Dr. Bower pointed out that the one NHP that died had developed anthrax meningitis, which is the presumed reason it had a high antibody titer but still died because the CNS is a privileged site and the antibodies were not getting in there. A good point is that if one develops almost any detectable level of antibody, there is protection.

Ms. Pellegrini inquired as to whether ACIP would be asked to express a preference on the dose-sparing schedule between 2 versus 3 and if 2, which schedule.

Dr. Bower clarified that he thought they were asking for permission to use either one depending upon the situation.

Dr. Romero recalled the 4th bullet on Slide 14 showing the WG's conclusions that states, "Individuals that experienced significant adverse events from AVA administered by the SC route of administration may elect to receive the subsequent vaccine dose(s) by the IM route in consultation with a provider." He wondered whether there was a plan to define what a "significant adverse event" entails.

Dr. Bower replied that while this was not discussed, it could be further clarified, and probably would be defined in consultation with the vaccine provider.

Dr. Frey pointed out that they must remember when trying to make up their minds about these very complicated questions with intricate data that they were only being asked to use this response if there are inadequate supplies in the midst of an event or events and depending upon the potential number of people who could be exposed. She asked whether they thought there would be a limited supply of ciprofloxacin in this situation, and if there are any data or there have been any models looking at the potential number of events that could occur simultaneously at any given time.

Dr. Bower replied that there are a lot of antimicrobials stockpiled, so the chances of those being a limited resource are very low. One situation would be if the organism used was resistant to one of the first line antimicrobials, which might result in an insufficient supply. The reason a decrease of antimicrobials was requested is because the data support decreasing it earlier, and getting people off of antimicrobials earlier will cut down on related AEs.

Henry Walker (SME) added that there are models from CDC, the Biomedical Advanced Research and Development Authority (BARDA), and others as the initial uptick in cases is seen to get an idea of how big an event might be. Of course, that is in one city at one point. There could be multiple cities.

Dr. Messonnier emphasized that this is contingency planning in case there is insufficient vaccine, but there also is a concern about the needles. There is a much larger stock of IM needles than SC needles. There is a potential that the right needles would not be available in the right settings. In addition, a new adjuvanted anthrax vaccine is expected to be licensed and should be in the stockpile soon. It is an IM vaccine given at Day 0 and Day 14. Therefore, operational complications are anticipated with both vaccines being in the field at the same time and the need to simplify in chaotic times.

Dr. Campbell indicated that AAP/COID recommends 60 days of antimicrobial PEP for children and does not support shortening this to 42 days. They agreed with the first two bullets in the proposed policy language in terms of IM and dose-sparing when necessary for children.

Ms. Pellegrini suggested that they consider expressing a preference for the 0, 14 schedule. Based on Slide 16, immunogenicity peaked most quickly with the 0, 14 full schedule. Based on human nature, the 0, 14 schedule is more likely to lead to higher levels of compliance. If people go a month without getting sick, some of them will not return. However, they might return in 2 weeks.

Dr. Bower agreed that waiting a month might result in losing some people, but in the type of mass event in which this would be implemented, they were not confident that they would be able to do it at exactly 0 and 14 days. This is why they suggested at 0 and between 2 to 4 weeks. However, he thought that if ACIP wanted to put either 2 full doses at 0, 14 or 3 half doses at 0, 14, 28 days that would be fine.

Dr. Stephens asked whether that was what Ms. Pellegrini was recommending.

Ms. Pellegrini clarified that she did not think they should rule out 0, 28 if for some reason statistically or otherwise that made the most sense. She was expressing a preference for 0, 14 based on the circumstances.

Dr. Messonnier asked whether this could go in the operational implementation guidance rather than the language of the recommendations.

Dr. Atmar emphasized that 0, 28 had the highest antibody levels achieved by Day 42.

Dr. Bennett advocated for not including this in the recommendation itself, but instead including it in the guidance. It could be clarified there that 0, 28 achieved higher levels, but that 0, 14 may be preferable.

Dr. Bower indicated that the way they were thinking about doing this was to put the data out to basically say 0, 14 higher/quicker and 0, 28 slower but longer.

For the second bullet point, Dr. Lee asked whether they were specifying SC or IM or if they were allowing flexibility.

Dr. Bower replied that they were not planning to be specific unless that was what ACIP wanted to do.

Dr. Bennett noted that it is possible that people would receive IM rather than SC and then also receive a dose-sparing dose. It is not known what the result would be. She thought it could be made clear in the guidance that if the IM ROA is used, one might consider either not using a dose-sparing regimen or continuing antibiotics for the full 60 days if a dose-sparing regimen is used.

Dr. Belongia agreed, given that there are no real data.

Dr. Lee thought the evidence tables were nicely presented to provide evidence for the SC approach, and because of the lack of data, for her it was a different question. On the operational side, it may be completely appropriate. However, she felt like the evidence had to be reflected in terms of the recommendation itself. She favored that the dose-sparing would be appropriate for SC ROA and acknowledging that there are no data for IM, but clarified that the recommendation had to align with the ETR tables functionally.

Dr. Messonnier thought this would be fine, emphasizing that they would see this again soon. In an effort to get consensus, if SC made everyone more comfortable, that would be fine. They will ask the WG to look at the data again in the context of the new vaccine and come back to ACIP if there is any desire to make a change.

Dr. Bennett expressed concern that they were creating permissive recommendations for an emergency in this country. She frankly thought they should give the best guidance they could, but make it as unrestrictive as possible because depending upon the scenario, they might have to use IM and dose-sparing regimen. This is not something for which they can make perfect recommendations.

Dr. Bower stressed that the reason they are doing this is because they know that getting vaccine into people's arms however possible will save lives. Therefore, they do not want to restrict getting vaccine into people's arms.

Regarding Dr. Lee's question, Dr. Bernstein did not think they needed this in the second bullet if they voted for the first. A preference is not needed one way or another because they were talking about an inadequate supply, which would then fall under one of the challenges. That is, if they voted for the first bullet, a ROA is not needed for the second bullet.

In support of Ms. Pellegrini's position and looking into the future when considering the new vaccine, Dr. Moore said she would love to be able to make a comment on the 0, 14 schedule being preferred when at all possible as supplies permit. It sounds like that would be harmonized with the new vaccine as well. Operationally, as a person who has been through PEP for anthrax in the past, anything that can be done to shorten antimicrobial and vaccine courses and go from 3 to 2 doses is going to increase the number of people adequately protected dramatically.

Public Comment

Andrea Woodruff
Concerned Parent

I have been quarantined a couple of times years ago in the Senate when there were some anthrax scares, so I've had time to think about this a little bit. A common topic that is brought up is that troops are vaccinated every single time that they are deployed, and so it would be nice to see some discussion instead of just revaccinating if titers can be checked or what can happen there. Considering it looks like the peak time for AEs is going to be a little bit later, I didn't know how that was going to be considered when people were reporting those numbers. Also, as a parent, with the mandates and everything, I would really like to have the choice of what doses. I would like to be in control over making the decisions and see if that vaccine is necessary for my child or not. That's it. Thanks.

Erika Geuser
Georgia Coalition for Vaccine Choice
Concerned Parent

This is my first meeting here, so thank you guys for your time and efforts on all of this. It's so very important what you guys are doing here. Listening to some of what you're talking about, I'm trying to wrap my head around it because I heard the lovely gentleman that presented talk about how we don't really know, you know, what the risks are for children. But, we still say that the benefits outweigh those risks. I'm just trying to, you know, understand and get how you guys come to that decision. I think it's an important decision and it must be such a hard job for you guys to make these decisions without the proper information that you need to do so. So, maybe if somebody could fill me in a little bit on that. I too hope there is choice involved when it comes to my child. If there is a mass event and you guys don't have safety information, I think it would hopefully be my choice as a parent to decide if that is going to be put in myself and my family.

Thank you so much. Dr. Bennett referred Ms. Geuser to some of CDC's previous publications about the risks of anthrax and ways of addressing them.

Motion/Vote: Anthrax Recommendations

Dr. Stephens made a motion to approve and Dr. Hunter seconded the following recommendation language: 1) The IM ROA may be used if the SC ROA presents clinical, operational, or logistical challenges that may delay or prevent effective vaccination; 2) Should there be an inadequate supply of anthrax vaccine available for PEP, either 2 full doses or 3 half doses of AVA may be used to expand vaccine coverage; and 3) In immunocompetent individuals 18-65 years of age, antimicrobials given in conjunction with vaccine may be discontinued at 42 days after the first vaccine dose or 2 weeks after the last vaccine dose, whichever comes later.

The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

14 Favored:	Atmar, Belongia, Bennett, Bernstein, Frey, Hunter, Lee, Moore, Pellegrini, Riley, Romero, Stephens, Szilagyi, Walter
0 Opposed:	N/A
0 Abstained:	N/A

Human Papillomavirus (HPV) Vaccines

Introduction

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

Dr. Szilagyi indicated that the ACIP HPV Vaccines WG is considering a new issue. An application to expand the age indication for 9-valent HPV vaccine (9vHPV) through age 45 years in males and females was submitted to the FDA in April 2018. The current licensure is through age 26 years. The FDA accepted the application and will give this a priority review. The focus of this HPV session was to begin the evidence review for policy considerations.

Before reviewing the agenda for this session, Dr. Szilagyi reviewed the past ACIP meeting and work of the WG. The HPV vaccine session at the last meeting focused on two issues. First, the WG presented an update on post-licensure HPV vaccine safety, specifically for 9vHPV. The WG and the Immunization Safety Office (ISO) at CDC periodically update ACIP on vaccine safety, and this was the first presentation of 9vHPV safety data to ACIP. In the second part of the session, there were presentations related to harmonization of the HPV vaccination age recommendations for females and males through age 26 years. The WG had been considering this issue, preparing to bring this to ACIP for a vote. Presentations included a review of burden and trends in HPV-associated cancers in males and females, the epidemiology of HPV infection in males, and WG plans.

The ACIP HPV Vaccines WG was informed about the application for the age expansion after the February 2018 ACIP meeting. WG calls have focused on background information related to the expanded age. There is strong support on the WG for harmonization, which will be part of the considerations going forward as the WG considers the evidence for the expanded age indication.

This session focused on a review of the background information related to the expanded age, HPV vaccine in mid-adults with results from clinical studies, WG considerations, and future WG plans.

Background: Application for Expanded Age Indication for 9-Valent HPV Vaccine

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 background for the application for an expanded age indication for 9vHPV. She gave some background information on the US program as well as HPV vaccine licensure related to the application for expanded age indication, and provided a brief overview of some of the clinical trials in persons over age 26 years.

In terms of the evolution of the vaccination program in the US, quadrivalent HPV vaccine (4vHPV) was licensed and recommended for use in females in 2006. Bivalent HPV vaccine (2vHPV) was licensed and recommended for females in 2009. While 4vHPV vaccine was licensed in males in 2009, it was not until 2011 when it was included the routine program. In 2015, 9vHPV was recommended for females and males. At that time, it was recommended that any of the three vaccines could be used in females and either 4vHPV or 9vHPV could be used in males. At present, three HPV vaccines are licensed for use in the US: 2vHPV produced by GSK and licensed for use in females 9 through 25 years of age, and 4vHPV and 9vHPV produced by Merck and licensed for use in females and males 9 through 26 years of age. Only 9vHPV has been available in the US since the end of 2016, while 2vHPV and 4vHPV continue to be available in other countries.

The current recommendations for HPV vaccination in the US are as follows:

- Routine HPV vaccination at age 11 or 12 years:
  - The vaccination series can be started beginning at age 9 years

- HPV vaccination is also recommended for the following persons if not adequately vaccinated previously:
  - Females through age 26 years
  - Males through age 21 years
  - Men who have sex with men (MSM), transgender persons, or persons with certain immunocompromising conditions, through age 26 years
  - Males aged 22 through 26 years may be vaccinated

The 9vHPV manufacturer filed a Supplemental Biologics License Application (sBLA) in April 2018 to expand the age indication for 9vHPV through age 45 years for females and males. The FDA accepted the application in June and will give it a priority review. The review is expected to be complete by early October. Because data from the 4vHPV efficacy trials are going to contribute to the 9vHPV application, Dr. Markowitz reviewed a brief history of these trials. Efficacy trials were conducted in females in two age groups. The first trials were in females aged 16 through 26 years. Data from these pivotal trials, along with immunogenicity data in 9 through 15-year-olds, led to licensure in females aged 9 through 26 years in 2006. A trial also was conducted in females aged 24 through 45 years.

With these data, Merck submitted an application to FDA in 2008 for an expanded age indication for females through age 45 years. The FDA did not approve an expanded age indication at that time, but allowed data from the clinical trial to be included in the label. The reasons this was not approved included lack of statistically significant efficacy for vaccine-type cervical intraepithelial neoplasia grade 2 or worse (CIN2+), and more cases in the vaccine group than in the control group in an intention-to-treat (ITT) analysis regardless of HPV type. On further analysis, this was considered to be caused primarily by an imbalance of infection and disease at randomization.

In 2009 and 2010, while FDA was reviewing the application for 4vHPV in mid-adult women, the ACIP HPV Vaccines WG considered data and options for use. But after the FDA decision in 2010, the WG did not bring this forward for a vote. A publication by Grant et al in *Vaccine* in 2011 reviewed some of the issues considered. As a reminder, at that time, the HPV vaccination program in the US was focused only on females, 4vHPV was being used in the US, and the vaccination program was less mature. More is known now about HPV vaccines and HPV natural history. Some of the same issues reviewed by the WG in 2010 will be reviewed for the current policy considerations.

While the age indication was not extended, information on 4vHPV in older women is included in the 4vHPV label as mentioned earlier. This is found in two places, in the safety section where it states that the adverse reaction profile in women 27 through 45 years was comparable to that in the younger females, and also in the clinical studies section where the results are summarized. The efficacy estimates for some endpoints are listed, which are high and statistically significant, such as prevention of vaccine type persistent infection, CIN of any grade, and genital warts. The lack of statistically significant efficacy against CIN2/3, AIS, or cervical cancer also is stated. A shorter section on 4vHPV trial data, but with basically the same information, is also included in the 9vHPV label.

While 4vHPV was not licensed for use in persons >26 years in the US, it has been by other regulatory agencies, as has been 2vHPV. 9vHPV has also been licensed for use over age 26. In Canada and Australia, all three vaccines are approved for use in females aged 9 through 45 years and 4vHPV and 9vHPV are approved for use in males aged 9 through 26 years. The European Medicines Agency (EMA) states that all three vaccines are approved for use “from the age of 9 years” implying no upper age limit. These are regulatory approvals. In most countries, HPV vaccination programs are limited to early adolescents, some countries have limited catch-up programs, and many countries do not include vaccination for males in their immunization program.

Dr. Markowitz gave a very brief overview of HPV vaccine clinical trials data in mid-adults that have led to regulatory approvals. Two efficacy trials have been conducted in mid-adult women, one for 4vHPV and one for 2vHPV. These were multi-national studies including women from 7 and 12 countries, respectively. This session addressed 9vHPV, for which the 4vHPV data are most relevant. The 4vHPV trial, also known as Future III, enrolled women aged 24 through 45 years and included over 3800 women. The 2vHPV trial, also known as Viviane, enrolled women older than age 25 and included over 5700 women. While the enrollment criteria varied somewhat, there was no exclusion for number of lifetime sex partners. The primary endpoints were similar: vaccine type 6-month persistent infection or vaccine-type related CIN1 or worse. The 4vHPV trial endpoint also included external genital lesions (EGL).

This table shows the per protocol efficacy results for the two trials for 16/18 related persistent infection, CIN, or EGL and for CIN2+ outcomes:

HPV 16,18-related	**4vHPV** Castellsagué et al. Br J Cancer 2011			**2vHPV** Wheeler et al. Lancet ID 2016		
	Cases			**Cases**		
	Vaccine	**Control**	**Efficacy (95% CI)**	**Vaccine**	**Control**	**Efficacy (96.2% CI)**
Persistent infection, CIN, EGL*	8	51	**84.7%** (67.5, 93.7)	7	71	**90.5%** (78.6, 96.5)
CIN2+	1	6	**83.4%** (-36.7, 99.6)	1	6	**83.7%** (-46.5, 99.7)

Per protocol: PCR negative and seronegative to relevant vaccine type, received 3 doses
CIN, cervical intraepithelial neoplasia, EGL, external genital lesions; CIN2+: CIN grade 2 or worse
Mean follow-up time 46 months for 4vHPV, 5.9 years for 2vHPV
*EGL included for 4vHPV endpoint

For the first endpoint, efficacy was statistically significant and similar in both trials at 84.7% and 90.5%. For 16/18 related CIN2+, the point estimates were very high, but were not statistically significant. There were very small numbers, with only 1 case in vaccine group and 6 in the control group in both trials.

There has been no efficacy trial in mid-adult males. A safety and immunogenicity study was conducted in men aged 27 through 45 years of age. This was an open label, single arm trial. Men received 3 doses of 4vHPV vaccine. Men were recruited from an ongoing natural history cohort study of HPV infection in men from sites in Florida and Mexico. About 150 men were enrolled, of whom 100% were seropositive to all 4 vaccine types after dose 3. Antibody titers were more than 10-fold higher than pre-vaccination titers among those seropositive on day 1, representing natural infection [Giuliano et al. Vaccine 2015].

In summary, since the end of 2016, 9vHPV is the only HPV vaccine available in the US. 9vHPV is licensed for use in males and females aged 9 through 26 years. A sBLA to expand the age indication for 9vHPV in males and females through age 45 years is being reviewed by the FDA. A 4vHPV efficacy trial was conducted in females aged 24 through 45 years showing high and statistically significant efficacy against persistent infection, CIN, and EGL due to the vaccine types. No 9vHPV efficacy trial has been conducted in males or females among persons >26 years, and no 4vHPV efficacy trial has been conducted among males in this age group. Bridging efficacy and immunogenicity data accepted for other HPV vaccine approvals will inform consideration of the expanded age application. The HPV Vaccine WG has just begun to review these issues.

.

9vHPV Vaccine for Mid-Adult Persons 27-45 Years of Age: Results from Clinical Studies

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

Dr. Luxembourg indicated that Merck is seeking an expanded indication for 9-valent HPV vaccine (9vHPV) in mid-adult women and men 27 through 45 years of age. They have been given priority review by the FDA, which underlines the importance of this extension. As a reminder, the upper age for the vaccine in the US is 26 years. In a number of countries outside the US (Canada, Australia, Europe), there is a higher adult age limit. There are no clinical trial data at this time for the 9vHPV vaccine in 27-45 year olds. However, given the importance of public health issues, need, and the fact that 9vHPV and quadrivalent HPV vaccine (4vHPV) are very similar in terms of the manufacturing process and their immunogenicity and efficacy, the data for 4vHPV are relevant to 9vHPV. Therefore, a number of regulatory agencies have concluded that 4vHPV vaccine efficacy and immunogenicity results can be bridged to 9vHPV vaccine. Dr. Luxembourg's presentation contained two parts: 4vHPV mid-adult studies and data supporting the similar efficacy and immunogenicity profile of 9vHPV versus 4vHPV.

A study that was begun in 2004 on 4vHPV has been ongoing for 10 years among women 24 through 45 years of age. There are two parts to this study. The first part, the base study, was placebo-controlled. The results of the base study were already published and were reviewed in the past by ACIP and the FDA. At the end of the base study, the group who received placebo was offered vaccination with 4vHPV. The study was then continued as a long-term follow-up (LTFU) extension. The primary analyses were conducted in the group that was vaccinated with 4vHPV in the base study. The group that received placebo in the base study and 4vHPV after the end of the base study was assessed in exploratory analyses.

The age range of the subjects in the base study was between 24 and 45 years at enrollment. The baseline HPV DNA prevalence was not very high, which underlines that these women continued to be susceptible to HPV as mid adults. It was possible to measure vaccine efficacy (VE) in the base study because there was a placebo control group. The study was mostly powered for HPV6/11/16/18-related 6 months persistent infection, and significance for other endpoints also was studied (e.g., CIN any grade, ≥ CIN 2, Condyloma related to HPV6/11/16/18) as reflected in this table:

Endpoint	qHPV Vaccine (N=1910)	Placebo (N=1907)	Efficacy (95% CI)
	Cases/ n	Cases/ n	
6-month PI	9 / 1581	85 / 1586	89.6% (79.3, 95.4)
CIN (any grade)	1 / 1581	17 / 1584	94.1% (62.5, 99.9)
≥ CIN 2	1 / 1581	6 / 1584	83.3% (-37.6, 99.6)
Condyloma	0 / 1600	7 / 1599	100% (30.8, 100)

As mentioned earlier, the study was not powered for HPV6/11/16/18-related CIN2/3. Although good efficacy was observed (83.3%), the analysis did not demonstrate statistical significance. The base study data have been published [Castellsague et al. *Br J Cancer.* 2011;105:28-37].

The safety profile of 4vHPV in adult women was consistent with the safety profile that was observed in clinical studies in younger females.

Regarding the long term follow-up (LTFU) extension, placebo recipients were offered vaccine after the end of the base study. The long-term extension was conducted in Colombia as it was the largest country in terms of enrollment and the investigators were very motivated to continue the study. A cohort of 685 Colombian subjects who received 4vHPV in the base study consented to participate in a long-term extension for a total of 10 years of follow-up, and 651 Colombian subjects who received placebo in the base study and 4vHPV after the base study were also followed in the extension for exploratory analyses. VE was evaluated in these subjects. The primary effectiveness endpoint for the long-term extension study was HPV6/11/16/18-related CIN or condyloma. The primary analysis population was the per-protocol population which included susceptible subjects. Subjects were not infected with HPV at baseline (i.e., Day 1 of the base study) and received 3 doses of 4vHPV within 1 year in the base study.

The LTFU study was conducted in women 24 through 45 years of age at enrollment in the base study. Since 9vHPV is already licensed and recommended in girls and women 9 through 26 years of age, Merck thought it was of interest to assess effectiveness in a subset of women 27 through 45 years of age at enrollment. There were 600 subjects 27 through 45 years of age at enrollment who received 4vHPV in the base study and continued in the LTFU study. Follow-up for effectiveness of these subjects in the base study and LTFU study combined is up to 10 years with a median of 9 years post-dose 3. When considering only this subset of women 27 through 45 years of age, 4vHPV efficacy in the base study was 95% for the composite endpoint of HPV6/11/16/18-related CIN and condyloma.

The data for the LTFU study were analyzed at 4-year intervals, to facilitate a comparison between the base study that was approximately 4 years and the LTFU study which extended over 6 additional years. This allowed Day 1 to Year 4 (base study) to be compared to Year 4 to Year 8 and Year 6 to Year 10. At year 4, there was only 1 case HPV6/11/16/18-related CIN and condyloma in the base study in the 4vHPV group, as reported previously. Looking at year 4 to year 8 and year 6 to year 10, there were zero new cases. Among participants from Colombia, there were zero cases in the base study and in the follow-up to 10 years. This speaks to sustained efficacy for 10 years. The efficacy analysis was based on HPV6/11/16/18, the four types in the vaccine. For the 10 types not in the vaccine (HPV31/33/35/39/45/51/52/56/58/59), there were a number of cases related to these types in the base study in both the placebo and 4vHPV groups, and cases were also observed in the LTFU study, suggesting that exposure to HPV was occurring in this population.

During the long-term follow-up, subjects remained exposed to non-vaccine types. Therefore, zero cases in the LTFU study for the vaccine types indicates real effectiveness. It is not due to lack of sexual activity or exposure to HPV. This LTFU study demonstrated durable effectiveness for 10 years among women who received 4vHPV between the ages of 27 and 45 years. Follow-up was through 10 years with a median of 9 years post-dose 3. No cases of HPV6/11/16/18-related cervical disease or condyloma occurred during the study extension in the presence of continuous exposure to HPV. Sustained immunogenicity also was demonstrated through 10 years post-vaccination. 4vHPV was generally well-tolerated, with no vaccine-related SAEs during the entire study.

Immunogenicity bridging analyses have been used to establish and/or support efficacy analyses. Merck reviewed all of the studies that were conducted in young and adult women and men to try to gain more insight by comparing immunogenicity. Data from the following studies were reviewed: 1) Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I[1] and II[2], which were efficacy studies of GARDASIL® in young women 16 through 26 years of age; 2) FUTURE III[3], which was an efficacy study in adult women 24 through 45 years of age; 3) Protocol V501-020, which was among young men 16 through 26 years of age[4]; and 4) the Mid-Adult Men (MAM) study, an external study among men 27 through 45 years of age[5] [[1]Garland et al. *N Engl J Med*. 2007;356:1928–1943; [2]FUTURE II Study Group. *N Engl J Med*. 2007;356:1915–1927; [3]Muñoz et al. *Lancet*. 2009;373:1949–1957; [4]Giuliano et al. *N Engl J Med*. 2011;364:401–411; [4]Palefsky et al. *N Engl J Med*. 2011;365:1576–1585; and [5]Giuliano et al. (2015) *Vaccine* 33:5640-5646].

Merck conducted two post-hoc immunogenicity bridging analyses (one in women, one in men) based on cross-study comparisons of 4vHPV trials. The objective was to compare HPV 6, 11, 16, and 18 GMTs at 1 month post-dose 3 between 27 through 45 year-olds and 16 through 26 year-olds. The non-inferiority criterion was the lower bound of the 95% CI of the GMT ratio of >0.67. The populations analyzed included women 27 through 45 years of age from FUTURE III; women 16 through 26 years of age pooled from FUTURE I, FUTURE II, and FUTURE III; men 27 through 45 years of age from the MAM study; and men 16 through 26 years of age from Protocol V501-020. When comparing GMTs at Month 7 in women 27 through 45 years of age in the per-protocol immunogenicity population versus women 16 through 26 years in the per-protocol immunogenicity population who received 4vHPV, non-inferiority was demonstrated for the 4 HPV types.

Based on these results, efficacy results previously established in women 16 through 26 years of age could be extended to women 27 through 45 years of age, including the endpoint of CIN2. The same analysis was conducted for men 27 through 45 years of age versus men 16 through 26 years of age. Non-inferiority was demonstrated for HPV types 6, 11, and 16. It is important to note that this is a small number of subjects and the main types causing disease in men are 6 and 16. Based on these results, efficacy results previously established in men 16 through 26 years of age could be extended to men 27 through 45 years of age.

As a reminder, other data already have been published and presented to CDC that support the similarity of the 9vHPV and 4vHPV. These data showed the efficacy of 4vHPV against HPV6/11/16/18-related disease was demonstrated in clinical studies in women16 through 26 years of age and women 27 through 45 years and men 16 through 26 years of age. Efficacy of 9vHPV against HPV6/11/16/18-related disease was inferred based on non-inferior HPV6/11/16/18 antibody response in the 9vHPV group versus the 4vHPV group regardless of age and gender. This was further supported by observation of a similar, low incidence of HPV6/11/16/18-related disease in a clinical study in women 16 through 26 years of age. The AE profiles of 9vHPV and 4vHPV vaccine are generally comparable. With 9vHPV, there are more injection-site AEs of mostly mild or moderate intensity. AEs are less frequent in men than in women [*Ref: Luxembourg A, Moeller E. Expert Rev Vaccines 2017; 16: 1119–39*].

A comparison at month 7 of 3 clinical studies in 3 demographic groups showed non-inferior immunogenicity of 9vHPV versus 4vHPV: Young Women 16 through 26 years of age[1], Girls 9 through 15 years of age[2], and Young Men 16 through 26 years of age[3]. The two vaccines continue to provide similar antibody responses, at least through 3 years post-vaccination (i.e., for the entire study period). Cases of cervical, vulvar or vaginal dysplasia or condyloma due to

the 4 vaccine types are very low in both vaccine groups[4] [[1]Joura et al. *N Engl J Med*. 2015;372:711–723; [2]Vesikari et al. *Pediatr Infect Dis J*. 2015;34:992–998; [3]Van Damme et al. *Vaccine*. 2016;34:4205–4212; [4]Huh et al. *Lancet* 2017; 390:2143-2159].

In conclusion, 4vHPV prevents HPV6/11/16/18-related CIN and condyloma through at least 10 years post-vaccination in women 27 through 45 years of age. Regarding immunogenicity, 4vHPV elicits HPV6/11/16/18 antibody responses in women and men 27 through 45 years of age that are non-inferior to antibody responses in women and men 16 through 26 years of age. These results support efficacy in women and men 27 through 45 years of age. In terms of safety, 4vHPV is generally well-tolerated in women/men 27 through 45 years of age. Clinical experience with 4vHPV is relevant to 9vHPV. The immunogenicity, efficacy, and safety profiles of the 2 vaccines are consistent. Both vaccines contain VLPs for HPV6/11/16/18 and are manufactured using similar processes. Therefore, the results obtained with 4vHPV are deemed applicable to 9vHPV.

Merck is conducting a 9vHPV study, Protocol V503-004 (CT.gov identifier: NCT03158220) in women 27 to 45 years of age. This ongoing study is a post-marketing commitment that was requested by the EMA. The primary objective is to demonstrate non-inferior GMTs at Month 7 in women 27 through 45 years of age versus women 16 through 26 years of age for the 7 high-risk types in the vaccine. The study population includes women 27 through 45 years of age (N=600) and a control group of women 16 through 26 years of age (N=600). Vaccine administration includes a standard 3-dose regimen (day 1, months 2 and 6) of 9vHPV vaccine. Analyses are expected in the second quarter of 2019.

Discussion Points

Dr. Hunter asked whether there are any data to suggest what the biological mechanism of the efficacy of HPV vaccine is in decreasing cervical intraepithelial neoplasia rates in women 27 through 45 years of age, especially whether it is due to preventing infection from HPV strains they have not been exposed to already versus preventing progress from an initial infection, to chronic infection, and then on to neoplasia.

Dr. Luxembourg replied that there are now new data from long-term clinical studies for 2vHPV and 4vHPV. The time of progression from persistent infection to low and high-grade cervical dysplasia has been assessed. These data are published. Interestingly, the rate of progression is similar in mid-adult women and in young women. These are very useful data because they show that during the studies, in a very controlled environment, natural history can be observed and it is very similar between young women and mid-adult women. Certainly, there are grounds to say that the mechanism of protection elicited by HPV vaccination is the same in both age groups. Moreover, mid-adult women continue to be exposed, especially if they have new sexual partners. It is difficult to answer the question regarding whether these could be existing infections that are reawakened and maybe the vaccine helps, because it is difficult to distinguish a latent infection from a re-infection. This is talked about a lot, but there are very few data. Merck can say that after 10 years of follow-up, they did not see any evidence of infections reemerging in the LTFU study in mid-adult women. It is a possibility, but the likelihood seems low. Certainly, there is a lot of benefit for protection against new infections in mid-adult women.

Dr. Bennett asked whether there was significant loss to follow-up in the LTFU studies.

Dr. Luxembourg said he thought they retained most of the Columbian women at about 75% to 80% of the initial enrollment in the LTFU studies. Attrition was similar to what has been seen in other studies at about 4% to 5%.

Dr. Riley inquired as to whether there were any plans for a cost analysis.

Dr. Markowitz indicated that she would go over this in the next presentation.

Dr. Lee asked whether Merck was able to look at the data by type-specific disease to get a sense of any difference in efficacy rate, and what proportion of women 25 through 49 years of age potentially would benefit.

Dr. Luxembourg replied that there were analyses by type in the base study. In the LTFU study, there were zero cases of all types. In terms of the proportion of women who would benefit, there was infection at baseline for all four types, but 6 and 16 were higher, which is very usual.

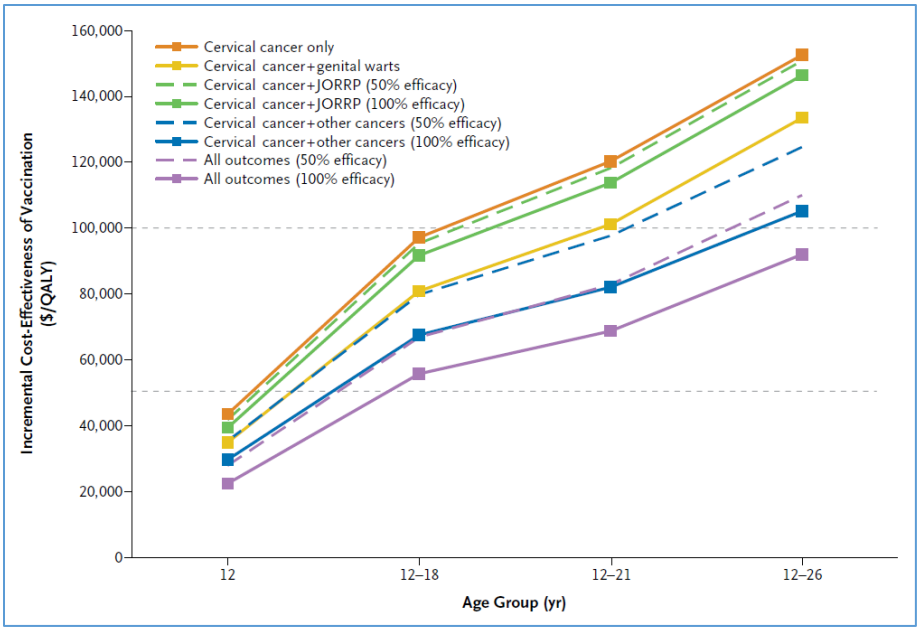
Considerations and ACIP HPV Vaccines WG Plans

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

In this talk, Dr. Markowitz reviewed some general consideration and the ACIP HPV Vaccine WG plans. Again, the WG just started to consider this as they were just recently made aware of the request to expand the age indication for 9-valent HPV vaccine (9vHPV) through age 45 years. During the October 2018 meeting, they will have more data and specific plans to share with the committee. She provided a brief introduction to policy considerations, followed by a high-level overview of the evidence that would help assess the burden and benefits in this population and age group, including epidemiology and some general concepts that would be important to think about. In addition, Dr. Markowitz presented the range of policy options that might be considered and plans for the October meeting.

In considering policy related to an extended age indication, it is important to emphasize that the available HPV vaccines are prophylactic. These vaccines will prevent new infections, and there are plenty of data from the vaccine trials showing that if someone was infected at the time of vaccination in the efficacy trials, vaccination did not prevent progression to a pre-cancer lesion and did not enhance clearance. Although additional evidence is coming out, this is still the basic understanding of these vaccines. Therefore, vaccination will have the greatest impact and is most cost-effective when administered before onset of sexual activity and HPV exposure. It is known that over 90% of men and women are sexually active before their mid-20s.Many modeling studies of HPV vaccination have been done, which show that the cost-effectiveness of vaccination becomes less favorable as age at vaccination increases* [*Kim et al. *NEJM* 2008; Kim et al. *Ann Intern Med* 2009; Canfell et al. *Vaccine* 2012].

To provide an idea of these data, Dr. Markowitz shared the following figure of some modeling done at the very beginning of policy considerations when there was a female-only vaccination program:



Kim et al. *NEJM* 2008

This figure shows the incremental cost-effectiveness of including older age groups in the vaccination program as well as different health outcomes. The main point of sharing this is to show that the cost per quality-adjusted life-year (QALY) increases quite dramatically with inclusion of older age groups, and also shows that vaccination is more favorable when the models include more health outcomes. A lot of work has been done on modeling since the beginning of HPV vaccination program. CDC will be updating modeling work for the upcoming policy considerations.

An expanded age indication would not impact the routine age for vaccination in the US, or the focus of the HPV vaccination program in young adolescents. The recommended age for vaccination is 11 through 12 years of age. However, an expanded age indication could impact the recommendations for catch-up and recommendations for people who are older than the routine catch-up age determined. ACIP's basic task is to determine the benefit of vaccination beyond the current catch-up age of 26 years.

The WG has started to review evidence of this specific policy issue using the Evidence to Recommendation (EtR) framework, which includes the following elements:

- ❑ PICO question and background
- ❑ Problem
- ❑ Benefits and harms
- ❑ Values
- ❑ Acceptability
- ❑ Resource use
- ❑ Feasibility of implementation
- ❑ Balance of consequences
- ❑ Type of recommendation and recommendation text

During this talk, Dr. Markowitz gave an overview of some of the data needed to define the burden of disease in order to inform the problem and the potential benefit of vaccination in this age group. The burden of disease associated with HPV includes outcomes that are associated with oncogenic or high-risk types, with 16/18 being the most important. These outcomes include a variety of anogenital cancers, oropharynx (OP) cancers, and intraepithelial neoplasias, which are detected through cervical cancer screening. The outcomes due to non-oncogenic types, primarily 6 and 11, are mainly anogenital warts and recurrent respiratory papillomatosis.

An HPV-attributable cancer is a cancer that is probably caused by HPV. CDC has estimated that during 2010 to 2014, HPV caused about 32,500 cancers in the US each year, with 19,700 cancers in women and 12,800 cancers in men. Most HPV-associated cancers in women were cervical cancers while in men, most were oropharynx cancers. During the last ACIP meeting, a talk was provided on the trends in HPV-associated cancers. HPV-associated cancers attributable to HPV of the oropharynx are increasing in the US, particularly in men. Overall, about 92% of these cancers could be prevented by 9vHPV.

The benefit of vaccination at different ages depends on preventing infections that lead to these precancers and cancers, which occur years or decades after infection. The benefit and potential impact of HPV vaccination is influenced by many things, including the likelihood of already having had a vaccine type infection, risk of incident infection, risk of development of disease from that incident infection, immunity after natural infection, and vaccine efficacy against reinfection.

HPV is a very common sexually transmitted infection (STI) in females and males. While much is known about the epidemiology, there are still many unknowns. Recently, there has been increased understanding with regard to differences by sex. Prevalence and infection rates may differ by sex, and patterns also may differ by anatomic site of infection. For example, prevalence at the genital site is higher than the oral site. Immune responses differ by anatomic site of infection, and response to natural infection is stronger and appears to be more protective against re-infection in females than males. Some of these are unknowns and data are preliminary on some of these issues [Giuliano et al. *Int J Cancer* 2015].

To provide an understanding of some epidemiology in the US, Dr. Markowitz showed data from a nationally representative survey, NHANES, showing any HPV prevalence in self-collected cervical vaginal swabs in females and penile swabs in males. “Any HPV” in these data includes any of 37 types that are measured by one of the widely used PCR assays. These data include the first national data among males. HPV prevalence is high in males and females, but there are some differences by age. As in many other studies in females, these data show that prevalence peaks in the early teens and late 20s and then is lower in older age groups. In males, prevalence is similar in those 25 through 29 years of age and older. These differences by sex may be due to differences in incidence of new infection, differences in clearance of infection, or both, or could be due to cohort effects, since this is a cross sectional survey. If due to new infections, they could be due to differences in sexual behavior or immunity after infection. It is important to note that HPV infection in younger age groups is likely due to new infections, while infections in older age groups are more likely to be due to a persistent infection [Lewis et al, *JID* 2018; Gargano et al, *JID* 2017; NHANES (National Health and Nutrition Examination Survey)].

Many sexual behavior surveys in the US show that the percentage of persons with a new sex partner decreases with increasing age after age 20 for men and women. Data from NHANES show that the percent with at least one new partner in the past year, while higher for males than females, was lower in successively older age groups for both females and males. In spite of this, among males, prevalence was similar in successively older age groups.

Consistent with data from prevalence studies, prospective data show that among women, the risk of incident infection decreases with increasing age. In a study from Columbia looking at incidence among women 15 through 85 years of age, there was a decrease in incidence by age. While there were incident infections in all age groups, the highest cumulative risk was observed in individuals 15 through 19 years of age (43%). Incidence decreased with age and was lowest in women over 45 years of age [Munoz et al. *JID* 2004].

Much of the data on HPV in men come from one major study, which is a cohort study of HPV conducted in the US, Mexico, and Brazil known as the HPV Infection in Men (HIM) study. Based on data from this study of HPV incidence among males 18 through 70 years of age who were followed for 36 months, the cumulative risk of any HPV infection was similar across age groups, although somewhat lower in the oldest age. In this study, the number of new sex partners was also similar for the different age groups, and likely contributed to these findings. The Munoz findings in women cannot be directly compared with the study in males, but these two studies provide insight into the different patterns of HPV infection among females and males [Giuliano et al. Lancet 2011, HIM study].

Complicating interpretation of these incidence studies in adults is that incident HPV detection may be due to a newly acquired HPV infection or to redetection of a previously acquired infection. Redetection could be the result of a persistent infection that is intermittently below the level of detection of the PCR assay or it could be due to reactivation of a latent infection. These are difficult to distinguish methodologically. The relative proportion due to new infection versus redetection could have an impact on the potential benefit of vaccination in older age groups because vaccination is expected to prevent new infections. Several studies have been conducted in females to try to estimate the proportion of new detections due to new infection by evaluating risk factors for new HPV detection. Dr. Markowitz reviewed two of these studies, which are listed in the following table:

	Major U.S. cities Winer et al. JID 2016	**Baltimore, MD** Rositch et al. Cancer Res 2012
Population	On-line daters	OB/GYN clinic attendees
Age range, years	25–65	35–60
New male partner	50%	10%
Incident HPV detection	High risk HPV 29.5/100 women-years	Any HPV 14/100 women-years

The two studies listed above provide information on incidence in mid-adult women in the US, and also try to estimate the proportion of new HPV detection due to new infection. These studies looked at HPV detection and sexual behavior and used that to determine the attributable risk to new and past exposures. The characteristics were quite different in these two studies. For the first study listed, women were enrolled from multiple US cities and were on-line daters 25 through 65 years of age. Of these women, 50% had a recent new partner. Incidence of high risk HPV in this study was 29.5/100 women-years. The study in Baltimore included lower-risk women recruited from OB/GYN clinics; only 10% had a recent new sex partner. Incident detection was 14/100 women-years. Note that this was any HPV not high-risk HPV; the rate of HR-HPV would be even lower. Overall in both studies, most of the detections were attributed to past, not new, acquisition. However, based on the association between new detection and sexual risk behavior, it was estimated that among women with a new partner, 62% to 80% of new detections were attributable to a newly acquired HPV infection.

A study in Seattle included HPV serology at enrollment to characterize persons with potential past infection. In this study, incident HPV detection varied by serostatus and was higher in those seropositive to that type at baseline. An association between recent sexual behavior and incident DNA detection to that same type was found only among seronegative women—those without serologic evidence of exposure. This suggests that among seropositive women, re-detection of the same type is more likely due to reactivation or intermittent detection of persisting infection than a new infection.

To summarize briefly, the risk of incident infection declines with increasing age in females, likely due to more stable partnerships and fewer new sex partners. It also could be due to some acquired immunity. Sex with a new partner remains a risk factor for a new infection in older age groups. The proportion of new detectable HPV due to prior versus a new infection varies by population and depends on both past risk behavior and current risk exposure. Given that it is known that new infections do occur in this age group, it is important to determine what the risk is of these new infections developing into a pre-cancer lesion. As mentioned earlier by Dr. Luxembourg, data to address this are available from the control arms of the vaccine trials. There are some good data from the bivalent trial showing that over 48 months, about 3.6% of the new infections did progress to a CIN2+ lesion. Less is known about males than females. It appears that among males, the risk of incident infection is more constant with increasing age. Re-detection of the same type is common; it is less clear what proportion is due to a prior versus a new infection.

Type specific immunity after natural infection could explain some of the differences observed by sex in prevalence and incidence. It is also a very important question for consideration of the benefit of vaccination. If there is little immunity after natural infection, benefit of vaccination would be greater than if natural immunity provides protection against reinfection. Models have shown this to be a very important parameter in the modeling results. A systematic review and meta-analysis were conducted to address this question. Over 24,000 individuals were included from longitudinal studies evaluating natural immunity by serology and compared for risk of genital infection by seropositivity status. A total of 14 studies were included, including 11 in females and 3 in males. The conclusion was that HPV antibodies acquired through natural infection provide some type-specific protection against subsequent genital infection in females, but not in males. Included in this study were data from the control arms of efficacy trials in females, which also support the finding that there is modest protection from re-infection from natural infection for females [Beachler et al. *JID* 2016].

Modeling has provided some very important information for HPV policy, due to the complex nature of HPV natural history and the many unknowns and different outcomes of infection. A study was published late last year that used a well-documented cervical cancer natural history disease simulation model based on US data and tried to address the question: What proportion of cervical cancers are caused by infections acquired at different ages. This was under the assumption of the absence of screening or vaccination. The model projected that among all cervical cancers, 50% of women acquired their causal HPV infection by age 21 and 75% by age 31. This, of course, strongly supports routine vaccination at a young age to prevent most infections that lead to cancer, but also provides information on projected infections acquired at older ages that might result in cancers. It is important to note that this model projected cancers in the absence of screening and vaccination, and the percentages would appear different in the context of the current program [Burger at al. *CID* 2017].

In contrast to cervical cancers, much less is known about the natural history of some other HPV-associated cancers. There was a presentation during the February 2018 ACIP meeting on the epidemiology of HPV among males, with particular reference to oropharynx cancer. At that time, Dr. Chaturvedi from the National Cancer Institute (NCI) highlighted that there are very few natural history studies to look at the steps between oral HPV acquisition and development of HPV-positive oropharynx cancer, a cancer that happens to be increasing in the US linked to HPV. Among the other unknowns for this are the time from acquisition of infection to development of cancer and the disease-relevance of infections acquired at older ages. The lack of information about natural history prevents the projection of any estimate as was done for cervical cancer [Chaturvedi, Presented at the February 2018 ACIP meeting].

While in this talk Dr. Markowitz mainly presented data on genital infection in males and females, she emphasized that it is known that the epidemiology of HPV at other anatomic sites differs. Also, HPV prevalence, incidence, and HPV-associated disease due to HPV is higher in some populations. Anal prevalence is higher in MSM, and anal cancer is particularly high in MSM with HIV infection. There is a very large and increasing literature on this topic. Women with HIV/AIDS have significantly higher rates of cervical cancer and some other HPV-associated cancers than the general population of women. The WG will consider special populations, including immunocompromised persons and MSM at a later meeting.

In summary, based on the epidemiology of HPV, the population-level benefit of vaccination of mid-adults would be low compared to vaccination at younger ages. In general, new sex partners decrease with increasing age, but sex with a new partner remains a risk for HPV infection. There are differences by sex in prevalence, incidence, immunity after infection, and HPV-associated cancers. Immunity after natural infection is an important determinant of potential impact of vaccination. This might differ between males and females. Updated modeling and cost-effectiveness analyses will be very helpful due to the complex nature of HPV and HPV natural history.

The WG is continuing to review data to inform the burden of infection and disease due to infection in older age groups. This, of course, will affect policy considerations. There is a range of potential policy options that could be considered. For catch-up, the current catch-up age of 26 could be retained or catch-up could be extended through an older age. For persons older than the determined catch-up age decided upon, there could be no recommendation for vaccination at older ages, a recommendation for individual decision-making, and/or there also could be recommendations for vaccination of special populations.

As mentioned earlier, the WG has been considering harmonization of the upper age recommendation for males and females through age 26 years. There is strong support on the WG for harmonization. Among other evidence reviewed were surveys of the Association of Immunization Managers (AIM) and of primary care physicians. These indicated that over 90% support harmonization. Harmonization will be considered as the WG moves forward to review data on the possible extended age indication.

In terms of the WG plans, background, and clinical data submitted in the sBLA for an extended age indication, and WG consideration were described briefly. During the October 2018 ACIP meeting, the WG plans to further review the epidemiology and burden of disease and hopes to have modeling and cost-effectiveness completed. In addition, the WG will review values, acceptability, and other elements of the EtR framework and will have more specific policy options that the WG is considering.

In closing, Dr. Markowitz posed the following questions for ACIP's consideration:

- ❑ Are there specific data ACIP would like presented?
- ❑ Are there specific options or other considerations the Work Group should address?

Discussion Points

Ms. Hayes (ACNM) said she was curious about the insurance payer and rates on high-risk HPV. She asked whether the Major US Cities, Baltimore, and Seattle studies looked at what type of insurance the participants had. The variation is huge in terms of the risks of new partners, so she wondered what socioeconomic groups they fell into.

Dr. Markowitz explained that the Major US Cities study was from multiple studies and recruitment was from online dating sites, which is a higher risk population. Baltimore participants were comprised of people presenting for routine cervical cancer screening and other healthcare at OB/GYN clinics.

Ms. Hayes (ACNM) asked what the percent of Medicaid was.

Dr. Markowitz replied that she did not know what percent was Medicaid.

Dr. Lee asked whether there would be any information in terms of coverage for a risk-based strategy versus more of a global catch-up strategy, and whether it would be possible to further examine a risk-based strategy for the subgroup of men who are in that category to give ACIP a sense of how much coverage would be attained.

Dr. Markowitz indicated that they do have some information on coverage among MSM and would hopefully have more by October. Many MSM have not been vaccinated. As the WG delves more into this, they will look at some of those issues specifically about a general catch-up extension versus focusing on specific groups.

Dr. Bennett pointed out that it could be beneficial to think about the special risk groups that might be vaccinated through risk-based recommendations, and perform an incremental analysis comparing that to an age-based strategy. Sometimes they forget that many people in the age-based strategy would be vaccinated anyway because of their other risks.

Dr. Riley said she thought as a practicing obstetrician they should take into consideration other practice issues that are changing for which more protection may be important. Obviously, behaviors are changing. For example, sometimes online daters are presumed to be from the younger group when they are not. It is everyone, so they need to think about the fact that risk behaviors may be different from what they were 10 years ago. The reduction in Pap smears to every 3 years also is going to create a different level of risk within the same community, which also should be considered when thinking about the context in which this might be more useful to the population.

Dr. Frey inquired as to whether there are any data on sex workers that could be presented.

Dr. Markowitz replied that while this is an interesting question, they do not have data on sex workers in the US. They can try to find data on this question.

Ms. Pellegrini suggested that it would be interesting to track over time what happens in the teen population. She was struck by the figure that 50% of the causal infection is occurring by age 21, because studies are showing that teenagers are increasingly postponing sexual activity. If they continue vaccinating in the teen years, there may be higher effectiveness in the future if that trend continues.

Mr. Moore suggested that as the WG considers what to do about mid-aged adults, consideration be given to individual clinical decision-making and how difficult it is programmatically to deal with any kind of risk-based recommendations. Another way to think about it is to think about a lack of risk opt out consideration. In other words, an intermediate step to say under certain circumstances, consideration could be given to not administering it as opposed to only considering the vaccine if someone has risks. This may make it easier to implement programmatically

Dr. Frey said she worried about the risk of opt out for teenagers.

Dr. Moore emphasized that she was talking specifically about mid-aged women.

Recalling the Beachler systematic review and meta-analysis showing that protection from natural infection does not appear to be as strong in males as in females, Dr. Sun (FDA) asked whether that was a function of the serotype of infection or if it was something about males. It seems that this would mean that males would be less likely to benefit from vaccination if they do not develop immunity from exposure.

Dr. Markowitz clarified that this was from natural infection. There have been studies showing that after natural infection, a much smaller percentage of males will develop antibodies. It is known that among females, though it varies by type, that about 60% will develop an antibody response after natural infection compared to less than 20% among men. Part of it is due to the site of infection at which they are exposed. In general, there has been some work to suggest that the antibody developed after natural infection in males is less protective. With vaccination, efficacy in males has been very high.

Dr. Middleman (SAHM) indicated that SAHM is encouraging, and hopeful, that there will be harmonization soon for males and females. She did not get a sense from the WG meetings or presentation that much data would change regarding whether they would specifically want males to have the same recommendations as females through age 26 years. They have been hoping for a long time to catch up those males with the same fervor they do with females

through age 26 and protecting as many people as possible. She asked whether there was anything in the data that was preventing this, or what future data might change the idea of harmonization.

Dr. Messonnier replied that CDC appreciates the enthusiasm for harmonization and shares the goal of simplifying recommendations. They certainly know the value with HPV and other vaccines of not making too many changes at the same time or sequentially over the years, because recommendations are not just about what ACIP does during these meetings, but also impact the need for CDC to have an education campaign to communicate those changes to providers. CDC highly values harmonization and looks forward to having a single discussion with a single recommendation that considers harmonization and at what age group that harmonization would be for, so that this can be communicated all at once.

Update on NITAGs

Overview

Dr. Abigail Shefer
Immunization Systems Branch
Global Immunization Division
Center for Global Health
Centers for Disease Control and Prevention

Dr. Shefer provided a brief overview of CDC work on National Immunization Technical Advisory Groups (NITAGs). CDC has played a role in NITAGs for over 10 years. The primary group involved in the NITAG work at CDC is the Global Immunization Division (GID). GID provides technical assistance (TA) in the form of developing training materials, tools, and facilitation of trainings. In addition to working with WHO, GID works with specific initiatives such as the Partnership for Influenza Vaccine Introduction (PIVI) and the Rotavirus Accelerated Vaccine Introduction Network (RAVIN). This work primarily involves working with NITAG WGs that are planning and introducing those vaccines. GID also conducts research. There are a couple of projects underway that are assessing how NITAGs integrate into the policy process in different country contexts, and how NITAGs link with other expert advisory groups in countries such as the National Verification Committee (NVC) to collect, verify and submit country documentation related to measles and rubella elimination and the National Certification Committee (NCC) to collect, verify and submit country documentation related to polio eradication.

GID also provides funding to WHO Headquarters (HQ) to support NITAGs traveling to SAGE meetings, regional TAGs to support regional trainings, and to support the NITAG Resource Center (NRC). GID collaborates with the National Center for Immunization and Respiratory Diseases (NCIRD) on visits to ACIP and on a number of other activities and trainings. One example of recent training in which CDC and WHO were involved was China's National Immunization Advisory Committee (NIAC). Established in October 2017, NIAC has 19 WGs (3 permanent), 27 voting members, and 160 WG members. Training on evidence-based decision-making was held in December 2017, which was more of an experience-sharing opportunity rather than didactic. TA and faculty were supported by CDC/WHO, with over 200 participants. The first NIAC meeting was convened in April 2018 during which two significant schedule

changes were approved, including a second inactivated polio vaccine (IPV) dose and a 2-dose mumps schedule. This was a very collaborative and successful training.

CDC and WHO/partners developed a simplified tool for NITAGs to use to assess NITAG functionality, quality of work processes and outputs, and integration into the policy process. This can either be done as a self-assessment by the NITAG or an external assessment. ACIP recently underwent a similar evaluation or assessment using a longer tool. The NITAG tool is currently being pilot tested. The hope is that it will be a simple enough tool that it can be used as part of an Expanded Programme on Immunization (EPI) review or part of a Global Alliance for Vaccines and Immunisation (GAVI) Joint Appraisal.

Global NITAG Activities and the Global NITAG Network (GNN)

Dr. Joachim Hombach
Senior Advisor
Immunization, Vaccines, and Biologicals
Secretary, SAGE
World Health Organization

Dr. Hombach explained what WHO is doing with partners such as CDC in order to support country-level decision-making on vaccines among the NITAGs, and how this connects to the work they are doing at the global level, forming the rationale that global-level policy work is only as good as it shows impact in countries. At the global level, WHO works along a continuum of the vaccine value chain. At the center is SAGE, which is WHO's top-level advisory group on immunization policy and strategy. It connects to work that WHO is doing upstream and downstream. What is important in relation to the vaccine recommendations that WHO issues through SAGE is to have a lever. Manufacturers may only submit for WHO prequalification once WHO has made a recommendation on the use of the vaccine. Only prequalified vaccines can be procured through the United Nations Children's Fund (UNICEF) and then eventually also can benefit from GAVI support. There is a nice situation of coherence of policy, which provides further impact to the recommendations that SAGE makes.

SAGE is WHO's principal advisory group for vaccines and immunization as mentioned earlier, which engages in similar activities as ACIP, but there are some substantive differences. SAGE reports to the Director-General at WHO and has working procedures and so forth. SAGE has 15 members, makes public calls for nominations, conducts two plenary sessions annually, and makes periodic declarations of interest. As with ACIP, the bulk of SAGE's work occurs within WGs. These are time-limited groups that work on proposing recommendations on very specific issues for deliberation at the SAGE plenary meetings. What is important to note is that SAGE's scope is relatively broad, so they are engaged in much more than vaccine-specific recommendations. They recently completed their last 8 years' worth of work; during this time only about 40% of the work was vaccine-specific. A lot of reports relate to progress on elimination and eradication strategies, adjustment to strategies, and support activities.

The way in which WHO has set up its immunization policy advisory framework is to try to connect to country-level work. Over the last years, Regional Immunization Technical Advisory Groups (RITAGs) have been established in all 6 WHO regions. These essentially have the role of monitoring and refining strategies in the regions, have much closer contact with the countries, and identify and interpret global recommendations for the regional context. The NITAGs are independent expert advisory bodies and are mainly tasked with making recommendations to Ministries of Health on use of the vaccine in the respective countries. The role of the NITAGs

was recognized to be of a very high priority and as part of the Global Vaccine Action Plan (GVAP, 2011-2020), every country should have a NITAG to assist with evidence-based decision making. These are process indicators that are monitored globally to assess how NITAGs are functioning. A NITAG is considered functional when it meets all six of these process indicators:

1. Legislative or administrative basis for the advisory group.
2. Formal written terms of reference.
3. At least five different areas of expertise represented among core members.
4. At least one meeting per year.
5. Circulation of the agenda and background documents at least one week prior to meetings.
6. Mandatory disclosure of any conflict of interest.

The importance of these NITAGs is also mirrored by various resolutions and work that is being done on GVAP. Here are some quotes recognizing the importance of NITAG support:

GVAP midterm review (2016)

- ❑ Good progress but additional efforts are needed to achieve GVAP 2020 target on NITAGs

70th World Health Assembly (2017)

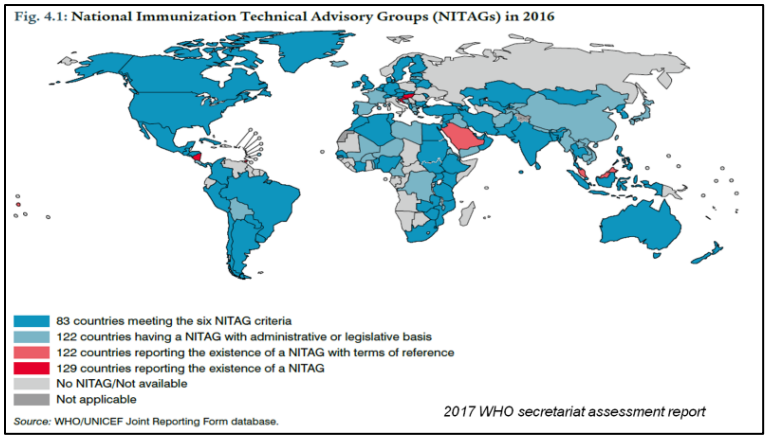
- ❑ Urges Member States to demonstrate stronger leadership and governance of national immunization programmes by strengthening national processes and advisory bodies for independent, evidence-based, transparent advice including on vaccine safety and effectiveness

- ❑ Requests the Director General to support Member States in strengthening NITAG to inform national decisions based on national context and evidence to achieve national immunization goals

71st World Health Assembly (2018)

- ❑ NITAGs, while supporting decision-making, can contribute significantly to building in-country ownership and credibility for immunization programmes

This map is from the last assessment of reports in 2016, at which time there were 83 countries meeting the six NITAG process indicators, which is more than double the baseline in the beginning in 2010:



There has been particularly good progress in the African Region, even though there has been some levelling off in the last couple of years. While there is progress, more needs to be done since the current measures are only process indicators. To be fully effective the NITAG must also produce quality recommendations that are evidence-based and be integrated into a country's policy process, both which indicators which are currently more difficult to measure.

In terms of specific work at the global level, resources include the NRC, guidelines, and training materials. Networking and collaboration occur through the Global NITAG Network (GNN), peer learning, and exchanges with SAGE. Support to Regional Offices is provided for SAGE-Regional Immunization Technical Advisory Group (RITAG) interactions and there is support for regional NITAG networks (there is a network in the Southeast Asian regions and there is potential in other regions). NITAGs may also be invited to RITAG meetings. There are sub-regional trainings for NITAG strengthening, and there is sub-regional collaboration between small countries. There also is the idea of having sub-regional collaboration, particular between small countries where it is virtually impossible to have functional NITAGs in every small country. In the Caribbean such a network was recently established. There are plans in the Pacific Region among small islands to have these types of collaboration. At the country level, there is ad hoc support for NITAG establishment and strengthening; sharing of work plans, recommendations, and best practices; peer-to-peer exchanges to build capacity; and the execution of NITAG evaluations.

The idea of the NRC is to have a web-based interface where all of the information for NITAGs can be centralized, such as good practices, systematic reviews, scientific publications, technical reports, updates from partners, upcoming immunization events, et cetera. Launched in 2015, the NRC is currently managed and run by WHO HQ with the support of a network of focal points. This has enormous potential for growth. It is not just for low-income countries. Middle- and high-income countries have asked for certain pieces of information and support as well. While there needs to be country adaptation, there are many valuable materials and analyses that can be shared among NITAGs. This is clearly an area that needs more work, but it is resource-intense if done right.

There was a plan about two years ago to launch the GNN. It was officially established in Berlin last year. This is a voluntary gathering of the NITAGs to share information and conduct advocacy in this important area. Regarding the terms of reference, the vision of the GNN is for each country, using the best practices and data available, to make sound and evidence-based recommendations on immunization that are most appropriate for their context in order to facilitate their adoption and implementation. The mission is to enhance the ability of NITAGs to efficiently make evidence-informed recommendations on immunization through global collaboration and cooperation with input from regional networks. The GNN's specific objectives are to:

- Provide a global platform to enable NITAGs to efficiently share and access knowledge, technical reviews, data, lessons learned, trends and innovations
- Liaise with regional NITAG networks to flag needs, develop relevant tools to address needs, and identify, evaluate, and document best practice and innovation (GNN does not replace regional networks)
- Help develop standards for processes to ensure evidence-based decision making and evaluate NITAGs
- Facilitate evaluations and capacity building of NITAGs
- Advocate for NITAGs

The next GNN meeting will be convened in Ottawa, Canada on December 6-7, 2018. The agenda is based on 2017 survey data in which two technical items were identified: 1) off-label recommendations of vaccination, and 2) the legal context for implementation of NITAG recommendations. The agenda also will address COIs, NITAG evaluation, NITAG agenda setting, and there will be a side session for long-established and recently established NITAGs.

To summarize key issues, immunization is leading in the field of evidence-based decision-making in public health. Global normative guidance is only as good as it shows impact at the country level. Global, regional, and country level collaborations are therefore essential for vaccine decision-making. NITAGs have been identified as a centerpiece to advance the immunization agenda, and there is overall good progress. Country level evidence-based decision making is increasingly important as vaccine policy choices increase. Allocation of scarce resources will face increased scrutiny in countries graduating from the GAVI subsidies, and evidence-based decision-making will increase sustainability and ownership. Countries will have to pick up pretty much the totality of the bill for the vaccines recommended, so they need to have very good justification, go through a very thorough review, and prioritize in order to make recommendations. This requires NITAGs to have a strict evidence base. Otherwise, there will be very haphazard recommendations of vaccines dropping off of the schedule, which is the worst that could happen. Partner technical support and predictable financial support will be essential to successfully drive establishment and fostering of NITAGs.

Discussion Points

Dr. Szilagyi asked whether technical support includes economic and other types of evaluation.

Dr. Hombach replied that in terms of economic evaluation, they are very often in a situation where there are mathematical models. Mathematical models need to be populated with data, and there needs to be confidence and trust in the models. Some work has been done in this area, and it is clearly an area where technical support is helpful.

Ms. Pellegrini asked whether a country can have more than one NITAG. For example, would National Vaccine Program Office (NVPO) be a NITAG.

Dr. Wharton (NVPO) responded that NVPO provides guidance about the overall program rather than specific vaccine recommendations. The way she envisions NITAGs is that it is exactly the kind of work ACIP does in terms of making specific recommendations about the use of specific vaccines, such as whether HPV vaccine should be added to a national program.

Dr. Hombach added that in many other countries, this distinction is probably not really made.

Dr. Hunter said it seemed that, especially in the smaller countries, the NITAGs are a lot more closely aligned with the actual implementation and financial decisions and there is much more interplay between the resources of the MoH and what the advice will be. ACIP is somewhat more separated from that because of the way the financing is done in the US.

Dr. Hombach replied that NITAGs have to be informed by the realities. ACIP did address some of this in their HPV discussions, and still has to connect to the realities of what it means in terms of financing and support. There also needs to be some type of independence, so that the evidence, science, and cost-effectiveness come first. The second step are the issues of implementation and affordability.

Dr. Moore said she appreciated the value of NITAGs around the world after serving on ACIP and given increasingly complex immunization policy decisions. She asked how the members of ACIP could be supportive of the work to expand expert advice around the world.

Dr. Hombach said he thought collectively, their expertise had contributed in one way or another. ACIP is a very functional committee from which other advisory groups under development could benefit, so there could be a strong element of peer learning.

Dr. Shefer pointed out that this presentation was an introduction of these issues, but that opportunities would be found for ACIP to share expertise, potentially engage in peer mentoring, twinning, et cetera.

Dr. Bennett said she thought there were a lot of opportunities for ACIP to be of assistance to countries that are trying to develop something modeled on what ACIP does.

Dr. Bernstein observed that 83 countries met the 6 criteria to be a NITAG and wondered whether the goal was to have every country on the globe that fit those 6 criteria to be a NITAG, and who was guiding those groups.

Dr. Hombach replied that the goal is for every country to have this capacity. He does not think it is acceptable for countries to make decisions without having gone through this process. In some instances, the NITAGs can be done through more of a network approach in which countries cooperate and collaborate. For many countries, this is the objective. If it takes more time, then it takes more time, but it is an important objective to be achieved. WHO tries to provide global support through certain resources and opportunities within the GNN where there are guidelines, tools, and self-evaluation resources. Ultimately, these things cannot happen just globally. They also must be fed and nourished in regional and sub-regional structures, and it is a long-term objective.

Dr. Bennett said that ACIP wishes them great luck in achieving this and stands ready to help in any way.

Mumps

Introduction

Kelly L. Moore MD, MPH
Director, Tennessee Immunization Program
Chair, Mumps ACIP Work Group

Dr. Moore reminded everyone that the objective for the Mumps WG is to evaluate and propose policy options to prevent or control mumps outbreaks in the US. The activities associated with that were to: 1) Review the epidemiology of mumps in the 2-dose vaccine era, including the international experience; 2) Review the available evidence on duration of immunity for mumps after 2 doses of MMR and other risk factors for vaccine failure; 3) Review the available evidence on benefit provided by a third dose of MMR for mumps outbreak control; and 4) Evaluate the programmatic implications and cost of various policy options for a third dose of MMR to prevent or control mumps outbreaks.

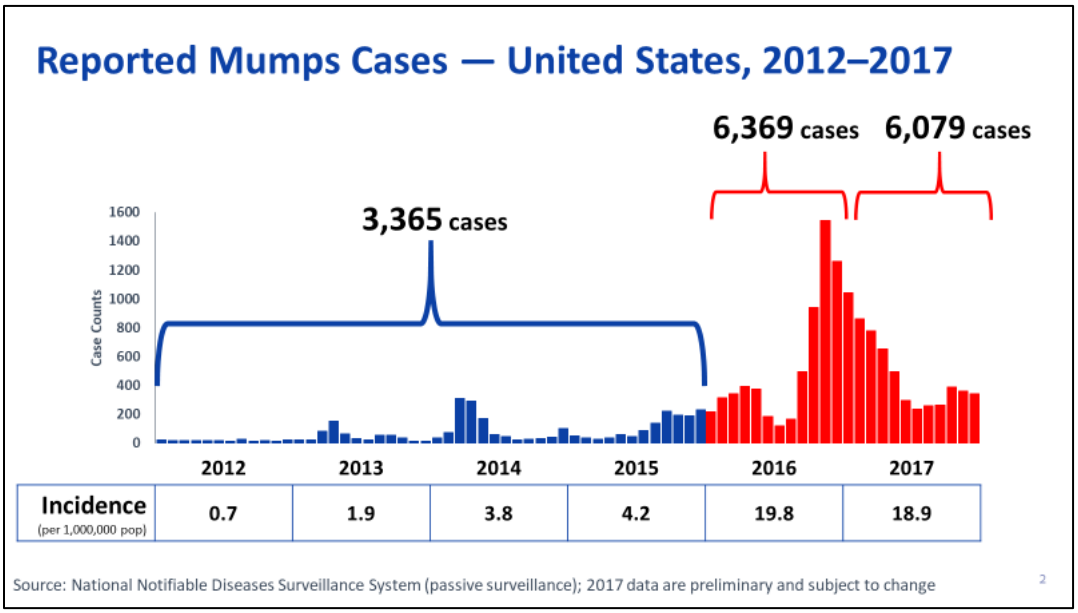
Between March and October 2017, the WG engaged in 13 calls and completed 4 online surveys to complete the evidence assessment of mumps epidemiology, 2-dose MMR vaccine impact, data on and experience with third dose MMR vaccine use, and critical review of published and unpublished data regarding mumps outbreaks. The outcome of this work wrapped up in October 2017 when ACIP recommended use of a third dose of mumps virus-containing vaccine for persons in the groups identified at increased risk for mumps during an outbreak. Between January and June 2018, the WG has engaged in 4 calls, 1 online survey, and 3 rounds of document review focused on providing technical consultation, discussion, and feedback to finalize CDC guidance for use of a third dose of MMR vaccine during mumps outbreaks. The objective of the session is to present to ACIP this proposed guidance.

At this point, the Mumps ACIP WG has accomplished its terms of reference with the evidence available to them to date. Therefore, they are announcing a temporary hiatus of WG activities. However, CDC will continue to monitor mumps epidemiology in the US and new scientific evidence that can inform better control of mumps going forward. WG calls will be scheduled as needed as new information becomes available.

Current US Mumps Epidemiology and Proposed CDC Guidance for Implementation of the ACIP Recommendations for a Third Dose of MMR Vaccine During Outbreaks

Mariel A. Marlow, PhD, MPH
Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

As presented during ACIP meetings last year, a substantial increase in the number of mumps cases has occurred in the US since late 2015. This graph shows the number of reported mumps cases by month from 2012 to 2017, with incidence per year shown below the graph:



The number of cases in 2016 and in 2017 were nearly double the total number of cases from 2012 through 2015. Incidence was 19.8 per million in 2016 and 18.9 per million in 2017, which

is the first time since the 1980s that the incidence has stayed higher than 10 per million for 2 consecutive years. Also since 2013, at least 70% of cases with known vaccination status had received 2 or more doses of MMR. In addition to the increase in the number of cases reported, there also was an increase in the number of outbreaks from 1 in 2012 to 88 in 2017. Beginning in 2013, over half of all reported cases were outbreak-associated.

In response to this increased burden, last October, ACIP recommended that persons previously vaccinated with two doses of a mumps virus-containing vaccine who are identified by public health authorities as being part of a group or population at increased risk for acquiring mumps because of an outbreak should receive a third dose of a mumps virus-containing vaccine to improve protection against mumps disease and related complications. A key part of this recommendation is that public health authorities determine which groups or populations are at increased risk.

To assist public health authorities with implementing the ACIP recommendation, CDC developed guidance in collaboration with the Mumps ACIP WG and in consultation with other partner organizations, including the Council of State and Territorial Epidemiologists (CSTE), the National Association of County and City Health Officials (NACCHO), and the American College Health Association (ACHA). Additional feedback was received during several partner meetings and national conferences and included in the guidance presented during this session.

The proposed guidance includes three sections:

- ❑ Identifying groups of persons at risk for acquiring mumps during an outbreak (mumps outbreak is defined as ≥3 cases linked by time and place)
- ❑ Assessing transmission in the settings to determine if these groups are at increased risk, and thus should receive a third dose of MMR vaccine
- ❑ Implementing a third dose recommendation

The first part of the guidance, identifying groups of persons at risk for acquiring mumps, starts by defining persons at risk and close contact. Persons at risk for mumps during an outbreak are those who may be exposed to mumps virus through close contact with a mumps patient. “Close contact” is defined as either direct contact with infectious respiratory secretions or droplets, which generally travel 3 feet or less when an infected person talks, coughs or sneezes; or close proximity for a prolonged period of time with a mumps patient during their infectious period, which is 2 days prior to 5 days after parotitis onset or other salivary gland swelling.

Risk for acquiring mumps depends on the likelihood of close contact exposure, which can be classified as: 1) known exposure for a group of persons with reported close contact with a mumps patient, such as a roommates or partners; 2) likely exposure for a group of persons with either likely close contact with a mumps patient or close contact with persons with known exposure (a group that is likely to be exposed to future cases); these are typically persons who share a social network with a mumps patient; and 3) potential exposure for a group of persons with any contact (other than known or likely) with mumps patients or persons with known exposure, such as persons sitting in the same lecture hall or cafeteria.

To maximize the benefit of added protection of a third dose and get ahead of transmission during an outbreak, public health authorities should focus their investigation on groups of persons with known and likely exposure to determine if they are at increased risk. To determine if the known and likely exposure groups are at increased risk during an outbreak, the next step is to assess transmission in the setting. Public health authorities can assess transmission in the setting (location, activity, or event where known or likely exposures are occurring) based on evidence of transmission in the setting (close contact exposures within a setting resulting in transmission); and risk for transmission in the setting (likelihood for continued transmission). They can then use these two factors in a decision matrix, shown here, to determine if a group is at increased risk:

Decision Matrix for Determining if a Group is at Increased Risk

Evidence for transmission	Risk for transmission in the setting		
	Low	Moderate	High
No evidence of transmission	Not at increased risk	Not at increased risk	May be at increased risk
Evidence that transmission occurred	Not at increased risk	May be at increased risk	At increased risk
Evidence of sustained or extensive transmission	May be at increased risk	At increased risk	At increased risk

Evidence of transmission can be stratified into three stages: no evidence of transmission, evidence that transmission occurred, and evidence of sustained or extensive transmission. Public health authorities can determine the stage by either the number of incubation periods since parotitis onset in the first case, or by epidemiologic links among cases. In the guidance, the criteria are provided to make this assessment. The second factor in the decision matrix is risk for transmission in the setting. Risk for transmission in the setting results from close contact behaviors and interactions among persons in a group, and increases with the intensity of close contact exposures (physical contact, such as dancing or sharing of sports equipment or drinks) and the frequency of these exposures (prolonged contact such as sharing living spaces, or repeated contact such as meeting regularly or sharing daily habits).

Given the complexity of mumps outbreaks, risk for transmission can vary widely across settings and between outbreaks. Health departments will need to assess behaviors and interactions for each setting to determine the level of risk. The written guidance provides examples of low, moderate and high risk for transmission from previous community, university, school, and workplace outbreaks for health departments to compare against their own outbreak.

As mentioned in the beginning of this section, once public health authorities have assessed evidence of transmission and risk for transmission in the setting, they can then enter them into a decision matrix to determine whether a group is at increased risk, may be at increased risk, or is not at increased risk.

Groups determined to be at increased risk should be recommended to receive a third dose of MMR. However, there may be additional epidemiologic factors to consider when deciding to make a third dose recommendation. For example, a third dose may be more likely to be indicated for a small, definable versus a large dispersed group or population, or when there is an increasing versus decreasing case count or attack rate. Other considerations are if the group at increased risk includes persons who may potentially transmit to a susceptible population (e.g., students who volunteer in child care centers), or if the setting is known to be high risk for transmission based on previously reported outbreaks (e.g., fraternities, sports teams, or close-knit communities).

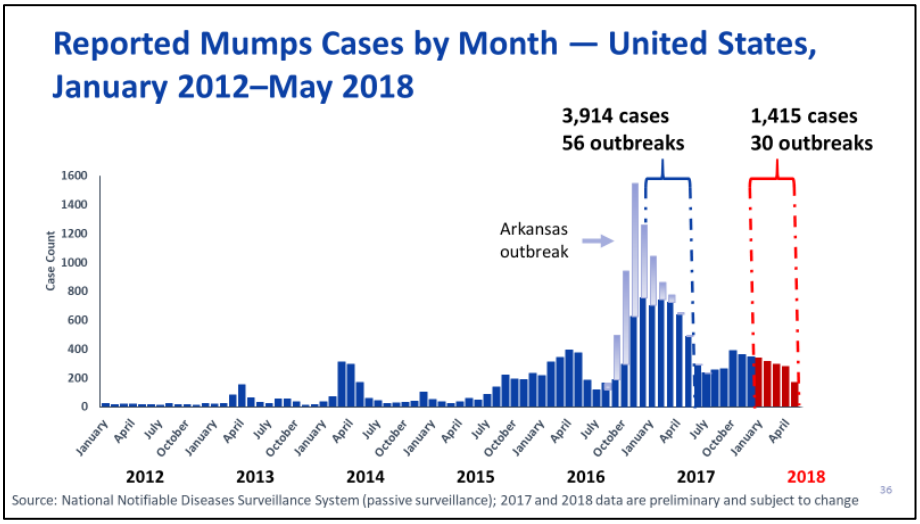
The third section provides additional guidance for public health authorities when implementing a third dose recommendation. First, persons in the groups identified at increased risk should be advised to seek vaccine through routine immunization channels. However, public health authorities might choose to expand their response to include vaccination campaigns or clinics in certain situations, such as when case counts are increasing despite a recommendation already having been made, there is poor vaccine access or low vaccine uptake among the group at increased risk, or the group at increased risk includes hard-to-reach or vulnerable populations.

Additional implementation guidance indicates that persons with unknown vaccination history, less than 2 doses, or other evidence of presumptive immunity should receive a dose if they are part of the group at increased risk. No additional dose should be given to persons who received 3 or more doses before the outbreak or their second dose during the outbreak. Persons vaccinated with 2 MMR doses before the outbreak should receive a third dose regardless of time since the second dose. In studies and during recent outbreaks, cases have been reported in persons with intervals less than 2 and less than 5 years since receipt of their second dose. Public health authorities should follow ACIP General Recommendations for the minimum interval for administration of live virus vaccines (≥28 days). Particularly during an expanded response, public health authorities may recommend a dose for all persons at increased risk without verification of vaccination history to avoid delays. Persons who receive a dose can be referred to their health care providers to assess the need for additional age-appropriate vaccination. This concluded the presentation on the proposed CDC guidance.

Dr. Marlow next provided a brief update on CDC activities and mumps epidemiology in 2018. As Dr. Moore mentioned, CDC will continue to monitor mumps epidemiology and new scientific evidence. Additionally, CDC has several ongoing or planned priority activities to improve the understanding of outcomes related to use of third dose, which are to:

- ❑ Develop transmission models to examine factors that impact the size and duration of an outbreak
- ❑ Measure duration of antibody response five years after the third dose
- ❑ Evaluate antibody avidity, or the quality of antibodies, after the third dose compared with after the second dose of MMR
- ❑ Assess differences between antibody responses to vaccine versus circulating wild-type mumps strains
- ❑ Monitor mumps incidence among populations with third dose vaccine recipients to better characterize duration of protection after the third dose

The following graph shows the number of reported mumps cases by month from January 2012 through May 2018:



So far in 2018, 1415 cases and 30 outbreaks have been reported. This is about half as many cases and outbreaks than was reported during the same period in 2017. However, it is important to note that a large number of cases that occurred in late 2016 and early 2017 were linked to one outbreak in the Marshallese community in Arkansas that later seeded outbreaks in other states in 2017. Also, the lower number of cases in 2018 may reflect some delay in reporting. CDC will continue to monitor mumps epidemiology and provide updates when available.

Discussion Points

Dr. Zahn (NACCHO) thought that from a local public health standpoint, these changes made a lot of sense. His sense was that the way in which third doses have been used at a national level have been in large outbreaks in universities. Less has been reported about 3 cases in one gym class or 3 or 4 cases among a football team. It makes sense to consider in such situations, and the guidance potentially opens the door to do that. He wondered if this was being done on a routine basis, or if it was new and different.

Dr. Moore replied that from personal experience, Tennessee has implemented a third dose in smaller outbreaks in a university in Tennessee. Part of the reason it may not have been seen in smaller outbreaks until now is because there was not a lot of guidance available on the use of a third dose, and people were on their own to try to figure it out. She said she believed that about half of the university outbreaks were fewer than 10 cases based on a survey of outbreaks around the country. The smaller an outbreak is, the more targeted the third dose recommendation can be. This guidance is intended to allow public health to be more focused and narrower in the application of a third dose, and potentially in an earlier stage in a high-risk transmission setting where the risk and opportunity for it to become larger exist.

Dr. Hunter added that the ability for accommodation of the ACIP recommendation, plus the local health department guidance, allows local health departments to quickly refer individuals to their local provider rather than having to go out and give the vaccine themselves.

Dr. Moore said that in her experience, they have recommended that people go through routine channels. If there is a student health opportunity, the student health center would make it available to the students who were directly impacted.

Zoster Vaccines

Introduction

Edward Belongia, MD
Chair, Herpes Zoster Work Group
Center for Clinical Epidemiology & Population Health
Marshfield Clinic Research Foundation

Dr. Belongia reminded everyone that following FDA licensure of Shingrix, ACIP made the following recommendations in October 2017: 1) Recombinant zoster vaccine (RZV, Shingrix) is recommended for the prevention of herpes zoster (HZ) and related complications for immunocompetent adults aged ≥50 years 2) RZV is recommended for the prevention of HZ and related complications for immunocompetent adults who previously received zoster vaccine live (ZVL, Zostavax®); and 3) RZV is preferred over ZVL for the prevention of HZ and related complications. These recommendations were published in January 2018. The CDC 2018 Herpes Zoster Policy Note recommendations serve as a supplement to the existing recommendations for the use of ZVL in immunocompetent adults aged ≥60 years [Dooling et al. *MMWR* Jan 25, 2018].

Since October 2017, the WG reviewed and approved the *Herpes Zoster MMWR Policy Note-Recommendations of the ACIP for Use of Herpes Zoster Vaccines*. In addition, WG meetings were convened to address the burden and pathophysiology of HZ in immunocompromised persons, HZ vaccine performance in immunocompromised persons, and post-licensure monitoring of RZV. This session focused on the enhanced safety, effectiveness, and coverage to monitor the impact of the preferential recommendation.

Dr. Belongia indicated that this would be his last meeting as Chair of this WG. Dr. Moore will be stepping in as the Chair going forward. He said it has been a great privilege for him to be part of this WG, and that he is proud of the WG's accomplishments over the past four years as they dealt with some complicated issues. He thanked all of the WG members and CDC support staff for their commitment, particularly Drs. Dooling and Harpaz.

Herpes Zoster Vaccination Update

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 indicated that the presentation she would give during this session reflected the work of numerous groups at CDC who are responsible for various aspects of post-licensure monitoring of vaccines. She first presented information regarding GSK's post-marketing

commitments for RZV, followed by CDC post-marketing monitoring of RZV safety and effectiveness, zoster vaccine coverage, RZV supply, and clinical guidance.

There are three principle post-marketing commitments of RZV study undertaken by GSK as outlined in the October Biologics License Application (BLA) approval letter from FDA. The protocol submission and study completion deadlines are subject to change. First, GSK is committed to assess the safety, reactogenicity, and immunogenicity of RZV in adults ≥50 years of age with a prior episode of HZ (Protocol submission: Q2, 2018 | Study complete:Q4, 2020). In addition, there will be a targeted safety study to evaluate the safety of RZV in adults ≥50 years (Protocol submission: Q4, 2020 | Study complete:Q2, 2024); as well as a study to assess the long-term efficacy, immunogenicity, and safety of RZV in adults ≥50 years of age (Protocol submission: Q4, 2021 | Study complete: Q3, 2023).

In terms of CDC safety monitoring of RZV, as a reminder, VAERS is the first pillar in safety monitoring. VAERS is a national early warning system to detect possible safety problems in US licensed vaccines. VAERS is co-managed by the CDC and the FDA. The system relies on passive reports of AEs following immunization. The strengths of the system are that the data are national in scope, the system accepts reports from anyone, it is possible to detect safety signals and rare AEs rapidly, and the data are available to the public. The system has limitations as well. There are reporting biases, inconsistent data quality and completeness, lack of an unvaccinated comparison group because the system only collects AEs following vaccination, and the system cannot assess causality. Keeping that in mind, it is important to highlight that VAERS is a hypothesis-generating system. It identifies potential vaccine safety concerns that can then be studied in more robust data systems.

From RZV licensure on October 20, 2017 through April 27, 2018 there were 680 reports submitted to VAERS. No unusual patterns or unexpected AEs were observed. Of these reports, 48 (7%) involved co-administration with another adult vaccine including pneumococcal polysaccharide (14), pneumococcal conjugate (12), quadrivalent inactivated influenza (7), Tdap (tetanus, diphtheria, acellular pertussis) (6), or adjuvanted inactivated influenza (1). The majority (63%) of the reports were among female vaccinees, 95% were adjudicated as non-serious, and 5 (1%) reports involved a death. During the same time period in the 5 months following vaccine licensure, the most commonly report symptoms among the 680 reports received included: injection site pain (25%), pyrexia (22%), injection site erythema (21%), chills (19%), pain (17%), headache (16%), pain in extremity (15%), injection site swelling (14%), erythema (10%), myalgia (10%), rash (10%), injection site warmth (9%), nausea (8%), herpes zoster (7%), and rash/erythematous (6%). Of these top 15 most common symptoms, 14 may represent the reactogenicity that has been characterized in clinical trials. HZ itself will be expected in some portion of older adults as either a vaccine failure or before the vaccine has had sufficient time to have the necessary immunologic effects to be protective.

A second pillar of safety monitoring is the VSD. Established in 1990, the VSD is a collaboration between CDC and several integrated healthcare plans. There are data on over 10 million persons per year, with links between vaccination records and health outcome data. As of May 31, 2018 over 37,000 doses of RZV were administered at the 6 VSD sites that are participating in safety monitoring. That included 35,431 first doses and 1872 second doses. The VSD RCA is under review at VSD sites. The first data extraction is anticipated in early August 2018 with a 3-month lag for risk windows and thus will include doses administered up to April 2018. VSD monitoring for RZV includes high priority short-term RCA outcomes (e.g., GBS, anaphylaxis, acute myocardial infarction); lower priority short-term outcomes for descriptive analysis (e.g.,

gout, local and systemic reactions); and longer-term outcomes (e.g., potential immune-mediated diseases).

An *MMWR* was published in late May 2018 based on early reports to VAERS. It is a descriptive paper outlining early administration errors involving RZV. During the first 4 months following RZV monitoring, VAERS received 155 reports, 13 of which documented an administration error including some reports documenting more than one error. Most errors involved giving RZV by the SC route rather than by the IM route. Other reports included administration of RZV instead of intended varicella vaccine, administration of RZV after incorrect frozen storage, and errors involving reconstitution of the vaccine [[1] Shimabukuro TT, Miller ER, Strikas RA, et al. Notes from the Field: Vaccine Administration Errors Involving Recombinant Zoster Vaccine—United States, 2017–2018. *MMWR* Morb Mortal Wkly Rep 2018;67:585–586. DOI: http://dx.doi.org/10.15585/mmwr.mm6720a4].

With regard to CDC communication pertaining to administration errors and RZV reactogenicity, CDC has engaged providers with the above *MMWR*, online continuing medical education (CME), Medscape expert commentary videos, HCP web pages, multiple webinars and conferences, and fact sheets. With regard to public outreach, CDC has created a Vaccine Information Sheet (VIS), web pages, and a fact sheet.

In terms of monitoring for RZV effectiveness, CDC and partners are exploring opportunities to study the real-world VE of RZV via large health systems and administrative claims data. The objective of observational studies in these settings is to evaluate VE of 1 and 2 doses of RZV among adults ≥50 years, prior ZVL recipients, and immunocompromised persons.

Regarding zoster vaccine coverage and 2-dose completion, there are a number of systems in which CDC will monitor the zoster vaccine program including: Trends in Immunization Practice System (TIPS), which is an immunization information system (IIS); National Health Interview Survey (NHIS); Behavioral Risk Factor Surveillance System (BRFSS), which provides estimates at the state level; and the VSD, which contains electronic health records (EHRs). All of these systems can provide information on HZ vaccine coverage and three (TIPS, NHIS, VSD) can provide information on 2-dose completion of RZV.

With respect to vaccine supply, due to high levels of demand for RZV (Shingrix), GSK has implemented order limits and providers have experienced shipping delays which will continue throughout 2018. GSK indicates that they have increased the number of doses available for the US market in 2018. GSK plans to release doses to all customer types on a consistent, predictable schedule for the remainder of the year. Supply of RZV is sufficient to support the vaccination of more patients in the US than were vaccinated against shingles last year.

CDC guidance on the use of HZ vaccines is as follows:

- **Recombinant Zoster Vaccine** (Shingrix, GSK) is the preferred shingles vaccine. Every effort should be made to ensure that two doses are administered within the recommended interval. If more than 6 months have elapsed since the first dose of RZV, administer the second dose when possible. Do not restart the vaccine series and do not substitute Zoster Vaccine Live (ZVL) for the second dose of RZV.

- **Zoster Vaccine Live** (Zostavax™, Merck) is a recommended shingles vaccine for immunocompetent adults ≥60 years. A decision to vaccinate with ZVL may be made after an informed discussion between patient and healthcare provider, considering

factors such as patient preference for ZVL or a desire for immediate vaccination when RZV is unavailable. Persons who have received ZVL are recommended to subsequently receive RZV. Age and time since receipt of ZVL may be considered to determine when to vaccinate with RZV (minimum interval of 8 weeks).

In summary, CDC safety monitoring will proceed primarily in VAERS and VSD. Assessment of effectiveness is being planned in the settings of large health systems and administrative claims data. Coverage and adherence will be monitored via IISs, surveys, and EHRs. In addition to the monitoring plans for the current recommendations, evidence of safety and effectiveness of HZV vaccine use in immunocompromised persons is currently being reviewed by the WG.

Discussion Points

Dr. Hunter asked when early results are expected on the 2-dose completion rate, and whether there will be any way to know whether the limited supply of vaccine impacted the lack of completing the second dose.

Dr. Weinbaum replied that CDC is hoping to use a variety of EHR data sources to assess 2-dose completion rates. It probably will be a year before good estimates are available on 2-dose completion. While they will be able to examine the time between the first and second dose, they will not be able attribute that to whether supply impacted second dose uptake.

Dr. Belongia added that it would be difficult in this first time period of 6 to 12 months to parse that out because of the limited supply. There probably will not be a good sense of the 2-dose completion rate until next year.

Dr. Lett (CSTE) complimented CDC on its provider and public communication efforts, which they have utilized a lot and which have been very helpful.

Day 1: Public Comment

Dr. Paul Offit
Children's Hospital of Philadelphia
Read on Behalf of Dr. Stanley Plotkin

I was sent an email by Dr. Plotkin. He wanted me to read this on behalf of him. This is Dr. Plotkin without the Brooklyn accent: "Of course, a third dose of mumps vaccine should be given to stop outbreaks as recommended by the working group. However, that does not go far enough as I have argued previously and recommended in an article just published in the *Journal of the Pediatric Infectious Diseases Society*. A new mumps vaccine would be desirable, but what we can do now is to give a third dose to those likely to be exposed to mumps in colleges. Recently, that recommendation has been echoed in an article from Greg Poland at the Mayo Clinic. Recent papers documenting outbreaks in students in Scotland and Canada also concluded that the current circulating strain differs from the mumps vaccine strain and that a new vaccine should be considered, but also show that these outbreaks will continue unless third doses are ROUTINELY recommended in college populations. Complications of mumps are occurring even in students who have received two doses of MMR." Thank you.

Rebecca Hastings
Mom, Grandmother, Breastfeeding Counselor

Hi. My name is Rebecca Hastings and I am a mom, a grandmother, a volunteer breastfeeding counselor, and I'm passionate about healthy babies. Thank you for this opportunity. I grew up with a lot of respect for the CDC since my dad worked here as a scientist his entire career. So, it's an honor for me to address this committee. In light of this committee's mandate to re-evaluate all recommendations as new scientific data emerges, and with its known ability to evaluate complex issues and conflicting opinions, and implement up-to-date decision-making, I would like to highlight four recent areas of study which demonstrate complex, non-specific effects from the current recommended vaccine schedule.

Firstly, Dr. Yao, who has a PhD from the University of Pittsburg, authored 33 peer-reviewed studies. He noted that the HepB vaccine is administered to more than 70% of neonates worldwide, yet whether this impacts brain development is unknown. Dr. Yao and his team from China studied mice and they published a paper in 2016. They showed how they injected them with hepatitis B vaccine and they conclude, "This work reveals for the first time that early HBV [Hepatitis B] vaccination induces impairments in behavior and hippocampal neurogenesis. This work provides innovative data supporting the long suspected potential association of HBV with certain neuropsychiatric disorders such as autism and multiple sclerosis." So, in light of this evidence, it would seem prudent for the committee to consider a delayed hepatitis B vaccine rather than recommend it on the first day of life.

Secondly, I want to focus on small fragment homologous replacement (SFHR), a technique used in gene therapy studies. This same mechanism is suggested as inadvertently operative in vaccines manufactured using human fetal cell lines, which contain fetal and retroviral contaminants. In a 2014 study by Dr. Theresa Deisher and her team, she showed that cells take up human DNA fragments into their own DNA sequence, causing mutations. There are clear and specific changepoints in the autism prevalence curves seen in multiple countries coinciding directly with human cell lines used in MMR II, varicella, and hepatitis A instead of the previously used animal mediums. Now Pentacel® also has these human cell lines, but they were not able to look at that at the time of their study.

Thirdly, there is a growing body of research on aluminum dangers. As the committee should be well-aware, the accumulative amount of aluminum in the current vaccine schedule is 4925 micrograms in the first 18 months of life. That is not counting the preschool boosters or the shots they get as adults or teenagers. Aluminum has never been clinically approved or clinically demonstrated to be safe. An evidence-based study is urgently needed to look at the impact of this aluminum.

Finally, Anthony Mawson from the University of Mississippi in 2017 published a vaccinated versus unvaccinated study. His did show that non-vaccinated children had a higher risk of chickenpox and whooping cough; however, surprisingly he found that the vaccinated had more doctor's visits, more otitis media (OM), more pneumonia, more allergies, more eczema, and more neurodevelopmental disorders (NDDs). By far the largest risk group that he found was pre-term vaccinated babies had a 6.6-fold increased risk of neurodevelopment disorders than pre-terms who did not receive vaccines. At the very least, this committee needs to urgently reverse the vaccination recommendation for pre-term babies. So, do you have working groups investigating these complex non-specific effects from HepB, human cell lines, aluminum, and pre-term babies?

Tiendra Severino
Concerned Parent

This is my son, Luke. He is 11 years old. He has autism. Based on what I've observed today and also based on the on-line viewing of previous ACIP meetings that this panel is tasked with making very important decisions to affect a lot of people. Perhaps you're making those decisions without fully understanding how these decisions may affect some people, especially children. From what I can ascertain, the datasets that you have to go on are epidemiological studies that do not look at placebo-based control groups and the passive reporting system known as VAERS. My son is vaccine-injured. He has autism. I also have two other members of the family who have vaccine injury, myself included. My last Tdap vaccine gave me severe nerve damage. Back in 2008, my son was one of the first participants in the Study to Explore Early Development (SEED). That is a CDC-sponsored study called the SEED Study. My son participated in that. They followed him for about 3 years. They took extensive medical histories, evaluations, complete vaccination records, everything. I know how extensive that data was. Okay? So, this study was exhaustive. It looked at the vaccination records of both autistic and neurotypical children, and I believe there were six locations where they looked at these children. The study has been referred to by one of CDC's top scientists, Dr. William Thompson, as the "motherload of data." A massive amount of data, which to date has not been examined for clues to the relationship between autism and vaccines. I would like to encourage this panel to examine that data, because the thousands of us mothers who watched our children regress after vaccines are simply not satisfied with being told that the science is settled—vaccines don't cause autism. We know what we saw happen to our kids. Thank you.

Del Bigtree
Informed Consent Action Network (ICAN)

I want to thank the members of ACIP for the incredible job you do. For those of you leaving us, I want to thank you for your time. Certainly, Dr. Bennett, thank you for making this such an enjoyable experience. I just want to address the idea of adding a third MMR vaccine. In this case, I partially do agree with Dr. Plotkin that we should be looking at better vaccines and I wonder why we don't hear that discussion here more instead of adding a vaccine that is clearly failing. Why is it failing? Where is the discussion on why we are seeing a failure of a vaccine? I think that it is also important when we think about ACIP, again, how you are recognized by the public. We have an ongoing case now where two scientists, Drs. Krahling and Wlochowski, have come forward and said they were forced to lie and commit fraud on exactly that, the effectives of the mumps strain being used in the MMR vaccine. So that is an ongoing case and we have workgroups here working on it. It seems to me that it would be very intelligent to think about waiting for that decision to be made. Imagine if ACIP decides to add a third vaccine and then suddenly we find out that it is true that fraud was committed. I also think it's ironic that in 2010 when these scientists came forward, they predicted we would see exactly the problem we are seeing. I don't think in normal circumstances we would let whistleblowers go without attention. Maybe it's because there is no relevance, but we have real relevance here given the case that is being looked at. I would hate to see ACIP have the look and opinion by the public be diminished because of a decision and then the case show that maybe perhaps they should not have made that decision. Thank you very much for your time.

Patricia Neuenschwander
National Association of Pediatric Nurse Practitioners (NAPNAP)

I have been a nurse for nearly 25 years and I have witnessed an increase in NNDs and chronic disease in our children over those 25 years. The literature also reflects that this increase is happening. The vaccine schedule has rapidly increased from 12 doses n 1993 to 72 doses in 2017. We have gone from a 12% rate of chronic disease in our children to a rate of 54% in 2011. Although it feels really good to protect children by preventing infectious disease, what if it is at the cost of chronic disease? There have not been any placebo-controlled studies done, as they are considered unethical for vaccines. There are no long-term safety studies that look at the schedule or the combination of vaccines that are given to children. There is an urgent need for long-term higher quality studies that look at the long-term effects of neurological and immune system outcomes in children. Can this committee ask or demand from the CDC that they conduct a large study using the VSD to evaluate health outcomes in children fully vaccinated compared to children who are completely unvaccinated to try to give us an idea if we may be trading infectious disease for chronic disease and is it worth that cost. I care very much about the health of children. Thank you.

Catharine Layton
Informed Consent Action Network (ICAN)

Thank you all very much for allowing me to speak. I beg to call to attention a newly published study in the *Journal of Toxicology and Environmental Health* entitled, “A lowered probability of pregnancy in females in the USA aged 25–29 who received a human papillomavirus vaccine injection.” It looked at data from the National Health and Nutrition Examination Survey (NHANES). The study looked at 8 million married and unmarried women ages 25-29 between 2007 and 2014, their history of pregnancy, and HPV vaccination status. It found that within both married and unmarried groups, women who were given HPV vaccine were 25% less likely to have been pregnant at least once. This is unmarried and married groups. It calls for further studies on the influence of HPV vaccine and infertility. It is known that the birth rates in the United States for women under age 30 are at record lows according to the most recent NCHS Data Brief. Therefore, I urge this work group and ACIP to take these findings into consideration in their discussions when considering a recommendation for this vaccine in older age groups. Thank you.

Jeffrey Jackson
Independent

I have a couple of points regarding the HPV vaccine as well, particularly the 9-valent. This is in regard to ACIP’s WG on that vaccination, as well the FDA’s priority review on the vaccination. A couple of data points that I saw from slides in today’s presentation: HPV vaccination will have its greatest impact when administered before onset of sexual activity; over 90% of males and females are sexually active by their mid-20s; and based on epidemiology of the population benefit of the adults would be low in comparison to younger adults. Given those data points, I would urge both the WG and FDA priority review to consider looking at all of the data and taking that into account while expanding that into the greater population. Regarding HPV vaccination, particularly the 9-valent, there is a whole decade of a global consensus, or I shouldn’t say consensus, but a global body that has been growing on the effects of injected aluminum. I would wish for the ACIP WG and the FDA to both consider the global scientific body which is relevant for this vaccine and not to overly rely on the science that is done by the manufacturer of that vaccine. Thank you for your attention.

Andrea Woodruff
Woodruff Family

I'll be honest, there are a lot of policies that this committee has made that I am not very happy about. However, one thing I am very impressed about is your transparency. You have allowed everyone to come here and give their opinion. I have been looking around the world, including watching the World Health Organization, and it is not as transparent as you are. As you continue to work with the World Health Organization, I ask that you bring this value to them and open up their decision-making processes so we can see how things go. Thank you.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Messonnier reported that CDC has been investigating an outbreak of Group A *Streptococcus pneumoniae (S. pneumoniae*) in Colorado. These are cases associated with injection drug use among homeless people. Infectious diseases associated with injection drug use is a new phenomenon for CDC. Questions that have been raised regard whether there is any association with the opioid epidemic, and the utility of vaccines to prevent these cases. The National Immunization Conference (NIC) was held May 15-18, 2018. More than 1500 local, state, federal, and private sector immunization stakeholders and partners gathered to explore science, policy, education, and planning issues. This year's conference was held in conjunction with the National Adult and Influenza Immunization Summit (NAIIS). The presentations for the NIC are available online. CDC is working to improve immunization rates among Medicaid-covered children and pregnant women. CDC's Immunization Services Division (ISD) hosted a special meeting on May 31, 2018 entitled "Opportunities and Barriers to Improve Immunization Rates among Medicaid-Covered Children and Pregnant Women: A Federal-State Partnership." This is part of a CDC-funded cooperative agreement focused on immunization barriers. The meeting brought together members of the community of practice states (Colorado, Indiana, Kentucky, Montana, and New Mexico), project partner CMS, and leaders in Medicaid and public health immunization from around the country.

This is the 100-year commemoration of the 1918 pandemic. A variety of related CDC-sponsored, state and local health department, and partner organization events are anticipated throughout the year. On May 7, 2018, CDC and Emory University convened a panel of experts from academia and government to mark the 100-year commemoration of the 1918 influenza pandemic and to discuss and debate current pandemic influenza threats and the future of pandemic preparedness. Sessions included historic overviews of the 1918 pandemic, current threats and challenges, and a panel of former CDC Directors who reflected on meeting a variety of high profile outbreaks. There is a great exhibit at the Smithsonian National Museum of National History (NMNH) called "OUTBREAK: Epidemics in a Connected World." The exhibit uses case studies of HIV/AIDS, Ebola, and influenza to highlight the social, emotional, and cultural impacts of epidemics. A variety of special events are being planned in conjunction with the exhibit, and they also are working on a traveling exhibit. This exhibit will be open to the public for the next three years.

In terms of staff updates, Dr. Sonja Rasmussen, who is currently Director of the Office of Infectious Disease (OID), is retiring from CDC after 20 years of federal service. After leaving CDC, Dr. Rasmussen will be joining the University of Florida as a Professor in Pediatrics where she will be providing clinical care to patients with genetic conditions, teaching, and continuing her research in public health. One of her passions is diseases and vaccination in pregnant women. Beginning July 2, 2018, Dr. Michael Iademarco, who is currently the Director of the Center for Surveillance, Epidemiology, and Laboratory Science (CSELS), will be serving as Acting Director of OID. A search is planned for a new Director. Dr. Messonnier encouraged everyone to send candidates to CDC. Ms. Brooke Barry has accepted a position as Associate Director of Policy for NCIRD. She will be overseeing the policy office and providing strategic advice, guidance, and direction to programs. Her most recent role has been as the Associate Director for Policy with NCIRD's ISO since 2012.

Department of Defense (DoD)

The Centers for Disease Control Epidemic Intelligence Service Team contributed to the Army EPICON team investigation pertaining to a cluster of 4 myo/pericarditis cases located at one site within DoD. Collectively, there were no deficiencies identified with regard to handling, management and administration of the smallpox vaccines and a number of best practices were noted. Final report and recommendations are pending as of 4 June 2018.

The Immunization Healthcare Branch continues to follow the mumps and measles outbreaks in HI, AK, and Japan. To date, no Service Members have developed disease. There is question of a beneficiary with measles in Japan, but this has not yet been confirmed.

DoD continues due diligence in managing Yellow-Fever vaccine requests during manufacturer shortage. No changes from June 2017 report.

DoD has completed all of Japanese Encephalitis vaccine FDA-required post-licensure studies and is awaiting FDA comment.

Vaccine redistribution continues to be a widely successful program. Individual DoD immunization sites have the capability to communicate near-expiring vaccine surplus or a vaccine deficit through personnel at the Immunization Healthcare Branch (IHB) at the Defense Health Agency. IHB staff then can reach out to other immunization site to redistribute vaccine as needed. In Fiscal Year 2017, $771,000 worth of vaccine was successfully redistributed.

Tracking of vaccine loss due to temperature compromise has continued to evolve. Potential vaccine loss, which vaccines were ultimately cleared vs discarded, etiology for potential vaccine loss (ex power failure, human error, etc.) and trends are identified. These metrics not only provide valuable information to the services with regard to lessons learned, but present an opportunity to standardize best practices across the DoD.

Publications:

Authored by IHB Staff:

- **McClenathan BM**, Stewart DA, **Spooner CE**, et al. Metabolites as biomarkers of adverse reactions following vaccination: A pilot study using nuclear magnetic resonance metabolomics. Vaccine. 2017 Mar 1:35(9):1238-1245.
- Dumas EK, Gross T, Larabee J, Pate L, Cuthbertson H, Charlton S, Hallis B, **Engler RJM**, **Collins LC Jr**, **Spooner CE**, Chen H, Ballard J, James JA, Farris AD.. Anthrax

Vaccine Precipitated induces Edema Toxin-neutralizing, Edema Factor-specific antibodies in human recipients. Clin Vaccine Immunol. 2017 Sep 6.

Funded by IHB Intramural Studies Program:

- Lee RU, Won SH, Hansen C, Crum-cianflone NF. 25-hydroxyvitamin D, influenza vaccine response and healthcare encounters among a young adult population. PLoS ONE. 2018;13(2):e0192479.
- Khodr ZG, Bukowinski AT, Gumbs GR, Conlin AMS. Tetanus, diphtheria, and acellular pertussis vaccination during pregnancy and reduced risk of infant acute respiratory infections. Vaccine. 2017;35(42):5603-5610. Intramural Studies Program funded.
- Hang J, Zavaljevski N, Yang Y, et al. Composition and variation of respiratory microbiota in healthy military personnel. PLoS ONE. 2017;12(12):e0188461. Intramural Studies Program funded.
- Conlin AMS, Sevick CJ, Gumbs GR, Khodr ZG, Bukowinski AT. Safety of inadvertent anthrax vaccination during pregnancy: An analysis of birth defects in the U.S. military population, 2003-2010. Vaccine. 2017;35(34):4414-4420. Intramural Studies Program funded.
- Khodr ZG, Bukowinski AT, Gumbs GR, Conlin AMS. Tetanus, diphtheria, and acellular pertussis vaccination during pregnancy and reduced risk of infant acute respiratory infections. Vaccine. 2017;35(42):5603-5610. Intramural Studies Program funded.
- Pittman PR, Barrera-Oro JG, Xiaofei, et al. Time course of the early antibody response to the priming doses of anthrax vaccine adsorbed. Under review at Military Medicine. Intramural Studies Program funded.

Food and Drug Administration (FDA)

Dr. Sun reported that the FDA convened a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting in May 2018 in which Dr. Carol Baker was a very important participant. This meeting focused on the development of Group B *Streptococcus* vaccines to prevent neonatal sepsis invasive disease. A couple of topics were discussed during that particular meeting, one of which was the use of various clinical endpoints for the pivotal trials such as early onset disease, late onset disease, or a combination of other clinical entities. There also was discussion regarding the use of immunologic endpoints to demonstrate VE as a potential approach, the need to develop standardized assays and serologic correlates of projects from animal studies as well as epidemiologic studies. They also discussed a potential role for colonization as a way to evaluate effectiveness. In terms of other activities, the FDA is working closely with the CDC on the topic of the use of anthrax vaccine in mass vaccination event scenarios and working through the regulatory mechanisms to make the vaccine available to all age groups. That work is ongoing and ACIP's vote the previous day will be a very important part of those considerations. Because of the increasing importance of the role of the use of real-world evidence in informing VE post-marketing, there are numerous ongoing activities related to vaccines and real-world evidence and what could be used to inform VE through these types of data other than RCTs.

Health Resources and Services Administration (HRSA)

Dr. Rubin reported that NVPO has continued to process an increased number of claims. In FY17, there were 1243 claims filed with the Vaccine Injury Compensation Program (VICP). In that same fiscal year, $2.52 million was awarded to petitioners and $29.8 million was awarded in attorney fees and costs. These fees include compensated, dismissed, and interim attorney cases. Thus far in FY18, as of April 30th, $115.4 million has been awarded to petitioners and

$16.6 million has been paid in attorney fees and costs. More data can be obtained on the HRSA website. As of April 30, 2018, the Countermeasures Injury Compensation Program (CICP) has compensated 39 claims totaling $5.5 million. VICP outreach efforts continue to focus on making providers and the public aware of this safety net program.

Indian Health Service (IHS)

Dr. Weiser reported that IHS administered 352,866 doses of influenza vaccine during the 2017-2018 influenza seasons to patients seen in IHS Tribal and Urban Health facilities. Influenza vaccine coverage among children 6 months through 17 years was 39.1% and coverage among adults 18 years of age and older was 35.5%. These numbers have not changed too much in recent years. IHS facilities now have a mandatory HCP influenza policy. Influenza vaccine coverage among federal IHS HCP was 95.8% for the 2017-2018 influenza season. IHS is very pleased about that change. IHS participated in the Region 5 and Region 9 NVPO meetings in Chicago and San Francisco, where they presented information on IHS efforts to implement NVAC and CDC *Standards for Adult Immunization Practice* in its facilities and to improve access to adult immunization in American Indian/Alaskan Native (AI/AN) communities. IHS is very proud of the development and implementation of its adult immunization composite measure, which is consistent with age-based ACIP recommended immunizations for all adults 19 years of age and older across all of IHS. The measure includes Td/Tdap, zoster, and pneumococcal vaccines and has been developed as a Government Performance Results Act (GPRA) measure, as well as being included in the IHS IIS for this year. IHS will report on coverage with this measure during the next ACIP meeting.

National Institutes of Health (NIH)

Given the focus on influenza vaccines during this meeting, Dr. Beigel thought it would be appropriate to give a few updates on NIH influenza studies. A strategic plan was released in February 2018, A Universal Influenza Vaccine: The Strategic Plan for the National Institute of Allergy and Infectious Diseases, that was published in the *Journal of Infectious Diseases* (*JID*) that maps NIAID's vision about how to get from current vaccines to a point at which there would be universal influenza vaccines. To develop a universal influenza vaccine, NIAID will focus on three key research areas:

- ❑ Improving the understanding of the transmission, natural history and pathogenesis of influenza infection
- ❑ Precisely characterizing how protective influenza immunity occurs and how to tailor vaccination responses to achieve it
- ❑ Supporting the rational design of universal influenza vaccines, including designing new immunogens and adjuvants to boost immunity and extend the duration of protection.

In March, NIAID launched two new clinical trials testing inactivated 2017 H7N9 influenza vaccines in the NIAID-funded network of Vaccine and Treatment Evaluation Units (VTEUs). NIAID funded previous research on an earlier version of the H7N9 vaccine. The new vaccine candidate uses an inactivated form of H7N9 influenza virus collected in 2017, to increase the likelihood that the vaccine will provide immunity against a newly-evolved strain of H7N9. Combined, these trials are expected to enroll up to 570 volunteers ages 19-64, and up to 300 volunteers > 65 years of age. One of the trials is testing different dosages of the inactivated influenza vaccine candidate, with or without AS03 adjuvant manufactured by GSK Biologicals. The second trial is testing the H7N9 vaccine candidate with the AS03 adjuvant when co-administered with seasonal influenza vaccine.

In May, NIAID began a clinical trial testing a universal influenza vaccine, called M-001, for safety and its ability to produce potentially broad protective immune responses, both on its own and when followed by a licensed seasonal influenza vaccine. Theoretically, it could protect against many current and emerging strains of influenza. The study will enroll up to 120 healthy volunteers between the ages of 18 and 49 years and is being conducted at four VTEUs.
In June 2018, NIAID's Advisory Council approved several FY19 concepts that may be of interest to ACIP. The first is entitled "Collaborative Influenza Vaccine Innovation Centers (CIVICs)." The program's objective is to support a new consortium focused on developing innovative influenza vaccines that provide robust, durable, broadly protective immunity (universal influenza vaccines) and improve the immunogenicity and durability of licensed seasonal influenza vaccines.

The second is for a new funding mechanism to support clinical trials evaluating vaccines. This would entail the establishment of a Leadership Group for an Infectious Diseases Clinical Research Consortium that will support planning and implementing clinical trials and studies, and a new funding mechanism for the VTEUs that will be part of the Leadership Group. This infrastructure should foster collaborative approaches to addressing NIAID priorities and provide a more streamlined mechanism for NIAID to evaluate and advance the development of vaccines, therapeutics, biologics, diagnostics, and other products. A webinar and FAQ page can be found at https://www.niaid.nih.gov/research/future-infectious-disease-research.

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

Dr. Wharton reported that NVPO collaborated with a number of partners (CDC, NIH, FDA, and other agencies) in responding to a request written into the 21st Century Cures legislation for a report on vaccine innovation barriers and how to address them. Since the February ACIP meeting, that report was posted online on the NVPO website. NVPO recently wrapped up a series of stakeholder meetings organized in collaboration with regional health administrators in Dallas, Omaha, Denver, Philadelphia, Chicago, and San Francisco. These meetings convened stakeholders around adult immunization. These were generally well-received and some planning came out of those. NVPO hopes to be able to support some similar meetings in the future. The next NVAC meeting will be on June 25, 2018 from 2:00 PM to 5:00 PM via webcast. This meeting will include a presentation from the HPV Implementation WG on a draft report that is expected to be discussed and voted on by the committee. In terms of personnel, CAPT Angela Shen who has been with NVPO for a number of years will be retiring from the US Public Health Service (USPHS) this summer. Her last day on the job will be later in June.

Discussion Points

Dr. Bennett expressed sadness that ACIP would be losing another extremely valuable member after this meeting with the departure of Dr. Sun, who has served as the FDA liaison for many years. She wished him the best and thanked him for all of his contributions. She thought it was fair to say that over the course of Dr. Sun's tenure, ACIP had come to better understand and has had a much stronger sense of continuity with the FDA.

Dr. Sun indicated that in August 2018, he would be departing the FDA. He thanked all of the ACIP Executive Secretaries: Dr. Larry Pickering and Dr. Amanda Cohn; Chairs: Dr. Carole Baker, Dr. Jon Temte, and Dr. Nancy Bennett; Directors: Dr. Anne Schuchat and Dr. Nancy Messonnier; Staff who have made all of these meetings so smooth: Dr. Jean Smith, Jessica McNeal, Stephanie Thomas, Natalie Greene, and others; and the WG leaders with whom he has worked closely: Dr. Marc Fisher, Dr. Lisa Groskopf, Dr. Lauri Markowitz, and Dr. Erin

Staples. Dr. Sun said he always looked forward to attending ACIP meetings because he knew that he would learn so much, but he also had some trepidation in that he might have to explain some FDA decision or was uncertain about whether he would be able to answer the questions asked of him. However, he stressed that this is a necessary and good thing, because ACIP is a forum for making evidence-based vaccine recommendations and policy. As someone pointed out the previous day, there is accountability and transparency. He has come to appreciate the importance of the close collaboration and partnership between the FDA, ACIP, and CDC in promoting public health through vaccines. He emphasized that it has been a real pleasure and privilege for him to have served with ACIP for the last 8 years.

Japanese Encephalitis Vaccine

Introduction

Chip Walter, MD
Chair, ACIP Flavivirus Vaccines WG

Dr. Walter reminded everyone that Flavivirus Vaccines WG's objectives with respect to Japanese encephalitis (JE) are to: 1) review the newly available safety and immunogenicity data for JE vaccine; 2) review the epidemiology and risk of JE in travelers; 3) review ACIP recommendations for use of JE vaccine in consideration of updated data; and 4) update the *MMWR Recommendations and Reports*. He indicated that the presentations during this session would include the following:

- GRADE for inactivated Vero cell culture-derived JE vaccine (JE-VC)
- Background to comparative analysis of JE vaccination strategies
- Comparative analysis of JE vaccination strategies
- Summary and conclusions

GRADE for Inactivated Vero Cell Culture-Derived JE Vaccine (JE-VC)

Dr. Susan Hills, MBBS, MTH
Arboviral Diseases Branch
Division of Vector-Borne Diseases
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention
Fort Collins, Colorado

Before commencing on the GRADE for JE-VC, Dr. Hills began with a reminder of some key issues related to JE and JE vaccine. JE is caused by a mosquito-borne flavivirus. It occurs in most of Asia and the Western Pacific and is the leading vaccine-preventable cause of encephalitis in Asia. [1]Most JE virus infections in humans are asymptomatic, with <1% of infected people developing neurologic disease. However, when disease does occur, it is often severe. Overall, about 20% to 30% of patients die, and 30% to 50% of survivors have significant neurologic, cognitive, or behavioral sequelae. There is no specific antiviral therapy, and treatment consists of supportive care. [2]There are about 68,000 JE cases annually in Asia, with an overall incidence for all age groups of approximately 1.8 cases per 100,000 population. The highest risk for infection is in rural, agricultural areas. Because of the ongoing risk for the local

population, national vaccination programs have been implemented in some endemic countries.[3] For most travelers to Asia, the risk for JE is very low but varies on the basis of travel destination, duration, season, and activities. The overall incidence is estimated to be less than 1 case per million travelers. A JE vaccine for travelers was first licensed in the US in 1992. In the 25-year period following licensure, 12 travel-associated JE cases were reported among travelers or expatriates, or less than 1 case reported per year [[1]Vaughn DW. Epidemiol Rev 1992; [2]Campbell GL. Bull World Health Organ 2011; [3]Hills SL. CDC Yellow Book 2018].

The inactivated JE-VC manufactured by Valneva, Ixiaro®, is the only JE vaccine currently licensed and available in the US. The vaccine was licensed for adults 17 years of age and older in 2009. The licensure was subsequently extended in 2013 to children ages 2 months through 16 years. The primary series is 2 doses administered 28 days apart. The vaccine costs approximately $600 for the 2-dose primary series.

There are no efficacy data for Ixiaro®. Because several effective JE vaccines were available in Asia, RCTs to evaluate new JE vaccines for efficacy would have been logistically difficult and potentially unethical. However, there is an established immunologic correlate of protection which is a JE virus with 50% plaque reduction neutralization test ($PRNT_{50}$) titer of ≥10 [Hombach J. Vaccine 2005; Markoff L. Vaccine 2000].

The vaccine was licensed based on its ability to induce neutralizing antibodies and comparison with a licensed inactivated mouse brain-derived JE vaccine (JE-MB). JE-MB had 91% efficacy in an RCT in more than 65,000 children in Thailand in 1984-1986. In the pivotal non-inferiority study for JE-VC, the neutralizing antibody response to JE-VC was non-inferior to the response to JE-MB. In addition, seroprotection rates of at least 95% for JE-VC recipients were achieved in all clinical trials that were submitted for licensure. The vaccine had a good safety profile in pre-licensure studies among about 5,000 recipients and no safety concerns have been identified since licensure in 2009, when more than 1 million doses have been distributed in the US [Hoke CH. N Engl J Med 1988; Tauber E. Lancet 2007; Tauber E. J Infect Dis 2008].

In terms of the timeline for ACIP recommendations for use of JE-VC, in 2009, recommendations for use in adults were approved. In 2011, adult booster dose recommendations were approved. In 2013, a GRADE was presented to ACIP for use of JE-VC in children, and recommendations for pediatric use of JE-VC were subsequently approved.

Moving on to the GRADE for JE-VC, the WG is conducting a routine review of JE vaccine recommendations in light of newly available safety and immunogenicity data that have become available since the previous recommendations for JE-VC were approved and published. The overarching policy question for the GRADE review was, “Should JE-VC be recommended for use in persons aged ≥2 months at risk of travel-related exposure to JE virus?” The components of the policy question are: 1) the population, which is persons aged 2 months and older traveling to JE risk areas; 2) the intervention, which is JE-VC administered as a 2-dose primary series; and 3) the comparison, which is no JE vaccine recommended.

In terms of the WG’s ranking and inclusion of outcome measures, the benefits that were considered critical were VE to prevent JE and seroprotection at 1 and 6 months after vaccination. There are no efficacy data available for JE-VC preventing inclusion of these data, but the vaccine was licensed based on an established immunologic correlate of protection, so data considered critical on seroprotection at 1 and 6 months after vaccination were included. The harms that were considered critical were SAEs and AEs of special interest, and these data

were included. Injection site reactions and interference with other vaccines were considered important but not critical outcomes, so these were not included in the evidence profile.

To collect the evidence for the GRADE evaluation, a systematic search and review was performed of the published literature. The WG searched Medline, Embase, CINAHL, and Cochrane Library databases for papers in any language using the keywords Japanese encephalitis AND Vaccine AND IXIARO or JESPECT or IC51 or JEEV or Vero or Purified inactivated. These latter terms are trade names in different countries, or terms used in clinical trials at different points of development of JE-VC. After papers were identified, the title and abstract were reviewed to identify relevant articles. If no abstract was available, the full paper was reviewed. In total, there were 21 studies that reported primary data relevant to the critical outcome measures. The following unpublished data also were included:

- ❑ VAERS data for JE-VC administered from May 2012 through April 2016 to adults and children in the US or to US military personnel
- ❑ Post-marketing AE surveillance data from US military personnel from the Defense Medical Surveillance System (DMSS) database
- ❑ Two clinical trials of a similar JE-VC which is manufactured and licensed in India under the trade name JEEV™

For the first critical outcome, 12 studies provided seroprotection data at 1 month after the 2 dose primary series, including four RCTs with comparative immunogenicity data for another JE vaccine. The comparator JE vaccines used in the controlled trials included JE-MB from Korea and Japan and JEEV™ from India. In all four studies, seroprotection rates were greater than or equal to 95%. Overall, of the 460 JE-VC recipients in the combined RCTs, 97% were seroprotected at 1 month after the 2-dose primary series. In all of these studies, seroprotection rates were similar to or higher than seroprotection rates for recipients of the comparator vaccines.

There were 8 additional observational studies with data on seroprotection at 1 month after the primary series. Of these studies, 4 were actually randomized trials but had no comparative immunogenicity data, so these were considered observational studies for this analysis. In these 8 observational studies involving over 1200 subjects who received JE-VC, seroprotection rates were similar to those in the controlled trials and rates in all but one study were higher than 95%. The one study with a lower seroprotection rate of 65% was conducted among older subjects aged 64 to 83 years. These data on immunogenicity in older adults were considered by the WG and presented to ACIP in October 2015 and were submitted to the FDA. While there are lower seroprotection rates in older adults compared to younger adults, there are no data on safety, immunogenicity, or optimal timing of a possible third primary series dose or early booster dose for older adults.

In terms of the results of a weighted random effects model to provide a pooled risk ratio by combining data from the 4 RCTs, the risk ratio was calculated by dividing the proportion seroprotected in the JE-VC group by the proportion seroprotected in the other JE vaccine group. The risk ratios from the individual clinical trials were weighted and combined to provide an overall comparison across the studies. A risk ratio of >1.0 favors JE-VC over the other JE vaccine. Overall, the combined risk ratio was 1 so there was no significant difference in seroprotection rates at 1 month between JE-VC recipients and the other JE vaccine recipients.

The second critical outcome was seroprotection at 5 to 6 months after a primary series of JE-VC. For the adult studies, follow-up was at 5 months after completing the 2-dose primary series, and for the pediatric studies it was at 6 months. Evidence for this outcome was from 6 studies, including 2 RCTs and 4 observational studies. Again, 2 studies were actually randomized trials without comparative immunogenicity data and were considered observational studies for this analysis. Of the 941 JE-VC recipients in the 6 studies combined, 92% had a PRNT titer of 10 or greater at 5 to 6 months after the 2-dose primary series. The results of the weighted random effects model of the 2 RCTs showed that a significantly higher proportion of JE-VC recipients were seroprotected at 5 to 6 months following vaccination compared to subjects who received JE-MB.

Regarding the outcomes related to potential harms of JE-VC, the control vaccines used in the various studies included JE-MB vaccines from Japan or Korea, JE-VC from India, hepatitis A vaccine, 7-valent pneumococcal conjugate vaccine, purified chick embryo cell culture rabies vaccine, or a placebo of phosphate buffered saline with aluminum hydroxide adjuvant. The AEs were reported if they occurred within the relevant timeframe, but were not necessarily causally related. Within 1 month of either dose of JE-VC, SAEs were reported in 1% or fewer of JE-VC recipients in each of the 8 studies with comparative safety data for a control vaccine or placebo, other than in one study where the rate was 9%. Unfortunately, the study authors did not describe the SAEs that were reported in that study, but only described one event that was considered related to vaccination. Overall in the 8 RCTs combined, 0.6% of the 4141 JE-VC recipients in the RCTs had an SAE reported. There were additionally 4 observational studies with data on SAEs reported within 1 month of either dose of JE-VC, and serious events were reported overall in 0.9 % of the 548 JE-VC recipients in these studies. Four studies provided data for SAEs reported within 6 to 7 months after the first does of JE-VC or control vaccine, including 2 RCTs and 2 observational studies. One study pooled data from several clinical trials in adults. Among a total of 5269 subjects, 1.4% had SAEs reported.

Regarding data from evaluations of AEs reported through post-marketing surveillance, the importance of post-marketing surveillance is that the larger numbers of subjects involved increases the likelihood of detection of rare SAEs that might not be detected with the relatively small numbers of subjects in the clinical trials. Three evaluations were reviews of passive surveillance systems, and one was a retrospective chart review for medical visits following administration of JE-VC to children in a travel clinic. One study included reports from the US, Europe, and Australia for April 2009 through March 2010 during which time almost 250,000 doses of JE-VC were distributed in those countries. Two studies were reports from VAERS analyses covering the periods May 2009 through April 2016, when more than 1 million doses of JE-VC in total were distributed in the US. Approximately 85,000 doses distributed in the US from May 2009 through March 2010 are included in 2 of the 3 evaluations of passive surveillance systems. There was no overlap in the 9 SAEs identified in these 2 evaluations.

The 3 large post-marketing surveillance evaluations provided indirect but reassuring data with 1.1 to 1.8 SAEs reported per 100,000 doses distributed, and the final study from November 2011 through August 2014 supports this although the numbers are much smaller. These rates are similar to or lower than rates of SAEs from post-marketing surveillance for other vaccines including quadrivalent human papillomavirus vaccine, 23-valent pneumococcal polysaccharide vaccine, yellow fever vaccine, and live attenuated herpes zoster vaccine, where rates in similar VAERS analyses were 1.9 to 4.4 SAEs per 100,000 doses distributed. It is important to remember that unlike in the clinical trials where JE vaccine was administered alone, the assessments of surveillance systems often include AE reports where one of more vaccines were co-administered with JE vaccine. In addition, causality often cannot be assessed from

information submitted and available in passive surveillance systems and the events might not be causally related. With the SAEs reported in the clinical trials and surveillance data overall, no patterns in the timing or types of SAEs were identified.

Regarding the results for pooled risk ratio after combining data from the 8 RCTs with data on SAEs within 1 month after either dose of JE-VC, the AE risk ratios were calculated by dividing the proportion with the AEs in the JE-VC group by the proportion with the AE event in the control group. A risk ratio <1.0 favors JE-VC over the control vaccine or placebo. Overall, the combined risk ratio was 1.2 and the confidence interval crossed 1, indicating there was no significant difference in the proportion of subjects who reported SAEs within 1 month after doses of JE-VC or comparison vaccines. In the 2 randomized controlled trials with data on SAEs at 6 to 7 months, the pooled risk ratio was 0.7 and the confidence limits indicate there was also no significant difference in the proportion of subjects who reported events following JE-VC or comparator vaccines.

For the other outcome considered critical by the WG, AEs of special interest, the events included were fever, rash, hypersensitivity or urticaria, neurologic events, and medically attended events. Data used to evaluate fever as a solicited AE reported within 7 days of JE-VC or control vaccine came from 7 studies, including 4 RCTs and 3 observational studies. Fever within 7 days was reported overall in 8% of the 3892 subjects in the 7 clinical trials, with proportions ranging from 0% to 21%. The substantial differences in proportions were likely related to several factors including the different age groups studied; variable locations of study sites from Europe, the US, Australia, India, and the Philippines; differences in study methodology; and the different sizes of study populations with potentially less precision in some smaller studies. The 2 studies showing higher rates of fever were the study that showed fever among 15% of children in the Philippines and a similar rate of fever among recipients of the control vaccines, and a Phase ll study in the US with only 24 recipients of JE-VC and a non-significant difference in rate of fever compared with the control group. In the 4 RCTs with data on fever within 7 days, there was no significant difference in the proportion of subjects who reported events following JE-VC or comparator vaccines.

Rash as a solicited AE within 7 days after either JE-VC dose was reported in 2% of the 3892 subjects who received JE-VC in the 4 RCTs and 3 observational studies, with proportions in individual studies all less than or equal to 4%. In the 4 RCTs, there was no difference in the incidence of rash between subjects who received JE-VC and comparison vaccines.

Hypersensitivity or urticaria within 1 month of either dose was reported in less than 1% of the 3868 JE-VC recipients in the 3 controlled trials and 3 observational studies. Proportions were less than or equal to 5% in all studies. The highest rate of 5% was in the observational study among US children travelers. The events reported included asthma in 2 subjects with a history of asthma; 1 subject with episodes of pruritis or rash 1 day, 5 weeks, and 3 months after vaccination; contact dermatitis in 1 subject, and pruritus and erythematous rash in 1 subject. In the 3 RCTs that included data on hypersensitivity or urticaria, there was no significant difference in the incidence of these reactions between recipients of JE-VC and control vaccines.

Neurologic AEs, excluding headache, within 1 month of either dose of JE-VC were reported in only 1 of the 5 clinical trials, or overall 1% of the 3668 JE-VC recipients. No cases of meningitis, encephalitis, or GBS were reported. In the 3 RCTs, there was no difference in the incidence of neurologic AEs between recipients of JE-VC and control vaccines.

Medically attended AEs within 1 month after either dose of JE-VC were reported in 14% of almost 4000 subjects overall in the 3 controlled trials and 3 observational studies. The proportion of subjects with medically attended AEs in individual studies ranged from 0% to 19%. The 2 studies with the highest percentage of subjects with medically attended AEs were conducted among children in the Philippines where the same rates of events occurred among the JE-VC and control vaccine recipients and among elderly adults in Europe. When data from the 3 RCTs were combined and weighted, there was no difference in the incidence of medically attended AEs between JE-VC and comparison vaccines recipients.

Additional data on some of the AEs of special interest were available through post-marketing surveillance reports from the 3 passive surveillance systems, and the post-marketing surveillance study that utilized the DMSS to actively and retrospectively identify pre-defined, potential SAEs in the 42 days following administration of JE-VC, based on ICD-9 codes. For the 3 reviews of passive surveillance systems, rates of hypersensitivity reactions were from 3.0 to 4.4 events per 100,000 doses distributed. In the active surveillance study, the rate was 24.8 per 100,000 doses administered. This much higher rate reflected the different methodology of this study with active and retrospective identification of events based on ICD-9 codes. Unfortunately, there was typically insufficient information available to assess the complete clinical presentation or why a certain ICD-9 code had been applied. However, information indicated that some events were likely unrelated, including for 1 case the report indicating a large area of erythema after a bee sting or bug bite, and for 3 cases, occurrence of the event at least 3 weeks after vaccination. In addition, 3 events occurred after co-administration with other vaccines including anthrax and rabies vaccine, precluding attribution to a particular vaccine.

Based on data on neurologic AEs reported through the same post-marketing surveillance systems, the incidence rates from the passive surveillance systems ranged from 0.2 to 1.1 neurologic events reported per 100,000 doses distributed. Again, in the active surveillance study, the rate was substantially higher at 22 events per 100,000 doses administered, reflecting the different methodology of this study. Clinical information was not available to adequately assess the events, although 1 event followed surgery and was unrelated. The timing of 3 events reported as convulsions and 1 event reported as meningitis at 3 weeks or later after vaccination suggested they were also likely unrelated. One other event occurred in a JE-VC recipient who had also received several reactogenic vaccines including smallpox and anthrax vaccines.

In addition to the studies of JE-VC, the WG also reviewed evidence for seroprotection, SAEs, and events of special interest from an RCT of a similar JE vaccine which is manufactured and licensed in India under the trade name JEEV™. JEEV™ is manufactured by Biological E using technology transferred from Valneva and is licensed for use in India. The vaccine used as a control was JenceVac, the inactivated mouse brain-derived JE vaccine from Korea. In an RCT comparing JEEV™ and JenceVac in children aged 1 through 2 years, 92% of the 280 children who received JEEV™ had protective neutralizing antibodies at 1 month after the second dose. SAEs were reported in less than 1%t of recipients. Fever within 7 days after either dose was reported in 11% of children and rash in 1%. Although JEEV™ and JE-VC are not identical vaccines, these data provide some additional evidence of immunogenicity and safety of JE-VC.

The final step in the GRADE analysis was assessing the quality of the evidence for each of the four critical outcomes. The initial evidence type is classified based on the study design and can be downgraded based on limitations including risk of bias, inconsistency, indirectness, and imprecision. As a reminder, these are the standard GRADE classifications:

- ❑ Evidence Type 1: RCTs or overwhelming evidence from observational studies
- ❑ Evidence Type 2: RCTs with important limitations or exceptionally strong evidence from observational studies
- ❑ Evidence Type 3: Observational studies or RCTs with notable limitations
- ❑ Evidence Type 4: Clinical experience, observational studies with important limitations, or RCTs with several major limitations

In terms of the evidence type for studies that support the critical outcomes related to the benefits of vaccination, for seroprotection at 1 month post-vaccination, for the 4 RCTs the initial evidence type was 1 and for the 8 observational studies the initial evidence type was 3. No downgrading was needed as no serious limitations were identified. For seroprotection at 6 months, there were 2 RCTs and 4 observational studies. The initial evidence types were again 1 for the RCTs and 3 for the observational studies, and no downgrading was needed for any serious limitations. For both outcomes, imprecision was a factor in some individual studies. But when combined data from the RCTs were reviewed, this was not a serious limitation overall. Other factors that could have an effect on evidence type (publication bias, strength of association, dose response, and residual confounding) were not considered to be factors that would alter the evidence type.

With regard to the evidence type for studies that support the critical outcomes related to harms of vaccination, including SAEs and events of special interest, for SAEs 8 RCTs started at evidence type 1 but were downgraded to evidence type 2 because of risk of bias due to inadequate blinding. Eight observational studies started at evidence type 3 and no serious limitations were identified. For events of special interest, the evidence provided by 5 RCTs was again downgraded to type 2 because of risk of bias due to inadequate blinding. Seven observational studies started at evidence type 3 and no serious limitations were identified. For both outcomes, there was some concern about imprecision in the RCTs. However, complementary information from surveillance assessments and observational studies supported the results of the RCTS and therefore imprecision was not considered a concern overall.

In terms of the overall quality of evidence for JE-VC, while RCTs and observational studies are considered in the body of evidence, the final evidence type is based on the RCTs because they provide the higher quality of evidence. The available data suggest the overall evidence type for benefits or seroprotection is 1 and for harms or adverse events is 2.

The next step in regard to this GRADE analysis is to incorporate the information into the EtR framework. The WG anticipates presenting the framework and proposed recommendations during the next ACIP meeting.

Discussion Points

Dr. Belongia requested further information about the history of this vaccine prior to licensure in the US in terms of whether it was licensed in other countries. It sounded like the manufacturer transferred the technology to India, and he wondered how long it had been used there.

Dr. Hills replied that it was licensed in the US and subsequently was licensed in Australia, Thailand, and Europe. The first licensure was in 2009. JEEV™ has been licensed in India but not really used beyond the private market in India. It has not been used extensively in national vaccination programs where other types of JE vaccines have been used.

Dr. Belongia pointed out that in terms of reporting the pooled effectiveness for the variety of measures the WG was considering, it would be helpful also to show a measure of heterogeneity across those, especially given the use of inconsistency as an outcome in the GRADE analysis.

Background for a Comparative Analysis of JE Vaccination Strategies for US Travelers to Asia

Marc Fischer, MD, MPH
Arboviral Diseases Branch
Division of Vector-Borne Diseases
Fort Collins, Colorado

Dr. Fischer provided background for a comparative analysis of JE vaccination strategies for US travelers to Asia. For most travelers to Asia, the risk for JE is very low but varies based on travel destination, duration, season, and activities. Travelers with longer trips or increased rural and outdoor exposures are at higher risk of acquiring JE virus infection. JE vaccine was first licensed in the US in 1992. In the 25 years from 1992 through 2017, 12 JE cases were identified among US travelers or expatriates. Among the 12 cases, 8 had traveled for a month or longer. Three cases traveled for less than a month but spent at least one night in a rural area. One case traveled for less than one month, but there is no information on their itinerary or activities. These low numbers of JE cases are not likely related to JE vaccination. In two studies performed in 2007 and 2009 through 2012, 11% and 28% respectively of adult higher risk, longer-term US travelers to Asia had received JE vaccine for their current or previous trips. Only 2% to 4% of lower risk travelers had received JE vaccine.

In terms of the current ACIP recommendations for prevention of JE among travelers, all travelers to Asia should be advised of the risk of JE and the importance of avoiding mosquito bites to reduce the risk for JE and other vector-borne diseases. For some travelers who will be in a higher-risk setting, JE vaccine can further reduce the risk for infection. Providers should assess a traveler's risk based on their planned itinerary, including location, duration, season, and activities. The decision whether to vaccinate should weigh the risk of travel-associated JE, the high morbidity and mortality when JE does occur, the low probability of serious AEs following vaccination, and the cost of the vaccine. JE vaccine is recommended for longer-term travelers who will live in or visit endemic areas for a month or longer during the JE virus transmission season, including expatriates and recurrent travelers who will be based in an urban area but are likely to visit rural areas. JE vaccine also should be considered for short-term travelers to endemic areas if they plan to travel outside an urban area and have an itinerary or activities that will increase the risk of JE virus exposure. JE vaccine is not recommended for short-term travelers whose visit will be restricted to urban areas or times outside of a well-defined JE virus transmission season.

The analysis to be presented after this talk compares JE vaccination in three groups of US travelers. Risk Group I includes travelers who plan to spend a month or longer in JE endemic areas and approximates the group for whom JE vaccine is currently recommended. Risk Group II includes travelers who will spend less than a month in JE endemic areas with at least 20% of their time doing outdoor activities in rural areas. This group approximates travelers for whom JE

vaccination should be considered after evaluating their itinerary and weighing the benefits, risks, and costs. Risk Group III includes the remainder of shorter-term and lower-risk US travelers to Asia for whom JE vaccination is not recommended.

In terms of how the estimated incidence of JE for each risk group was calculated, the number of JE cases by risk group comes from US surveillance data for the 10 years from 2007 through 2016. This time period was used because it most closely approximates the JE risk for current travelers and includes the best data for total travelers to Asia and the proportion of travelers in each risk group. From 2007 through 2016, 9 JE cases were identified among US travelers or expatriates. Of those, 5 spent a month or more in JE endemic areas and fit Risk Group I, 3 were shorter-term travelers with rural exposures who fit Risk Group II, and 1 case had no information on their itinerary and was conservatively assigned to Risk Group III. The proportion of all US travelers by risk group was estimated from a survey of US travelers to Asia performed at three US airports in 2007. Using data from that study, approximately 20% of US travelers to Asia are in Risk Group I, 25% are in Risk Group II, and the remaining 55% are in Risk Group III. The number of US travelers to Asia was approximated from US National Travel and Tourism Office (NTTO) data for the number of the total number of trips to Asia by US citizens from 2007 through 2016. During this 10-year period, US citizens made 48 million trips to JE endemic countries in Asia. By applying the proportions derived from the airport study, it was estimated there were 9.4 million trips among travelers in Risk Group I, 12.2 million trips among travelers in Risk Group II, and 26.5 million trips among travelers in Risk Group III. From the number of reported cases and total travelers to Asia, the incidence of JE among Risk Group I is 0.53 cases per million travelers, the incidence of JE for Risk Group II is 0.25 cases per million travelers, and the JE incidence for Risk Group III is an estimated 0.04 cases per million travelers.

There have been no previous cost-effectiveness studies of JE vaccine among travelers. In addition, ACIP has not considered cost-effectiveness analyses for other rare travel-associated vaccine-preventable diseases, such as rabies or meningococcal disease. JE vaccination is cost-effective or cost-saving for local populations in JE endemic countries. Two factors account for expected differences in the cost-effectiveness of JE vaccine between local populations and travelers. First, there is a substantially higher incidence of disease in endemic areas. There are 1 to 10 cases of JE per 100,000 people per year in endemic areas without vaccination compared to less than 1 case per million US travelers. In addition, substantially lower cost vaccines are used for most routine or mass vaccination programs in Asia. A live-attenuated JE vaccine manufactured in China and used widely throughout Asia costs less than $1.00 per dose. By comparison, a 2-dose primary series of JE-VC for US travelers costs approximately $600 dollars.

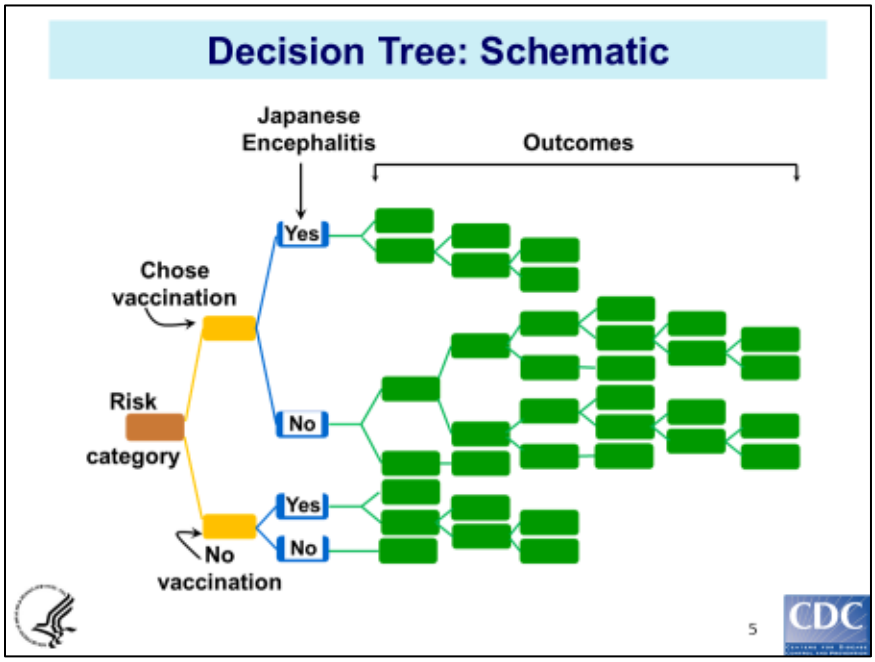
In 2010, the ACIP WG decided not to evaluate cost-effectiveness when it considered the current recommendations for JE vaccine in US travelers. This was because it was clear that vaccination of travelers would not be cost-effective due to low disease incidence and high vaccine cost. In addition, travel vaccines are usually paid for by the travelers themselves. They are not covered under the Vaccines for Children (VFC) program or by most private insurance plans. For this routine review of the current recommendations, the WG decided to perform a comparative analysis of different vaccination strategies. The rationale for the analysis was to: 1) provide perspective on the numbers of travelers needed to be vaccinated and associated costs to avert a case; 2) compare the relative costs of vaccination for travelers with different itineraries and disease risk; and 3) better understand the cost implications of possibly expanding the current JE vaccine recommendations to a broader group of travelers.

Comparative Analysis of Strategies for JE Vaccination for US Travelers to Asia

Martin Meltzer, PhD, MSc
Senior Economist
Lead, Health Economics Modeling Unit
Distinguished Consultant, Division of Preparedness and Emerging Infections
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Meltzer indicated that, in order to conduct a comparative analysis of vaccinating different groups of US travelers against JE, a cost-effectiveness analysis was performed. The design was a Decision Tree and a hypothetical population was used in which a comparison was made of cases in vaccinated and unvaccinated cohorts of 1 million individuals in each of the 3 risk groups that Dr. Fischer outlined. It was assumed that each traveler would receive 2 doses of primary vaccination as per the recommended schedule, all individuals would travel in year 1. Further, some individuals would travel again after year 1, and some of those repeat travelers may receive a booster dose. The analytic horizon was 6 years with one exception. For those people who obtained clinical illness, the productivity losses associated with severe illness and/or death were extended out over average life-expectancy of those patients. Two analytic perspectives were examined. One was societal, which is an umbrella perspective including all benefits and all costs regardless of who pays. The other was that of the travelers. Of particular note, it was assumed that most travelers would have some form of healthcare insurance so that should they become clinically ill with JE, the short-term and long-term medical costs would be paid by the existing healthcare insurance and would not come out of the traveler's pocket.

This is a schematic of the Decision Tree Model used to compare, adjudicate, and estimate all of the inputs into the model:



Reading from left to right, there is first a given traveler risk category, which is one of the 3 traveler risk categories described by Dr. Fischer. The first split in the Decision Tree pertains to whether someone chooses to get vaccinated or not. Having made that decision, the next split in the Decision Tree described the risk of getting JE, Yes/No. Even if one is vaccinated, the vaccine is not 100% effective and there is some risk of getting JE, albeit greatly reduced because of the vaccination. The green boxes are the outcomes. The point here is that, in a model that is considered to be simple, those green boxes represent a lot of different outcomes and the probabilities associated with them.

There are different risks of obtaining a clinical case of JE by risk group, as follows: A risk of 0.53 clinical cases of JE per million travelers in Risk Group I, 0.25/million travelers in Risk Group II, and 0.04/million travelers in Risk Group III. If a traveler does contract a clinical case of JE, it is assumed that there is a 32% chance of having a fatal outcome. Even if a clinically ill traveler experiences a non-fatal outcome, there is a large percentage probability of obtaining a lifelong, or at least severe, sequalae. Overall, there is a greater than 50% chance, among those travelers that have a clinical case of JE, of experiencing either a fatal outcome or severe sequalae.

Keeping in mind that protective neutralizing antibodies are a proxy for effectiveness, vaccine effectiveness (VE) in Year 1 is approximately 91%. Without a booster dose, by Year 6 VE decreases to 64%. With a booster dose in Year 2, VE for the remaining 6 years will be approximately 96%. It is assumed that in Year 1, all travelers receive the 2 doses as per recommendations. It also was assumed, initially, that about 40% of travelers would return annually to areas where JE is endemic and that those travelers would receive a booster dose. Later in the analysis the impact of changing these assumptions are extensively examined.

In terms of the economic data, the following medical costs were used:

	Estimated Costs (US 2016 Dollars)
Vaccine cost per dose	$ 292
Vaccine administration fee per dose	$ 46
Vaccine adverse effects per vaccinee	$ 0.01†
Short-term medical costs of JE treatment*	$29,992
Long-term medical costs of mild sequelae*	$ 1,687
Long-term medical costs of severe sequelae*	$ 8,437

†See appendix for details
***Assumes clinical syndrome of encephalitis**

Sources: ***Drug Topics Red Book. Medical Economics Co, 1995, online; Coleman MS. Vaccine 2005; Staples JE. Am J Trop Med Hyg 2014.***

Most people are surprised in that these numbers can seem to be “pretty low”. But, in fact, most of the long-term costs associate with treating clinical cases of JE occur within 5 years. For most people with medical costs associated with JE-related treatments, those medical costs are over within 5 years. That is not the same as productivity costs.

The following productivity costs were used:

		Estimated Costs (US 2016 $)
Short-term productivity costs†:		
	Complete recovery	$ 59,090
	Mild sequelae	$ 59,090
Lifetime productivity costs:		
	Severe sequelae†	$1,183,294
	Death‡	$1,688,566

***Assumes median age of JE case is 33 years**
†Based on market productivity
‡Based on total productivity (household + market)

Sources: ***Grosse SD. Med Care 2009; Staples JE. Am J Trop Med Hyg 2014 (Table 5).***

Dr. Meltzer emphasized that these are productivity costs, not an absolute value of life. This is the economic value of lost productivity due to lost work and household functions.

Regarding the results in terms of the Numbers Needed To Treat (NNT) to prevent one case, 735,994 Risk Group I travelers would have to be vaccinated to prevent one case of JE. To prevent one death in that risk group, which has an incidence or risk of 0.53 cases per million travelers, 2.2 million travelers would have to be vaccinated. Just under 30 million travelers would have to be vaccinated to prevent one death in Risk Group III. When the costs of vaccination and healthcare treatments prevented due to vaccination are considered, from a societal perspective there are more costs than benefits regardless of who pays and who benefits. To prevent one case of JE in Risk Group I, it would cost $596 million per case averted, increasing to just over $1.8 billion dollars per death averted in Risk Group I. It would cost $7.9 billion per case averted to prevent one case of JE amongst Risk Group III travelers and increases to $23.9 billion per death averted in that risk group. The numbers are very similar from the traveler's perspective.

Obviously, there is a great deal of uncertainty in some of the input values. A lot of time was spent on sensitivity analyses varying the values of inputs. For example, in the base case for the Risk Group I (societal perspective), it would cost $596 million to prevent one case of JE. If JE incidence was increased by 100-fold from 0.53/million to 53/million, the cost for a case averted in that risk group would decrease to $5 million per case averted. If the medical costs are increased by 100-fold, the cost per case averted would decrease from $596 million to $592 million. If the probability of death is increased from 33% to 60%, approximately doubling the risk of death, the cost per case averted decreases by approximately $1 million per case averted.

The risk of disease is a very important input. Detailed consideration was given to the impact of increasing or altering the risk of disease by risk group on the cost per clinical case averted by risk group, allowing for differences in disease incidence. In Risk Group I. who experience a base incidence of 0.53 cases/million travelers, the cost would be $596 per case averted. If a base incidence of 100 times higher, this decreases to $5 million per case averted. Similarly, the $7.9 billion per case averted for Risk Group III decreases to $78 million per case averted if

incidence or risk is increased by 100 times. Increasing medical costs by factors of 10 and 100, the changes in the costs per case averted are far less. For example, in Risk Group III base case medical costs are $7.905 billion per case averted. Increasing medical costs for the treatment of people in that risk group with JE by a factor of 100 decreases the cost per case averted to a factor of $7.902 billion per case averted, which is not a very large change in the cost per case averted. In a sensitivity analysis that changed incidence and medical costs simultaneously, incidence was found to be a far more important input variable than medical costs, relatively speaking.

With regard to what would happen if vaccine costs were reduced, an analysis was performed that kept vaccine administration at $45 and treatment of vaccine-related Adverse Events (AEs) at an average of $0.01 per dose administered. When the base case of $292 per dose was reduced by 50% (to $146/dose) and 90% (to $29/dose), the impact on the cost per case averted from the societal perspective in Risk Group I went from $596 million per case averted to $338 million per case averted when cost per dose was reduced by 50%, and to $131 million dollars per case averted when the cost per dose was reduced by 90%. For a given, fixed probability of repeat travel past Year 1, increasing the probability of getting a booster dose increases the cost per case averted. The greatest change is seen when the probability of repeat travel in Years 2 through 6 is increased, with greater increases in repeat travel being associated with greater reductions in the cost per case averted. In other words, of those two variables, the probability of repeat travel beyond Year 1 is the greater impact in the cost per case averted.

A sensitivity analysis also was done with a mixed cohort, taking 1 million travelers comprised of a mix of all three risk groups according to the number of travelers: 19% in Risk Group I, 25% in Risk Group 2, and 55% in Risk Group III. Consideration was given to what would happen if only those in Risk Group I were vaccinated, those in Risk Groups II and II were vaccinated, and all of those in the cohort were vaccinated. As the number of people vaccinated is increased, the number of cases averted per million travelers in this mixed cohort increases from 0.26 to 0.43 if Risk Groups I and II are vaccinated, and to 0.48 cases averted per million travelers if all three risk groups are vaccinated. As the number of people vaccinated in that cohort is increased, the cost for vaccination increases from $185 million for vaccinating just Risk Group I to $949 million if all three risk groups in the cohort are vaccinated. The average cost per case averted increases from $596 million per case averted if just Risk Group I is vaccinated to approximately $1.7 billion per case averted if all three groups are vaccinated. The incremental cost, or the additional cost for additional cases averted because additional people have been vaccinated in the mixed cohort is as follows: If Risk Group I is vaccinated and then Risk Group I and II are vaccinated, it would cost approximately an additional $1.6 billion to prevent one additional case of JE amongst the mixed cohort. Similarly, if Risk Group III was added to Risk Groups I and II, it would cost an additional $14.6 billion to prevent one additional case due to that additional increase in travelers vaccinated.

In terms of limitations, the results are affected by uncertainty regarding JE incidence. This has been addressed with extensive sensitivity analyses, altering the assumed level of incidence and risk amongst travelers. The proportion of travelers who get JE vaccine is also unknown. In this analysis, it was assumed that all of the travelers were vaccinated at least in the first year. The study includes only the possibility of a vaccine booster dose in Year 2. Long-term medicals costs include only costs for the first 5 years for those people who have long-term sequelae treatment. That was based on the limited data available that most medical treatment is completed within the first 5 years.

The study was performed according to ACIP guidelines and underwent peer-review inside CDC. The main comments from the peer-review were to: 1) clarify assumptions regarding number of doses administered to vaccinees; 2) increase the breadth of the sensitivity analyses regarding vaccine administration costs and medical costs; and 3) explain why medical costs were not discounted. These issues were addressed.

In conclusion, the cost per JE case averted ranged from $596 million for Risk Group I per case averted to approximately $7.9 billion for Risk Group III from the societal perspective. The NNV ranged from approximately 736,000 to prevent one case of JE in for Risk Group 1 to just under 10 million for Risk Group III. The single most important variable is the incidence or risk of getting JE while traveling. There is smaller impact of other variables including increased likelihood of returning travel, increased medical costs, and decreased likelihood of getting a booster dose of vaccine.

Summary and Conclusions

Dr. Susan Hills, MBBS, MTH
Arboviral Diseases Branch
Division of Vector-Borne Diseases
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention
Fort Collins, Colorado

Dr. Hills summarized the WG's conclusions from the comparative analysis of JE vaccination strategies for US travelers to Asia. As a reminder, the objectives for the comparative analysis were to: 1) provide perspective on numbers of travelers needed to be vaccinated and cost per case averted; 2) compare the relative costs of vaccination for travelers with different itineraries and disease risk; and 3) understand the cost implications of expanding the current JE vaccination recommendations to a broader group of travelers.

To prevent one case of JE among US travelers in the highest risk group for JE, which approximates those for whom JE is currently recommended, about 0.7 million travelers need to be vaccinated. For travelers in Risk Group II, or those in the category for whom vaccination should be considered, about 1.6 million travelers need to be vaccinated. For remaining travelers in the lowest risk group, almost 10 million travelers will need to be vaccinated to prevent one case of JE.

With the baseline assumptions used in the cost-effectiveness analysis, the cost to prevent one case of JE in travelers in the highest risk category is about $0.6 billion. Comparatively, for those in Risk Group II the cost per case averted is $1.3 billion and for those in Risk Group III, it is $7.9 billion. Because there is some uncertainty about the sensitivity of surveillance for JE and therefore true incidence among travelers, a sensitivity analysis was conducted increasing incidence 100 times. Although it is very unlikely 100 cases of JE are occurring among US travelers each year when fewer than 1 case is reported, this figure was used as a very high estimate. With incidence 100 times higher, the cost per case averted in each of the three risk groups was $5 million, $12 million, and $78 million respectively. When expanding recommended JE vaccination from Risk Group I to Risk Group I + II, it will cost society an additional $1.6 billion to prevent 1 additional case of JE. Similarly, expanding JE vaccination recommendations from Risk Groups I + II to all (Risk Groups I + II + III), it would cost society an additional $14.6 billion to prevent an additional JE case.

In conclusion, the comparative analysis provided information that indicated that the number of travelers needed to vaccinate and cost per case averted varied greatly related to disease risk group. It also showed the cost per case averted was at least $2 million even when extensive sensitivity analyses were conducted including increasing incidence and medical costs and decreasing vaccine cost, and these costs were substantially higher when travelers in the lower incidence groups were considered. The WG plans to use the results of the comparative analysis of vaccination strategies to assist with considerations as part of the EtR assessment. Importantly, the findings are only one piece of data that will be considered comprehensively with the other important disease and vaccine data, including considerations about the high morbidity and mortality when JE occurs, and the availability of a safe and effective vaccine which is typically paid for by individual travelers.

To complete the remaining Workgroup objectives, the following items will be addressed at one or more upcoming ACIP meetings:

- ❑ Presentation of the EtR framework
- ❑ Presentation of proposed ACIP recommendations for use of JE vaccine in consideration of the updated safety, immunogenicity, and traveler risk data
- ❑ Presentation of a draft of an updated *MMWR Recommendations & Reports*

Discussion Points

Dr. Riley asked whether there are any patient-specific risk factors for either being more likely to get the disease or more likely to do poorly from the disease.

Dr. Hills replied that there are no particular patient-specific risk factors other than being immunocompromised, for example, for which the risk would be expected to be increased. Because US travelers are typically not immune, cases are seen among all age groups unlike in developing countries where immunity through asymptomatic infection develops fairly early such that most cases are seen among younger age groups. The risk really is exposure to mosquito bites in rural areas, such as camping, hiking, et cetera. These are by far and away the critical factors that are important in the cases that occur among US travelers.

Dr. Lee said that when this session started, she wondered whether it was worth it to perform the economic analysis. However, at the end she thought it was really helpful as it provides support for the common-sense approach for why ACIP made the recommendation they did already. The other reason she thought it was important is because the NNV is incredibly useful at the clinician and individual patient level. Often people are told they are at higher or lower risk, but there are no numbers to give them to show what the risk really is. Having that number to share is important for that conversation a doctor might have with a patient. In terms of the risk-benefit balance for the individual patient, she wondered whether it would be possible to assess how many AEs might be occurring in that same population of 700,000 patients to prevent one case of JE. From a population-level, the answer is clear.

Dr. Meltzer replied that vaccine-related AEs is included in the calculation, though they had not produced a table. It would not be particularly difficult to do so.

Dr. Stephens asked of the 12 cases that have been identified in the last 25 years, how many were vaccinated, the age distribution, and whether they thought that there was a larger pool of individuals who have not been identified who have had disease.

Dr. Hills replied that among the 12 JE cases that have occurred over that 25-year period, they are not aware of any of them who have been vaccinated. The age range is from a very a young infant who was an expatriate living overseas at the time through cases at least in their 60s. Regarding whether they are missing cases, there are two separate issues which are reporting and diagnosis. There are very few places in the US that can actually perform JE testing. The majority of cases are actually tested at CDC, so they are confident that they are aware of those who have a confirmed diagnosis. They do not know how much detection there might be in terms of clinicians actually thinking about the diagnosis in somebody returning from overseas and ordering the test to diagnose a condition. As Dr. Meltzer mentioned, to address that in the cost-effectiveness analysis, incidence was increased 100-fold though it is unlikely that many cases are occurring.

Dr. Bernstein asked whether most of the 68,000 cases annually in Asia are in individuals who have been vaccinated or not.

Dr. Hills indicated that the 68,000 cases are primarily among those who have not been vaccinated. For decades in Asia, there was not much access to immunization because the vaccine that was available required 3 doses and it was relatively expensive for many countries in Asia, so they did not introduce vaccination programs. Countries such as Japan, Korea, and Thailand did begin to introduce vaccine. The real progress with JE control in Asia has been the availability of an affordable vaccine that is produced in China. Over the last 10 years, there has been an enormous expansion of vaccination programs and reduced numbers of JE cases. However, countries like Myanmar, Cambodia, and Laos have introduced vaccines in recent years. Other countries like the Philippines, Bangladesh, Indonesia, and others have not yet introduced a national vaccination program. They are seeing a lot of cases in those countries that have not yet been able to introduce vaccination programs.

Dr. Scott Halstead of the Uniformed Services University of the Health Sciences (USUHS) said he admired the effort that Drs. Meltzer and Hills went through to go through the cost-effectiveness analysis and congratulated them. The problem is that it is not clear what to make of it. This is certainly the most important human viral zoonosis. Roughly 40% of the people who live in South Asia are at risk. Many people like to visit Asia. This a very complex zoonosis. He spent many years in Japan trying find out where JE went in the winter time, so he studied many different species. Finally, they thought they had to start tapping trees but it could be found anywhere—bats, snakes, frogs. This is a very complex zoonosis that is largely fueled by rice paddy breeding mosquitoes, of which there are many different species. There is going to be risk and there has to be a way to mitigate that risk. The vaccine used in the US is antibody-based and probably is okay. While they have gotten a long way, they do not really understand vaccines very well. They are made and administered and empirically they work or do not work. JE vaccine is one that works and is known to work because the vaccine he was talking about (mouse brain-derived vaccine) has been given for 40 or 50 years to countries that are highly vaccinated (Japan, Korea, Taiwan) and the disease has virtually disappeared. Nothing is understood about booster doses. It is known that this vaccine works because it produces antibody. It does not produce T-cell immunity, which is largely derived from non-structural proteins. Given the protective efficacy of antibody, the question regards whether a detectable titer is needed. The 6 months of effectiveness is based on whether the titer is above or below 10, but it probably does not work that way. Having spent many years in Asia, JE vaccine is largely given to children on a very expected schedule. However, they no longer receive it at 20 years or older. There are 50 years of data on JE vaccine in Japan where most of the protection in people over the age of 20 is in people whose titers are probably less than 10, because the vaccine produces an antibody response that disappears. The issue of how this vaccine works

needs to be seriously revisited. It is not even clear that a 2-dose schedule is needed. This really is in scientific limbo. A vaccine is needed. Americans and others who visit Asia are always going to be at risk, and younger people are likely to go back. Increasingly more people are becoming very adventurous and are not just staying in air-conditioned hotels. A vaccine is needed that is comprehensively understood and that it is available. There is still a philosophical strategic question regarding how much this vaccine will be given and how much it will be pushed.

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:

- ❑ Review current data on efficacy, effectiveness, immunogenicity, and cost-effectiveness of pneumococcal vaccines
- ❑ Review current recommendations considering up-to-date (UTD) evidence, including epidemiological studies conducted post-licensure, and assess strength of the evidence
- ❑ Revise or update recommendations for pneumococcal vaccine use, as needed.

As a reminder, ACIP recommended pneumococcal conjugate vaccine (PCV)7 for children in 2000. That was replaced by PCV13 in 2010. In 2012, ACIP recommended PCV13 for individuals with immunocompromising conditions. In 2014, there was a recommendation for PCV13 in series with PPSV23 for adults ≥65 years of age. Currently, the WG is evaluating the use of PCV13 in adults ≥65 years of age. The rationale for that was in 2014 when ACIP recommended PCV13 in series with PPSV23 for adults ≥65 years old the thinking was that short-term, the recommendation was needed because while indirect effects had decreased vaccine-type IPD, there was still a significant burden of pneumonia, especially among older adults.

However, there was a recognition that the long-term public health benefits were expected to be limited because of anticipated continued indirect effects from pediatric PCV13. Therefore, the recommendation was made in 2014 with a commitment to re-evaluate this policy 4 years later and revise as needed, which is where they are in 2018. The re-evaluation of PCV13 for adults ≥65 years has included the following tasks: 1) monitor pneumococcal disease, including both invasive disease and non-invasive pneumonia among adults ≥65 years; 2) evaluate the impact of direct and indirect effects on pneumococcal disease among adults ≥65 years; and 3) continue to monitor vaccine safety.

This table illustrates the complexity of the recommendations:

Table 1. Medical conditions or other indications for administration of PCV13 and PPSV23 for adults

Medical indication	Underlying medical condition	PCV13 for ≥ 19 years	PPSV23* for 19 through 64 years		PCV13 at ≥ 65 years	PPSV23 at ≥ 65 years
		Recommended	Recommended	Revaccination	Recommended	Recommended
None	None of the below				✓	✓ ≥ 1 year after PCV13
Immunocompetent persons	Alcoholism Chronic heart disease[1] Chronic liver disease Chronic lung disease[2] Cigarette smoking Diabetes mellitus		✓		✓	✓ ≥ 1 year after PCV13 ≥ 5 years after any PPSV23 at < 65 years
	Cochlear implants CSF leaks	✓	✓ ≥ 8 weeks after PCV13		✓ If no previous PCV13 vaccination	✓ ≥ 8 weeks after PCV13 ≥ 5 years after any PPSV23 at < 65 years
Persons with functional or anatomic asplenia	Congenital or acquired asplenia Sickle cell disease/other hemoglobinopathies	✓	✓ ≥ 8 weeks after PCV13	✓ ≥ 5 years after first dose PPSV23	✓ If no previous PCV13 vaccination	✓ ≥ 8 weeks after PCV13 ≥ 5 years after any PPSV23 at < 65 years
Immunocompromised persons	Chronic renal failure Congenital or acquired immunodeficiencies[3] Generalized malignancy HIV infection Hodgkin disease Iatrogenic immunosuppression[4] Leukemia Lymphoma Multiple myeloma Nephrotic syndrome Solid organ transplant	✓	✓ ≥ 8 weeks after PCV13	✓ ≥ 5 years after first dose PPSV23	✓ If no previous PCV13 vaccination	✓ ≥ 8 weeks after PCV13 ≥ 5 years after any PPSV23 at < 65 years

*The PPSV23 column only refers to adults 19 through 64 years of age. All adults 65 years of age or older should receive one dose of PPSV23 5 or more years after any prior dose of PPSV23, regardless of previous history of vaccination with pneumococcal vaccine. No additional dose of PPSV23 should be administered following the dose administered at 65 years of age or older.

[1]Including congestive heart failure and cardiomyopathies

[2]Including chronic obstructive pulmonary disease, emphysema, and asthma

[3]Includes B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease)

[4]Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy

In 2012, there was a recommendation to continue PCV13 use in adults ≥19 years of age for patients considered immunocompromised, with functional or anatomic asplenia, with Cochlear implants, or with cerebrospinal fluid leak (CSF) leaks. In addition, in 2014 the recommendation for PCV13 at ≥65 was recommended for those with no medical conditions and those who are immunocompetent.

In the past, the WG has presented on nasopharyngeal carriage before and after PCV13 introduction in adults ≥ 65 years of age to identify serotypes circulating in the community. Of note, for children < 5 years PCV13-serotype carriage had declined from 8% in 2011 to <1% in 2017, while the overall total carriage remained about the same at about 30%. For adults ≥ 65 years of age, it is somewhat different. Declines have been seen in PCV13-serotype carriage. It was estimated to be about 0.2% in 2015-2016, but overall the total *S. pneumoniae* carriage rate is also quite low at 1.8% [Thomas, ACIP meeting Oct 2017; Lessa, ACIP meeting Oct 2017].

Evidence has been presented to ACIP since 2014 on PCV13 coverage in adults. For adults ≥65 years of age and older, coverage increased to about 40% through 2017 where the most recent estimates are represented. For the population 19 through 64 years of age with other PCV13 indications, coverage is lower and varies by indication. This is important to consider, given the complexity of the recommendation already [Pilishvili, ACIP meeting Oct 2017; Black, MMWR 2017].

PCV13-type invasive pneumococcal disease (IPD) declined in all age groups from 2007-2016. Overall and PCV13-type IPD incidence in adults ≥65 years old declined by 40% and 68%, respectively, but then plateaued from 2014 to 2016. During the February ACIP meeting, a mathematical model was presented to estimate the contribution of direct versus indirect PCV13 effects on observed trends in IPD among adults ≥65 years old. The model estimated that approximately 580 IPD cases were prevented since 2014 among adults ≥65 years old in the US,

with benefits decreasing over time due to herd immunity [Matanock, ACIP meeting Oct 2017; Pilishvili, ACIP meeting Feb 2018].

PCV13 effectiveness against PCV13-type IPD ranges from 47% to 65%. These studies were presented during the February meeting. These confidence intervals overlapped with the pre-2014 Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) PCV13 efficacy estimates of 75% (95%CI 41–91%) against PCV13-type IPD. PCV13 effectiveness against PCV13-type pneumonia was approximately 73% (95% CI 13–92) in a test negative case-control study design. Those confidence intervals overlapped with the pre-2014 CAPiTA PCV13 efficacy estimates of 45% (95%CI 14–65%) against PCV13-type pneumonia [Pilishvili, ACIP meeting Feb 2018; McLaughlin, ACIP Feb 2018].

Dr. Lee indicated that during the June 2018 pneumococcal session, presentations would focus on the following topics:

- ❑ Safety of PCV13 in adults aged ≥65 years old
- ❑ Pneumococcal pneumonia burden and PCV13 impact among adults aged ≥65 years old in Louisville, Kentucky
- ❑ Pneumococcal carriage, invasive disease, and hospitalizations following community acquired pneumonia (CAP) among Native American populations
- ❑ Racial disparities in invasive pneumococcal disease and PCV13 impact and Overview of the Evidence to Recommendations Framework for the ongoing review of the PCV13 recommendation for adults ≥65 years old

In conclusion, Dr. Lee posed the following question for ACIP's consideration:

- ❑ What additional information will the committee need to help determine whether continued PCV13 use in adults ≥65 years is warranted?

Safety of PCV13 in Adults Aged ≥65 Years Old

Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Shimabukuro presented information on the background of PCV13 recommendations in adults; AEs following PCV13 reported to VAERS in adults aged ≥65 years old; and PCV13 safety in adults aged ≥65 years old in the VSD.

In August 2014, ACIP recommended both PCV13 and PPSV23 should be administered routinely in series to all adults aged ≥65 years [https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6337a4.htm]:

- Pneumococcal vaccine-naïve persons. Adults aged ≥65 years who have not previously received pneumococcal vaccine or whose previous vaccination history is unknown should receive a dose of PCV13 first, followed by a dose of PPSV23. The dose of PPSV23 should be given 6–12 months after a dose of PCV13. If PPSV23 cannot be given during this time window, the dose of PPSV23 should be given during the next visit. The two vaccines should not be co-administered, and the minimum acceptable interval between PCV13 and PPSV23 is 8 weeks.

- Previous vaccination with PPSV23. Adults aged ≥65 years who have previously received ≥1 dose of PPSV23 also should receive a dose of PCV13 if they have not yet received it. A dose of PCV13 should be given ≥1 year after receipt of the most recent PPSV23 dose. For those for whom an additional dose of PPSV23 is indicated, this subsequent PPSV23 dose should be given 6–12 months after PCV13 and ≥5 years after the most recent dose of PPSV23.

The safety of PCV13 was evaluated in pre-licensure randomized controlled trials in PPSV23-naïve and PPSV23-experienced adults aged ≥50 years[1,2]. The most common AEs did not differ between PCV13 and PPSV23 [[1]Jackson LA, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine compared to a 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naive adults. Vaccine. 2013; 31:3577–8; [2]Jackson LA, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in adults 70 years of age and older previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Vaccine. 2013;31:3585–93].

There have been two post-licensure studies of adults aged ≥50 years. The findings from those observational studies are reassuring. Injection site pain and mild systemic reactions were most common, and there were lower rates of the most common systemic reactions compared to pre-licensure clinical trials[1]. There was a VAERS review of reports in adults aged ≥19 years from 2012-2015. Injection site reactions and fever were most commonly reported, and the safety profile was consistent with safety data from pre-licensure clinical trials[2] [[1] Durando P, et al. Immunization campaign with 13-valent Pneumococcal Conjugate Vaccine in adults in Liguria Region, Italy: one year post-introduction preliminary results. Hum Vaccin Immunother. 2015;11:172-7; [2] Haber et al. Post-licensure surveillance of 13-valent pneumococcal conjugate vaccine (PCV13) in adults aged ⩾19years old in the United States, Vaccine Adverse Event Reporting System (VAERS), June 1, 2012-December 31, 2015. Vaccine. 2016;34:6330-6334].

The objective of the VAERS review was to describe the safety profile of reports submitted to VAERS following PCV13 in adults aged ≥65 years. As a reminder, VAERS is a national spontaneous reporting system that is co-managed by CDC and FDA. It strengths are that it can rapidly detect safety signals and rare AEs. It is subject to the limitations of spontaneous reporting or passive surveillance, which means generally causality cannot be assessed from VAERS data alone.

Regarding the methods for the review, the VAERS database was searched for PCV13 reports from August 2014 through December 2017. The search was restricted to US reports in adults aged ≥65 years. Serious reports were defined as those documenting death, life-threatening illness, hospitalization, prolongation of hospitalization, or permanent disability[1]. Signs and symptoms of AEs were coded using MedDRA[2] Preferred Terms (PTs). PTs are not mutually exclusive, which means that a single report may be assigned more than one PT. A descriptive analysis was conducted that included a clinical review of reports for select pre-specified

conditions of interest (GBS, anaphylaxis, and death). FDA colleagues conducted empirical Bayesian data mining to detect disproportional reporting [[1] Based on the Code of Federal Regulations 21 CFR 600.80; [2] https://www.meddra.org/].

The review identified 5822 VAERS reports in adults ≥65 years of age following PCV13. Of these, 75% were in females, 6% met the regulatory definition for an SAE, the median age was 72 (lowest age was 65), the median onset interval was the day after vaccination, and PCV13 was administered alone in 72% of the reports. In reports documenting co-administration of vaccines, the most common were high-dose inactivated influenza (n=884), zoster vaccine live (n=204), and Tdap (n=87). The most common signs and symptoms are shown in the following two tables, which were very similar in those receiving PCV13 alone and those receiving PCV13 with other vaccines:

Most common signs and symptoms[1] in reports to VAERS following PCV13 in adults ≥65 years, Aug 2014-Dec 2017

PCV13 given alone (72%)	N (%)
Injection site erythema	1,176 (28)
Erythema	815 (20)
Injection site pain	771 (18)
Injection site swelling	735 (18)
Pain	582 (14)
Fever	577 (14)
Pain in extremity	569 (14)
Injection site warmth	487 (12)
Chills	389 (9)
Pruritus	378 (9)

PCV13 given w/other vaccines	N (%)
Injection site erythema	413 (25)
Injection site swelling	271 (17)
Injection site pain	263 (16)
Erythema	254 (16)
Pain in extremity	246 (15)
Pain	189 (12)
Injection site warmth	185 (11)
Fever	171(11)
Peripheral swelling	148 (9)
Pruritus	136 (8)

[1] Coded using the MedDRA Preferred Terms; more than one MedDRA Preferred Term may be assigned to a single report (i.e., not mutually exclusive)

14

Regarding the clinical review of reports for select pre-specified conditions of interest, 39 GBS reports were identified. The median age was 73 and the median onset interval in days was 11. As a reminder, the biological risk window used for GBS is 0 to 42 days. In 23% of reports, there was documentation of a viral respiratory illness 2 to 4 weeks prior to the onset of GBS symptoms. Viral upper respiratory illnesses (URIs) are a known risk factor for GBS. Of these reports, 67% met the Brighton Collaboration criteria[1] for GBS[2]. In 64% of the reports, PCV13 was administered alone [[1]Sejvar et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011;29(3):599-612; [2] Remaining reports (13) had insufficient information to confirm diagnosis and apply Brighton Collaboration criteria for GBS].

Four reports of anaphylaxis were identified. Of these, 1 anaphylaxis case report met the Brighton Collaboration[2] Level 1 criteria, which is the highest level of diagnostic certainty. This was in a 94-year-old female who received PCV13 only and within a few hours began to experience symptoms of angioedema, upper airway swelling, and respiratory distress. The remaining 3 case reports had insufficient information to confirm diagnosis and apply Brighton Collaboration criteria for anaphylaxis [[2] Ruggeberg et al. Anaphylaxis: Case definition and

guidelines for data collection, analysis, and presentation of immunization safety data Vaccine. 2007 Aug 1;25(31):5675-84].

There were 26 reports of deaths identified. In 25 of these, it was possible to confirm that a death occurred through an autopsy report or death certificate. The median age was 80 years and the median time from vaccination to death was 13 days. In 81% of these death reports, PCV13 was administered alone. The following were the causes of death among the verified deaths after PCV13 in adults ≥65 years reported to VAERS between August 2014 and December 2017 (n=25):

- Cerebrovascular accident (6)
- Septic shock (5)
- Coronary artery disease (3)
- Chronic obstructive pulmonary disease (3)
- Myocardial infarction (1)
- Congestive heart failure (1)
- Colon infarction (1)
- Pulmonary embolism (1)
- Influenza (1)
- Medullary paralysis (1)
- Parkinson's disease (1)
- Cryptococcal meningitis (1)

In the review, no unusual or concerning patterns or any unusual or concerning clustering were identified in the post-vaccination period.

Empirical Bayesian data mining did not show any unexpected disproportional reporting for PCV13-MedDRA PT pairings for adults aged ≥65 years old compared to other vaccines in that age group [Data provided by FDA/CBER Division of Epidemiology].

In summary, VAERS received 5822 reports following PCV13 vaccination in adults aged ≥65 years during August 1, 2014 through December 31, 2017. Most (94%) of the reports were non-serious, which is similar to other vaccines given in this age group. The most frequently reported AEs were injection site reactions (i.e., swelling, erythema, and pain) and fever. There were no unexpected data mining findings, and no new safety signals or unexpected patterns were observed. During the analytic period, approximately 29 million PCV13 doses were distributed for the ≥65-year-old US population[1] [[1] Pfizer, personal communication].

Moving on to the VSD study, VSD is CDC's large linked database system that has data on over 10 million persons per year. Active surveillance and epidemiologic studies are conducted using VSD data. The VSD links vaccination data to health outcome data. Vaccination records, health outcomes, and patient characteristics are all linked using a unique identifier.

The objective of the VSD study was to examine a large cohort of adults aged ≥65 years old for evidence of an increased risk of AEs requiring medical attention following vaccination with PCV13 compared to PPSV23. This was a cohort study that involved 6 VSD sites. The study period was from January 1, 2011 through September 30, 2015. "Exposed" doses were the first dose of PCV13 received by active members aged ≥65 years old during January 1, 2015 through August 15, 2015. "Unexposed" doses, which can be considered control doses for the purpose of this study, were the first dose of PSV23 received by active members of the same age group during January 1 through August 15 of each year between 2011 and 2015.

Outcomes included cardiovascular events, Bell's palsy, GBS, syncope, erythema multiforme, thrombocytopenia, cellulitis and infection, allergic reaction, and anaphylaxis. Risk windows varied by events, and were censored at membership disenrollment or receipt of another vaccine. Possible confounders included age at vaccination, sex, VSD site, healthcare utilization, Charlson comorbidity score[1] (predicts one-year mortality), concomitant vaccination, and calendar month. The analysis included the inverse probability of treatment weighting (IPTW) approach to adjust for the differences between the exposed (PCV13) and the unexposed (PPSV23) that may be associated with the risk of AEs [[1]Charlson ME et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83].

These are the VSD study sites and doses:

Study population / VSD sites

	PPSV23 (N=232,591)	PCV13 (N=313,136)
HMO Site		
NCK	85794 (36.89%)	77382 (24.71%)
KPC	15278 (6.57%)	23875 (7.62%)
MFC	4604 (1.98%)	12645 (4.04%)
NWK	12256 (5.27%)	25063 (8%)
SCK	96227 (41.37%)	160958 (51.4%)
GHC	18432 (7.92%)	13213 (4.22%)

- NCK (Norther California Kaiser Permanente), KPC (Kaiser Permanente Colorado), MFC (Marshfield Clinic), NWK (Northwest Kaiser Permanente), SCK (Southern California Kaiser Permanents), GHC (Group Health Cooperative, now Kaiser Permanente Washington)
- Six subjects with missing or other gender were excluded

28

This is the results table:

Results: RRs for medically attended AE for PCV13 v. PPSV23

Adverse Event (risk window)	PPV23 AE counts (N = 232591)	PCV13 AE counts (N = 313136)	Unadjusted RR	95% Wald Confidence Limits		IPTW Adjusted RR	95% Wald Confidence Limits	
G1. Cardiovascular events (1-42)								
Acute myocardial infarction	375	534	1.05	0.92	1.19	0.73	0.61	0.88
Acute pericarditis	8	6	0.55	0.19	1.59	0.90	0.27	2.94
Atrial fibrillation	430	702	1.20	1.06	1.35	0.67	0.57	0.80
Cardiomyopathy &heart failure	566	838	1.09	0.98	1.21	0.62	0.54	0.72
G2. Bell's Palsy (1-42)	57	69	0.89	0.63	1.26	0.69	0.41	1.15
G3. Guillain-Barre Syndrome (1-42)	8	4	0.37	0.11	1.22	0.21	0.05	0.78
G4. Syncope (day 0)	75	22	0.22	0.14	0.35	0.13	0.07	0.25
G5. Erythema multiforme (1-42)	2	2	0.73	0.10	5.22	0.94	0.13	6.71
G6. Thrombocytopenia (1-28)								
Thrombocytopenia I	21	17	0.60	0.31	1.13	0.66	0.25	1.76
Thrombocytopenia II	100	96	0.71	0.53	0.94	0.44	0.31	0.61
G7. Cellulitis and infection (1-7)	1393	1915	1.02	0.95	1.09	0.89	0.81	0.98
G8. Allergic reaction (1-7)	70	49	0.52	0.36	0.75	0.47	0.30	0.73
G9. Anaphylaxis (0-1)	4	5	0.93	0.25	3.46	1.32	0.30	5.79

All anaphylaxis diagnoses at 0-1 days following vaccination were chart reviewed and one patient receiving 5 vaccines concomitantly, including PCV13, was confirmed as anaphylaxis

29

Focusing on the red highlighted area, none of the relative risks for all of the pre-specified AEs reached 1 except for anaphylaxis. For anaphylaxis, 1 is in the 95% confidence interval so there is no increased risk for medically attended AEs following PCV13 compared to PPSV23. In fact statistically, there appears to be a protective effect for some of these outcomes.

A sensitivity analysis was conducted that included alternative comparison groups of those who received PPSV23 during 2015 (N = 25,536) and those who received PPSV23 from 2014 to 2015 (N=77,597). This analysis did not affect the overall results.

In conclusion, the results of this VSD study of PCV13 safety in adults aged ≥65 years old do not support an increased rate of AEs for the AEs studied following PCV13 compared to PPSV23. These findings should provide reassurance regarding continued use of PCV13 in this age group.

Pneumococcal Incidence in the US

David L. Swerdlow MD (CAPT. USPHS, retired)
Senior Director, Clinical Epidemiology & Early Candidate Vaccines Medical Lead, Vaccines Medical Development & Scientific/Clinical Affairs
Pfizer

In terms of background, Dr. Swerdlow first reviewed the 2014 ACIP age-based PCV13 recommendation for adults ≥65 years of age. Community-acquired pneumonia (CAP) incidence is critical for understanding the burden of disease and the cost-effectiveness of the pneumococcal vaccination program. Cost-effectiveness calculations in 2014 were based on an assumed hospitalized CAP incidence rate of 1375/100,000 based on administrative claims data[1]. Two previous population-based surveillance studies, the Etiology of Pneumonia in the Community (EPIC) study from CDC and the Ohio Project, estimated the incidence of hospitalized CAP to be 900-1000/100,000 for adults ≥65 years of age[2,3]. Pfizer conducted active population-based surveillance for hospitalized CAP and determined the proportion of CAP due to PCV13 serotypes. They determined that the incidence of CAP is higher than previously recognized, PCV13 serotypes persist, there is evidence for direct impact of PCV13 in adults ≥65 years of age, and disparities in vaccine uptake are evident [[1]Tomczyk S, et al. MMWR Morb Mortal Wkly Rep. 2014;63:822-825; [2]Jain S, et al. *N Engl J Med 2015;372:835-45*; and [3]Marston BJ, et al., *Arch Intern Med*. 1997;157 (15):1709-18].

During this presentation, Dr. Swerdlow discussed the incidence of hospitalized CAP based on the Louisville Pneumonia Study, PCV13 serotypes in CAP patients and PCV13 impact based on the US Multisite Serotype-Specific Urinary Antigen Detection (SSUAD) Study and Louisville Pneumonia Study, and disparities in PCV13 uptake based on merged IQVIA™ claims data with Experian data.

The Louisville Pneumonia Study[1,2] prospectively enrolled all adults 18 years of age and older living in Louisville, Kentucky who were hospitalized with CAP based on clinical and radiographic criteria. All 9 adult acute-care hospitals were enrolled, which was the full catchment in that area. Incidence was estimated during the 2-year period from June 1, 2014 through May 31, 2016. For all patients with CAP, the PCV13 SSUAD assay was performed to determine if they had PCV13 serotypes as a cause of their pneumonia. Overall, incidence of hospitalized CAP by age group was about 700/100,000 for all persons 18 years of age and older. However, the incidence was 2300/100,000 for adults 65 years of age and older.[1] That is higher than was previously seen in

the claims-based surveillance, EPIC, or Ohio studies [[1]Ramirez et al. *Clin Infect Dis*, 2017;65(11):1806–1812; [2]Alexander R, et al. *Univ Louisville J Respir Infect*. 2017;1(4):35-39].

Pfizer has thought a lot about why the incidence rates seen in Louisville were higher than the incidence rates in the EPIC and Ohio studies. This table shows the selection criteria as well as the three studies:

Louisville Pneumonia Study *vs* Other Prospective CAP Studies: Explained by Inclusion of HCAP and Immunocompromised

Selection Criteria	Louisville[1]	EPIC[2]	Ohio[3]
Pneumonia diagnosis confirmed with Chest Radiograph	✓	✓	✓
No alternative diagnosis to Pneumonia	✓	✓	✓
Clinical criteria (ie, signs and symptoms)	✓ Acute Respiratory Illness OR Acute Infection	☒ Acute Respiratory Illness **AND** Acute Infection	✓ Acute Respiratory Illness OR Acute Infection
HCAP	✓ All Included	☒ Hospitalized in prior 28 days (90 days immunocompromised) ☒ Nursing home residents‡ ☒ Cystic fibrosis ☒ Tracheotomy ☒ PEG tube	☒ Hospitalized in prior 7 days ☒ Nursing home residents‡ ☒ LTC / institutionalized
Immunocompromised	✓ All Included	☒ Cancer with neutropenia ☒ Transplant within 90 days§ ☒ GVH disease ☒ Bronchiolitis obliterans ☒ HIV with CD4 <200 cu. Mm	✓ All Included
Annual CAP Incidence in ≥65y	**~2300 per 100,000**	**~900 per 100,000**	**~1000 per 100,000**

‡Functionally dependent nursing home residents. §Solid organ or hematopoietic stem cell transplant. Red text represents key differences between studies.

amirez et al. *Clin Infect Dis*, 2017;65(11):1806–1812. **2.** Jain S, et al. *N Engl J Med 2015;372:835-45*. **3.** Marston BJ, et al., *Arch Intern Med*. 1997;157(15):1709-18.

7

The first three criteria were not substantially different in terms of incidence rates between the Louisville, EPIC, and Ohio studies. However, there were differences in healthcare-associated pneumonia (HCAP) and for immunocompromised patients. HCAP was included in the Louisville study, but those were excluded in the EPIC and Ohio studies. Immunocompromised patients were included in the Louisville and Ohio studies, but were excluded in the EPIC study. This raises the question regarding whether that is enough to explain the differences in the incidences seen.

The incidence rate of HCAP in the Louisville study was 2327/100,000. If the selection criteria used in the Ohio study were applied and HCAP was excluded, the incidence rate in Louisville would have been 1291/100,000. This is pretty close to what the Ohio study found with 1000/100,000. In the same manner, if the selection criteria used in the EPIC study were applied and HCAP and immunocompromised patients were excluded, the incidence rate would have been 798/100,000. This is again very similar to the rates seen in the EPIC study. Therefore, Pfizer feels that the differences in incidence rates can be explained by the inclusion of HCAP and immunocompromised patients in its study.

In terms of why it is important to include HCAP and immunocompromised patients in estimates of vaccine-preventable CAP incidence, both HCAP and immunocompromised patients make up a substantial portion of CAP hospitalizations. The updated 2016 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines no longer recognize HCAP as a relevant clinical entity separate from CAP[1]. Immunocompromised patients have always been at the highest risk of pneumococcal disease. A similar proportion of PCV13 serotypes were identified in adult HCAP patients and in immunocompromised patients as

compared to patients without HCAP or immunocompromising conditions in a US multisite SSUAD study [[1]Kalil AC, Metersky ML, Klompas M et al. *CID*, 63(5), e61-e111 (2016)].

Dr. Swerdlow pointed out that while he talked about the Louisville and SSUAD studies as being separate, the SSUAD study is an expansion of the Louisville project. The SSUAD expansion was a prospective, multicenter, surveillance study conducted at 21 hospitals in 10 geographically dispersed US cities from October 2013 through September 2016. The objective of the study was to assess the proportion of HCAP in US adults caused by *S. pneumoniae* and specifically by PCV13 serotypes over time. The time period is slightly different because they were able to include surveillance for a 3-year period.

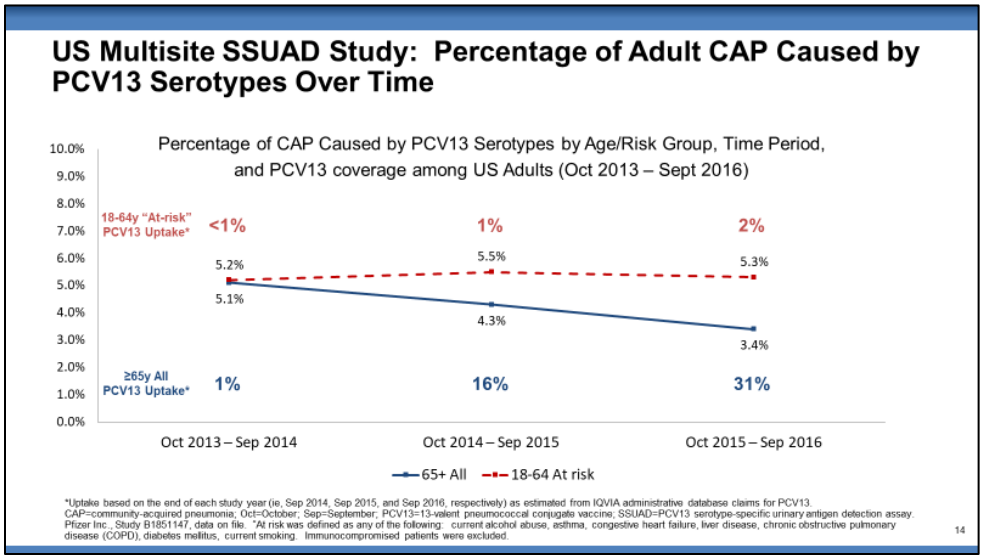
This table shows the percentage of CAP caused by PCV13 serotypes from the entire 21-hospital surveillance system:

Patient Group	≥65y	18–64y
All	4.2	5.1
HCAP	4.8	4.8
No HCAP	3.8	5.2
Immunocompromised	3.7	5.1
Immunocompetent	4.5	5.0

PCV13 serotypes are similarly present in HCAP and immunocompromised patients and there are not any great differences between the percentage positive for HCAP and No HCAP or immunocompromised and not immunocompromised. Therefore, excluding HCAP or immunocompromised patients excludes potentially PCV13-preventable adult CAP disease burden.

In terms of measuring the impact of PCV13, the proportion of CAP caused by PCV13 serotypes was used from both the US Multisite SSUAD Study and the Louisville Pneumonia Study. For PCV13 coverage, the numerator is comprised of monthly administrative claims data projected to national estimates (IQVIA, formerly IMSHealth) and the denominator is comprised of US Census population size estimates (monthly interpolation). Any impact against PCV13-type CAP seen among adults ≥65 years of age who had direct vaccination and also indirect impact from the pediatric program but not in adults 18 through 64 years of age “at-risk” group who had only indirect impact (control group) was assumed to be direct impact above and beyond pediatric indirect effects.

This graphic shows the percentage of adult CAP caused by PCV13 serotypes over time:

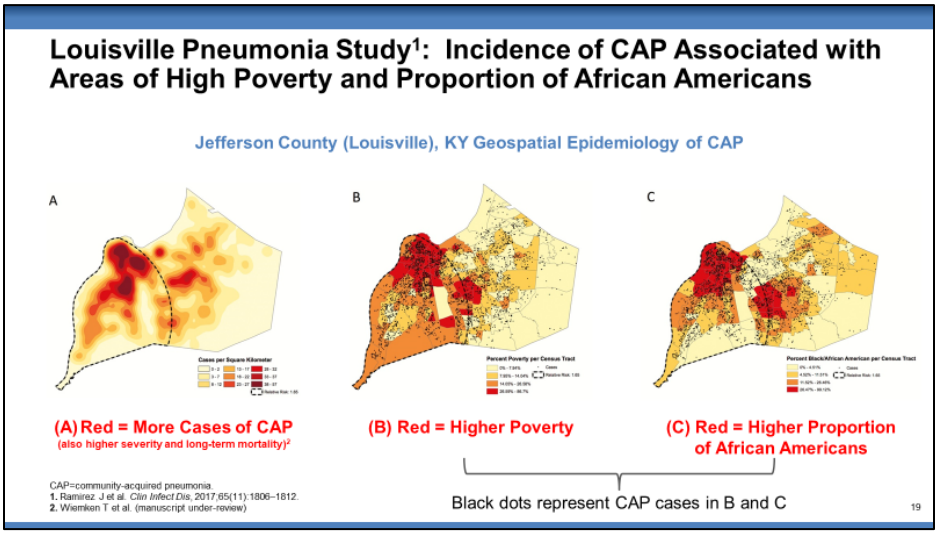


There are a couple of things to see in this table. One is that for adults 18 through 64 years of age who do not get vaccinated, the percentage of CAP that is due to PCV13 serotypes has not changed. The time period of October 2013 to September 2014 is when the ACIP recommendation came out, so the first point is pre-recommendation. Among adults 65 years of age and older, there was a substantial difference and decrease in the percentage of CAP caused by PCV13 serotypes over time. Pfizer thinks that the difference seen is equal to the direct impact of vaccination. Another thing to observe with regard to the above table is that there is a plateau of about 5% for adults 18 through 64 years of age for PCV13 serotypes. There was not very much uptake among adults 18 through 64 years of age because it is not recommended for that age group. However, uptake increased for adults ≥65 years of age during this time period.

The WG asked Pfizer if they could present this same data, but in terms of incidence rather than percentage. For this study, only the Louisville data were used. It was not possible to use the entire 21-hospital data, because they had incidence data only from Louisville. Year 1 is 2014 to 2015 and includes the time period of the ACIP recommendation. Year 2 is after the ACIP recommendation. From Year 1 to Year 2, for PCV13-type CAP there was a 31% reduction that was statistically significant in the incidence of PCV13-type CAP for adults over 65 years of age. For all adults 18 through 65 years old and at-risk adults 18 through 65 years of age, there was no significant difference. To Pfizer, this is more evidence that there was a direct impact of vaccination. The other thing interesting about this analysis is the incidence rate of 76/100,000 for Year 2 of PCV13-type CAP. This is in the range of influenza hospitalizations per year and they think it is still significant.

In terms of disparities in PCV13 uptake, Pfizer examined disparities in PCV13 uptake among adults ≥65 years of age by merging IQVIA™ claims data with Experian ConsumerView™ sociodemographic data[1]. They were able to match 60% of the claims data information from IQVIA™. They looked at income level decile, race/ethnicity, urban and rural versus suburban, and education level. Overall PCV13 uptake was 43% by the end of November 2017. PCV13 uptake is considerably lower among older adults who are in poverty or are African American. From the lowest income decile, uptake of PCV13 was 31% and for the highest decile was 54%.

That is a pretty substantial difference. The same is true for uptake by race/ethnicity. Uptake was 30% for Hispanics, 36% for black non-Hispanics and Asian and other Hispanics, and 46% in white non-Hispanics. The results were very similar for education level, high school or not, and for being in a rural or inner-city area versus a suburban locale [[1]Manuscript submitted April 2018 (currently under review)]. There clearly are very large disparities in terms of uptake of PCV13 as reflected in the following heat maps:



In terms of why this matters, Pfizer was able to show in the far left heat map of Jefferson County where the most cases of CAP are reflected in red. In the next two heat maps, red is equal to higher poverty or to a higher proportion of African Americans. In the areas where there are cases are the same areas where there is higher poverty, a higher proportion of African Americans, and disparities.

In summary, the Louisville study showed high incidence or burden of 2300/100,000 in hospitalized CAP[1] in those ≥65 years of age. A significant reduction in vaccine-type (VT-CAP) has been observed in those ≥65 years of age following PCV13 introduction in adults, but VT disease persists. In contrast, during the same period, among those 18 through 64 years of age where PCV13 was not recommended, VT-CAP remained stable and in fact has plateaued. These findings suggest a direct impact of PCV13 on VT-CAP beyond pediatric indirect effects. PCV13 uptake in those ≥65 years of age has increased steadily since the 2014 age-based recommendation to 43% by November 2017. Continuing PCV13 vaccination in adults ≥65 years of age will allow more time to increase uptake in the general population and address the existing disparities in PCV13 uptake in the very communities at increased risk for pneumococcal disease [[1]Ramirez J et al. *Clin Infect Dis*, 2017;65(11):1806–1812].

Discussion Points

Dr. Romero asked whether the heat maps were run using Latinos and Hispanics as was done for the African American population.

Dr. Swerdlow indicated that a paper will be published that looks at even more details in this area, and the Census tracts were divided into Census groups and performed a lot more review of this. They looked at several different groups and severity. Those areas were likely to have more severe disease and higher mortality as well.

Dr. Szilagyi asked whether they have CAP hospitalization rates by race and ethnicity comparing adults over and under 65 years of age. In terms of the heat maps, he wondered if it would look the same if they plotted just the population density.

Dr. Swerdlow replied that he could forward the CAP hospitalization rates by race and ethnicity to Dr. Szilagyi. Regarding the heat maps, the Census tracts were all about the same population, so they did not do it per population. He thought it was a good question and that it would be interesting to do it per population.

Dr. Messonnier asked whether Pfizer has additional studies planned that will be available within the timeframe for which ACIP is going to make a decision.

Dr. Swerdlow responded that they are still collecting data and performing analyses. They are performing a meta-analysis of serotype 3 effectiveness, and there are other studies they would be happy to present and discuss in October.

Dr. Whitley-Williams (NMA) asked whether they have any data regarding whether persons in the Louisville area actually get their vaccinations, and if they had looked at influenza and pneumococcal vaccination histories prior to discharge for individuals who were hospitalized. She noted that she was trying to get at where intervention efforts possibly could be applied.

Dr. Swerdlow indicated that they do have these data. They went back to every patient during a certain time period to find out their exact vaccination history. Because of that, they know exactly. This turned out to be a lot more complex than they thought. They had to call insurance companies and primary care physicians. The results of that analysis were presented during the last ACIP meeting. In terms of hospital discharge pneumococcal vaccination histories, they could ask what happens in each of the 9 hospitals. He said he thought that was critical in terms of trying to decrease disparities to think about how to reach certain populations.

Dr. Hunter noted that some hospital systems have decided to stop doing routine discharge pneumococcal vaccination with the introduction of the conjugate vaccine, because it was complicated and because Medicare stopped including pneumococcal rates in hospitals as a variable they were measuring.

Dr. Paradiso (Paradiso Biologics Consulting) said he was interested in Dr. Swerdlow's comment about the rate of PCV13 disease and the comparative cases per 100,000. He asked whether that could be translated into numbers of cases for pneumonia for adults over 65 years of age or even a group of at-risk individuals, and how big the burden would be if they were to reduce the 5% to 3% or follow the same pattern.

Dr. Swerdlow replied that while 4.2% or 3.8% sounded like a very small number, Pfizer thinks this is a tremendous burden. There are approximately 49 million US adults ≥65 years of age according to the US Census. Using the current hospitalization rate of 2300/100,000; the in-hospital 30-day mortality from Louisville of 6.5% to 12.7%; a PCV13-type of 3.7% in unvaccinated people; and the results from the analysis presented during the last ACIP meeting with a VE of 72.8% translates to a tremendous burden in the entire US population of adults ≥65 years of age. Translated, that is an absolute rate reduction of 62/200,000. The number of hospitalizations averted over 5 years is 137,000. To him, that is equivalent to the averted hospitalizations in the influenza vaccine program. Papers from CDC that have talked about

averted cases and averted hospitalizations are approximately 20,000 to 40,000 hospitalizations per year averted. Deaths of 17,500 over 5 years is a lot.

Pneumococcal Carriage and Disease in Native Americans in the Era of Routine Use of PCV13

Laura Hammitt, MD
Director, Infectious Disease Prevention Program
Center for American Indian Health
Johns Hopkins Bloomberg School of Public Health

Dr. Hammitt shared data on pneumococcal carriage and IPD from the Center for American Indian Health (CAIH) site among Native Americans in the Southwest US, data from Alaska Native populations shared by the CDC's Arctic Investigations Program (AIP), and data on community-acquired pneumonia from the Southwest US.

To understand and interpret vaccine impact, it is important to know something about PCV13 coverage. Among children, the IHS immunization registry reports show coverage at 80% to 85% for children aged 3 through 4 months (1 dose ~85%), 7 through 15 months (3 doses ~80%), and 24 through 27 months (4 doses ~85%). Coverage among Alaska Native children is slightly higher. For adults, the IHS reports do not currently differentiate between polysaccharide and conjugate vaccine, but other data sources provide an estimate of coverage. From 2015 to 2017, PCV13 was 60% to 80% among Native Americans ≥65 years who participated in various CAIH studies. PCV13 coverage Among Alaska Natives was somewhat lower at ~24% in 2016 [https://www.ihs.gov/NonMedicalPrograms/ihpes/Immunizations/index.cfm?module=immunizations&option=reports; Alaska data courtesy of Mike Bruce CDC/AIP].

A carriage study funded by Pfizer conducted early in the infant PCV13 era showed that PCV13-type carriage among children <5 years of age carriage declined from 12% when PCV13 was first rolled out in early 2010 down to 4% two years later. Among adults, PCV13 type carriage prevalence decreased from about 2% at the start of the study down to about 1% after one year of infant PVC13 use and staying at about 1% through early 2012 [Grant et al, Pediatr Infect Dis J 2016;35:907–914].

A follow-up carriage study was conducted in 2015-2017. Overall carriage prevalence was about 50% during each period and PCV13-type carriage prevalence remained stable at about 4% to 5% between the two time periods. The main PCV13-serotypes in circulation now are 19F and 3. Before moving on to the adult data, it is worth noting key similarities and differences between the two studies. A concerted effort was made to enroll adults in the second study, with 300 participants enrolled into each of 3 adult age categories. This is reflected in a higher median age of adult participants in that second study. This was done to get a more robust understanding of what carriage looked like in adults in the era of adult and infant PCV13. The second study also collected OP swabs in adults and used Sequetyping for serotyping. Overall adult pneumococcal carriage prevalence ranged from about 6% in those 65 years of age and older to about 11% in younger adults. That was similar across the two time periods. PCV13-type carriage was about 1% and was similar between the two groups. Looking at OP swabs and use of PCR on OP swabs, which is thought to be a more sensitive technique, the estimates of PCV13-type carriage increased to about 3%.

Dr. Hammitt noted that Mike Bruce from the CDC's AIP in Anchorage shared data from annual surveys of nasopharyngeal carriage that have been conducted in rural Alaska villages. In terms of PCV13-type carriage prevalence among Alaska Natives from 2008-2015, carriage in children declined nicely after PCV13 introduction in infants. Data from adults also declined and was ~1% in 2015. These data from 2015 are prior to widespread use of PCV13 in adults, so there is only 1 adult in this study who received a PCV13 vaccine.

The conclusion from the carriage data is that PCV13-type pneumococcal carriage in adults was very low following infant PCV13 introduction and remains low.

Turning to IPD, the CAIH collaborates with tribes in the Southwest and IHS facilities serving those tribes to conduct active, laboratory-based, population-based surveillance for invasive bacterial disease, including IPD. For reference, the Navajo Nation is about the size of the State of West Virginia and the population is about 250,000. Identified pneumococcal isolates are serotyped at the CDC's field station in Anchorage and chart reviews are conducted to review underlying medical conditions and vaccination history.

This surveillance system and another system in Alaska are comparable to CDC's Active Bacterial Core Surveillance (ABCs) system, which allowed the investigators to make comparisons on rates of disease between these populations. Across the age groups. Native Americans and Alaska Natives continue to experience disease at rates 3 to 5 times higher than the general US population. The majority of this is attributable to non-PCV13 serotypes.[1] Despite this persistent disparity in disease, it is important to note the tremendous impact that conjugate vaccines have had, especially in high-risk populations. PCV use in children has virtually eliminated PCV-type disease in children [[1]Navajo/White Mountain Apache data from CAIH ABS; Alaska Native data courtesy of CDC/AIP; CDC data from ABCs surveillance reports].

As has been seen in other populations, there have been indirect benefits as well in non-vaccinated age groups. Comparing the pre-PCV era to the infant + adult PCV13 era, there have been substantial reductions in PCV13 IPD incidence. Looking at the impact of the recommendations for vaccines in adults compared to the infant PCV13 era, there was not substantial change over that period. Rates of disease in adults 50 through 64 years of age is similar to that in adults ≥65 years of age and older.

Looking at specific serotypes causing disease among adults ≥65 years of age, there was a nice decline in the case count in the years immediately following infant PCV13 introduction for infants in 2010. By the time PCV13 was introduced for adults ≥65 years of age, most of the serotypes had disappeared with the exception of serotype 3. This has been observed in other populations as well. In the setting of this study, serotype 3 disease is increasing. This is leading the plateau of rates.

Looking again at data from Alaska, courtesy of the AIP, a nice decline in observed in the rates of disease among adults 50 through 64 years and ≥65 years following infant PCV13 introduction in 2010, with rates plateauing after that point. Looking at the serotype distribution in Alaskans ≥65 years of age, there was a decline in the case count following infant PCV13 introduction in 2010 and following PCV13 in adults ≥65 years of age. As discussed earlier, this has not penetrated in that population as well as it has in the Southwest Native American populations, where there is still circulation of serotype 3 and 19A.

The conclusion regarding the IPD data is that substantial indirect effects had been achieved by 2014-2015, which left little opportunity to assess impact of PCV13 in adults ≥65 years of age on carriage or IPD.

Regarding the Native American Adult Pneumonia Etiology Study funded by Pfizer and conducted between March 2016 and March 2018, the era of PCV13 use in adults, cases were identified through surveillance at 5 IHS hospitals. Cases were required to have a provider diagnosis of pneumonia and two or more clinical signs and symptoms. Controls were aged-matched individuals who had no suspicion of CAP. A variety of specimens were collected. For this discussion, Dr. Hammitt focused on the blood cultures obtained per the clinical team and tested in the IHS laboratories at the study facilities and the urine specimens tested by Pfizer using two assays, the SSUAD for 24 serotypes and the BinaxNOW® assay.

The SSUAD is a clinically validated and FDA approved assay for research studies that can detect PCV13 serotypes. Pfizer's SSUAD 2 assay adds an additional 11 serotypes. This assay was well-characterized but not yet clinically validated at the start of the study. The UAD is a limit assay. For most populations, the published thresholds are appropriate. However, there are certain population for which the values in controls are shifted toward the values for CAP cases, as has been seen in children and in HIV-infected individuals.[3] This study provided an opportunity to collect urine from 400 Native America adults in the study community and to use the SSUAD results to establish the thresholds for this specific population. This exercise resulted in the need to reset the positivity cut-off for serotype 14 for this population [Pride et al, Clin Vaccine Immunol 2012; 19:1131–1141].

Over 800 cases have been enrolled in this study, but laboratory testing is still ongoing for the second year of enrolment, so Dr. Hammitt shared results for the first 355 chest x-ray (CXR)-confirmed cases. Demographics were similar between cases and controls, with two exceptions. Cases were split pretty evenly between males and females, but there were about 74% females among the controls. Cases also were more likely to have a smoker residing in the household compared to controls. In terms of clinical characteristics, underlying conditions were very common, more so among cases compared to the controls. Among adults less than 65 years of age, 66% of cases and 48% of controls had received polysaccharide vaccine. Among adults ≥65 years of age, over 90% had polysaccharide vaccine and over 80% had PCV13 vaccine.

Turning to the results for CXR-positive cases with any pneumococcal test performed, overall pneumococcus was detected in 26% of CAP cases. The SSUAD increased the detection of pneumococcal cases by 57%. There was 100% concordance between the SSUAD and blood culture serotype. Because of concerns in the past regarding specificity of urine assays, the urine test results were compared among the CXR-positive cases in the community controls. The SSUAD was positive in 19.5% of cases compared to 2.8% of controls. BinaxNOW® was positive in 15.5% of cases compared to 3.2% of controls. While specificity is not perfect, it is excellent for these assays.

The serotype data were available for 72 of the 91 pneumococcal cases that were detected. A third of them were PCV13-type. The vast majority of the PCV13-type cases were serotype 3. When serotype 3 is excluded, this leaves just over 6% being PCV13-type among those pneumococcal cases.

To compare the data presented by Dr. Swerdlow and this study, PCV13 types were responsible for approximately 6% of overall CAP admissions. Among the PCV13-type cases that had vaccination status available, 62% had received PCV13 in the past and all of those had received PPSV23 first and then PCV13. Nobody received the recommended sequence of PCV13 before PPSV23. This is not a matter of IHS providers not following recommendations. This is a matter of providers having done an excellent job vaccinating people with risk conditions with PPSV23 prior to the advent of the ACIP recommendations for PCV13 in adults. The vast majority of the cases had received PPSV23 before PCV13, many of whom had received more than one dose. Better understanding is needed regarding the implications of the order of vaccination on the immune response. More work also is needed to understand the impact of serotype 3 disease at an individual and population level.

In conclusion, pneumococcus remains an important cause of CXR-positive CAP among Native American adults. Non-PCV13 serotypes and serotype 3 predominated. The SSUAD assay was useful in increasing the detection of pneumococcal pneumonia over conventional methods. It did not reveal a substantial burden of PCV13-type disease, with the exception of serotype 3. However, this is in the context of high PCV13 use in infants and adults ≥65 years of age.

Discussion Points

Dr. Bernstein asked whether they are doing molecular typing on the isolates, given the replacement issues that have been seen previously. Serotype can be helpful, but molecular typing can be more informative, particularly with regard to serotype 3. He wondered if Dr. Hammitt could say more about that.

Dr. Hammitt responded that they are particularly interested in that as well. One of her colleagues at the CAIH just received a research grant to perform some molecular characterization of serotype 3 isolates. They have done this previously in collaboration with colleagues and have seen some of the same patterns there that they have seen in other places with the change between Clade 1 and Clade 2. That was from several years ago and they are now going to look at those isolates again to see what is circulating and perhaps causing what appears to be an increase in serotype 3 disease.

Dr, Grabenstein (Merck) noted that IHS had a great PPSV23 program for many years. Regarding people receiving PPSV23 first and PCV13 second, he wondered whether they were able to assess the interval in time between the two vaccinations.

Dr. Hammitt indicated that they do have those data and she looked at each case. Of those who had their polysaccharide vaccine prior to PCV13, 70% had multiple doses of polysaccharide vaccine ahead of time. Some people had their first polysaccharide vaccine in the 1990s and would have had three vaccines prior to getting PCV12, so they do want to take a more careful look at the intervals to see if that could help inform what is occurring.

Incidence of Invasive Pneumococcal Disease by Race, United States, 2008–2016

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

Dr. Matanock pointed out that IPD rates historically have been higher in some racial minorities. Race is sometimes used as a proxy for socioeconomic status (SES), but in terms of risk for disease, SES might not account for all of the differences in IPD incidence between races. An alternative theory is that some of the increased risk among people of the black race is driven by higher prevalence of certain chronic medical conditions, such as sickle cell disease and HIV. Based on the most recently published analysis using ABCs data for children <5 years of age, overall at pre-PCV7 introduction there were approximately 100 cases/100,000 population absolute difference in IPD incidence among children of black race as compared to white race. This corresponds to a rate ratio of 2.5. Just before PCV13 introduction, the absolute difference had been reduced to approximately 20 cases/100,000 with a rate ratio of 2.2.

The overall objective in this analysis was to evaluate racial disparities in IPD incidence since PCV13 introduction. ABCs data were used from the 10 active laboratory and population-based surveillance sites. Pneumococcus was isolated from sterile sites. Race was defined as a single race reported in the medical chart. Race was imputed, for the 13% of IPD cases where it was not reported, from other patient characteristics such as age, location, syndrome, and underlying medical conditions. US Census population estimates were used as denominators.

Isolates were serotyped by Quellung or PCR at reference laboratories and grouped for analysis. For children <5 years of age, there are PCV13 serotypes[1] that include 6C due to cross-protection[2] and non-PCV13 types. For adults, there is an additional category of PPV11 serotypes[3], which includes the 11 serotypes unique to PPSV23, and all other non-vaccine types. Overall and serotype-specific IPD incidence before and after PCV13 introduction [[1]Serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F; [2]Cooper et al. 2011; and [3]Serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F].

This table shows the distribution of race and the major invasive syndromes caused by pneumococcus, and reflects differences between the age groups:

Race and Syndrome by Age among IPD Cases, 2008–2016

Age in Years:	<5	≥65
Race n (%)		
Black	776 (32%)	1,234 (12%)
White	1,438 (59%)	8,845 (84%)
Other	229 (9%)	434 (4%)
Syndrome n (%)		
Meningitis	224 (9%)	399 (4%)
Bacteremia without Focus	1,074 (44%)	1,618 (15%)
Pneumonia with Bacteremia	813 (33%)	7,998 (76%)

In terms of trends in IPD incidence by serotype group among children <5 years of age from 2008–2016, the incidence reduced for all children after PCV13 introduction. The absolute incident rate difference between children of black and white races went from 8.5 in 2008-2009 to less than 1 case/100,000 in 2015-2016 with an unchanged incidence ratio of 1.8 to 1.7. Looking at the non-PCV13 serotypes, the incidence over time has remained stable with similar disparities between groups. When including a relatively higher incidence year of 2008 and a relatively lower incidence of 2016, there appear to be some reductions in the absolute rate difference in the incidence rate ratio. But overall, there does not appear to be any increase or decrease in the trend.

Regarding the trends in IPD incidence by serotype group among adults ≥65 years of age from 2010 to 2014, the majority of adults were only experiencing indirect or herd effects from pediatric vaccination. After the PCV13 recommendation in 2014, there were combined direct and indirect effects for adults ≥65 years of age. Looking only at the PCV13-type IPD, incidence was reduced for all adults after pediatric PCV13 introduction. The absolute rate difference between older adults of black and white race went from 2.1 in 2008-2009 to equal in 2015-2016, with an unchanged incidence rate ratio of 1.1 to 1.

The unique PPSV serotypes over time are different from the PCV serotype disease in older adults in that there has not been a dramatic decrease in incidence. The incidence by race is similar and is relatively unchanged from 2008-2016. For non-vaccine type in older adults, the incidence has been stable over time, but there remains a persistent gap between older adults of white and black race with those of black race consistently experiencing at least 5 cases/100,000 more than whites with an incidence rate ratio of approximately 1.5.

This table summarizes the absolute rate difference and incidence rate ratios. Persons of white race are not shown because they are used as the reference group:

Incidence Comparisons Before and After PCV13 Introduction

	2008–2009		2015–2016	
	Black*	All Other Races*	Black*	All Other Races*
Children <5 Years Old				
PCV13 IPD Absolute Rate Difference (ARD)	8.5	4.9	0.8	1.2
PCV13 IPD Incidence Rate Ratio (IRR)	1.8	1.5	1.7	2.0
Total IPD ARD	17.8	8.6	5.5	2.5
Total IPD IRR	2.0	1.5	1.7	1.3
Adults ≥65 Years Old				
PCV13 IPD ARD	2.1	-1.9	-	-2.9
PCV13 IPD IRR	1.1	0.9	1.0	0.5
Total IPD ARD	8.5	-3.8	7.9	-5.6
Total IPD IRR	1.2	0.9	1.3	0.8

*Incidence among persons of white race used as reference group

Again, the PCV13 type absolute rate difference between children of white and black races went from 8.5 in 2008-2009 to 0.8 in 2015-2016. The decline of PCV13-type IPD drove a reduction in the absolute difference between whites and blacks from 17.8 to 5.5 in all IPD. Looking at adults ≥65 years of age, the PCV13-type absolute rate difference went from 2.1 to equivalent between blacks and whites. However, with a significant proportion of the remaining non-PCV13-type disease, the overall IPD incidence was similar in 2008-2009 to 2015-2016.

Preliminary conclusions are that as with other analyses, IPD incidence has dramatically declined after PCV introduction for all racial groups. This is driven by reductions in PCV13-type IPD. PCVs have nearly eliminated the absolute difference in PCV13-type IPD incidence between people of black and white races. The disparities in IPD that remain are due to non-vaccine type IPD, which is seen especially in older adults. Further analysis is planned to look at the contribution of SES and underlying medical conditions by race.

Discussion Points

Dr. Bernstein observed that it was interesting that race was imputed and that it was only 13% of the IPD. He asked whether that was a multiple imputation, if there was a reason to do that, and if they looked at it without the imputation.

Dr. Matanock replied that they did look at this both ways, with and without the imputation. They imputed to make it more complete for the entire set, and there were multiple imputations. In the future, they can present it both ways.

Dr. Paradiso (Paradiso Biologics Consulting) pointed out that it is a really interesting result in the US that there has been a dramatic reduction in the vaccine serotypes without a significant increase in replacement of other serotypes in children or adults; whereas, many other countries are fighting replacement disease significantly. This is interesting scientifically in that the US recommended 3 doses in the first year and 1 dose in the second year, while many other countries used a 2 + 1 schedule. This has been a very successful program in the US, in part because replacement has not occurred. Though the US is benefitting from that success, many people are trying to figure out why that disparity is occurring.

Dr. Bresnitz (Merck) asked whether Dr. Hammitt could provide some context by giving an estimate of the percentage of individuals who had been vaccinated with PCV13 between 2014-2016 and then received PPSV23 per the recommendation.

Dr. Hammitt indicated that an *MMWR* was published in 2017 by lead author Carla Black. Among older adults, there was a difference in vaccination rates. It is difficult to assess adult vaccination because there are not standardized registries. The way that information is obtained through multiple channels has limitations. This *MMWR* looked at Medicare beneficiaries ≥65 years of age with claims submitted for pneumococcal vaccination. Between those of black and white race, there was a 10% difference. At that time point, 33% of blacks and 44% of whites had been vaccinated with 1 dose of PPSV23. About 33% of whites and 19% of blacks had received 1 dose of PCV. Receiving both PPSV23 and PCV was about 19% amongst whites and about 10% amongst adults of black race. However, the order and timing of the vaccines is not known from this source.

Dr. Atmar recalled that at the beginning of the presentation, Dr. Hammitt set up the possibility that the racial disparities in incidence might be related either to SES or due to actual racial differences. His interpretation of the data presented was that as the incidence of PCV13 disease has declined, the racial differences have disappeared. He could not tell if this actually answered the question regarding whether this was due to SES or race.

Dr. Hammitt replied that SES and race was somewhat linked and that she had brought it up because they are still planning to look at this by SES, and they know that different results have been observed depending upon whether it is examined by race or SES. She clarified that she made that point because she did not want it to get lost that one could be a complete proxy for the other. The overall message is that through vaccination, whichever one of those things is causing the difference for PCV13-type IPD with the vaccination program in place, the disparity and absolute difference of cases by race has pretty much been eliminated.

Overview of the Evidence to Recommendations (EtR) Framework for the Ongoing Review of the PCV13 Recommendation for Adults ≥65 Years

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

Dr. Matanock reminded everyone of the elements for the EtR framework:

- Statement of problem
  - Public health priority
  - Burden of disease
- Benefits and harms
  - Balance of desirable and undesirable effects
  - Certainty in evidence
- Values and preferences of the target population
- Acceptability to stakeholders
- Resource use
  - Health economic analyses
- Feasibility
  - Implementation considerations

As a reminder, in 2012 ACIP recommended PCV13 in series with PPSV23 for adults ≥19 years old with immunocompromising conditions, asplenia, cochlear implants, or cerebrospinal fluid leaks. In 2014, ACIP added an age-based recommendation for PCV13 to be given in series with the previously recommended PPSV23 for all PCV13-naïve adults ≥65 years old. In 2014, there was a commitment to re-evaluate this recommendation given the ongoing indirect or herd effects, which brought them to this session and the EtR question:

Should PCV13 be administered routinely to all immunocompetent adults aged ≥65 years given sustained indirect effects? The supporting PICO elements are:

- *Population: Immunocompetent adults 65 years and older*
- *Intervention: PCV13 at ≥65 years old in series with PPSV23 in the context of indirect effects*
- *Comparison(s): PPSV23 alone at ≥65 years old*
- *Outcomes: pneumococcal disease, mortality, and vaccine safety*

As part of the EtR, the WG is considering the following outcomes as part of the GRADE process:

- *PCV13-type IPD*
- *Non-bacteremic pneumococcal pneumonia (NBPP) as measured by all-cause pneumonia, NBPP, and PCV13-type pneumonia*
- *Mortality due to IPD and NBPP*
- *Serious or systemic events associated with PCV13*

Within this framework, the information that has been added at this time includes safety data for PCV13 among adults. No new safety signals or unexpected patterns have been observed in VAERS surveillance. No increase in AEs were observed in the VSD cohort. The WG will continue to monitor and provide updates as needed.

Pneumococcal pneumonia still causes a relatively high burden of disease, especially relative to IPD. As presented earlier in the session, from June 2014 to May 2016, PCV13-type pneumonia in adults ≥65 years of age decreased. However, this observation is limited to only 2 years. Additionally, the time period after 2014 is difficult to disentangle in terms of direct and indirect effects. The proportion of pneumonia caused by PCV13 serotypes was 4% among adults ≥65 years of age in Louisville and 6% among American Indian adults in the Southwest. In Louisville, 66% of pneumonia incidence in adults ≥65 years of age was in patients with immunocompromising conditions or HCAP. Population characteristics and case definitions contribute to variations in pneumonia incidence. Studies estimating all-cause and pneumococcal pneumonia incidence and vaccine impact are anticipated in October 2018.

Pediatric PCV introduction has reduced racial disparities in IPD. IPD incidence has dramatically decreased for all racial groups driven by reduction in PCV13-type IPD, nearly eliminating the absolute difference in PCV13-type IPD incidence between people of different races. Carriage of PCV13 serotypes in American Indian children and adults are similar overall to carriage in the US presented to ACIP in October 2017. Among American Indians in the Southwestern US, 26% of chest x-ray confirmed pneumonia was caused by pneumococcus, but PCV13-types did not predominate.

In terms of the tentative timeline, outstanding data will be shared with ACIP during the upcoming meeting in October 2018. These include PCV13 impact on all-cause pneumonia and NBPP from studies examining administrative and clinical surveillance data, as well as the potential public health impact and cost-effectiveness of changing the PCV13 policy for adults ≥65 years old. The WG hopes to have the EtR with GRADE finalized by the following meeting in February 2019 and anticipates a potential vote in February, or if additional time needed, in June 2019.

In conclusion, the WG is in the process of re-evaluating the 2014 PCV recommendation for adults aged ≥65 years in terms of whether PCV13 should be administered routinely to all immunocompetent adults ≥65 years of age in a setting of sustained PCV13 indirect effects. Dr. Matanock asked ACIP what additional evidence should be included in future presentations in terms of the GRADE review to help the committee with decision-making.

Discussion Points

Dr. Moore said that Dr. Hammitt's presentation brought to mind the fact that the vaccine includes serotype 3 but does not work very well against it. It would be incredibly helpful whenever possible to examine the burden of preventable disease in terms of what is remaining with regard to serotype 3 that actually could be impacted. That is, if they are trying to decide whether to retain a recommendation for immunocompetent older adults, what amount of disease remaining, other than serotype 3, do they think they actually could prevent with that policy?

Dr. Stephens said he would like to hear more about the next generation of pneumococcal vaccines and the potential for expanded PCVs, as well as when to give conjugate vaccine or boost with a polysaccharide at a younger age.

Dr. Lee noted that even though she had heard the presentations previously, it was helpful to hear them side-by-side during this session because it illustrated the challenge in disentangling the direct from indirect effects. Based on Dr. Swerdlow's presentation, it seemed like there were some potential direct effects just by there being an overall less than 50% vaccination rate in that population. In contrast, Dr. Hammitt's presentation illustrated that despite very high vaccination rates, there was really no gain after 2014 in terms of IPD presumably because of serotype 3. It was helpful to have all of this information in one place.

Dr. Bennett indicated that this would be Dr. Cindy Whitney's last meeting. She said that for her personally, this was particularly painful because she felt like all of her work with the CDC started with Dr. Whitney. More than that, Dr. Whitney has been an incredible leader of the Pneumococcal WG and the work that the Pneumococcal WG has done over the last 10 years has been extraordinary. She thanked Dr. Whitney for her tremendous leadership and stressed that she would be sorely missed. This was followed by applause and a standing ovation.

Vaccine Supply

Dr. Jeanne M. Santoli
Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Santoli presented an update on Hepatitis A (HepA) and Hepatitis B (HepB) vaccine supplies and provided a reminder about CDC's supply web page during this session.

During 2017, large outbreaks of HepA among adults in several US cities resulted in increased demand for vaccine and resulted in constrained supplies of vaccine. Actions taken included collaboration between CDC and public health officials in affected jurisdictions to target vaccine based on local epidemiology; implementation of ordering controls to maintain an equitable distribution of vaccine in unaffected jurisdictions; and modification of CDC's vaccine contracts to support additional vaccine purchase. In addition, both GSK and Merck have increased the amount of vaccine available in the US market for outbreaks and routine use. Vaccine continues to be directed toward jurisdictions with outbreaks. In addition, as vaccine supplies have improved, the vaccine supply strategy has evolved, making more vaccine available for routine use and/or prevention activities in jurisdictions without large, ongoing outbreaks. CDC and

vaccine manufacturers are continuing to monitor ongoing demand for and usage of adult HepA vaccine closely.

Merck is not currently distributing its adult HepB vaccine or the dialysis formulation and will not be distributing vaccine through the end of 2018. GSK has a sufficient supply of adult HepB vaccine to address the anticipated gap in Merck's adult HepB vaccine supply during this period; however, preferences for a specific presentation (i.e., vial versus syringe) may not be met uniformly during this period. Merck has not been distributing its pediatric HepB vaccines since mid-2017 and will continue to have a limited supply of pediatric HepB vaccine during 2018. Together, Merck and GSK are able to supply the US market with approximately 10% less of the monovalent pediatric HepB vaccine compared to normal during 2018. This expected monovalent supply is fortunately sufficient to cover the birth dose for all children as well as additional vaccine for some second and third doses. There also are combination vaccines that are meeting the rest of the need for HepB vaccine in children. CDC has implemented controlled vaccine ordering in the public sector using both Merck's and GSK's monovalent vaccines. In addition, GSK is providing monovalent vaccine to the private sector aligned with CDC's clinical guidance for emphasizing and continuing with the birth dose. GSK's DTaP-HepB-IPV combination vaccine, PEDIARIX™, continues to be available in the public and private sectors.

CDC has a vaccine supply page that is kept updated to make sure that it is in sync with all of the updates made during ACIP meetings. The Vaccine Supply/Shortage Webpage can be found at: http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm

Discussion Points

Dr. Schaffner (NFID) noted that another recently approved HepB vaccine, HEPLISAV-B®, is now available.

Dr. Santoli responded that in terms of the website, that was not an option at the point where these updates came up. However, when updating it this time they certainly will make note of that.

Day 2: Public Comment

Lynette Barron
Concerned Parent

Hello. I'm Lynette Barron and I am here representing my children. I have two vaccine-injured children. I had no idea vaccine injury was even a possibility. I have 5 kids. I always followed the schedule with my 3 oldest ones and never even imagined it could happen. When my 4-year old was 15 months took to the doctor for thrush. I did not take her in for vaccinations that day. I took her in because she was sick. The doctors told me that my child had to get vaccinations that day. I told them I did not think this was a great because she was in there for thrush. I'm not a doctor. I'm not a scientist. But, I have Google. I can read that that means your immune system is down. But, they kept telling me that if my child would get something that she could have had that would have prevented by those vaccines, that I would be in trouble so I needed to go ahead and do this that day. So, my daughter got 6 vaccines that day—2 were triples. From that day for we went through 26 days straight of fever. We spent 7 weeks in Children's in Birmingham. We had

bone marrow aspiration and biopsies. We went through all kinds of—sorry. Anyway, it's just really hard when you're a parent and have to go through this. I give my daughter NEUPOGEN® injections now every three days of her life, and I have ever since this happened. Two weeks prior to her injury, I cut my finger. Two tiny little stiches is what I needed. I was 26 weeks pregnant and I was told that I had to have Tdap vaccine. I received that Tdap vaccine. Her 2-year old sister has severe autism, development delay, epilepsy, and the list goes on and on. I can't even tell you how many diagnoses this child has received and she is not even 3 years old yet.

I have 5 kids. My older kids didn't get a schedule like this and we didn't see problems like this. The schedule keeps growing, and keeps growing, and keeps growing and we're creating people like me. I don't want to have to know all of this vaccine science. I don't want to have to read every book about this stuff. Every medical journal. I'm a mother. I mean, seriously. I turned my life around in order to try to help other people avoid the same thing my family has to go through. If you had all of the proper science, like this sweet woman just said, find actual scientists other than just the people who are being paid to do these things. Pharmaceutical companies aren't thinking about people like me. They are not thinking about those children who don't need to be vaccinated again. I'm sitting here listening to Paul Offit earlier, the same man who says if you're not going to vaccinate children, they should be taken by the state. I will never vaccinate my children again, and the state will not come take my children because I will fight tooth and nail for my kids. This is not the way this should be. You shouldn't feel pressured to do something like this. You should have all of the proper information. If you don't have all of the science, then how will we have all of the science? It just doesn't make any sense. I will be at every meeting that comes. I will be right here. I really hope that things start getting better and the science starts improving, because the saddest part is I hear more data that makes more sense about what's going on everywhere else than I do in this room. So, I just really hope that improves for people like us who don't want to have to do this. We don't want to be in your space in your face. I want to be at home with my children. I had to pay over $500 to make this trip today to come here from out of state just to talk to you guys to let you know we don't want to be forced. We don't want to be told it's okay when they're sick, "It's okay. We do this all the time. It's not going to do anything. If you don't want to do it and something happens to them, you're responsible." Who is responsible when something happens to my children? Nobody, because they deny it in the VICP. Nobody cares. They don't want to hear your story. They don't want to hear it. They tell me to find my own experts and find my own lawyers. How do I find my own experts? Somebody please tell me that. I mean, it's just insane. The system is not set up to help people. It's damaging and it needs to stop.

Rebecca Hastings
Mom, Grandmother, Breastfeeding Counselor

Hi. I'm Rebecca Hastings and I am in here on my own in my private capacity, paying my own expenses. I really appreciate the opportunity to have this public comment. At the risk of beating a drum and making music that no one wants to listen to, I hope to narrow my comment a little bit today. My guess is that probably everyone in this room understands the priority and significance of breastfeeding. Some of you theoretically and some of you have had personal experience, either yourself or someone close to you, with a breastfeeding mom and baby, health diet, just getting it right. Well, as a breastfeeding counselor trying to help thousands of moms over 25 years, I often see moms really struggle. Some of the main struggles have to do early on with latching, and that often prevents them from developing a good milk supply. So, over the years I've looked at this and I've noticed and have read some studies that point out a correlation between HepB vaccine and difficulty with breastfeeding. Non-vaccinated babies often do better

with breastfeeding, so could only HepB, that birth dose, be playing a role in sabotaging the breastfeeding of newborns. Further, Dr. Yao's study using animal models notes a long-term impact on the brains of mice that received early vaccination with HepB. That caused neurobehavioral impairments, not right away, but in early adulthood. So, the original HepB studies prior to the inclusion on the schedule tracked infants for less than two weeks amongst a growing incidence of anxiety, violence, and social disorders amongst the youth in our country today.

It is no small thing to review the long-term impact that this routine shot may be having on our children. I understand there are many branches in the CDC that are all looking at various aspects of health. I'm sure you have specialists who are working to improve breastfeeding rates and trying to understand the anxiety, depression, violence, and suicide rates amongst youth. Increased communication amongst these various branches of the CDC may increase our understanding of the complex, non-specific effects that could be associated with vaccines. For the layperson, that's unintended consequences. So, the vaccine schedule currently has 3 categories to which physicians refer regarding administration of HepB: Positive Mothers, Negative Mothers, and Mothers of Unknown Status. I would suggest that to delay the HepB vaccine for negative mothers, at least until breastfeeding is well-established, would be a great idea. I would also like to have more representation in your working groups from people who are studying non-specific effects, experts such as Dr. Christopher Exley, Dr. Theresa Deisher, Dr. Mawson. These people can inform your working groups just as you currently have the pharmaceutical industries representing their work and their studies in your working groups. I think that will give you the evidence base. Many have said here today you don't have enough evidence. You're making decisions without evidence. Well, there is evidence available. I think if you access it, it will be better for everyone. Thank you.

Tiendra Severino
Concerned Parent

Hello again. Tia Severino. I just want to say the hepatitis B vaccine is one of the vaccines that injured my son. When he was brought to me after a 5-hour delay after an emergency C-section, he could not latch. He could not nurse. I ended up having to supplement even though it was my desire to exclusively breastfeed him. I thought I was going to take the cautionary approach to vaccinations. He only received 4 vaccines—4 individual separate vaccines separated by 3 to 4 weeks and he still ended up injured. Okay? I'm sitting here listening to you guys talk about a shortage in the hepatitis B vaccine for newborns, and I for the life of me cannot understand why you are recommending this vaccine for a sexually transmitted disease for day 1 old infants. I would like to point out for this panel that the United States has the highest day 1 infant mortality rate in the world. Why? We are supposed to have the best medical system in the world. Why are babies dying the first day right here in this country? Why do we have the highest rates of infant mortality? We have the highest vaccination rates. We should not have children dying. Babies go in at 2, 4, and 6 months and are routinely injected with up to 23 antigens. I'm standing right here representing a friend of mine name Pricilla and her husband Will whose daughter died after receiving her 4-month vaccines. This was determined to be caused by vaccines. Now, with the hepatitis B vaccine, by the time my son is sexually active, guess what? That vaccine is not going to be protecting him. It lasts maybe 8 to 10 years. So, you're telling me that I needed inject my newborn child with a sexually transmitted disease vaccine that is going to wear off before he is ever even sexually active? It makes no sense to me. If you guys are worried about a shortage in hepatitis B vaccines, why don't you just stop giving them to babies? Then you'll have more to go around. Thank you.

Britney Valos
Concerned Parent

Hello. Thank you so much for everything everybody is doing, and for the wonderful presentations, and for explaining to everybody what you guys have been working on for such a long time. I do have a couple of questions about the JE vaccine and the presentation with that earlier. You guys were able to answer the questions, but I just wanted to give a comment and maybe a line of thought to see what your thoughts would be on that. My understanding is that there were 12 cases of JE in about a 19-year span. In those 12 cases, that boils down to less than one case per year. So, if I'm looking at that, you also mentioned that the death rate in JE is 33% in one case. So, in less than one case per year, the possibility of dying is about 33% of that. The purpose and idea behind vaccines is to save lives, so I'm going to focus on the high-risk group, which is the Risk Group I, which is recommended for all travelers staying over a month and also focusing on the deaths on that as well. So, 12 cases over the course of 19 years and a 33% chance of dying in that less than 1 case. In that situation, it would take 2,230,284 people to be vaccinated to save that potential 1 life. If we're looking at that and then we also look at the cost standpoint at that higher rate of $292 per vaccine, you're looking at $651,242,928 to potentially save less than one third of one life, less than 1 life of actually contracting JE in that possible year. Even with the reduced cost of vaccine of $131 per vaccine, then we're looking at $292,167,204 of vaccinating that number of people to potentially save that one life in one year. So, I'm looking at that as far as cost goes. Then one other thing I wanted to point out is that you mentioned that there are 64,000 cases of JE in Asia that have not been vaccinated. Two things. Number one, we're looking at a population of I think 4 or 5 billion people, so the chances of them even getting not being vaccinated we figured up is .00000-it's like 5 zeros, so the chance of them getting it is extremely rare even without the vaccination. Then as you mentioned, the people that are in that area, they receive natural immunity from the symptoms of getting it. So, I wanted to mention those two things.

The next aspect of it, you mentioned the boosters and you're not really sure how efficacious that is. I noticed that the efficacy really went down as far as the number of boosters. It definitely wears off. It doesn't last. So, when we're looking at people to return to this country and possibly getting disease, then my question becomes: What would be better for them if they get it? To achieve natural immunity from getting those basic symptoms and then they have the immunity for a lifetime, versus maybe getting a booster shot or not getting a booster shot. So, I wanted to present that as one idea. Then the second idea is in looking at the study, you're comparing vaccine-to-vaccine as far as the safety profile and the adverse events, so if you're comparing two vaccines, I would want to know from the second vaccine what the safety profile on that vaccine compares to a saline placebo. We don't really know. What if this vaccine has a ton of adverse events. You know, we're not really looking at how safe this vaccine is if we're comparing it to another vaccine that could potentially cause a lot of adverse events. So basically, at the end of the day I understand that this might be an inconvenient illness for that less than 1 person maybe a year who may get it but is probably not going to die from it. But, is this vaccine even needed? I mean, is it even necessary? To go through the cost of having to produce this and then to require or recommend, strongly recommend, for that Class I in people that stay over there a month to get this vaccine when we don't even really know the safety profile of it, because you're just comparing it to another vaccine, that's a lot of unanswered questions. When you're looking at the general public, when they're going to this other country and they're being told, "You might get this. You might get this. You might get this," they're going to just follow suit and we really don't know the safety profile and the disease is really not a big deal. So, I just wanted to see if not vaccinating would be an option.

Andrea Woodruff
Woodruff Family

Hi and thank you. For the Center for Disease Control organization, I've always been pretty impressed with, but I'm starting to really doubt how much we can control disease. I think at best we can manage it. I've been watching data issues and have been asking for models. I haven't gotten them. I've been reading that strain replacement for a combination of viruses or combination of bacteria and contamination issues and manufacturing issues. These things seem to be out of our control. I think we can try to manage and we can report what is being found, but it ultimately comes down to my choice as a person and as a parent what my data points are and what I'm seeing. I love to hear your information and I am grateful that you provide it, but I don't think we can control it. I think that we need to look at these things a little differently. Thank you so much. Take care.

Certification

Upon reviewing the foregoing version of the June 20-21, 2018 ACIP meeting minutes, Dr. Nancy Bennett, ACIP Chair, certified that to the best of her knowledge, they are accurate and complete. Her 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 27, 2017 – June 30, 2018

CHAIR
BENNETT, Nancy, MD, MS
Professor of Medicine and Public Health Sciences Director,
Center for Community Health
Co-director, Clinical and Translational Science Institute
University of Rochester School of Medicine and Dentistry
Rochester, NY
Term: 07/01/2015-06/30/2018

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 Interim Chief,
Section of 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

BELONGIA, Edward, MD
Director
Center for Clinical Epidemiology & Population Health
Marshfield Clinic Research Foundation Marshfield, WI
Term: 07/01/2014-06/30/2018

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

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

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

MOORE, Kelly, MD, MPH
Director, Tennessee Immunization Program
Tennessee Department of Health
Assistant Clinical Professor, Department of Health Policy
Vanderbilt University School of Medicine
Nashville, TN
Term: 07/01/2015-06/30/2019

PELLEGRINI, Cynthia
Senior Vice President
Public Policy and Government Affairs
March of Dimes
Washington, DC
Term: 07/01/2013-06/30/2018

RILEY, Laura E, MD
Associate Professor, Obstetrics, Gynecology and Reproductive Medicine
Harvard Medical School
Maternal Fetal Medicine
Massachusetts General Hospital
Boston, MA
Term: 07/01/2014-06/30/2018

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: 07/01/2014-06/30/2018

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

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)
SUN, Wellington, MD
Director, Division of Vaccines and Related Product Applications
Office of Vaccines Research and Review
Food and Drug Administration
Rockville, 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)
GROOM, Amy, MPH
Immunization Program Manager
Indian Health Service Albuquerque, NM

National Vaccine Program Office (NVPO)
SHEN, Angela K., ScD, MPH CAPT,
U.S. Public Health Service
Senior Science Policy Advisor
Co-Chair National Adult and Influenza Immunization Summit
National Vaccine Program Office, Office of the Assistant Secretary for Health
Washington, DC

National Institutes of Health (NIH)
LAMBERT, Linda C., Ph.D.
Chief, Respiratory Diseases Branch
Division of Microbiology and Infectious Diseases
NIAID/National Institutes of Health
Bethesda, MD

LIAISON REPRESENTATIVES

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

American Academy of Pediatrics (AAP)
BYINGTON, Carrie L, MD
Chair, AAP Committee on Infectious Diseases
The Jean and Thomas McMullin Professor and Dean of Medicine
Senior Vice President Health Science Center
Vice Chancellor for Health Services
Texas A&M University
Bryan, TX

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)
AULT, Kevin A, MD, FACOG
Professor and Division Director
Department of Obstetrics and Gynecology
University of Kansas Medical Center Kansas City,
KS

American College of Physicians (ACP)
FRYHOFER, Sandra Adamson, MD, MACP
Adjunct Associate Professor of Medicine
Emory University School of Medicine
Atlanta, GA

American College of Physicians (ACP) (alternate)
POLAND, Gregory A., MD
Mary Lowell Professor of Medicine and Infectious Diseases Mayo Clinic
Rochester, MN

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) (Alternate Susan Lett)
HAHN, Christine, MD State
Epidemiologist
Office of Epidemiology, Food Protection and Immunization Idaho
Department of Health and Welfare
Boise, ID

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)
NEUZIL, Kathleen M, MD, MPH
Professor of Medicine
Director, Center for Vaccine Development
University of Maryland School of Medicine
Baltimore, MD

Infectious Diseases Society of America (IDSA) (alternate)
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

National Vaccine Advisory Committee (NVAC)
THOMPSON, Kimberly, ScD Chair,
NVAC
Professor of Preventive Medicine and Global Health University of
Central Florida, College of Medicine
Orlando, FL

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)
JOHNSON, David R, MD, MPH
Associate Vice President, Global Medical Affairs, 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

Attachment A: Liaison & Public Comment Letters Submitted

Department of Defense (DoD) Updates for 20-21 June 2018
Advisory Council for Immunization Practices Meeting in Atlanta, GA

The Centers for Disease Control Epidemic Intelligence Service Team contributed to the Army EPICON team investigation pertaining to a cluster of 4 myo/pericarditis cases located at one site within DoD. Collectively, there were no deficiencies identified with regard to handling, management and administration of the smallpox vaccines and a number of best practices were noted. Final report and recommendations are pending as of 4 June 2018.

The Immunization Healthcare Branch continues to follow the mumps and measles outbreaks in HI, AK, and Japan. To date, no Service Members have developed disease. There is question of a beneficiary with measles in Japan, but this has not yet been confirmed.

DoD continues due diligence in managing Yellow-Fever vaccine requests during manufacturer shortage. No changes from June 2017 report.

DoD has completed all of Japanese Encephalitis vaccine FDA-required post-licensure studies and is awaiting FDA comment.

Vaccine redistribution continues to be a widely successful program. Individual DoD immunization sites have the capability to communicate near-expiring vaccine surplus or a vaccine deficit through personnel at the Immunization Healthcare Branch (IHB) at the Defense Health Agency. IHB staff then can reach out to other immunization site to redistribute vaccine as needed. In Fiscal Year 2017, $771,000 worth of vaccine was successfully redistributed.

Tracking of vaccine loss due to temperature compromise has continued to evolve. Potential vaccine loss, which vaccines were ultimately cleared vs discarded, etiology for potential vaccine loss (ex power failure, human error, etc.) and trends are identified. These metrics not only provide valuable information to the services with regard to lessons learned, but present an opportunity to standardize best practices across the DoD.

Publications:

Authored by IHB Staff:

- **McClenathan BM**, Stewart DA, **Spooner CE**, et al. Metabolites as biomarkers of adverse reactions following vaccination: A pilot study using nuclear magnetic resonance metabolomics. Vaccine. 2017 Mar 1:35(9):1238-1245.
- Dumas EK, Gross T, Larabee J, Pate L, Cuthbertson H, Charlton S, Hallis B, **Engler RJM**, **Collins LC Jr**, **Spooner CE**, Chen H, Ballard J, James JA, Farris AD.. Anthrax Vaccine Precipitated induces Edema Toxin-neutralizing, Edema Factor-specific antibodies in human recipients. Clin Vaccine Immunol. 2017 Sep 6.

Funded by IHB Intramural Studies Program:

- Lee RU, Won SH, Hansen C, Crum-cianflone NF. 25-hydroxyvitamin D, influenza vaccine response and healthcare encounters among a young adult population. PLoS ONE. 2018;13(2):e0192479.
- Khodr ZG, Bukowinski AT, Gumbs GR, Conlin AMS. Tetanus, diphtheria, and acellular pertussis vaccination during pregnancy and reduced risk of infant acute respiratory infections. Vaccine. 2017;35(42):5603-5610. Intramural Studies Program funded.

- Hang J, Zavaljevski N, Yang Y, et al. Composition and variation of respiratory microbiota in healthy military personnel. PLoS ONE. 2017;12(12):e0188461. Intramural Studies Program funded.
- Conlin AMS, Sevick CJ, Gumbs GR, Khodr ZG, Bukowinski AT. Safety of inadvertent anthrax vaccination during pregnancy: An analysis of birth defects in the U.S. military population, 2003-2010. Vaccine. 2017;35(34):4414-4420. Intramural Studies Program funded.
- Khodr ZG, Bukowinski AT, Gumbs GR, Conlin AMS. Tetanus, diphtheria, and acellular pertussis vaccination during pregnancy and reduced risk of infant acute respiratory infections. Vaccine. 2017;35(42):5603-5610. Intramural Studies Program funded.
- Pittman PR, Barrera-Oro JG, Xiaofei, et al. Time course of the early antibody response to the priming doses of anthrax vaccine adsorbed. Under review at Military Medicine. Intramural Studies Program funded.

IHPM INSTITUTE FOR HEALTH AND PRODUCTIVITY MANAGEMENT

WPWA WORK PLACE WELLNESS ALLIANCE

IHPM-MENA

IHPM-CHINA

Advancing Health & Performance Globally

June 15, 2018

Chair: Dr. Nancy Bennett, MS
Professor of Medicine and Public Health Sciences
Director, Center for Community Health
Co-director, Clinical and Translational Science Institute
University of Rochester School of Medicine and Dentistry
Rochester, NY

Executive Secretary: Dr. Amanda Cohn
Senior Advisor for Vaccines
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA

Dear Dr. Bennett and Dr. Cohn:

International business travelers are estimated to now constitute from at least 15 to as much as 30 percent of all international travelers, with Asia now their leading destination. The unique risks of business travel and the full impact of lost health and productivity from illness, however, have not heretofore been recognized in the Advisory Committee on Immunization Practices (ASIP) recommendations.

The ACIP recommendations for Japanese Encephalitis (JE) vaccine are under review, and currently include only travelers who spend a month or longer. While expatriates as well as assignees and recurrent travelers to a site may stay for 30 days, the great majority of international business trips are for two weeks – but with multiple trips to at-risk areas common in a year and for a period of years.

In the current recommendations, however, the only considerations for short-term travelers are for leisure and wilderness activities. International business travelers will work and live in peri-urban and rural areas, where there is significant risk. In the recent study of high-risk travelers receiving JE vaccines, more than half listed a work-related reason for their trip.

Institute for Health and Productivity Management | Work Place Wellness Alliance
17470 N Pacesetter Way | Scottsdale, AZ 85255 | p: +1.480.305.2100 | f: +1.480.305.2189
website: www.ihpm.org/ihpm-global

JE is a rare but devastating disease that is spreading geographically in Asia. Leaders of the international business community expect recommendations from ACIP that address any and all potential risks with all possible preventive measures – particularly a safe and effective vaccine. The heath and productivity of international business travelers should be considered in the revision of the currently outdated recommendations for vaccination against JE.

It was announced at the February 2018 ACIP meeting that a Cost Effectiveness Analysis (CEA) would be performed. No such formal CEA had been conducted in connection with previous JE vaccination recommendations, or recommendation for any other travel vaccine. Travel vaccine costs are paid – and purchase decisions made – by the employer or business traveler. The cost effectiveness of vaccination for international business travelers may be different than for leisure or other travelers.

This letter transmits a detailed analysis of the full economic cost burden of Japanese Encephalitis from an employer health and productivity perspective. The Institute for Health and Productivity Management (IHPM), with financial support provided by Valneva USA Inc., commissioned the analysis to be done by the Institute for Clinical Research and Health Policy Studies, Center for Health Solutions: Program on Health, Work and Productivity at Tufts University Medical Center. Dr. Debra Lerner, Director and Founder of the Center, is the acknowledged global leader in the field of functional health and productivity measurement.

IHPM and its WorkPlace Wellness Alliance (created by the World Economic Forum and now managed by IHPM) is a global non-profit enterprise dedicated to establishing the full economic value of employee health as an investment in human capital productivity. The Institute is engaged with employers worldwide, and has a particular interest in Asia because of its China Chapter – which includes such leading multinational companies as Dow Chemical, GE, IBM, Johnson & Johnson, Pfizer, Procter & Gamble, Shell Oil and Unilever. IHPM supports and conducts research on workplace health, and publishes the *International Journal of Health & Productivity* -- the only scientific journal focusing exclusively on health and productivity.

Self-funded American employers assume a unique responsibility for the overall health and wellbeing of their workers, which increasingly means overseas – and especially Asia. While this clear business interest in protecting its travelers to Asia ultimately will be a decision for employers and the travelers themselves, IHPM believes it significant enough to be acknowledged by ACIP in its recommendations.

Institute for Health and Productivity Management | Work Place Wellness Alliance
17470 N Pacesetter Way | Scottsdale, AZ 85255 | p: +1.480.305.2100 | f: +1.480.305.2189
website: www.ihpm.org/ihpm-global

IHPM appreciates the opportunity to enter the accompanying analysis into the record, and would be pleased to engage in further discussion concerning vaccination against JE.

Sincerely,

Sean Sullivan, JD
President & Chief Executive Officer
Co-Founder
Institute for Health and Productivity Management
WorkPlace Wellness Alliance

Dr. William C. Williams III
EVP, National Association of Managed Care Physicians
Medical Directors Institute
Co-Founder of IHPM

Name: Rebecca Hastings Address: 302 Watermarke Lane, Anderson, SC
Organizational affiliation: Independent Email: beckyspd@gmail.com
Topic: Recent scientific studies on vaccine safety

Significant studies have been published which shed light on some unintended consequences of vaccines. I would like to ask the ACIP members specific questions in light of recent findings.

1.Dr Yao (PhD, University of Pittsburgh, and the author of 33 peer-reviewed studies) and his team from China studied the hepatitis B vaccine administered to mice.
"The hepatitis B vaccine (HBV) is administered to more than 70% of neonates worldwide. Whether this neonatal vaccination affects brain development is unknown."
Their conclusion:
"This work reveals for the first time that early HBV vaccination induces impairments in behavior and hippocampal neurogenesis. This work provides innovative data supporting the long suspected potential association of HBV with certain neuropsychiatric disorders such as autism and multiple sclerosis." [Kawahara, Masahiro, and Midori Kato-Negishi. "Link between Aluminum and the Pathogenesis of Alzheimer's Disease: The Integration of the Aluminum and Amyloid Cascade Hypotheses." *Advances in Pediatrics.*, U.S. National Library of Medicine, 8 Mar. 2011, www.ncbi.nlm.nih.gov/pmc/articles/PMC3056430/.]
What steps are being taken by ACIP members to protect infants from the possible harm to the brains from the Hepatitis B shot recommended for the first day of life?

2. Small Fragment Homologous Replacement (SFHR) is known to occur with adult stem cells and is being used in gene therapy studies. This same mechanism is being investigated as operative after injection by vaccines which contain aborted human fetal cell fragments whereby the stem cells readily take up the human DNA fragments into their own DNA sequence, which causes mutations. There are clear and specific change points in the autism prevalence curve seen in multiple countries which coincide directly with the change of vaccines to using aborted human fetal cell lines as a growth medium instead of previously used animal mediums.
What is being done by ACIP to further understand and seek to protect infants from the deleterious impact of injected aborted human DNA fragments?

3. A growing body of research raises questions on the safety of the aluminum adjuvants in vaccines. Since aluminum has never been clinically approved, or clinically demonstrated to be safe, and aluminum is implicated in a host of brain related conditions, **what steps is the ACIP taking to ascertain the safety of the current vaccine schedule in light of the fact that it requires the injection of around 4,925 mcg in the first 18 months of life, not including the preschool, middle school, teen, and adult boosters?**

4. **In light of the Mawson study that clearly demonstrates the robust health of nonvaccinated children, what further studies on vaccinated versus nonvaccinated children are planned by the NIH, CDC, or other governmental bodies? Lacking a safety study for the entire vaccine schedule, how can more vaccines be added?**