

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

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



**Summary Report
October 25-26, 2017
Atlanta, Georgia**

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Final - October 19, 2017

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
October 25-26, 2017

<u>AGENDA ITEM</u>	<u>PURPOSE</u>	<u>PRESIDER/PRESENTER(S)</u>
Wednesday, October 25		
8:00 Welcome & Introductions		Dr. Nancy Bennett (ACIP Chair) Dr. Amanda Cohn (ACIP Executive Secretary; CDC)
8:30 Herpes Zoster Vaccine		
Introduction		Dr. Edward Belongia (ACIP, WG Chair)
Review of GRADE (ZVL, HZ/su)	Information &	Ms. Angela Guo (CDC/NCIRD)
Cost effectiveness analysis	Discussion	Dr. Lisa Prosser (University of Michigan)
Considerations and proposed recommendations		Dr. Kathleen Dooling (CDC/NCIRD)
Public comment		
Vote	Vote	Dr. Kathleen Dooling (CDC/NCIRD)
10:30 Break		
10:45 Hepatitis Vaccines		
Introduction		Dr. Arthur Reingold (ACIP, WG Chair)
HEPLISAV-B	Information &	Dr. Robert Janssen (Dynavax)
Work Group considerations: HEPLISAV-B	Discussion	Dr. Noele Nelson (CDC/NCHHSTP)
Hepatitis A outbreaks		Dr. Noele Nelson (CDC/NCHHSTP)
12:15 Lunch		
1:15 Influenza Vaccines		
Introduction		Dr. Chip Walter (ACIP, WG Chair)
Surveillance update		Ms. Lynnette Brammer (CDC/NCIRD)
Coverage update	Information &	Dr. Carla Black (CDC/NCIRD)
LAIV Efficacy/Effectiveness 2016-17 and strain selection update	Discussion	Dr. Raburn Mallory (MedImmune)
Vaccine Safety Datalink Pregnancy Study		Dr. James Donahue (Marshfield)
Work Group considerations: Influenza vaccines		Dr. Lisa Grohskopf (CDC/NCIRD)
2:30 Break		
2:45 Mumps		
Introduction		Dr. Kelly Moore (ACIP, WG Chair)
Update on mumps epidemiology in the United States	Information &	Dr. Mona Marin (CDC/NCIRD)
GRADE: third dose of MMR vaccine	Discussion	Dr. Mariel Marlow (CDC/NCIRD)
Considerations and proposed recommendations		Dr. Mona Marin (CDC/NCIRD)
Public comment		
Vote	Vote	Dr. Mona Marin (CDC/NCIRD)
VFC vote	VFC Vote	Dr. Jeanne Santoli (CDC/NCIRD)
4:30 Vaccine Safety: Shoulder Injury After Vaccination		
Introduction		Dr. Andrew Kroger (CDC/NCIRD)
Data from HRSA Vaccine Injury Compensation Claims	Information &	Dr. Narayan Nair (HRSA)
Data from the Vaccine Adverse Event Reporting System	Discussion	Dr. Tom Shimabukuro (CDC/NCEZID)
Communication and Education Campaign		Dr. Andrew Kroger (CDC/NCIRD)
5:00 Human Papillomavirus (HPV) Vaccines Update		
Introduction	Information	Dr. Peter Szilagyi (ACIP, WG Chair)
Update		Dr. Lauri Markowitz (CDC/NCIRD)
5:15 Public Comment		
5:30 Adjourn		

Final - October 19, 2017**Thursday, October 26**

8:00 Agency Updates & Unfinished Business CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NVPO	Information	Dr. Nancy Messonnier (CDC/NCIRD); <i>Ex Officio</i> Members
8:30 Adult Immunization Schedule Introduction Proposed changes in the 2018 adult immunization schedule	<u>Vote</u>	Dr. Laura Riley (ACIP, WG Chair) Dr. David Kim (CDC/NCIRD)
9:00 Child/Adolescent Immunization Schedule Introduction Proposed 2018 child and adolescent schedule revisions	<u>Vote</u>	Dr. José Romero (ACIP, WG Chair) Dr. Candice Robinson (CDC/NCIRD)
9:30 Japanese Encephalitis Vaccine Introduction JE among U.S. travelers JE-VC post-marketing adverse event surveillance among U.S. military Adverse events following JE-VC reported to VAERS, 2012-2016 JE Vaccine Work Group summary and plans	Information & Discussion	Dr. Chip Walter (ACIP, WG Chair) Dr. Susan Hills (CDC/NCEZID) Dr. Christian Taucher (Valneva) Dr. Susan Hills (CDC/NCEZID) Dr. Susan Hills (CDC/NCEZID)
10:30 Break		
10:50 Pneumococcal Vaccines Introduction PCV13 impact on nasopharyngeal carriage among children and adults PCV13 impact on invasive pneumococcal disease: update from Active Progress of the research agenda to inform potential policy change for	Information & Discussion	Dr. Arthur Reingold (ACIP, WG Chair) Dr. Fernanda Lessa (CDC/NCIRD), Ms. Stephanie M. Thomas (Emory University School of Medicine) Dr. Almea Matanock (CDC/NCIRD) Dr. Tamara Piliushvili (CDC/NCIRD)
11:50 Anthrax Vaccines Introduction Preparedness/Operational concerns Anthrax vaccine (BioThrax®) new safety and reactionogenicity data Information on immunogenicity and reactogenicity given by Summary	Information & Discussion	Dr. David Stephens (ACIP, WG Chair) Dr. William Bower (CDC/NCEZID) Dr. Kate Hendricks (CDC/NCEZID) Mr. Jarad Schiffer (CDC/NCIRD) Dr. William Bower (CDC/NCEZID)
1:00 Evidence Based Recommendations	Information	Dr. Wendy Carr (CDC/NCIRD)
1:15 Respiratory Syncytial Virus (RSV) Vaccine	Information	Dr. Gayle Langley (CDC/NCIRD)
1:20 Vaccine Supply	Information	Dr. Jeanne Santoli (CDC/NCIRD)
1:25 Public Comment		
1:40 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 vaccine
NCHHSTP	National Center for HIV, Hepatitis, STD and TB Prevention [of CDC/OID]
NCIRD	National Center for Immunization & Respiratory Diseases [of CDC/OID]
NCEZID	National Center for Emerging and Zoonotic Diseases [of CDC/OID]
NVPO	National Vaccine Program Office
PCV13	13-valent pneumococcal conjugate vaccine
VFC	Vaccines for Children
WG	Work Group

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
ACNM	American College of Nurse Midwives
ACOG	American Congress of Obstetricians and Gynecologists
ACP	American College of Physicians
ACS	American Cancer Society
ACS	American Community Survey
ADEM	Acute Disseminated Encephalomyelitis
ADL	Activities of Daily Living
AE	Adverse Events
AFI	Acute Febrile Illness
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
AIM	Association of Immunization Managers
AMI	Acute Myocardial Infarction
AN	Alaska Natives
ANA	Anti-Nuclear Antibody
ANA	American Nurses Association
ANCA	Anti-Neutrophil Cytoplasmic Antibody
Anti-dsDNA	Anti-Double-Stranded DNA
AOA	American Osteopathic Association
APhA	American Pharmacists Association
APLA	Antiphospholipid Antibodies
ARI	Acute Respiratory Illness
ASH	Assistant Secretary for Health
ASTMH	American Society of Tropical Medicine and Hygiene
AVA	Anthrax Vaccine Adsorbed
AVRP	Anthrax Vaccine Research Program
<i>B anthracis</i>	<i>Bacillus anthracis</i>
BARDA	Biomedical Advanced Research and Development Authority
BIO	Biotechnology Innovation Organization
BLA	Biologics License Application
BRFSS	Behavioral Risk Factor Surveillance System
CAP	Community-Acquired Pneumonia
CDC	Centers for Disease Control and Prevention
CDPH	California Department of Health
CDSi	Clinical Decision Support for Immunization
CEU	Continuing Education Credit
CFR	Code of Federal Regulations
CLD	Chronic Liver Disease
CMS	Center for Medicare and Medicaid
COI	Conflict of Interest
COID	Committee on Infectious Diseases (AAP)
COPD	Chronic Obstructive Pulmonary Disease

CRFs	Case Report Forms
CSTE	Council of State and Territorial Epidemiologists
CV	Cardiovascular
CVD	Cardiovascular Disease
DBD	Division of Bacterial Diseases
DHA	Defense Health Agency
DICP	Division of Injury Compensation Programs
DMSS	Defense Medical Surveillance System
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DTaP	Diphtheria and Tetanus Toxoid and Pertussis
DVA	Department of Veterans Affairs
DVH	Division of Viral Hepatitis
EAP	Expanded Access Program
EBRWG	Evidence-Based Recommendations WG
ED	Emergency Department
ED ₅₀	Effective Dose 50
EHR	Electronic Health Record
EIP	Emerging Infections Program
EIS	Epidemic Intelligence Service
ELISA	Enzyme-Linked Immunosorbent Assays
EMR	Electronic Medical Record
Epi-X	Epidemic Information Exchange
EtD	Evidence to Decision
EtR	Evidence to Recommendation
EU	European Union
FAQ	Frequently Asked Questions
FDA	Food and Drug Administration
FFS	Fee-For-Service
FluSurv-NET	Influenza Hospitalization Surveillance Network
FY	Fiscal Year
GBS	Guillain-Barré Syndrome
GCC	(Tom Harkin) Global Communications Center
gE	Glycoprotein E
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HAV	Hepatitis A virus
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCP	Healthcare Personnel
HCUP	Healthcare Cost and Utilization Project
HD	High-Dose
HEDIS	Healthcare Effectiveness Data and Information Set
HepA	Hepatitis A
HepB	Hepatitis B
HHS	(Department of) Health and Human Services

HHS	(County of San Diego) Health and Human Services Agency
HI	Hemagglutinin Inhibition
Hib	<i>Haemophilus influenzae type b</i>
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
hSBA	Human Complement Serum Bactericidal Antibody
HZ	Herpes Zoster
HZ/su	HZ Subunit Vaccine
IAC	Immunization Action Coalition
ICD	International Classification of Diseases
ICER	Incremental Cost-Effectiveness Ratio
IU	Intensive Care Unit
ID	Identification
IDSA	Infectious Disease Society of America
Ig	Immunoglobulin
IHB	Immunization Healthcare Branch
IHS	Indian Health Service
IIS	Immunization Information Systems
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
ILINet	Influenza-like Illness Surveillance Network
IM	Intramuscular
IND	Investigational New Drug
IOM	Institute of Medicine
IPD	Invasive Pneumococcal Disease
IPV	Inactivated Polio Vaccine
ISO	Immunization Safety Office
IT	Information Technology
IV	Intravenous
JEV	Japanese Encephalitis Vaccine
<i>JID</i>	<i>Journal of Infectious Diseases</i>
LAIV	Live Attenuated Influenza Vaccine
LMP	Last Menstrual Period
LTx	Lethal Toxin
LTPS	(SPS) Long-Term Persistence Study
<i>lytA</i>	<i>N</i> -acetylmuramoyl-l-alanine amidase
MACE	Major Adverse Cardiovascular Events
MDHHR	Michigan Department of Health and Human Resources
MedDRA	Medical Dictionary for Regulatory Activities
MenB	Serogroup B Meningococcal Disease
MHS	Military Health System
MI	Myocardial Infarction
MMR	Measles, Mumps and Rubella
<i>MMWR</i>	<i>Morbidity and Mortality Weekly Report</i>
MSM	Men Who Have Sex With Men
NACCHO	National Association of County and City Health Officials
NACDS	National Association of Chain Drug Stores
NAPNAP	National Association of Pediatric Nurse Practitioners

NAS	National Academy of Sciences
NTTO	National Travel & Tourism Office
NCAI	National Coalition of Adult Immunization
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
NCPA	National Community Pharmacists Association
NF ₅₀	Neutralization Factor 50
NFID	National Foundation for Infectious Diseases
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Study
NHP	Non-Human Primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIS	National Immunization Survey
NIS-Flu	National Immunization Survey-Flu
NNDSS	National Notifiable Diseases Surveillance System
NNV	Number Needed to Vaccinate
NP	Nasopharyngeal
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
NVT	Non-Vaccine Types
O/E	Observed Over Expected
OP	Oropharyngeal
OPV	Oral Polio Vaccine
ORISE	Oak Ridge Institute for Science and Education
PCP	Primary Care Physician
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PDUFA	Prescription Drug User Fee Act
PEP	Post-Exposure Prophylaxis
PHL	Public Health Laboratories
PHN	Post Herpetic Neuralgia
PhRMA	Pharmaceutical Research and Manufacturers of America
PIDS	Pediatric Infectious Disease Society
pIMDs	Potential Immune Mediated Diseases
PIR	Post-Injection Reaction
PrEP	Pre-Exposure Prophylaxis
PRNT	Plaque Reduction Neutralization Test
PSP	Primary Safety Population
PTC	Papillary Thyroid Carcinoma
QALYs	Quality-Adjusted Life-Years
QIV	Quadrivalent Influenza Vaccine
RA	Rheumatoid Arthritis
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RIV	Recombinant Influenza Vaccine
RNA	Ribonucleic Acid

ROM	Range of Motion
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
<i>S. aureus</i>	<i>Staphylococcus aureus</i>
<i>S. pneumoniae</i>	<i>Streptococcus pneumoniae</i>
SAB	Spontaneous Abortion
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunization (WHO)
SAHM	Society for Adolescent Health and Medicine
SC	Subcutaneous
SES	Socioeconomic Status
SIRVA	Shoulder Injury Related to Vaccine Administration
SLE	Systemic lupus Erythematosus
SME	Subject Matter Experts
SPR	Seroprotection Rate
SPS	Shingles Prevention Study
STGG	Skim Milk Tryptone, Glucose, Glycerol
STPS	(SPS) Short-Term Persistence Substudy
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis
THS	Tolosa-Hunt Syndrome
TIV	Trivalent Influenza Vaccine
TLRs	Toll-Like Receptors
TNA	Toxin Neutralization Activity
UAD	Urinary Antigen Detection
UAT	Urinary Antigen Test
UK	United Kingdom
UNC	University of North Carolina
US	United States
USPS	United States Postal Service
UTD	Up-To-Date
VA	(US Department of) Veteran's Affairs
VAERS	Vaccine Adverse Event Reporting System
VBA	Veterans Benefits Administration
VE	Vaccine Efficacy
VFC	Vaccines For Children
VICP	Vaccine Injury Compensation Program
VRBPAC	Vaccine and Related Blood Products Advisory Committee
VSD	Vaccine Safety Datalink
VT	Vaccine Type
VZV	Varicella Zoster Virus
WG	Work Group
WHO	World Health Organization
YF	Yellow Fever
YF-Vax®	Yellow Fever Vaccine®
ZVL	Zoster Vaccine Live

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

Call To Order / Welcome

Nancy Bennett, MD, MS
ACIP Chair

Dr. Bennett called the October 2017 Advisory Committee on Immunization Practices (ACIP) meeting to order and welcomed those present.

Overview / Announcements

Amanda Cohn, MD
Executive Secretary, ACIP / CDC

Dr. Cohn welcomed everyone to the October 2017 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 several 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 announced that the new Deputy ACIP Executive Secretary is Jessica McNeil, MPH who also will be in charge of ACIP work groups (WGs).

She noted that handouts of the presentations were distributed to the 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 to 120 days following this meeting.

The next ACIP meeting will be convened at the Centers for Disease Control and Prevention (CDC) on Wednesday and Thursday, February 21-22, 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 January 24, 2018 and for US citizens registration closes February 5, 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.

Guests, member substitutions, and new Liaison and *Ex-Officio* representatives announced during this meeting included the following:

Guests

- Ms. Hope Peisley, Director, Immunisation Policy Section, Immunisation Branch, Office of Health Protection, Australian Government Department of Health

Liaison Representatives

- Dr. Scott Cyrus, representing American Osteopathic Association (AOA)
- Dr. Susan Lett, representing the Council of State and Territorial Epidemiologists (CSTE)
- Dr. Bonnie Maldonado, American Academy of Pediatrics (AAP)
- Dr. Corey Robertson, representing Pharmaceutical Research and Manufacturers of America (PhRMA)
- Ms. Amy Walker, representing Biotechnology Innovation Organization (BIO)
- Dr. Victoria Statler, Association for Prevention Teaching and Research (APTR)

Ex-Officio Members

- Dr. Barbara Mulach, National Institutes of Health (NIH)
- Dr. Melinda Wharton, National Vaccine Program Office (NVPO)

Update on ACIP Membership

- Dr. Arthur Reingold, Ms. Cindy Pelligrini, and Dr. Allison Kempe have been extended through December 31, 2017
- Nominations for membership beginning July 1, 2018 are under review
- Applications for membership beginning July 1, 2019 will open in January 2018
- Any questions: acip@cdc.gov

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

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. Registration for public comments is solicited in advance of meetings. 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, each comment was limited to three minutes. 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 those vaccines,

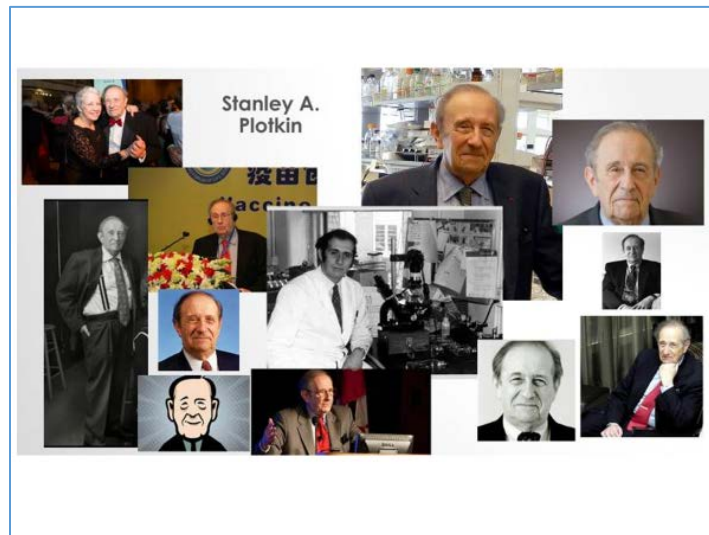
but these members are prohibited from participating in committee votes on issues related to those vaccines. Regarding other vaccines of the concerned company, a member may participate in discussions, with the provision that he/she abstains on all votes related to the vaccines of that company. It is important to note that at the beginning of each meeting, ACIP members state any COIs.

Dr. Cohn announced that during this meeting, electronic voting would be utilized. She explained that ACIP members would vote simultaneously, with results displayed on the screen at the close of the voting process. Voting would then be verified verbally around the table and ACIP members could add comments if they chose.

Farewell to Dr. Stanley A. Plotkin

Dr. Larry Pickering ACIP Executive Secretary, Retired

I appreciate this opportunity to recognize our good friend and colleague, Dr. Stan Plotkin, who knows nothing about this, which is unusual (applause / standing ovation):



Dr. Plotkin has attended ACIP meetings for as long as many of us can remember, and has been a constant source of knowledge and information. After many years of sharing his wisdom and guidance, Dr. Plotkin has announced that he will no longer attend ACIP meetings in person. All of us have been influenced by Dr. Plotkin. Every time Stan approaches the microphone at an ACIP meeting to offer comments, we know that we are about to learn something from his sage advice and massive insight.

The honors and achievements of Dr. Plotkin are many, but I'm going to just mention a few of them. He was involved in pivotal trials on anthrax, oral polio, rabies vaccine; inventor of the RA27 strain rubella vaccine; and co-inventor of the pentavalent rotavirus vaccine. He was founding father of the Pediatric Infectious Disease Society (PIDS). He is a member of the Institute of Medicine (IOM) and the French Academy of Medicine, and has many awards from numerous societies and organizations, which I will not mention at this time. He developed the standard textbook for vaccines in 1988, now in its 7th edition and aptly titled *Plotkin's Vaccines*.

Many of us are fortunate to be or have been pediatricians and to have worked very closely with Dr. Plotkin during his 8-year tenure on the AAP's Committee on Infectious Diseases (COID), and when he served as the *Red Book*® Associate Editor for two editions. Indeed, the 2015 edition of the *Red Book*® is dedicated to Dr. Plotkin.

So, to ensure that Dr. Plotkin continues to be an active part of future ACIP meetings, we present to the ACIP an engraved Stanley Plotkin knocker. It reads "Stanley A. Plotkin ACIP Gavel."



Beginning today, Dr. Bennett can ring the Sam Katz bell—many of you remember Sam Katz when he used to attend the meetings—and ring the Sam Katz bell to notify everyone to be seated and then use the Stanley Plotkin gavel to officially begin the meeting. Stan, at ACIP, your influence will never, ever be forgotten. Thank you (applause / standing ovation). Dr. Cohn invited Dr. Plotkin to officially open the meeting with the gavel.

Dr. Stanley Plotkin Vaccine Consultant

Well, obviously, I'm very touched. Fortunately, I did ask to make comments later in the day and while I'm here today, I don't plan to shut up. But since there's a 3-minute limit, I will stay within that limit. Excuse me for what I have to say. I apologize for taking a few minutes of your time to say that this is probably the last ACIP meeting I will attend in person. I have come to ACIP meetings since the 1980s, either as a liaison member from the *Red Book*® or as an observer. I will cease to be here after this meeting, even though the meetings are very worthwhile. The work done by ACIP is admirable and sets a standard for the world. However, although I am not yet retiring, at age 85, I may be excused for not wanting to go through Hartsfield Airport again. I will be watching ACIP on the web and, indeed, someday I may come back if and when vaccines for Lyme disease or cytomegalovirus are on the agenda. But in the way of personal recommendations, I have the following suggestions for the ACIP:

- Give ACIP's views on future vaccine needs, which will greatly influence how vaccine companies decide which vaccines to develop.
- In WGs, include more representatives of industry to offer their expertise. Even if they can't vote, don't exclude them from deliberations.

- ❑ Conduct more reviews of vaccine safety.
- ❑ Don't be shy of giving preferential recommendations when more than one vaccine against a disease exists. For example, multiple influenza vaccines are available and there is evidence that high-dose, adjuvanted, and cell culture vaccines have advantages over standard ones.
- ❑ Finally, hold discussions about how to implement higher immunization coverage.

Whatever the value of these ideas may be, I regret that I will see less of the people here on the ACIP committee, the staff of CDC to which I belonged long ago in the 1950s, and those here in the audience. But the toll of increasing age is inevitable, and so I close with the ancient Roman goodbye Ave Atque Vale. Hail and Farewell. Thank you (applause / standing ovation).

Roll Call

Nancy Bennett, MD, MS
ACIP Chair

Pointing out that this should be done for the first time in Dr. Plotkin's presence, Dr. Bennett officially called the meeting to order using the Stanley A. Plotkin ACIP gavel. She thanked him for his many years of sage advice, emphasized how much he would be missed, and expressed hope that he would call into future meetings. She called the roll to determine whether any ACIP members had COIs. No COIs were declared. She then requested that the Liaison and *Ex Officio* members introduce themselves. A list of Members, *Ex Officio* Members, and Liaisons is included in the appendixes at this end of the full document from the October 2017 ACIP meeting.

Herpes Zoster Vaccine

Introduction

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

Dr. Belongia reported that the Herpes Zoster WG has been highly engaged and productive over the past two and a half years in preparation of the introduction of a new zoster vaccine. The WG has convened 34 conference calls since January 2015 and has received a variety of presentations by manufactures and researchers on the effectiveness, safety, immunogenicity, cost-effectiveness, and programmatic barriers of HZ vaccines. The WG has considered the body of evidence regarding both vaccines, and has identified key zoster vaccine policy questions and discussed options. SHINGRIX herpes zoster subunit (HZ/su) vaccine by GlaxoSmithKline (GSK) was licensed by the Food and Drug Administration (FDA) on October 20, 2017 for immunocompetent adults 50 years of age and older—the focus of this session.

There have been a number of presentations to ACIP in preparation for the discussion during this session, include presentations on general epidemiology [of herpes zoster], the efficacy and safety of HZ/su vaccine, the effectiveness of zoster vaccine live (ZVL), GRADE (Grading of Recommendation Assessment, Development and Evaluation) results for HZ/su and ZVL, the immunogenicity results of HZ/su long-term and post-ZVL, and cost-effectiveness analyses. This led to three policy questions that the WG defined for input from ACIP:

- Should ACIP recommend HZ/su for vaccination of immunocompetent adults 50 years and older?
- Should ACIP recommend HZ/su for individuals previously vaccinated with ZVL?
- Should ACIP recommend HZ/su be preferred over ZVL?

The WG will continue to meet and HZ will continue to be on the agenda for future ACIP meetings. Both HZ/su and an investigational vaccine by Merck are currently under evaluation for use in immunocompromised populations. As more data become available regarding the safety and efficacy of these vaccines in immunocompromised individuals, they will be presented to ACIP for further consideration.

Review of GRADE (ZVL, HZ/su)

Angela Guo, MPH

Oak Ridge Institute for Science and Education (ORISE) Fellow

Division of Viral Diseases

National Center for Immunization and Respiratory Diseases

Centers for Disease Control and Prevention

Ms. Guo indicated that this presentation would be a summary of the GRADE evaluation of HZ vaccines. Two separate GRADE assessments were performed for existing HZ vaccines and the newly licensed HZ/su, and the currently licensed and recommended live-attenuated herpes zoster vaccine (ZVL Zostavax[®]). The results of these analyses were presented to ACIP on February 22, 2017 and June 21, 2017, respectively. As a reminder, the steps of the GRADE process executed by the WG were to develop policy questions, consider critical outcomes, review and summarize evidence of benefits and harms, and evaluate the quality of evidence. For both GRADE analyses, the WG deemed the prevention of HZ and post-herpetic neuralgia (PHN) as critical outcomes. Duration of protection was considered important. For harms, serious adverse events (SAEs) were deemed critical and reactogenicity important.

Specifically regarding the GRADE results for the HZ/su vaccine, the policy question for consideration was, "Should Herpes Zoster subunit vaccine (HZ/su) be routinely used to prevent herpes zoster?" A systematic review of the literature was conducted to find articles in which the population of interest was immunocompetent adults aged 50 years or older, the intervention of interest was a 2-dose series of HZ/su administered intramuscularly at 0 and 2 months, and the intervention was compared to placebo or no vaccine. Ten studies that met inclusion criteria were included in the GRADE analysis. The estimate of effects of the benefits of HZ/su include vaccine efficacy (VE) against HZ and PHN and duration of protection against HZ, of which only data up to 4 years post-vaccination were available. The estimates of efficacy come from 2 Phase III clinical trials. VE against HZ for HZ/su is 96.6% in adults 50 through 59 years of age, 97.4% in adults 60 through 69 years of age, 91.3% in adults 70 through 79 years of age, and 91.4% in adults 80 years of age and older. VE against PHN was reported to be 91.2% in adults 50 years of age and older and 88.8% in adults 70 years of age and older. VE against HZ remained at or above 85% 4 or more years post-vaccination in all age groups.

The harms outcomes included the assessment were SAEs and reactogenicity. Based on estimates from the Phase III clinical trials, there is no imbalance of SAEs between vaccine and placebo groups and no reported SAEs related to vaccination. Grade 3 reactions, or reactions deemed to prevent normal daily activities, were more commonly reported in vaccinated groups compared to placebo. Any Grade 3 reaction was noted in 16.5% of the vaccinated group compared to 3.1% of the placebo group. Grade 3 injection-site reactions were reported in 9.4% of the vaccinated group compared to 0.3% of the placebo group. Grade 3 systemic reactions were reported in 10.8% of the vaccinated group compared to 2.4% of the placebo group. The remaining 7 studies administered HZ/su to a total of 616 participants and found no SAEs related to vaccination and similar rates of reactogenicity.

Regarding the GRADE summary for this analysis, the critical outcomes of HZ, PHN, and SAEs were all supported by at least one good quality large randomized controlled trial (RCT). The overall evidence type supporting the critical outcomes is 1, with evidence type 1 being the highest level of evidence and evidence type 4 being the lowest. In other words, the level of certainty of the estimate of effects of these outcomes is high. For important outcomes, the evidence types for reactogenicity and duration of protection were both 1. In summary, the findings were that HZ/su is significantly efficacious in preventing HZ and PHN up to 4 years post-vaccination. No safety concerns or SAEs related to the vaccine were observed in clinical trials. Grade 3 reactions were more common among vaccine recipients.

In terms of the GRADE analysis for the ZVL, the policy question for consideration was, "Is the live attenuated herpes zoster vaccine (ZVL) safe and effective at preventing herpes zoster?" A systematic review of the literature was conducted to find articles in which the population of interest was immunocompetent adults aged 50 years and older, the intervention of interest was one dose of ZVL, and the intervention was compared to placebo or no vaccine. Forty studies met inclusion criteria and were included in the GRADE analysis. The estimate of effects for benefits of ZVL include VE or effectiveness of HZ and PHN and duration of protection against HZ defined as VE 4 or more years post-vaccination.

Based on clinical trials data, VE against HZ for ZVL was 70% in adults 50 through 59 years of age, 64% in adults 60 through 69 years of age, 41% in adults 70 through 79 years of age, and 18% among adults 80 years of age and older. VE from observational studies in adults 60 years of age and older ranged from 33% to 51%. In clinical trials, VE against PHN was reported to be 65.7% in adults 60 through 69 years of age and 66.8% in adults 70 years of age and older. VE from observational studies in adults 60 years of age and older ranged from 41% to 69%. ZVL protection wanes year-by-year. All studies estimated a VE against HZ of 40% or less 4 or more years post-vaccination.

Regarding the estimate of effects of harms of ZVL, in 8 placebo-controlled RCTs with over 36,000 participants receiving ZVL, there were no imbalances in SAEs between vaccine and placebo groups. An addition 20 studies with no comparison groups also found no SAEs associated with ZVL. For reactogenicity, injection-site reactions were the most common reaction reported. In Phase III clinical trials, 48% of vaccine recipients reported injection-site reactions compared to 17% among placebo. Similar rates were reported in other clinical studies. The majority of injection-site reactions were mild. Four studies reported Grade 3 injection-site reactions that ranged between 0% to 4% of vaccine recipients. Seven studies reported any systemic AEs, with reactions reported among 0% to 8% of vaccine recipients. Also of note, several cases of varicella zoster virus (VZV) rash caused by Oka/Merck strain were reported in clinical trials and in Merck's 10-year post-marketing review [FDA; Willis, 2016].

In terms of the GRADE summary for this analysis, the critical outcomes of HZ, PHN, and SAEs related to vaccination were all supported by at least one good quality large RCT and were given an evidence type 1. For these critical outcomes, the overall evidence type is 1. In other words, the WG's level of certainty in the estimate of effect of these outcomes was high. For important outcomes, reactogenicity and duration of protection were assigned an evidence type of 1 and 2, respectively. In summary, the findings were that ZVL is effective in preventing HZ and PHN. Effectiveness of the vaccine drops in the first year following vaccination and continues to wane year-by-year. No safety concerns or SAEs related to the vaccine were observed in real-world and clinical settings. Injection-site reactions were more commonly reported among vaccine recipients compared to placebo, but tended to be mild.

In conclusion, GRADE analyses were performed separately for the two existing HZ vaccines HZ/su and ZVL. For both vaccines, the evidence type for critical outcomes is 1. The WG has high confidence in the estimates of effect for these outcomes for both vaccines.

Cost-Effectiveness Analysis

Lisa Prosser, PhD
University of Michigan

Dr. Prosser presented the results from a University of Michigan/CDC economic evaluation of vaccination for the prevention of HZ and related complications. This study represents research that the University of Michigan and CDC have been working on together for the last year and a half.

The overall study questions were to evaluate the cost-effectiveness of a HZ/su and no vaccination, using both healthcare and societal perspectives; examine revaccination scenarios with HZ/su; and directly compare the cost-effectiveness of HZ/su and ZVL in the context of a preferential recommendation. The intervention strategies included in the analysis were vaccination with HZ/su, vaccination with ZVL, and no vaccination. The target population included 5 age groups: 50-59, 60-69, 70-79, 80-89, and 90-99. The analytic time horizon was lifetime; that is, from age of vaccination until death. For the base case, 100% adherence to a 2-dose regimen for HZ/su was modeled. This is consistent with CDC practice to evaluate a policy recommendation consistent with the recommended dosing schedule. Lower levels of completion were explored in detail in the sensitivity analyses.

Simulation modeling was utilized to project lifetime costs and health outcomes for each age group. The primary outcome measure for the model was the incremental cost-effectiveness ratio (ICER). Secondary outcomes included disaggregated costs; disaggregated health outcomes, including quality-adjusted life-years (QALYs) gained; number needed to vaccinate (NNV). The cycle length was annual, the costing year was 2016, and the discount rate was 3%. The model inputs included published evidence, primary data, and expert opinion. In the model, an individual could be vaccinated with HZ/su, vaccinated with ZVL, or remain unvaccinated. Individual cohorts were assigned to each of these strategies in the model, so there were identical cohorts of simulated individuals. If vaccinated with HZ/su, there was a probability that they would receive two doses of the vaccine or just one dose. This probability was set to 100% for the base case analysis, but was relaxed in sensitivity and scenario analyses.

Each year, an individual had some probability of remaining disease-free, experiencing zoster infection, or dying from other causes. If they experienced HZ, they could have had an uncomplicated HZ episode of less than a month, PHN, or other complications. There was a very small probability of dying from HZ infection. As simulated individuals traveled through the model, they accumulated costs and losses in QALYs in each of the health states experienced. Each probability and QALYs adjustment was represented by a range of values. These were coded into the model so that confidence intervals could be generated. Also included in the model though not shown were AEs associated with vaccination, including reactogenicity, systemic reactions, and SAEs. These events are also associated with costs and losses in quality of life depending on the severity of the AEs.

In terms of the key parameter inputs into the model, the incidence of HZ and PHN both increase with age. The incidence of HZ ranges from 0.005 to 0.015 and PHN ranges from 0.4/1000 to 3.5/1000. VE for the cohort aged 60 through 69 years was based on published data and various plausible assumptions for waning. The assumptions for VE were based on the initial 4 years of data available from clinical trials and extrapolated over those, and then assumptions were developed based on those data for different estimates of waning duration. VE for HZ/su was close to 100% in the first year and seemed to wane over 19.4 years extrapolating from the 4 years of data in the trials. VE for ZVL in the initial year was 78% and waned over a period of 10 years, which is consistent with published data. Additional protection against PHN was assumed in the model for ZVL.

Dr. Prosser shared the following tables with the results for VE of HZ/su and ZVL for other age groups, pointing out that effectiveness is greater for the younger age groups and wanes more quickly for older age groups:

Vaccine Effectiveness, HZ/su			
Variable	Base Value	Range	Source
Initial Year, 2 doses			
Age 50-69	1.00	0.95-1	Cunningham et al 2016, Lal et al 2015
Age 70+	0.97	0.92-1	
Initial Year, 1 dose			
Age 50-69	0.90	0.85-0.95	Unpublished post hoc analysis by GSK from ZOE 50/70
Age 70+	0.69	0.64-0.74	
Waning Duration, 2 doses (years)			
Age 50-69	19.4	10-30	Cunningham et al 2016, Assumption
Age 70+	18.8	10-30	
Waning Duration, 1 dose (years)			
Age 50-69	11.0	1-17.5	Assumption
Age 70+	4.0	1-13.4	

Vaccine Effectiveness, ZVL			
Variable	Base Value	Range	Source
Initial Year			Morrison et al 2015, Oxman et al 2005, Schmader et al 2012, Rohan 2005
Age 50	0.781	0.703-0.860	
Age 60	0.779	0.701-0.857	
Age 70	0.659	0.593-0.725	
Age 80	0.385	0.346-0.423	
Waning Duration (years)			
Age 50	12	10-15	
Age 60	10	9-12	
Age 70	7	6-8	
Age 80	4	3-5	

The model also included the additional inputs of direct medical costs, productivity losses, vaccination-related costs, AE event costs, and QALY losses. The primary outcome measure is the ICER, which divides the incremental cost of vaccination by the incremental QALY gained comparing vaccination to no vaccination. This metric measures the gain in health benefits associated with the additional investment of vaccination and accounts for offsets due to averted illness. Analyses were conducted from both healthcare and societal perspectives. The societal perspective is considered as the primary perspective for this analysis. A wide range of sensitivity analyses were conducted (probabilistic, univariate and multi-way, scenario), which Dr. Prosser presented in the context of the three policy questions being considered (vaccination with HZ/su, revaccination of individuals who previously received VZL, preferential recommendation).

Turning to the results, the following table shows the projected cases of HZ for both vaccines by age cohort:

Projected Cases (per 1000)			
	No Vaccine	Vaccinated: HZ/su	Vaccinated: ZVL
Herpes Zoster			
50-59 years	265	186	231
60-69 years	204	117	170
70-79 years	138	61	119
80-89 years	81	23	77
90-99 years	42	7	42
Post-herpetic Neuralgia (PHN)			
50-59 years	32	27	29
60-69 years	31	21	25
70-79 years	27	13	20
80-89 years	21	6	17
90-99 years	14	2	12

It is important to keep in mind that these cases are projected over the lifetime of the cohort so that although incidence rates are higher for the older age groups, the period of analysis is shorter and yields different numbers of projected cases across the different age groups. For all cohorts, HZ/su is projected to avert a greater proportion of cases than ZVL. It is important to

note that this does not directly represent the loss in QALYs because there is a higher proportion of PHN cases in the older age groups, which are associated with a higher loss in QALYs.

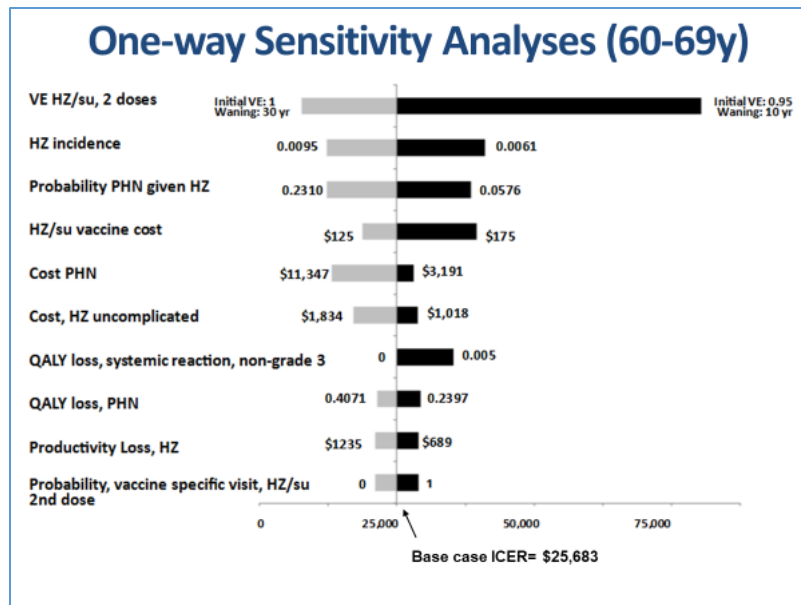
In terms of projected costs with and without vaccination, for the cohort aged 60 through 69 disease-related costs are projected to be \$474,000 in the absence of vaccination. For HZ/su, total costs are higher. Vaccination costs are approximately \$350,000 and \$244,000 in remaining disease costs, yielding \$594,000 in total costs. For ZVL, total cost of vaccination for the same age group are higher at \$619,000. This indicates that vaccination requires an additional investment for all age groups; that is, total costs are higher under vaccination scenarios compared with no vaccination and ZVL results in higher incremental costs than HZ/su across all age groups.

The following table shows the incremental cost-effectiveness ratios in dollars per QALY by age group. Using base case assumptions, this is the most likely value for each of the parameters in the model. Cost-effectiveness ratios range from approximately \$47,000 to \$10,000 to per QALY for the most favorable age group:

Base Case Analysis, HZ/su vs No Vaccination	
Age	Societal Perspective \$/QALY
50-59 years	\$46,824
60-69 years	\$25,683
70-79 years	\$11,561
80-89 years	\$9,739
90-99 years	\$27,310
50+ years	\$30,797

ZVL was dominated for all age groups evaluated; that is, as a vaccine strategy it was overall most costly and yielded lower health gains when compared directly with HZ/su. This table does not include the confidence intervals, which will be presented later in the uncertainty analysis. The bottom row of the slide represents a population analysis which pools results across the age groups representing the proportion in each age group. The overall cost-effectiveness ratio for a pooled cohort is approximately \$31,000 per QALY.

In terms of how these results change in response to changes in the underlying parameter values and whether the results are robust to changes in these inputs, the following tornado diagram displays the changes in the incremental cost-effectiveness ratios as each parameter was varied across the 95% confidence interval determined for the input assumption:



This diagram shows the top 10 parameters to which the results are most sensitive. There is a univariate sensitivity analysis for every parameter input into the model. The 4 most influential parameters are VE, HZ and PHN incidence, and the cost of PHN. This slide was created before the cost of the vaccine dose was known for certain, so it is fixed at this point. Even under the lower bound assumptions for HZ/su, looking at the top bar in this figure, with initial 95% effectiveness and 10-year duration, vaccination with HZ/su is below \$100,000 per QALY. Looking more broadly across all of the other sensitivity analyses represented here, vaccination with HZ/su is below \$50,000 per QALY for all of the univariate parameter changes except waning. Overall, the results are robust to univariate changes in the parameter inputs.

A scenario analysis was performed to explore the cost-effectiveness of vaccinating individuals with HZ/su who already received ZVL. In terms of how VE was derived for this scenario, three intervals were evaluated: 8 weeks, 1 year, and 5 years. For the 8-week interval, a scenario was modeled for immediate vaccination since the cycle in the model is 1 year. This is a slightly more conservative assumption than an 8-week interval between the two vaccinations. First, the full VE for ZVL was considered. Assuming an individual is revaccinated with HZ/su at roughly the same time, approximately 8 weeks following vaccination with ZVL, a linear relationship is observed between VE and the difference between ZVL and HZ/su is seen as attributable to a revaccinated individual but with full vaccination cost. For the 1-year interval, there was additional incremental protection for revaccination. The 5-year interval again resulted in greater incremental effectiveness attributed to revaccination with HZ/su. Using these input assumptions, the ICER for revaccination was highest for the 50- to 59-year cohort and lowest for the 80- to 89-year cohort. Revaccination yielded incremental cost-effectiveness ratios lower than \$60,000 per QALY gained for all age groups except for the 50- to 59-year cohort.

A scenario analysis was performed comparing HZ/su and ZVL directly to no vaccination instead of incrementally to each other. The results also were compared to three other available analyses of zoster vaccination. The following table represents a quick primer on the definition of “dominance” in economic evaluation:

Age	Strategy	Costs	QALYs	Incr. Costs	Incr. QALYs	\$/QALY
60-69 years	Not vaccinated	\$473,485	12138.8			
	Vaccinated- HZ/su	\$593,527	12143.5	\$120,042	4.67	\$25,683
	Vaccinated- ZVL	\$614,476	12141.4	\$20,949	-2.11	Dominated

This table shows the detailed outcomes for the 60 to 69 cohort. The third column shows that both HZ/su and ZVL have higher total costs for vaccination and are placed in order of increasing cost. The incremental costs were calculated to the next least expensive strategy, so \$120,000 comparing HZ/su to no vaccination and about \$21,000 comparing ZVL incrementally to HZ/su. Comparing incremental QALYs are evaluated in the same way. ZVL yields higher incremental costs but lower health gains as measured in QALYs, which would be defined as dominated in a cost-effectiveness analysis. It is important to keep in mind that that each of the costs and QALYs presented in the table are associated with a confidence interval that is not shown here. These results also can be evaluated comparing both strategies directly to vaccination.

Comparing results across models for base case estimates among the 60- to 69-year age group, the cost per QALY for HZ/su is \$26,000 compared to no vaccination. In a scenario in which HZ/su is not available, ZVL was compared directly to no vaccination for a cost-effectiveness ratio of \$55,000 per QALY gained. Considering the results in comparison to the 3 other existing economic analyses, the results from Le and colleagues are very concordant with the CDC/Michigan model. Their results show \$30,000 per QALY gained for HZ/su and \$67,000 per QALY gained when comparing ZVL directly to no vaccination. In their model, ZVL is also dominated by HZ/su.

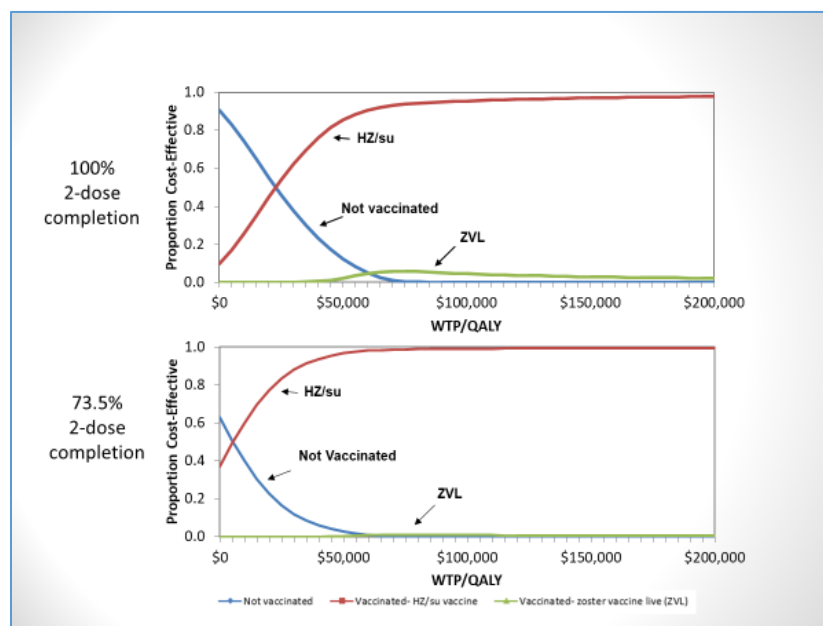
In the comparison to the GSK and Merck models, both manufacturers' models used an analytic perspective that included direct medical costs and productivity losses. They did not include time and cost of vaccination, which is why both the societal and healthcare perspectives were included in the comparison of results across models. The healthcare perspective includes only direct medical costs. The societal perspective, in addition to that, includes productivity losses and time costs for vaccination. The two other models fall in between those two perspectives because they include productivity losses, but do not include time costs for vaccination.

Comparing to the base case results for the GSK model, they report more favorable incremental cost-effectiveness ratios for HZ/su and less favorable compared to the CDC/Michigan model for ZVL. The Merck analysis presents scenarios in which ZVL is not dominated, but has similar results when looking at the CDC model compared directly to vaccination. The Merck model yields less favorable results for HZ/su. There are a number of differences across models, most importantly in assumptions for waning duration, initial vaccine effectiveness for a single dose of HZ/su, QALY losses associated with PHN, modeling of AEs, and 2-dose completion rates. Again, the CDC/Michigan model assumed 100% 2-dose completion rates. That is lower for both the GSK and Merck models. The CDC/Michigan model includes additional protection for ZVL against PHN, which is not included in any of the other models presented here.

	Le et al. model Societal Perspective	CDC model Societal Perspective	CDC model Healthcare Perspective	GSK model Healthcare + Prod. Loss	Merck model Healthcare + Prod. Loss
HZ/su*	\$30,000**	\$19,000	\$29,000	\$12,000	\$107,000
ZVL*	\$67,000**	\$80,000	\$89,000	\$120,000	\$83,000

The results of the uncertainty analyses present information relevant to the preferential recommendation question. In the probabilistic sensitivity analysis, 10,000 simulations are run using the parameter distributions in the model. In each run, a parameter value from that distribution is randomly drawn from all of the parameter inputs in the model and simultaneously calculates a new cost-effectiveness ratio. Therefore, a confidence interval can be projected for each of the base case cost-effectiveness ratios. There is some overlap among the confidence intervals for the younger age groups, but not for the older age groups. This indicates that there are some scenarios in which ZVL would be the preferred strategy in the younger age groups, but far less likely in the older age groups. When the assumption of 2-dose completion is relaxed to 73.5%, the results are quite similar. Cost-effectiveness ratios are slightly lower for the younger age groups because of the assumption for VE with 1 dose at 90%. Those individuals are receiving 1 dose at 90% VE, which wanes to 0 over 10 years, but for only half the cost. There are slightly higher ICERs for people over 70 when 73.5% 2-dose adherence is assumed because the initial VE for 1 dose for the older age groups is much lower.

The graphic shows the cost-effectiveness acceptability curves, which provides information on the proportion of scenarios in which HZ/su and ZVL would be the preferred strategy depending on the willingness-to-pay thresholds for a QALY:



After running 10,000 simulations, starting in the top panel at \$25,000 per QALY, HZ/su yields an ICER in about 50% of those simulations and in the other 50%, no vaccination would be preferred. At a higher willingness-to-pay threshold of \$75,000 per QALY and above, HZ/su would become the preferred strategy in more than 90% of simulations. Beyond \$75,000 per QALY, ZVL would be the preferred strategy in 4% of simulations or less. The curve looks similar at 73.5% 2-dose completion, again with slightly more favorable results for HZ/su because of the assumption around 1-dose vaccination of a higher VE with only half of the vaccination costs.

Multi-way sensitivity analyses were performed with a scenario in which both initial VE and duration were set to the lower bounds for individuals who received 1 dose of HZ/su. It is important to keep in mind that the probability of this combination of parameters is quite low in the simulations CDC/Michigan have done. Under 2-dose completion rates as low as 20%, HZ/su was the preferred strategy and ZVL was dominated looking at lower bound for VE and lower bound for waning duration for 1 dose of vaccine. The following table of multi-way sensitivity analyses presents worst-case and best-case scenarios for VE and waning duration for HZ/su:

Multi-Way Sensitivity Analysis: HZ/su 2-Dose Completion Rate, Vaccine Waning Duration, Initial Efficacy							
Age	1-dose initial VE=0.85; waning 1 y 2-dose initial VE=0.95; waning 10 y			1-dose initial VE=0.95; waning 17.5 y 2-dose initial VE=1.0; waning 30 y			
	2-dose completion rate			2-dose completion rate			
	20%	50%	100%	20%	50%	100%	
60-69 y	\$64,171	\$54,920*	\$569,324**	Cost Saving	\$403	\$7,902	
Age	1-dose initial VE=0.64; waning 1 y 2-dose initial VE=0.92; waning 10 y			1-dose initial VE=0.74; waning 13.4 y 2-dose initial VE=1.0; waning 30 y			
	70-79 y	\$51,493	\$49,865	\$48,050***	Cost Saving	Cost Saving	Cost Saving
	80-89 y	\$57,244	\$44,879	\$34,505	Cost Saving	Cost Saving	\$2,212
90-99 y	\$70,968	\$54,681	\$42,465	\$6,902	\$13,564	\$21,971	

* ZVL dominates HZ/su; ** No dominant strategy; *** HZ/su dominates ZVL by extended dominance

The left-hand side of the table is the worst-case scenario lower bounds of initial VE for both 1 dose and 2 doses of HZ/su, and lower bounds for waning duration for series completion. The right-hand side is the upper bound, with even higher initial VE for 1-dose of HZ/su and longer waning duration for 2 doses of HZ/su. These were assessed across 20%, 50%, and 100% completion rates. It is important to keep in mind that in the scenario analysis for 2-dose completion, the base case was 73.5% so this lower 20% bound was even outside of the 95% confidence interval for that. So, this really is the worst-case scenario.

Under lower bound conditions, HZ/su remains the preferred strategy under most variations in these parameters but no longer dominates ZVL in 2 cases: the 60-69 cohort under a 50% completion assumption and 100% completion assumption. What is happening here with this very high ratio of \$569,000 per QALY is that HZ/su no longer dominates ZVL. This is a ratio comparing HZ/su incrementally to ZVL, which has a cost-effectiveness ratio compared to no vaccination at \$54,000. This is very high because it is being compared incrementally to ZVL. Looking at the right side, best-case scenario and upper bounds for 1- or 2-dose VE, in some of

these scenarios vaccination with HZ/su becomes cost-saving and has much more favorable cost-effectiveness ratios. It is important to keep in mind that in terms of the cost-effectiveness acceptability curves, these are the scenarios that will be represented within the 4% for ZVL for the worst-case and upper bound above the 95% for HZ/su.

This is a simulation model, so there are a number of limitations in the available data, most notably for the incidence of AEs associated with HZ/su and specifically with the healthcare utilization associated with these AEs. Long-term effectiveness of vaccination for HZ/su is not known beyond 4 years yet, and the proportion of individuals likely to complete the 2-dose series and health care utilization associated with delivery of a second dose are unknown.

In summary, the cost-effectiveness results vary by age at vaccination, with HZ/su preferred under most conditions and dominating ZVL in the base case analysis. Results were most sensitive to assumptions regarding the duration of VE, incidence of HZ and PHN, and the cost of HZ. There were a number of differences across the models, including time costs for vaccination, incidence of PHN by age, VE, and the magnitude of QALY losses. Overall, the results are robust to most changes in the input parameters.

Discussion Points

Dr. Kempe requested clarity regarding whether HZ/su was more effective at 1 dose than ZVL for younger than 70 and older than 70 years. The input data showed 90% effectiveness of 1 dose for less than 70 and about 70% for 70+.

Dr. Prosser clarified that HZ/su initial VE was close to 100% and 96.6% for 2 doses of HZ/su [age 50-69 and age 70+], but 90% and 69% protection was assumed for 1 dose [age 50-69 and age 70+] [Based on post hoc analysis of ZOE 50/ZOE 70 trials]

Dr. Kempe noted that the data compared favorably with 1 dose of ZVL. There is no reason to think that duration would be less than ZVL and would likely be better with HZ/su.

Dr. Prosser indicated that they assumed a slightly lower duration compared with ZVL. ZVL has slightly different patterns across age groups, but they are similar. One dose of HZ/su is similar to ZVL, but higher for the 50 to 69 age group [initial VE of 90% whereas it starts at 78% for ZVL]. Slide 47 shows 2 doses in the top 2 panels and 1 dose in the bottom two panels.

Dr. Hunter did not recall being presented with much data about 1 dose effectiveness, so he expressed concern with the assumptions being made. In addition, he expressed confusion about the outcome of the assumptions of the sensitivity analysis on completion of the 2-dose series. One chart made it look like when the completion rate was lower, ZVL compared more favorably in the cost analysis. But, the graph with the crossing lines looked like a fairly high completion rate of 75% and HZ/su compared more favorably.

Referring to Slides 71 and 72, Dr. Prosser showed the one-way sensitivity analysis for 2-dose completion rates. They do end up running the opposite directions for the 50- to 69-year cohort compared to the 70 and older cohort. That is because moving from 100% down to 20% compliance, the assumption for 1 dose is that there is 90% effectiveness, but there is only half the dose cost and half the AE cost. The overall implication is that the cost-effectiveness results are not particularly sensitive to this assumption, which may be surprising. What is not seen here is a change in the overall number of cases. Because there are lower costs and lower VE

with 1 dose, it yields a similar cost-effectiveness ratio. Looking at the total number of cases prevented, it would be lower in the 20% completion scenarios compared to the 100%.

Dr. Hunter observed that the sensitivity analysis on completion rates is dependent upon the assumption of the 1-dose effectiveness, for which there is not very good data.

Dr. Prosser responded that when they modeled the completion rates, they had to include the reduced effectiveness for 1 dose.

Dr. Reingold asked whether anything was known about VE with revaccination of people who previously received ZVL, or if that was entirely based on assumptions or immunogenicity data? Regarding Slide 32, he inquired as to what was meant by “productivity loss” in the Merck model in the last column. He also asked what the two or three important factors are that make such large differences in the GSK and Merck models.

Dr. Prosser replied that they did not have direct data to derive the VE assumptions, but there are data looking at revaccination. She explained that “productivity loss” referred to an individual experiencing lost time from work or is unable to complete daily activities due to an episode of HZ or PHN, and a cost is assigned to those losses. Those are included in the cost side of the model in all of the analyses. Time costs are not included in the GSK and Merck models. In terms of the large differences, in the GSK model there were differences in VE, slightly more favorable duration for HZ/su compared with the other models, and different assumptions regarding VE for ZVL. The Merck model included scenarios with much lower 2-dose completion rates, higher VE assumptions for the ZVL vaccine, and a much quicker waning rate for HZ/su.

Dr. Dooling added that revaccination data were presented by the manufacturer in February 2017. In a small study that included individuals who had been previously vaccinated with ZVL 5 years prior, it did not affect safety or immunogenicity of the HZ/su vaccination.

Dr. Szilagyi thought 75% was very optimistic for the revaccination rate, certainly for some populations.

Referring to Slide 32, Dr. Ezeanolue requested further explanation of the difference between the GSK and Merck models.

Dr. Prosser emphasized that there are a number of differences across the models. In any set of simulation models, there are always a number of differences in assumptions which would be expected. There are differences as well in the structure of the models, especially as the different models have modeled AE rates and healthcare utilization associated with those. In terms of comparing the key inputs in the model, HZ incidence is slightly higher for GSK and Merck, but the incidence of PHN is slightly lower. This yields very similar overall incidence rates for the CDC/Michigan model compared with GSK, and slightly lower incidence rates for the Merck model. CDC/Michigan QALY losses associated with PHN are higher based directly on primary data collected in a study several years ago specifically for HZ, which yields differences in the model. Most importantly, the difference is around assumptions for VE. GSK assumptions for VE for the initial 2-dose and 1-dose of HZ/su are similar to CDC. The Merck model assumed a lower initial VE for HZ/su. They also assumed a shorter waning duration for HZ/su. There are major differences for ZVL VE assumptions, and the 2-dose compliance is different as well. Really what is driving the differences is primarily the assumptions around VE. All of the other differences contribute partly to the differences in the model.

Referring to Slide 37, Dr. Lee stressed that this was a 1-dose lower bound so that would be something around 85% VE for younger than 70 and 64% VE for 70 and older with the duration of immunity waning to 0 after 1 year. That would be the worst-case scenario. There is a lot of uncertainty regarding 1 dose. This is just a snapshot of the probability sensitivity analysis, but is helpful in understanding that even if we assume a very short duration of immunity it is not so dissimilar from the findings in the probability sensitivity analysis.

Dr. Prosser emphasized that even under the worst-case assumptions, the results are robust to changes in this input parameter.

Dr. Roberts (Merck) indicated that his team did the Merck model. There are a couple of reasons that their analysis shows different results, particularly with regard to HZ/su. One is that it is a 50% series completion rate versus 100% like some of the others, and the second is that they assumed a rapid waning after the first dose of SHINGRIX. He did not believe there was that much difference in the 2-dose, and that it is largely driven by assuming less series completion and much greater waning. In terms of the parameterization of Zostavax[®], the data they feel represents most of the real-world performance of Zostavax[®] are the data presented during the June 2017 ACIP meeting by Kaiser Permanente. That study includes 1.3 million individuals with 400,000 vaccinated and followed up to 8 years at this point, which shows pretty robust effectiveness in 60-69, 70-79, 80-89, and 90 and above as well as durability. There was some positive feedback during the June 2017 ACIP meeting about that study. He asked whether the CDC/Michigan investigators had seen those data and included that scenario in their model. That plays a big role, particularly in the older age groups, in the Merck model.

Dr. Prosser indicated that those data were considered and are represented as part of the overall distribution in the modeling with the effectiveness for ZVL, but were not included as the base case. They are certainly included in the sensitivity analyses.

Dr. Roberts (Merck) noted that the confidence intervals Dr. Prosser showed, particularly in the 50-59 and 60-69 cohorts, spanned not only the point estimate of Zostavax[®], but also the whole confidence interval of Zostavax[®]. There are a lot of assumptions regarding HZ/su at this point that are pure unknowns, such as the series completion and the 1-dose effectiveness and durability. He wondered if Dr. Prosser could reflect on the interpretation of these confidence intervals with regard to policy.

Dr. Prosser replied that there is some overlap for younger age groups, but not complete overlapping. It is not possible to translate these into statistical significance, but it implies that for the older age groups, the cost-effectiveness results are different for the older age groups. For the younger age groups, there is some overlap when running multiple simulations. That is seen in the cost-effectiveness analyses, but at higher thresholds per QALY, and the number of scenarios in which that overlap occurs is 5% or 10% depending upon the willingness to pay threshold.

Regarding the assumptions on ZVL durability in the CDC model, Dr. Annunziato (Merck) indicated that she was a member of the study team and a co-author on the Shingles Prevention Study (SPS) and the Long-Term Persistence Studies (LTPS) along with Dr. Kenneth Schmader. At the time the results were published for the LTPS, ACIP and CDC were actually somewhat critical of the study because of the limitations that the authors were very forthcoming about with regard to the lack of a concurrent control by which to estimate the actual effectiveness of the vaccine beyond the time period when the placebo recipients were offered vaccination. Because of that limitation, they created 3 different historical controls in an effort to account for the fact

that HZ incidence changes over years regardless of the age of the population. They recognized that this was clearly a limitation, but it was the best they could do at the time. Another limitation of that study was that only a subset of the sites participated. They were able to enroll 6800 subjects and had accrued about 25,000-person years. From an effectiveness standpoint, that is a fairly small study. She was surprised that CDC chose that set of data as the input for their base case on durability for the vaccine as opposed to the ongoing, very large, and well-controlled effectiveness study that Kaiser is conducting that Dr. Roberts mentioned.

Dr. Prosser responded that the assumptions used in the model incorporated data from several studies, including the SPS study, consistent with the GRADE summary conducted as part of the Zoster WG. Effectiveness rates are included from the Kaiser study as part of the sensitivity analysis.

Dr. Harpaz (SME) added that at the time the LTPS was presented to ACIP, CDC was quite critical because of the points made by Dr. Annunziato that there was a historic comparison group plus other biases in the study. At that time, historic rates of zoster in the general population had been increasing substantially for older adults for reasons that are still not understood. Over the last number of years, the best data from several different sources show that rates of zoster in the general population in the older population seem to have plateaued dramatically. In a sense, this makes the LTPS perhaps even a conservative assessment. In other words, it actually overstated the duration of protection rather than understating it, if that indeed is the case. The Northern California observational study was very well-done; however, it was based on health-seeking behavior for zoster and PHN. Health-seeking behavior for zoster and PHN is complex, and there is reason to be somewhat skeptical about some of the results from the different studies. On the other hand, ascertainment was extremely good for the LTPS in that it looked for every single case in the study population. Based on those kinds of considerations, CDC felt that it was quite reasonable to consider the LTPS to be the base case and to include the other studies, including the Northern California study, in the sensitivity analyses.

Dr. Dooling reiterated that the choice of using an RCT, albeit a follow-on study, over an observational study is consistent with GRADE principles. CDC recognizes that there are limitations, which is why they used the observational studies in the sensitivity analyses.

Considerations and Proposed Recommendations / Vote

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

Dr. Dooling presented considerations for the use of HZ vaccines, first providing a brief overview of HZ and PHN epidemiology in the US. The annual incidence is approximately 4 HZ cases per 1000 population or about 1 million cases annually^{1,2}. Incidence increases with age, ranging from <1 case/1000 in children to >15 cases/1000 population who are 80 years and older^{2,3,4}. For adults 50 years and older with HZ, 10% to 18% will go on to develop PHN. Similar to HZ, the incidence increases with age³. ZVL (Zostavax[®]) has been licensed in the U.S. since 2006. Approximately 31% of individuals 60 years and older report receipt of this vaccine⁵ [¹Jumaan et al., JID, 2005, 191:2002-7; ²Yawn, et al., Mayo Clin Proc. 2007; 82:1341-9; ³Insinga et al., J

Gen Intern Med. 2005, 20:748-53; ⁴Harpaz et al, IDWeek 2015; and ⁵Williams et al, MMWR 2017, 66:1-28].

HZ, which is commonly known as shingles, is caused by reactivation of latent varicella zoster virus, resulting in a rash which is usually unilateral and involves one to three adjacent dermatomes. About 90% of HZ episodes are associated with pain. Treatment with antivirals has been shown to reduce duration of rash and pain¹. PHN is the most common complication of HZ and is usually defined as pain that persists at least 90 days following resolution of the rash. Unlike HZ, the treatment has minimal or no efficacy and often results in side effects, especially in the elderly.²CDC frequently receives emails from the public regarding HZ and PHN. Here is an excerpt from one of them, "My PHN is worse than my cancer and chemotherapy... [it] has made me depressed and suicidal in the past" [¹Cohen et al, NEJM 2013; ²Johnson et al, NEJM 2014].

The following key HZ policy questions were put before ACIP during this session:

- Q1. Should ACIP recommend HZ/su for vaccination of immunocompetent adults 50 years of age and older?
- Q2. Should ACIP recommend HZ/su for individuals previously vaccinated with ZVL?
- Q3. Should ACIP recommend HZ/su be preferred over ZVL?

In order to address these policy questions, Dr. Dooling presented the WG's interpretation of the data, deliberations on the policy options, and perspective for each of these policy questions.

Regarding the WG's interpretation of the data for the first policy question (Should ACIP recommend HZ/su for vaccination of immunocompetent adults 50 years of age and older?), based on 1 large Phase III RCT, HZ/su demonstrated high VE against HZ of 97% among adults 50-69 years of age and 91% among adults ≥ 70 years of age. HZ/su also demonstrated high VE against PHN at 91% for adults >50 years of age. Efficacy was maintained at $\geq 85\%$ for 4 years following vaccination in adults ≥ 70 years of age. Based on the same large Phase III RCT and additional smaller studies, HZ/su demonstrated no differences between vaccinated and comparison populations for SAEs. However, Grade 3 reactions were more commonly reported in vaccinated groups at 17% compared to 3% in the placebo group.

In a small Phase II study with subjects ≥ 60 years of age, immunogenicity data at 4, 6, and 9 years post-HZ/su demonstrated a CD4+ T-cell response which was maintained from year 4 through year 9 at greater than 3 times the baseline. Immune response was maintained in the oldest age group >70 years. However, there is no established correlate of protection. The NNV to prevent 1 case of HZ varies by age from 11 to 17 and to prevent 1 case of PHN is from 70 to 187. The ICERs from the societal perspective comparing HZ/su to no vaccine ranged between \$9,700/QALY for adults 80 through 89 years of age to \$47,000/QALY for adults 50 through 59 years of age.

In terms of the health outcomes comparing HZ/su to no vaccine. There are two cohorts consisting of 1 million vaccinees each: adults 50 through 59 years of age and adults 60 through 69 years of age. Health outcomes are measured over the lifespan. Of the vaccine recipients, 100% completed the 2-dose series of HZ/su and effectiveness is assumed to wane to 0% in approximately 19 years. In the following table, the first two columns represent the number of cases expected under no vaccination versus vaccination with HZ/su and the third

column is the difference. In other words, the expected number of cases averted by vaccination over the lifespan:

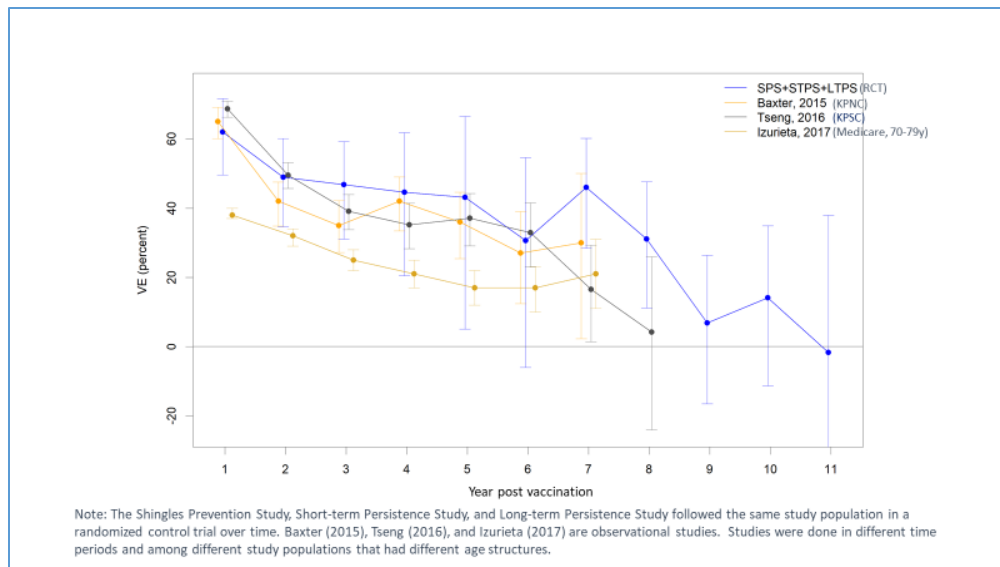
Outcome	Cases Expected		Cases Averted	Number Needed to Vaccinate*
	No Vaccine	HZ/su	No Vacc- HZ/su	
HZ cases	265,000	186,000	80,000	13
50-59 yo	204,000	117,000	87,000	11
60-69 yo				
PHN cases	32,000	27,000	5,000	187
50-59 yo	31,000	21,000	10,000	100
60-69 yo				

Between 80,000 and 87,000 averted cases of HZ and between 5,000 and 10,000 averted cases of PHN are expected. Therefore, between 11 and 13 people would need to be vaccinated in this age group to prevent 1 case of HZ and 100 to 187 people would need to be vaccinated to prevent 1 case of PHN.

In terms of the WG deliberations regarding the first question, based on a review of the GRADE assessment of the evidence for critical and important outcomes, the HZ WG felt that there was strong evidence that the vaccine is efficacious and durable and found no evidence that it is unsafe. There is minimal waning in the first 4 years, but effectiveness beyond 4 years is uncertain. However, durability has been demonstrated for immunological outcomes at 6 and 9 years. The vaccine is reactogenic, resulting in an excess of approximately 13% Grade 3 reactions in vaccinees. There are approximately 42 million adults 50 through 59 years of age, a group in which about 21% of all HZ episodes occur annually. Under almost all assumptions, HZ/su demonstrates NNV and cost-effectiveness similar to or more favorable than other adult vaccines for all age groups, including those 50 through 59 years of age. The majority of WG members favor a policy which recommends HZ/su vaccine for immunocompetent adults 50 years and older.

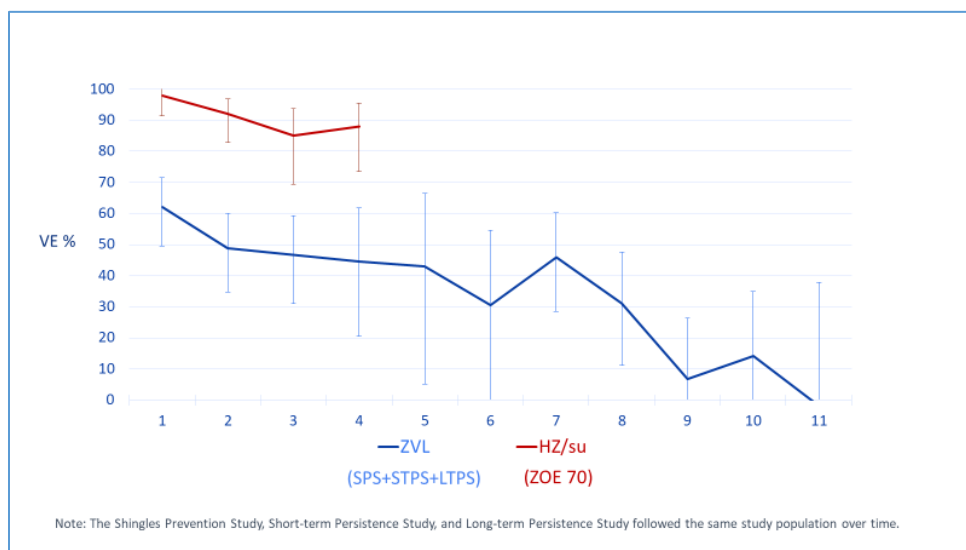
Regarding the WG's interpretation of the data for the second question (Should ACIP recommend HZ/su for individuals previously vaccinated with ZVL?), HZ/su is more efficacious than ZVL in all age categories. The differences are larger for older adults. Experimental and observational studies indicate significant waning of protection from ZVL. For example, VE drops the first year after receipt at approximately 15% to 25%. By 6 years post-vaccination, VE was less than 35% and there may be negligible protection by 10 years. HZ/su is significantly more efficacious over 4 years, with VE greater than 97% in the first year, which is maintained at or above 85% during the first 4 years for all ages. In a small study, vaccination with HZ/su 5 years following ZVL did not alter the safety or immunogenicity of HZ/su.

This graph depicts the duration of protection of ZVL against HZ by year. On the y-axis is VE and on the x-axis are the years post-vaccination. The 95% confidence interval for each estimate is represented by the error bars. The blue line represents the estimates from the RCTs discussed earlier (SPS, STPS, LTPS), while the other 3 lines represent data from large observational studies in individuals 60 years of age and older:



There is a steep drop in VE following the first year after receipt of ZVL. Thereafter, a slow waning is observed. Studies agree that protection is less than 35% by 6 years following vaccination, and the longest duration studies (SPS, STPS, LTPS) estimate VE below 20% with a high degree of uncertainty.

This graph depicts VE against HZ for ZVL and HZ/su by year following vaccination:



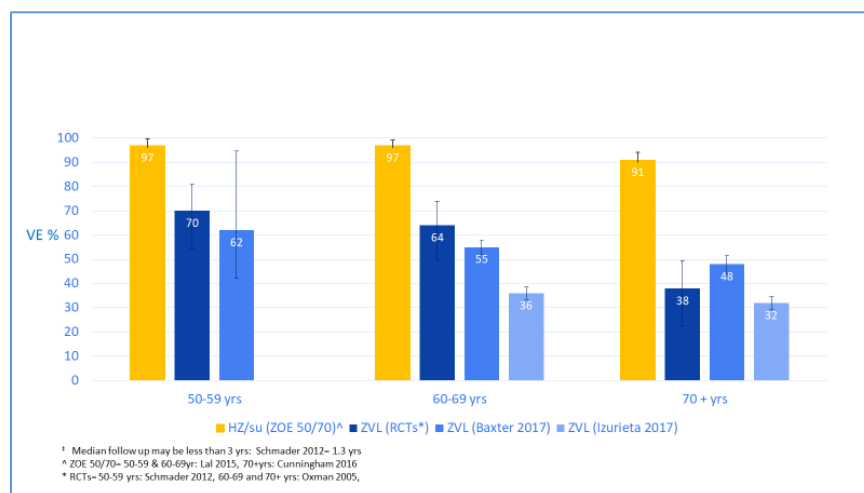
In red is VE for HZ/su from the ZOE 70 Phase III clinical trials, while in blue is VE for ZVL from the SPS, STPS, and LTPS studies. As reflected in the graph, there is a significant gap in the HZ protection provided between both of these vaccines over the first 4 years.

Regarding the WG's interpretation of the data, approximately 20 million people have been vaccinated with ZVL and would be potentially eligible for HZ/su¹. The ICERs from the societal perspective of revaccination, even at a minimal allowable interval of 8 weeks* post ZVL, is similar to or lower than other adult vaccines ranging from \$15,000/QALY among individuals 80 through 89 years of age to \$117,000/QALY among individuals 50 through 59 years of age [Source: IMS; * Revaccination at 8 weeks was approximated in the CEA model by revaccination immediately following ZVL].

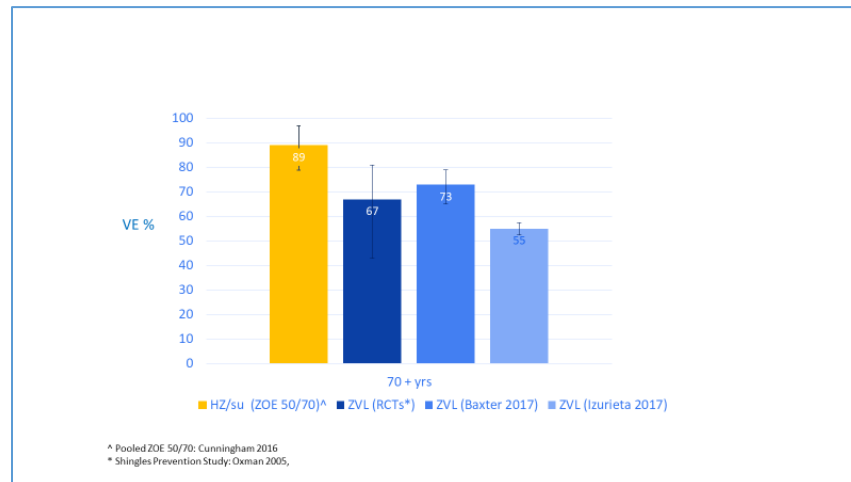
With respect to the WG's deliberations pertaining to the second question, the WG felt that prior ZVL receipt should not be a contraindication to receiving HZ/su. For prior ZVL recipients, HZ/su should be viewed as a new vaccine to prevent HZ and its complications. Substantial burden of HZ and PHN could be prevented by vaccinating this population with HZ/su, in particular among the elderly. Prior ZVL did not alter the safety or immunogenicity of HZ/su as measured at a 5-year interval. However, there are no efficacy data in this population, there are no established correlates of protection, and there are no data on other intervals. Of the US population 60 years of age and older, 31% followed ACIP recommendations and received ZVL. A significant fraction of ZVL recipients now have very low vaccine protection for HZ and PHN. Vaccination with HZ/su is a cost-effective strategy for individuals who have previously received ZVL. The majority of WG members favor a policy recommending HZ/su for individuals previously vaccinated with ZVL.

Regarding the WG's interpretation of the data for the third question (Should ACIP recommend a preference for HZ/su over ZVL?), it should be noted when interpreting the data, these vaccines have not been studied in a head-to-head efficacy trial. Based on the individual efficacy trials, HZ/su estimates of efficacy are significantly higher than ZVL estimates across all age groups at 97% vs 64% among individuals 60 through 69 years of age, 91% vs 41% among individuals 70 through 79 years of age, and 91% vs 18% among individuals 80 years and older. HZ/su appears to wane at a slower rate than ZVL over the first 4 years. The expected cases of HZ and PHN averted are far greater with HZ/su compared to ZVL. Neither vaccine is associated with SAEs in immunocompetent persons. HZ/su is more reactogenic than ZVL. The economic analyses showed that under almost all assumptions, HZ/su leads to more disease prevention and decreased overall costs (vaccine + expected disease costs) compared to ZVL.

This graph depicts VE against HZ for HZ/su and ZVL, by age group, during the first 4 years following vaccination:



The horizontal axis is separated into 3 age categories. Efficacy for HZ/su is depicted in the yellow bars, ZVL in the dark blue, and observational in the lighter blue. As shown, HZ/su is more efficacious in each age category and the difference is larger among older recipients. Similarly, this graph depicts VE against PHN for HZ/su and ZVL in adults 70 years and older during the first 4 years following vaccination. Once again, the difference is substantial, but the uncertainty is greater:



Returning to the cohort of 1 million people in their 60s, in terms of health outcomes comparing no vaccine, ZVL, and HZ/su with expected health outcomes measured over the lifespan, it was assumed that HZ/su recipients completed both doses and that VE wanes to 0% protection over about 19 years and that ZVL VE wanes to 0% over about 10 years. Under these assumptions, the differences in cases expected between the 2 vaccination strategies would result in an additional 53,000 HZ cases averted and 4,000 PHN averted in the HZ/su cohort. Looking at disease averted under two examples of vaccine uptake with those same cohorts, under Example #1 with 50% receiving ZVL and 50% receiving HZ/su, there would be approximately 144,000 expected cases of HZ and 23,000 cases of PHN. Under Example #2, with 10% receiving ZVL and 90% HZ/su, there would be approximately 122,000 cases of HZ and 21,000 cases of PHN. Therefore, Example #2 would result in an additional 21,000 cases of HZ and 1,600 cases of PHN averted over the lifespan.

The two policies under consideration by the WG are a preference for HZ/su or no preference for either vaccine. In terms of the pros and cons of each deliberated by the WG, under the preference for HZ/su option, the pros would be substantially more prevention of HZ, PHN, and other complications. This is especially important for the elderly, who are also most vulnerable and at highest risk for both HZ and PHN. HZ/su is more cost-effective than ZVL under almost all assumptions. The preference would promote patient access to the more efficacious vaccine. HZ/su is more refrigerator-stable, which may decrease some of the implementation barriers. The cons of a preferential recommendation are that HZ/su may be removed from the market if an unexpected safety problem is observed. If effectiveness or long-term protection are substantially less than expected, ACIP would need to reverse the preferential recommendation. This policy would lead to more Grade 3 reactions following vaccination. It requires 2 doses, which would increase implementation barriers. In terms of the no preference policy option, having 2 or more manufacturers of HZ vaccines will safeguard a stable vaccine supply. The cons are that a large difference in VE will result in 1000s of preventable cases of HZ and PHN

over the lifespan, and the onus is on providers to compare the evidence and determine vaccine choice.

Ultimately, there are a number of unknowns in this decision analysis in terms of vaccine characteristics and program implementation. First, there is always the possibility for rare safety events with HZ/su. VE of HZ/su beyond 4 years remains unknown, as do the VE and durability of 1 dose HZ/su. Moreover, real-world adherence to the 2-dose schedule of the vaccine is unknown, as is healthcare seeking among recipients who experience reactions. A minority of the WG members thought that the unknowns regarding safety, effectiveness, and 2-dose adherence in the real-world setting preclude a preferential recommendation at this time. In discussion of the key unknowns such as effectiveness and the possibility of an unexpected safety signal, the majority of WG members thought that adequate surveillance, pharmacovigilance, and long-term testing are in place to detect unexpected occurrences. ACIP will re-evaluate the benefit-to-harm ratio if steep waning or SAEs. With respect to 2-dose adherence and 1-dose VE, provider and patient education regarding expected reactogenicity may positively impact adherence. Observational studies will be required to estimate 1-dose VE.

In terms of the WG's deliberations pertaining to the third question, the majority of WG members thought a preferential recommendation for HZ/su is likely to prevent significantly more disease compared to a non-preferential recommendation. Moreover, HZ/su is more cost-effective than ZVL under almost all assumptions. A non-preferential recommendation puts the onus on clinicians to compare safety and efficacy literature to select a vaccine. A preference would promote access to the more efficacious vaccine; whereas, health systems or providers may choose to stock only the less expensive vaccine if no preference is stated. The WG acknowledged that although preferential votes are uncommon for new vaccines, they are warranted when ACIP believes there is sufficient evidence of superior benefit-to-harm ratio of one vaccine compared to another. Therefore, the majority of WG members favor a policy recommending a preference for HZ/su over ZVL.

Based on the information available regarding the 3 policy questions, the following three votes were proposed:

- Vote #1: HZ/su vaccine is recommended for the prevention of HZ and related complications for immunocompetent adults aged 50 years and older.
- Vote #2: HZ/su vaccine is recommended for the prevention of HZ and related complications for immunocompetent adults who previously received ZVL (Zostavax[®]).
- Vote #3: HZ/su vaccine is preferred over ZVL (Zostavax[®]) for the prevention of HZ and related complications.

Discussion Points

Dr. Kempe requested a review of the amount of data available regarding safety and reactogenicity of revaccination, as those data were presented a long time ago and were from a small study. She expressed concern with the small number of subjects in the study.

Dr. Dooling responded that those data were from a Phase II study that included 2 comparison groups: a vaccine naïve group and a group previously vaccinated with ZVL. Both groups were given HZ/su and the comparison showed no difference in immunogenicity, reactogenicity, or safety between the two groups.

Dr. Romulo Colindres (GSK) added that there were a little over 400 subjects in that revaccination study, and confirmed that there were no differences in safety and reactogenicity in the group that received ZVL or not.

Dr. Belongia added that the vaccinated subjects in the study had a 5-year interval from previous ZVL. Little is known, but ZVL is live and HZ/su is a adjuvanted subunit vaccine. There is no biological reason that he is aware of to expect any interaction of those that might be harmful. The data are limited and it is a relatively small study, but there are some data on that. While there may be some concerns about 2-dose completion and the unknown efficacy of a single dose, it is important to keep in mind that the vaccine is licensed for 2 doses rather than a single dose. VE and the waning trajectory are fixed characteristics of the vaccine and will not change with the modeling of different assumptions. However, implementation and 2-dose completion are not fixed characteristics of the vaccine. If 2-dose completion is not as high as they would like, steps can be taken to increase completion rates. While everyone would like to have additional observation real-world data, the reality is that over the next one to two years, there will not be that much more data available. Finding rare AEs that potentially could be observed will require long-term studies over several years and very large populations. While waiting for those data to accrue, tens of thousands of HZ cases and thousands of PHN cases will occur because healthcare systems and insurers will continue to give a vaccine that is not performing at the level of HZ/su. These are considerations to keep in mind as they think about 1-dose uncertainties and 2-dose completion rates.

Dr. Harpaz (SME) concurred that biologically, there is no reason to think that ZVL and HZ/su would interact in any particular way. The potential for added disease averted was substantial enough that given what is known known currently, it makes public health sense.

In terms of not having a correlate of protection in the context of revaccination, Dr. Reingold assumed that in clinical trials people collected specimens and attempted to assess that. He asked whether he was correct in thinking that immunogenicity data are basically antibody data and antibody is not the relevant clinical correlate of protection to look at.

Dr. Dooling confirmed that there is no correlate of protection. In the revaccination study, both cell-mediated immunity and antibody protection were studied and neither showed a difference between the newly vaccinated and previously vaccinated groups. CDC is anxiously awaiting analysis of an overall assessment of a correlate of protection. It is compounded somewhat by the paucity of cases in ZOE 50 and ZOE 70. She agreed that this information would be very helpful for decision-making.

Dr. Ezeanolue recalled how happy pediatricians were when they got the live attenuated influenza vaccine (LAIV), but then a follow-up decision had to be made. There is no head-to-head comparison of ZVL and HZ/su and there are no SAEs in terms of harm for either, but ACIP was being asked to consider a preference of one over the other. What most likely will happen is that ZVL will be discontinued and there will be nothing on standby should something happen with HZ/su. He was concerned with the damage that could be done. Since monitoring mechanisms are in place, there will be more data available to confidently make a preference determination, but there are insufficient data to make that determination at this point.

Dr. Romero noted that there was a paucity of minority populations in the licensing group, and he wondered what steps have been taken to remedy that in the follow-up.

Dr. Friedland (GSK) responded that GSK is committed in the post-licensure setting to generate effectiveness data in other populations who will be receiving this vaccine.

In terms of the significant reactogenicity issue with HZ/su, Dr. Stephens inquired as to whether the mechanism is known, if reactogenicity influences whether individuals receive a second dose, and whether there are any data on co-administration of nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen.

Dr. Dooling responded that the high rates of reactogenicity are thought to be associated with the adjuvant, which overall boosts the immune response of the antigen, which is an anti-IgE antibody found on the cell surface of varicella zoster virus. Co-administration of NSAIDs or acetaminophen has not been studied to her knowledge.

Dr. Riley asked whether there was a sense as to why only 30% of the population who is recommended for 1 dose of vaccine is getting it, and whether the expectation for 2 doses will make uptake even worse. She thought she read that the incidence of HZ is different in different ethnic populations and that potentially, African Americans have a lower incidence. She would like to see the safety data as well, because it makes her think that there is something different about the immune system.

Dr. Weinberg (CDC) responded that there are implementation challenges with all adult vaccines in the US, especially with HZ vaccine given the storage and price. There are challenges for providers to stock the vaccines and patients to access it. HZ vaccine coverage has been increasing in the US over the last several years and reached 30% this year, the Healthy People goal.

Dr. Bresnitz (Merck) pointed that there are a number of issues impacting why uptake is not great. One is the complex reimbursement scheme, which is probably one of the major reasons. At least for the population 65 years of age and above, this is a Medicare Part D benefit. This is not going to change for SHINRIX (HZ/su) either. In fact, it will be even more problematic because it is a 2-dose vaccine. Data show that most vaccine is given in the fall concomitant with influenza pneumococcal vaccines. If recipients of the first dose have to return in the early part of the next year for the second dose, they may have to pay full price because they will not have met their deduction. When people find out that their cost is going to be over \$50 at the pharmacy, they walk away.

Dr. Sun (FDA) asked whether the WG had an opportunity to review the final pharmacovigilance plan and approval letter. In the review of vaccines, the pharmacovigilance plan often is not finalized until relatively late in the review cycle. The pharmacovigilance plan and approval letter address certain safety issues that arose during the pre-licensure evaluation. If not, perhaps GSK could summarize it.

Dr. Dooling replied that the WG received a provisional presentation prior to licensure, but she invited GSK to provide more current information on the pharmacovigilance plan.

Dr. Colindres (GSK) responded that there is now a detailed pharmacovigilance plan, an outline of which has been shared with ACIP WG members. GSK is very committed to the continued close monitoring of safety as they enter the post-marketing setting. The pharmacovigilance plan is a 3-tiered plan. The first part is routine pharmacovigilance as would be done for any GSK-licensed vaccine, and includes safety signal detection. The second part would be enhanced pharmacovigilance, which would be for any events of interest and would include exercises such

as observed over expected (O/E) analyses. The third component, which is very specific, is a targeted safety study. This has been agreed upon with regulatory authorities who have provided input into this. This would be a large non-interventional prospective cohort study conducted in a large medical database system in which certain events of interest would be followed, such as potential immune-mediated diseases.

Dr. Walter asked at what ages people are getting vaccinated in terms of different efficacy based on different ages. In terms of Vote #2 and the fact that there are only data for the 5-year interval, he asked whether the WG gave any thought to including an interval in the recommendation.

In terms of rates of ZVL by age, Dr. Dooling indicated that from a National Health Interview Study (NHIS) of self-report of vaccine receipt, as of 2015 of the entire population of people over 60 years of age, 31% reported vaccine receipt. That is higher in individuals 60 through 69 years of age and lower in those 70 years of age and older. CDC has unpublished figures showing that 5% to 6% of individuals 50 through 59 years of age have been vaccinated. Regarding whether timing will be addressed in the recommendation, the WG discussed an interval and thought that the most straightforward recommendation would be to set a minimal allowable interval and then allow for CDC guidance to assist patients and providers to decide what might be an optimal interval. The minimal interval would be set at 8 weeks, but the optimal interval would be guided by such considerations as the age at which a person was vaccinated initially and the interval between when they were vaccinated and their presentation.

Dr. Moore acknowledged that the financial barrier is certainly a serious issue. However, it may be that it is the barrier to initiation rather than being more difficult with 2 doses. If able to overcome the financial barrier to get one dose, the second one will be easier based on figuring out how to access it potentially. The other thing that is encouraging about 2-dose coverage with this vaccine is that although initiation may occur in the fall with influenza vaccination, the people in the age groups who could be recommended to get this vaccine are ones who visit healthcare providers and pharmacies much more frequently and may have more opportunities to receive the second dose. Unlike hepatitis A or B, a travel vaccine for which a series is needed, or something people do not feel that personally threatened by, everyone knows someone who has had a horrible experience with HZ. HZ is very visible and painful, and it seems much more of an immediate threat that may motivate people in this age group in a way that has not previously been observed for the vaccines available. Regarding the history of LAIV, influenza differs significantly from anything else ACIP tackles. It is wily, changes all of the time, and there are many unknowns. Rather than trying to draw a correlation between an influenza product which has so many issues that are unrelated to HZ, she prefers to deal with them separately with the evidence. Certainly, it is the role of ACIP to address the evidence available to them and make changes to its recommendations if the evidence changes. They must address the data and evidence before them, which shows that the HZ/su vaccine performs in a superior fashion and will prevent much more disease than the other product that is available. It is not up to ACIP to figure out how to make sure that the public gets the 2 doses they need.

Regarding the second recommendation, Dr. Atmar asked whether other subgroups were considered by the WG such as persons who previously received vaccine and specifically the paper by Gadot in which 6 of 96 persons got HZ within the year after receiving HZ/su, and whether any consideration had been given to restricting the vaccination to those who have not previously had HZ.

Dr. Dooling replied that in the revaccination study, individuals who had a previous HZ episode were excluded. That was a true exclusion for the efficacy studies as well. The Phase III immunogenicity sub-study in subjects 50 years and older with a prior history of HZ was designed to examine immunogenicity endpoints, as well as safety. It met the immunogenicity endpoints. In other words, the subunit vaccine appeared to elicit the same immunogenicity in people who had a prior HZ episode, and the reactogenicity was similar in people who had a prior episode and people who had not. What was unexpected was that 6 participants reported 9 suspected episodes of HZ. Given the small number of expected HZ cases *a priori*, a rigorous case ascertainment procedure is mandated in the protocol. Of the episodes, 4 were medically attended and the remainder were self-reported. Interestingly, there is no laboratory confirmation and no photographs were taken, which would have been the standard ascertainment in an efficacy trial, for example. All 9 cases were reported at Canadian sites and none at the Russian sites, which is also difficult to explain in this study. Another study is underway to assess HZ/su recipients with a prior history of HZ. For example, several hundred individuals who received placebo in the efficacy trial and went on to get HZ have now been enrolled in the follow-on study. Hopefully there will be more clarity on this issue in time. In terms of restricting vaccination to those not having previously had HZ, Dr. Dooling responded that the WG felt that there was not sufficient evidence at this time to exclude individuals who had a prior HZ episode. These issues will be further deliberated on and considered in the guidance.

Dr. Lee commented that these decisions have been challenging to think through and expressed appreciation for Dr. Dooling's transparency about the pros and cons of these decisions. She agreed with each of them, which is what made it so difficult. That said, she thought ACIP's charge as a group was to be as transparent as possible in its decision-making and to focus on the benefits-risk balance at a population level. In this instance, it was helpful to have the cost-effectiveness analyses to make that transparent. It is always easy to look backwards in time and question whether they were making the right decision, but she agreed with Dr. Moore that they must make the best possible decision given the data they had at the moment. It is fine for ACIP's decision-making to be dynamic, and it should be. As more data become available and uncertainties are resolved, ACIP should reconsider the decision at a future date. It is important to recognize that they may have their own values and judgments how they want to make the decision, but she expressed her hope that as a group, regardless of differences in opinion, they would make the best possible decision on the whole.

Regarding the prevalence and severity of this disease and the need to do the right thing by the patient, Dr. Duchin (NACCHO) said that in his role as a clinician, infectious disease specialist, and public health practitioner, he could not imagine not giving a preferential recommendation for the effective vaccine based on the information presented during this session about VE, cost-effectiveness, and safety. He wondered how they would explain to a patient that they were not being advised to use a vaccine that is expected to prevent a serious disease more effectively than another product. He encouraged the ACIP members to make a preferential recommendation for this vaccine, and he will continue to make a preferential recommendation to his family, friends, and colleagues who ask.

Ms. Pellegrini expressed appreciation for the vigorous discussion. Thinking about this from the layperson perspective, from families and patients. She was struggling with the fact that she could easily envision people questioning a preferential recommendation for this vaccine even though it has never been administered outside of a research setting. Giving the number of unknowns, she was much more comfortable starting with a non-preferential recommendation and reconsidering a preferential recommendation in a couple of years when more is known.

Dr. Belongia reminded everyone that the Vaccine Safety Datalink (VSD) will also be conducting near real-time monitoring using pre-specified outcomes for this vaccine as it rolls out. That typically runs for a couple of years, so it will not provide quick information. However, this is an additional mechanism to monitor safety.

Dr. Baker (IDSA) agreed with Ms. Pellegrini's observations. She believes this vaccine is a terrific addition and would recommend it for herself and her family, and she was comfortable with the first two recommendations. Regarding a preferential recommendation and the potential for only one manufacturer of the vaccine, there is a potential for something to occur in the real-world setting. What if there is a preferential recommendation and there is a supply issue? Pediatricians were ensured when pneumococcal conjugate vaccine (PCV7) was introduced in 2000 that there would be no supply issues. From the beginning they could not use that vaccine in infants universally because there was not enough, and they had to keep using polysaccharide in children 2 years of age and older. LAIV is a bad analogy for the reasons stated, but there could be supply issues. In the real world, there are marketplace issues when there is a preferential recommendation. While the modeling is lovely and transparent, what vaccine even for babies, has 100% adherence to a 2- or 3-dose schedule at the outset? Even now, especially in certain states that are supposed to give 3 doses of diphtheria, pertussis, and tetanus (DPT), this does not manage to get done until the child is a year or more of age. The comments about the real-world and waiting for more data outside of a clinical trial, including ethnic diversity, are great. She is not that worried biologically about the adjuvant, but it is a brand-new adjuvant that has not been given to millions of people. She is a person who tries not to worry about lack of data on rare events, but she is cautious about making a preferential recommendation. Dr. Baker clarified that she was speaking for the IDSA as well as herself.

Dr. Bresnitz (Merck) indicated that he came to Merck with previous experience in public health and as a practitioner, so that experience informed his comments as well. He thought they all could agree that the subunit vaccine deserves a recommendation, and he congratulated the GSK team for the great work they have done to this point. He noted that for the GRADE analyses, both vaccines were graded as Type 1 evidence. He wished they could grade the inputs to the models, because he thought that would be a 4 or even a 5 if it existed. The evidence on the assumptions is very weak. There were clearly adequate pre-licensure data to make a recommendation, but he agreed with the issues regarding a preferential recommendation that Dr. Baker articulated very well. The WG has been split in its opinion, but it is the ACIP who must vote. In addition to the 3 explicit votes to be made, Dr. Bresnitz stressed that there was an implicit vote as well. That is, what will be ACIP's *effective* recommendation for Zostavax®? Right now, it is listed as a Category A recommendation. If ACIP were to make a recommendation for revaccination without a minimum time limit of 2 weeks, what would that actually say to the practitioner? The cost-effectiveness analyses are very complex and many of the analyses were based on assumptions that were based on assumptions. They are all projections of what might happen assuming A, B, and C. The base case assumptions were all basically favorable to the novel vaccine. However, he said he was not going to say that they were unfavorable to Zostavax® because there are real-world data for that—maybe not what they would have like in the base case, but those data were available to the WG as well. The issue of making a preferential recommendation now and coming back in a year or two to reverse it based on new data is a lot harder to do than making a neutral or equivalent recommendation for both vaccines now. During the last ACIP meeting, Dr. Dooling indicated how long it would take to collect various pieces of data, some of which would take only one to two years. ACIP could make a non-differential recommendation, because there were not a lot of data shown in the cost-effectiveness analysis for individuals 50 through 59 years of age. There is no recommendation for Zostavax® for adults 50 years of age and older. If ACIP was going to make

a recommendation for HZ/su for those 50 years of age and older, they should do that for Zostavax® as well. In conclusion, Dr. Bresnitz emphasized that ACIP could make a neutral recommendation and come back to it in a year or two when additional data are available. Mention was already made that ACIP would be evaluating other issues for which there may be additional votes. Based on his experience as a policy-maker, he suggested that the best approach was to be cautious about the recommendation because ACIP's votes have consequences. Occasionally, they have unintended consequences as well.

Dr. Bennett called for public comment on all three recommendations posed. With no public comments offered, she began the voting process. Of note, a new electronic voting mechanism was instituted during this session.

Motion/Vote #1: HZ/su for Immunocompetent Adults Aged 50 Years and Older

Dr. Belongia moved to approve the recommendation for HZ/su vaccine for the prevention of HZ and related complications for immunocompetent adults aged 50 years and older. Dr. Moore seconded the motion. The motion carried with 14 affirmative votes, 1 negative vote, and 0 abstentions. The disposition of the vote was as follows:

14 Favored: Atmar, Belongia, Bennett, Ezeanolue, Hunter, Kempe, Lee, Moore, Pellegrini, Reingold, Romero, Stephens, Szilagyi, Walter
1 Opposed: Riley
0 Abstained: N/A

Dr. Belongia moved to approve the second recommendation to give HZ/su for the prevention of HZ and related complications for immunocompetent adults who previously received ZVL, which Dr. Romero seconded.

Ms. Pellegrini asked whether they were concerned that if there is no interval, some clinicians might think they could give both vaccines simultaneously.

Dr. Belongia responded that the WG discussed this and the feeling was that it was best to have the interval in the guidance rather than in the recommendation itself. There is no recommended interval, but the minimum interval was somewhat arbitrarily decided to be 8 weeks. The vast majority of people who would be eligible were vaccinated 1, 2, 3, or more years in the past or not vaccinated at all.

Dr. Moore added that one of the considerations was that there are so many variable clinical considerations depending upon the age of the patient, it would be unfair to try to set a recommendation that is fixed. It was preferable to provide more detailed guidance that would allow a clinician and patient to make a decision that may be very different for someone 85 years of age than someone 55 years of age.

Given all of that, Dr. Hunter asked how this differed from a preferential vote.

Dr. Moore responded that it was quite clear that patients who received ZVL in the past have waning immunity and lack of protection against shingles and shingles complications. HZ/su is a completely different vaccine, which then enables them to receive protection against shingles.

Dr. Bennett said that from her perspective, these vaccines are different, so it is not really revaccination. They should clarify the point that if someone has received ZVL in the past, they would be eligible.

Dr. Walter said he continued to struggle with the issue of the minimal interval at the short time point of 8 weeks.

Dr. Bennett clarified that ACIP would not be voting on the interval. It will be included in the background information, but not in the formal recommendations.

Dr. Hunter emphasized that his point was that it is a preferential recommendation if the vaccine is given early, but it is not if given late. Dr. Belongia agreed.

Ms. Pellegrini asked if the schedule would state that everyone over a certain age should receive zoster vaccine, but those who received ZVL should be revaccinated.

Dr. Hunter said he thought what it would say is that those over 50 could receive HZ/su, and those over 60 could receive either.

Dr. Cohn clarified that if this vote passed, the schedule would then say that those who received ZVL in the past should get the HZ/su vaccine. There would be two separate parts of the schedule.

With that in mind, Dr. Atmar wondered whether the interval should be included in the recommendation rather than only in the guidance. Dr. Reingold concurred with this suggestion.

Dr. Messonnier noted the issue was that this is a vaccine for which aggressive data will be collected, and the WG and CDC staff thought that tying it down to an interval would make it difficult to stay up with the data as they continue to evolve. The ACIP statement will include information regarding the interval. They have been trying to get the language of the actual recommendation more precise and not include so many caveats in it. The complication with including an interval in the recommendation is that it would require multiple scenarios, because there are so many different iterations. Regardless of what happens around this, the full ACIP statement goes to everyone. The number of people who read the recommendation as precisely as ACIP writes it is probably smaller than the number of people who read the surrounding clinical guidance that comes from this. CDC will be working with all of the provider organizations and all of its partners to translate what ACIP says in the recommendations, including the concerns about the interval into the clinical guidance for providers.

Dr. Lee thought the vote should be based on the evidence that exists, and there is not sufficient evidence about the 8-week interval. As that is collected, she thought it should sit in the guidance as opposed to the recommendation. The discussion about one-size-fits all is a challenge in those over 50 years of age, because there is such heterogeneity in the population. The WG tried to go down the path regarding whether there could be recommendations for individuals 80 years of age and older, 70 through 79, and so forth. There was not sufficient evidence to break it down and say what the interval should be. There was a lot of clinical judgment and expert opinion that the WG hopes will be included in the guidance.

Motion/Vote #2: HZ/su for Immunocompetent Adults Who Previously Received ZVL

Dr. Belongia moved to approve the recommendation for HZ/su vaccine for the prevention of HZ and related complications for immunocompetent adults who previously received ZVL (Zostavax®). Dr. Romero seconded the motion. The motion carried with 12 affirmative votes, 3 negative votes, and 0 abstentions. The disposition of the vote was as follows:

12 Favored: Atmar, Belongia, Bennett, Ezeanolue, Kempe, Lee, Moore, Pellegrini, Reingold, Romero, Stephens, Szilagyi
3 Opposed: Hunter, Riley, Walter
0 Abstained: N/A

Those opposed were offered an opportunity to further comment on their dissent. Dr. Hunter maintained that without an interval, this would be a preferential vote. Dr. Walter underscored that there is insufficient evidence for subsequent vaccination.

Dr. Hunter made a motion to vote on the preferential recommendation for HZ/su vaccine over ZVL for the prevention of HZ and related complications. Dr. Romero seconded the motion.

Dr. Fryhofer (AMA/ACP) echoed the comments of Ms. Pellegrini and Dr. Baker that this is a new adjuvant. As a clinician, she sees patients every day. When clinicians see recommendations from ACIP, they put a lot of trust in ACIP having looked at the data. She had concerns about making a preferential recommendation for a vaccine with an adjuvant that has never been utilized in the real-world. It seemed to her to be somewhat impulsive, and she preferred that they wait for at least a few months.

Given the difference in performance in the clinical trials, it seemed to Dr. Moore to be almost like a permissive recommendation equivalent to not expressing any sort of acknowledgement of the substantial difference in performance of these two vaccines. Her concern is that clinicians would look at this and have the same kinds of concerns they typically do with any permissive recommendation. She feels like it is ACIP's responsibility, and clinicians do look to ACIP, to make recommendations based on the evidence in front of them. The evidence across costs and disease prevention is very strong. Reasonable people can disagree about the concerns regarding the unknown and whether they are more comfortable making decisions based on the evidence and saying that as the evidence evolves, so should the recommendations; whereas, others feel differently about those values and judgements. No one, concerned or not, has expressed a feeling that they do not believe that the HZ/su vaccine performed in a superior manner to the existing vaccine and would prevent more disease. As such, she thought that they all were leaning in the same direction. Some want the vaccine in the real-world longer for some indeterminant period of time to see if unknowns show up. For her conscience, she felt that a preferential recommendation was called upon to give people direction based on performance.

Regarding Dr. Fryhofer's comments, Dr. Kempe said she was thinking of this as a completely new vaccine. ACIP considers lots of new vaccines, many of which have a similar level of evidence even though they are always somewhat worried about unknowns, they frequently recommend new vaccines to the population with similar levels of evidence.

Ms. Pellegrini asked whether the guidance would include the discussion of the data on performance. She expressed that if they could trust that clinicians would go to the guidance for the interval information, they could also refer to guidance for performance information.

Dr. Messonnier replied that the ACIP statement includes all of this. When that is translated to clinical guidance, they try to follow the science and the intent of ACIP. Most clinicians will not look at that at the depth with which ACIP does, but they will look for how ACIP expresses the recommendation. The interval guidance will be proscriptive as opposed to the comparison of the differences in the vaccines. If ACIP decided that based on the discussions there was not a preference, the guidance will say something like, "CDC recommends these vaccines" and will provide decision-making clinical guidance about what to do for individuals who received one or the other. The details of vaccine performance data would not be reflected in the clinical guidance, but rather, will be in the ACIP statement.

Dr. Belongia noted that one of the concerns expressed in the WG is that there are situations in which physicians are not choosing a vaccine. If a healthcare system decides to stock a vaccine and there is no recommendation, they may choose to stock the lowest priced vaccine for their bottom line. They are not necessarily going to read through the literature to second guess ACIP's decisions. This will be similar with insurers. He completely agreed with the concerns and the wish to have more real-world data, but at the same time balanced that against the fact that cases of HZ and PHN will occur in people who may not even know this vaccine exists, may not know that it is better, and do not get it.

Dr. Hunter expressed appreciation for all of the work the WG has done on this very difficult issue. He thought they already had basically two preferential votes that they just made. One was for the 50 to 60 age group and one was for people who are already vaccinated. He thought it would be clear to clinicians and health systems that for certain people, there is a preference. Although that may or may not impact how administrators and insurance will actually work in the real-world, that does make him feel like there is going to be some push to use the new vaccine in those groups.

Dr. Fryhofer (AMA/ACP) said she understood how wonderful the new vaccine is in its increased effectiveness. However, she thought they discounted clinicians by thinking that if something is put in the first paragraph comparing the differences that they will not read that.

For the guidance regarding this particular vote, Dr. Lee re-emphasized something that came up in the WG, which is that there are a greater number of Grade 3 reactions and that it is important to reflect that in the guidance to providers to ensure that they are providing that information to their patients. This is not going to be anticipated by the average patient. They will think it is like every other shot.

Dr. Bennett added that it is particularly important in terms of completion of the second dose to warn people of the potential for increased reactions.

Dr. Messonnier stressed that this is a complicated issue and is one of the cases in which CDC has tasked ACIP with something completely different from anything they have had to deal with before. Regardless of what happens with this vote, she did not know that they could predict what would actually happen with clinicians. While she agreed with Dr. Belongia about stocking of vaccines, the second recommendation will require providers to stock new vaccine. Market forces will impact this either way, and it is not possible to predict all of the different scenarios. What CDC can promise is that regardless of what happens, the agency will be aggressive

through a variety of means to collect real-world data about how the vaccine is used, AEs, efficacy, and everything else they can.

Motion/Vote #3: Preference for HZ/su Vaccine Over ZVL (Zostavax®)

Dr. Hunter moved to vote on the preferential recommendation for HZ/su vaccine over ZVL (Zostavax®) for the prevention of HZ and related complications. Dr. Romero seconded the motion. There were 8 affirmative votes to make a preferential recommendation, 7 votes not to make a preferential recommendation, and 0 abstentions. The disposition of the vote was as follows:

- 8 Favored Preferential Recommendation:** Belongia, Bennett, Kempe, Lee, Moore, Reingold, Stephens, Szilagyi
7 Opposed Preferential Recommendation: Atmar, Ezeanolue, Hunter, Pellegrini, Riley, Romero, Walter
0 Abstained: N/A

Those opposed were offered an opportunity to further comment on their dissent. Dr. Walter cited potential longer-term safety and supply issues; Dr. Ezeanolue thought they should wait a year to accumulate more information, particularly since there is no head-to-head comparison of the two vaccines; and Dr. Riley would like to see safety data on a larger population that is not just research-based, especially because there are very little data on ethnic minorities.

Dr. Riley clarified that she inadvertently voted “no” for Motion/Vote #1 thinking that it pertained to the preferential recommendation for HZ/su vaccine over ZVL (Zostavax®) for the prevention of HZ and related complications. It was her intent to vote affirmatively for Motion/Vote #1 HZ/su vaccine for the prevention of HZ and related complications for immunocompetent adults aged 50 years and older.

Hepatitis Vaccines

Introduction

Art Reingold, MD Hepatitis Vaccines Work Group

Dr. Reingold offered his personal congratulations to Dr. Plotkin, stressing that he would certainly be missed at future meetings.

He reminded everyone that the Hepatitis WG terms of reference currently are to:

- Update ACIP recommendations for hepatitis A vaccine use:
 - ACIP Routine Recommendation for Hepatitis A Vaccine
MMWR 2006 May 19;55(RR-7):1-23

- Update: Prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the ACIP.
MMWR 2007 Oct 19;56(41):1080-4
- Updated recommendations from the ACIP for use of hepatitis A vaccine in close contacts of newly arriving international adoptees
MMWR 2009 Sep 18;58(36):1006-7

- Evaluate HEPLISAV-B™ efficacy and safety

WG considerations between July 2017 and October 2017 have included HepA routine vaccination, HepA post-exposure prophylaxis (PEP), HepA vaccination of international travelers, HepA vaccination of pregnant women, HepA outbreaks (homeless as a risk group for HepA), and HEPLISAV-B™ efficacy and safety.

Presentations for this session focused on the following:

- Dynavax HEPLISAV-B™
- WG considerations: HEPLISAV-B™
- HAV outbreaks

In terms of next steps, the WG ultimately plans to present the full updated HepA vaccine statement for a vote and will continue deliberations on adult HepB vaccination, including a GRADE evaluation of HEPLISAV-B™.

HEPLISAV-B™

Robert Janssen, MD
Chief Medical Officer
Dynavax Technologies Corporation

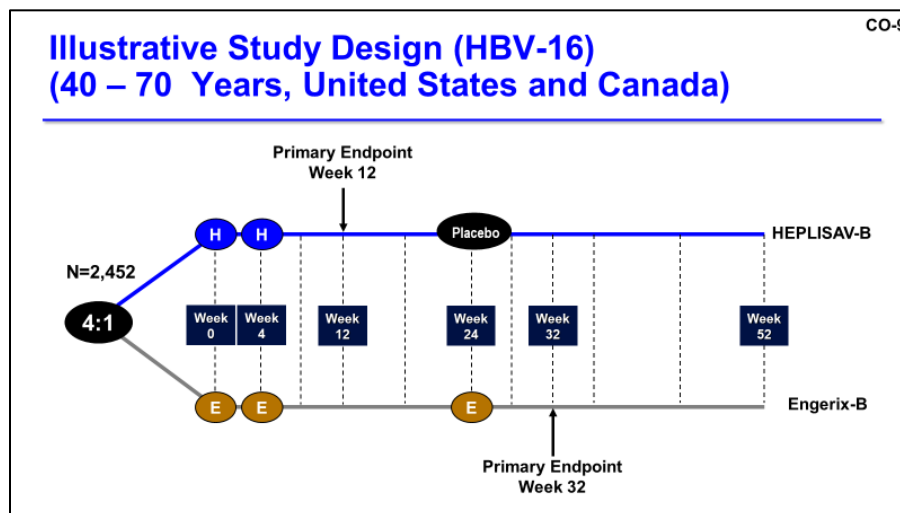
Dr. Janssen presented Dynavax Technologies Corporation's data on HEPLISAV-B™ during this session, which he indicated provides significantly higher and earlier protection among adults against HBV compared with an existing vaccine using fewer doses and with an acceptable safety profile. Like the currently approved HepB vaccines, HEPLISAV-B™ contains a yeast-derived recombinant hepatitis B surface antigen (HBsAg). The HBsAg in HEPLISAV-B™ is produced in *hansenula polymorpha*. Over a billion doses of this antigen have been administered worldwide. The major difference is in the adjuvant. HEPLISAV-B™ uses a Toll-like receptor 9 (TLR9) agonist that Dynavax calls "1018;" whereas, the currently licensed vaccines use aluminum salts. HEPLISAV-B™ is a sterile liquid dosage form supplied in half mL dose vials and contains 20 micrograms of HBsAg and 3 milligrams of 1018. It is administered in a 2-dose series 1 month apart by intramuscular injection (IM) compared with a 3-dose series over 6 months.

The adjuvant, 1018, is a small synthetic single-stranded oligonucleotide with specific CpG sequence motifs that mimic the natural innate immune response to bacterial and viral deoxyribonucleic acid (DNA). This innate response activates antigen-presenting dendritic cells, leading to enhanced B- and T-cell responses to co-administered vaccine antigens. The actions of 1018 are mediated by its interaction with a well-defined and highly specific receptor, TLR9, that is primarily expressed by plasmacytoid dendritic cells. The proposed indication for HEPLISAV-B™ is for active immunization against infection caused by all known subtypes of

HepB virus in adults 18 years of age and older. The Prescription Drug User Fee Act (PDUFA) action date is November 9, 2017.

The immunogenicity results for HEPLISAV-B™ are based on Dynavax's three pivotal, Phase 3 trials: HBV-10, HBV-16, and HBV-23. In each of these trials, different randomization ratios were used ranging from 2-to-1 to 4-to-1. The 3 trials shared common design features. All three trials were observer-blinded, randomized, active controlled, and multi-center. Trial participants could not have evidence of current or previous HepB infection, and could not have received a HepB vaccine prior to enrollment in the trial. Persons with human immunodeficiency virus (HIV), or immunosuppression, or a history of autoimmune disease were not eligible for the trial. The demonstration of seroprotection (% with anti-HBs ≥ 10 mIU/mL, the surrogate of protection for HepB) was based on head-to-head comparisons with Enderix-B®. Lastly, concentrations of antibodies to HBsAg were measured using an approved commercial assay.

All trials were designed and powered for the primary endpoint to demonstrate the non-inferiority of the seroprotection rate (SPR) of HEPLISAV-B™ compared with Enderix-B®. The non-inferiority criterion was met if the lower bound of the 95% confidence interval of the difference in SPRs was above -10%. A statistically significantly higher SPR was achieved if the lower bound of the confidence interval was greater than zero. The per-protocol population was used in these analyses. The following diagram is illustrative of the study design for the pivotal trials:



HBV-16 compared the immunogenicity and safety among healthy adults 40 to 70 years of age in the US and Canada, with 2452 adults randomized in a 4:1 ratio to receive HEPLISAV-B™ or Enderix-B® and were followed for 52 weeks after the first injection. Demographics within the 3 studies were balanced between treatment groups and were not expected to affect immunogenicity results. Across the studies, the average age varied from 40 years in HBV-10 to 54 years in HBV-16. In HBV-23, a higher proportion of subjects than in the other studies were of Black race or were obese.

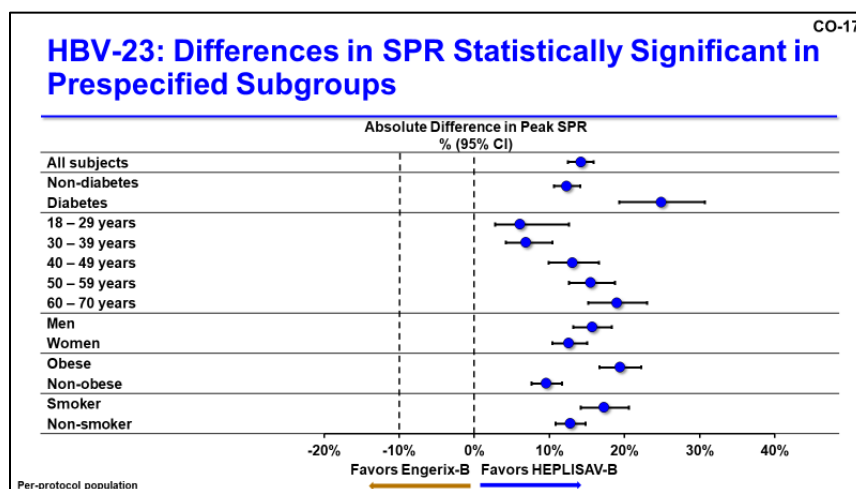
In HBV-10, the primary endpoint was met. The SPR in the HEPLISAV-B™ group was non-inferior to that in the Enderix-B® group and was statistically significantly higher. The SPR in the HEPLISAV-B™ group at Week 12 was 95.0% and in the Enderix-B® group at Week 28 was 81.2%. The difference between SPRs was 13.7%, with the lower bound of the 95% confidence interval of 10.4%. In a post-hoc analysis, the peak SPR within the trial occurred at Week 24 in

the HEPLISAV-B™ group and was significantly higher than the peak SPR in the Enderix-B® group, which occurred at Week 28. It is also important to note that HEPLISAV-B™ achieved the same SPR much earlier at week 8 than Enderix-B® achieved at week 28.

Similar to HBV-10, HBV-16 met its primary endpoint, demonstrating that seroprotection with HEPLISAV-B™ is non-inferior to that of Enderix-B®. In HBV-16, the SPR in the HEPLISAV-B™ group at Week 12 was 90.1% and in the Enderix-B® group at Week 32 was 70.5%. The difference between SPRs was 19.6% with the lower bound of the 95% confidence interval of 14.7%. Additionally, HEPLISAV-B™ achieved its key secondary endpoint of a statistically significantly higher SPR. Similar to HBV-10, in a post-hoc analysis, the peak SPR induced by HEPLISAV-B™ was significantly higher than the peak SPR induced by Enderix-B®. Again, HEPLISAV-B™ achieved the same SPR much earlier, at week 8, compared with week 28 for Enderix-B®.

HBV-23 also met its primary endpoint, demonstrating that seroprotection with HEPLISAV-B™ is non-inferior and statistically significantly higher than Enderix-B® in adults with type 2 diabetes. In this population, the SPR in the HEPLISAV-B™ group at Week 28 was 90% and in the Enderix-B® group at Week 28 was 65.1%. The difference between SPRs was 24.9% with the lower bound of the 95% confidence interval of 19.3%. In terms of the results of the secondary endpoints, seroprotection for HEPLISAV-B™ was higher than Enderix-B® in the total population and across a variety of prespecified subpopulations including in all age groups, from 100% versus 93.9% in the youngest adults to 91.6% versus 72.6% in the oldest group. Overall, the SPR in each of these prespecified sub-populations is consistently greater than 90% in the HEPLISAV-B™ group and was more variable in the Enderix-B® group.

Differences in seroprotection for HEPLISAV-B™ were also statistically significant in all of these prespecified subgroups compared with Enderix-B®. This forest plot shows the point estimates and 95% confidence intervals of the differences of the SPR described above. The vertical line at -10% is indicative of noninferiority and the vertical line at 0 is indicative of statistical significance:



The largest differences between HEPLISAV-B™ and Engerix-B® are in populations that previously have been reported to have reduced seroprotection from alum adjuvanted vaccines. However, the seroprotection rates are significantly higher in HEPLISAV-B™ recipients in all pre-specified subgroups. In summary, HEPLISAV-B met its primary and secondary endpoints in each study with higher SPRs early, at peak, and in all adult subpopulations.

Dr. Janssen presented Dynavax's safety data using 3 populations: HBV-10 and HBV-16 (N=3778), HBV-23 (N=5587), and Primary Safety Population (PSP) (HBV-10, HBV-16, HBV-23) (N=9365). It is important to remember when looking at the results, particularly in terms of numerator data, that none of the trials were randomized 1-to-1. The safety populations for HBV-10 and HBV-16 are used to show solicited reactogenicity results and unsolicited AEs. The safety population for HBV-23 will be used to show unsolicited medically attended AEs; that is, events for which subjects sought medical care. The PSP comprises adults 18 to 70 years of age in the 3 pivotal trials. The subject allocation ratio in this SPS is 2.4 to 1. This is used to evaluate deaths, SAEs, and immune-mediated AEs.

In terms of reactogenicity and AEs, around 55% of subjects in both vaccine groups had a solicited post-injection reaction or unsolicited AE. In HBV-23, the proportion of subjects who experienced a medically attended AE was balanced between the groups. HEPLISAV-B™ was generally well-tolerated with no cases of vaccine-associated anaphylaxis or other serious post-injection reactions (PIRs). Most solicited PIRs were mild or moderate in severity, self-limited, and resolved within 7 days after injection. In this analysis following all active injections, the frequencies of local post-injection reactions overall were balanced between the treatment groups. The most frequent local reaction in both treatment groups was injection site pain. In the HEPLISAV-B™ group, 32% of subjects had a systemic PIR compared with 37% of subjects who received Engerix-B®. The most frequent systemic reactions in both treatment groups were fatigue and headache, followed by malaise. With both vaccines, there was decreasing reactogenicity with subsequent doses.

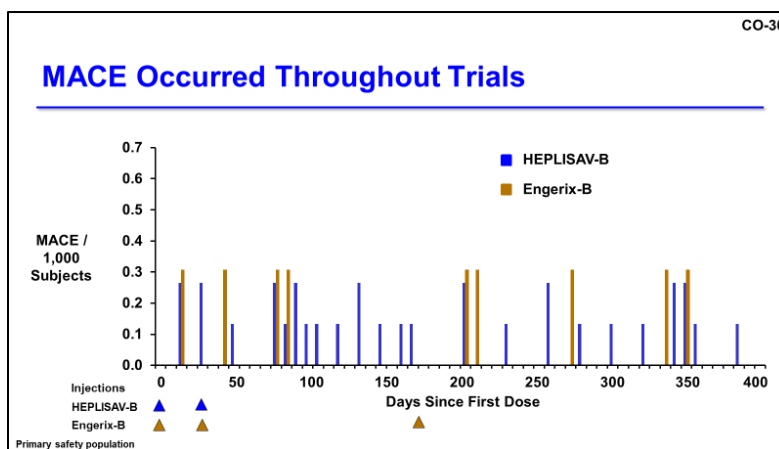
Overall in the PSP, deaths occurred in 0.28% of the HEPLISAV-B™ group and 0.21% of the Engerix-B® group. The only imbalance in causes of death was death due to illicit or therapeutic drug overdose with a higher frequency in the HEPLISAV-B™ group. SAEs were 4.8% in each vaccine group. Immune-mediated events occurred in 0.20% of the HEPLISAV-B™ group and 0.13% of the Engerix-B® group. In the PSP, the percentage of subjects reporting any SAE was similar in both groups. While SAEs were generally similar between the HEPLISAV-B™ and Engerix-B® groups, Dr. Janssen highlighted two notable imbalances. A higher proportion of HEPLISAV-B™ recipients than Engerix-B® recipients experienced an SAE of acute myocardial infarction (AMI) and a higher proportion of Engerix-B® recipients experienced an SAE of prostate cancer. The magnitude of the differences between treatment groups for these 2 events was similar, but in opposite directions. These are typical examples of observing unexpected post-hoc safety findings in a large database with over 1400 AE preferred terms.

Looking more closely at the numerical imbalance in AMIs in the individual trials, a numerical imbalance in safety events was identified in HBV-23 that were coded to the single Medical Dictionary for Regulatory Activities (MedDRA) preferred term of "acute myocardial infarction." However, in HBV-16, the same difference was not observed between groups. In fact, while the numbers were small, there was a lower proportion of subjects in the HEPLISAV-B™ group than in the Engerix-B® group who had an acute MI. There were no MIs in HBV-10, which enrolled a younger population than HBV-16 or HBV-23. The numerical imbalance in acute MI in HBV-23 was unexpected, given that there was nothing in the medical literature and nothing in Dynavax's preclinical or previous clinical studies that indicated myocardial infarction was a concern.

Because of the medical importance of the preferred term, this observation was thoroughly investigated. To explore the AMI imbalance observed in HBV-23, a typical analysis for cardiovascular (CV) outcomes was conducted. First, the investigators identified and had performed post-hoc, blinded adjudication of all potential atherosclerotic CV events that are included in the gold-standard composite outcome used in most atherosclerotic disease trials referred to as Major Adverse Cardiovascular Events (MACE). This entails analysis of the composite 3-point MACE outcome and each of its components, comprising time to the first event of death due to CV cause, non-fatal myocardial infarction, or non-fatal stroke. They then evaluated in whom the events occurred, at what rate they occurred, and when they occurred during the trials. In terms of the CV events confirmed by adjudication, 0.33% of subjects in the HEPLISAV-B™ group and 0.21% of subjects in the Engerix-B® group had adjudication-confirmed MACE outcomes. The incidence of CV death and non-fatal stroke were similar between the vaccine groups. The difference between groups was only seen in MI. If the difference in MI observed in HBV-23 was caused by HEPLISAV-B™, then one would expect to see differences across the spectrum of atherosclerotic CV disease outcomes such as CV death and stroke, which is not the case here. Analyses of the composite and component outcomes each yield 95% confidence intervals that include 1.

The CV risk profiles of patients with reported MACE outcomes were then assessed. Overall, CV risk factors were balanced between the two vaccine groups in the PSP. MACE outcomes were reported in subjects who were on average 10 years older than the overall cohort, with about twice the prevalence of hypertension, diabetes, and hyperlipidemia. In fact, most subjects who had a MACE event had 2 or more CV risk factors. In addition, cardiac catheterization in the majority of cases of MI showed multi-vessel, obstructive coronary artery disease. Thus, MACE outcomes occurred in persons expected to have them. The expected incidence of CV events was then estimated based on age, sex, and race, comparing observed versus expected event rates. In each comparison, the observed incidence rate per 1000 person years of follow-up in the HEPLISAV-B™ group was similar to or lower than predicted. The expected rate of MI in the studies was 2.6/1000 person years. It was 2.4 in the HEPLISAV-B™ group but only 0.7 in the Engerix-B® group, which was nearly 4-fold lower than expected. In HBV-23, it was nearly 7-fold lower than expected. Thus, MACE and MI events in the HEPLISAV-B™ group occurred at rates similar to or below expected.

This epidemic curve shows the timing of occurrence of MACE events in the PSP, presented as incidence per 1000 subjects to account for the 2.4:1 subject allocation ratio. The triangles along the horizontal axis reflect timing of vaccine administration:



MACE outcomes occurred over the entire duration of the trials, without clear evidence of clustering of events. Importantly, events in the HEPLISAV-B™ and Engerix-B® groups were similar between the groups shortly after each vaccination. The imbalance of MACE events only begins to emerge at study day 100 and beyond, with events occurring well beyond day 300 in both groups.

In conclusion, a thorough investigation was conducted of the CV events observed in the HEPLISAV-B™ program. A biologically plausible explanation was not identified for the imbalance in acute MI observed in HBV-23. The imbalance was observed only in one trial. MIs occurred in subjects in whom such events were expected at rates similar to expected with catheterization results showing typical events. There was no temporal association of events with vaccine administration. Thus, Dynavax believes that the imbalance is most likely due to random variation in the context of very small numbers of subjects having reported events when analyzing more than 1400 AE terms. Nonetheless, Dynavax will be conducting a post-marketing study to more definitively exclude any CV risk with HEPLISAV-B™.

Regarding immune-mediated events, the most frequent new-onset immune mediated event in the PSP was Bell's palsy, occurring in 0.06% of the HEPLISAV-B™ group and 0.05% of the Engerix-B® group. The only other event that occurred in more than 1 HEPLISAV-B™ subject was hypothyroidism. One of those events occurred in a subject who had papillary thyroid carcinoma (PTC). A variety of other immune-mediated events occurred in each group. They occurred in 1 subject each and were quite diverse, both in the time of onset as well as in their principal mechanisms of pathogenesis.

In the PSP that had a subject ratio of 2.4 to 1, rare, serious immune-mediated AEs were balanced with 3 in the HEPLISAV-B™ group and 1 in the Engerix-B® group. In the HEPLISAV-B™ group, 1 event of granulomatosis with polyangiitis occurred. The event of Guillain-Barré Syndrome (GBS) occurred more than 3.5 months after the last HEPLISAV-B™ dose and 5 days after an influenza vaccination. The event of Cavernous sinus syndrome, thought to be the inflammatory condition of Tolosa-Hunt Syndrome (THS) but not confirmed radiologically, occurred 8.5 months after the last HEPLISAV-B™ injection. In the Engerix-B® group, one rare, serious immune-mediated AE of microscopic polyangiitis, an anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis was reported.

Finally, as part of the immune-mediated disease assessment, similar autoantibody development was observed in HEPLISAV-B™ recipients compared with Engerix-B® recipients. ANCA testing was performed retrospectively because of the event of Granulomatosis with Polyangiitis in a HEPLISAV-B™ participant in HBV-10. More than 2500 subjects were evaluated and there were no confirmed positive results, other than the previously mentioned ANCA-positive vasculitis cases that occurred in each arm. Anti-nuclear antibody (ANA) testing was performed in several trials prospectively, with 5.5% HEPLISAV-B™ and 5.1% Engerix-B® recipients developing antibodies during a trial. Anti-double-stranded DNA (anti-dsDNA) testing was performed as a protocol-specified assessment similarly to ANA, with 1.2% of HEPLISAV-B™ and 1.0% of Engerix-B® recipients developing such antibodies. In HBV-23, development of antiphospholipid antibodies (APLA) was evaluated in 309 subjects. There was no difference in most of these antibodies, including anti-cardiolipin and lupus anticoagulant. The proportion of subjects who developed elevated anti-beta-2 glycoprotein 1 IgM levels was higher in the HEPLISAV-B™ group than in the Engerix-B® group only at Week 8. Isolated elevation of anti-beta-2 glycoprotein 1 IgM has not been associated with thrombotic events in the literature or in this study.

The safety data in more than 13,000 adults show that HEPLISAV-B™ is well-tolerated with an overall similar safety profile to an existing HepB vaccine. Rates of PIRs, AEs, and medically attended AEs were largely balanced between the HEPLISAV-B™ and Engerix-B® groups. The overall SAE rate was similar for the two arms, with imbalances in individual terms in both directions including acute MI for HEPLISAV-B™ and prostate cancer for Engerix-B®. Comprehensive analyses of all new-onset immune-mediated event rates were also balanced with the Engerix-B® group, with no increase in any specific condition. Autoantibodies were also similar between the groups.

Dynavax's post-marketing surveillance studies will be conducted by Kaiser Permanente Health care systems in both the Southern and Northern California regions. In these retrospective electronic medical record (EMR) analyses, acute MI and immune-mediated events will be analyzed specifically. For acute MI, 25,000 patients will be analyzed who receive HEPLISAV-B™ compared with a similar number of patients who receive another hepatitis B vaccine in the Kaiser Southern region. In this acute MI study, a non-randomized cluster design will be used where some facilities will use HEPLISAV-B exclusively and others will use Engerix-B® exclusively. For immune-mediated events, the 25,000 patients who receive HEPLISAV-B™ in the Kaiser Southern region and an additional 5,000 patients from the Northern region will be evaluated, and will be compared with a similar number of patients who receive another HepB vaccine.

In conclusion, HEPLISAV-B™ induces high rates of seroprotection in all adults, including populations with reduced response to current vaccines. Compared with Engerix-B®, HEPLISAV-B™ provides earlier seroprotection with a similar safety profile. HEPLISAV-B™ should increase adherence with a 2-dose schedule over 1 month. Dynavax believes that HEPLISAV-B™ can play an important role in helping to meet the National Academy of Sciences (NAS) goal of eliminating HepB as a public health problem by 2030.

Considerations for Use of HEPLISAV-B in Adults

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During this session, Dr. Nelson discussed the summary data reviewed by the WG for the use of HEPLISAV-B™ in adults, including: epidemiology and burden of HepB in adults, adult HepB vaccination coverage, HEPLISAV-B™ immunogenicity, HEPLISAV-B™ safety, and cost-effectiveness; and the policy options and WG considerations.

Adults recommended to receive HepB vaccination include the following:

- Household contacts of HBsAg-positive persons
- Persons with sexual risk factors:
 - Sexual contact of HBsAg-positive persons
 - Multiple partners
 - Persons seeking evaluation for a sexually-transmitted infections
 - Men who have sex with men (MSM)

Other

- Injection drug users
- Residents and staff of facilities for developmentally-disabled persons
- Healthcare and public safety personnel
- Hemodialysis patients and persons with end-stage renal disease
- International travelers to regions with high or intermediate HBV endemicity ($\geq 2\%$)
- Persons with chronic liver disease (CLD), including HepC virus
- Persons with HIV infection
- Adults with diabetes mellitus*

[Mast EE, et al.; *MMWR* Recomm Rep. 2006 Dec 8;55(RR-16); *Murphy TM, et al.; *MMWR* 2011 Dec 23;60(50):1709-11].

Vaccination has been very successful in the US. Vaccine was first introduced for high-risk groups in 1982, and in 1984 for infants born to HBsAg-positive mothers. The estimated number of new HepB virus (HBV) infections in 2015 was 21,900—a sharp decrease from almost 300,000 in the 1980s. From 2000 through 2015, the incidence of HBV cases reported in the US was consistently highest among the 30 through 39-year age group and lowest among the 0 through 19-year age group. From 2014 through 2015, the incidence of HBV cases reported in the US increased for persons in each of the age groups, except among those in the 0 through 19-year age group. In 2015, rates were highest for persons aged 30 through 39 years at 2.6 cases/100,000 population, while the lowest rates were among children and adolescents aged <19 years at 0.0 cases/100,000 population [Source: National Notifiable Diseases Surveillance System (NNDSS)].

Overall HepB vaccine coverage for ≥ 3 doses among adults 19 years of age and older in 2014 was 24.6%. Coverage was 31.6% among travelers, 27.4% among persons with chronic liver conditions, 64.7% among healthcare personnel (HCP), 24.4% among persons with diabetes aged 19 through 59 years, and 12.6% among persons with diabetes aged 60 years and above [National Health Interview Survey (NHIS) — United States, 2015; *MMWR* Surveill Summ. 2017 May 5;66(11):1-28].

To improve HepB vaccination of high risk adults, CDC funded 14 local and state health departments (Alabama, Chicago, Florida, Kentucky, Louisiana, Maryland, Michigan, Nevada, New York City, Oregon, San Antonio, Tennessee, Virginia, West Virginia) to implement HepB vaccination programs. Awardees provided CDC with standardized reports regarding vaccination activities, high-risk settings, partners, doses administered, 3-dose series completion, and program challenges and successes. From September 2012 through September 2015, 161,171 HepB vaccine doses were distributed and 139,110 doses (86.3%) were administered in 459 settings, including correctional facilities. Challenges included incorporating vaccination services and tracking vaccine doses administered in settings without dedicated vaccination staff. Of the 14 awardees, 6 were able to track dose series (Chicago, Michigan, Maryland, New York City, Oregon, San Antonio). Series completion is shown in the following table and illustrates that vaccine completion is low even when it is distributed to high-risk settings:

Dose	Total Doses Given	Range of percent receiving HepB series among those received 1 st dose	Average percent receiving HepB series among those received 1 st dose
1st dose	29,457	--	--
2nd dose	11,897	18.5% - 67.6%	40.4%
3rd dose	6,557	6.2% - 46.1%	22.3%

[Watson, et al. 2017 National Adult and Influenza Immunization Summit Posters.

https://www.izsummitpartners.org/content/uploads/2017/05/14-1_Watson_Hepatitis-B-Vx-Prog-Implementation-in-Settings.pdf].

Another study assessing compliance with multi-dose vaccine schedules among older children, adolescents, and adults using data from the VSD showed that 41.4% to 62.2% of persons completed the 3-dose series within 1 year of the first dose, 2.8% to 4.9% completed the 3-dose series 1 to 2 years after the first dose, and 2.0% to 4.6% completed 3-dose series more than 2 years after the first dose. Among persons who did not complete the 3-dose series, 15.1% to 25.7% received 1 dose and 12.5% to 21.2% received 2 doses, again showing the challenges in series completion [Nelson JC, et al. Compliance with multiple-dose vaccine schedules among older children, adolescents, and adults: results from a vaccine safety datalink study. *Am J Public Health*. 2009 Oct;99 Suppl 2:S389-97].

A cost-effectiveness study was conducted by Dynavax in 2013. The study shows that HEPLISAV-B™ has a favorable cost-effectiveness profile, with ICERs of less than \$25,000 across all populations studied. The ICERs were \$12,613 for patients with diabetes, \$11,062 for HCP, and \$5,564 for travelers. The cost of vaccine, regimen completion rates, and seroprotection rates were the sensitive variables in the models [Kuan RK, Janssen R, Heyward W, Bennett S, Nordyke R. Cost-effectiveness of hepatitis B vaccination using HEPLISAV™ in selected adult populations compared to Engerix-B® vaccine. *Vaccine*. 2013 Aug 20;31(37):4024-32].

The limitations of existing HepB vaccines is that they require 3 doses administered over 6 months, with a minimum interval between dose 1 and 3 of 16 weeks. In addition, there is reduced seroprotection in some populations: Diabetes ($\geq 90\%$ for aged ≤ 40 years; $< 40\%$ for aged ≥ 70 yrs)¹, renal disease (77% hemodialysis patients)², immunosuppressed persons, obese persons, the elderly, and smokers [1Murphy TM, et al.; *MMWR* 2011 Dec 23;60(1709-1811); ²Cordova E, et al; *Ann Ig* 2017;29(27-37)].

During their deliberations, the WG considered compelling evidence for HEPLISAV-B™ immunogenicity based on the data presented by Dr. Janssen, administration benefits of 2-dose over 1 month compared to the current 3 doses over 6 months, favorable cost-effectiveness based on the 2013 study by Dynavax, and the need for post-marketing CV surveillance to address major adverse cardiac event findings as presented by Dr. Janssen. The WG determined the pros of HEPLISAV-B™ to be its increased immunogenicity, particularly in high-risk populations; administration with a 2-dose series over 1 month; and the potential for increased series completion with the 2 doses over 1 month. The cons are that acute MI was reported in a higher proportion of HEPLISAV-B™ than Engerix-B® recipients in one study [<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM568489.pdf>].

The proposed policy option language for HEPLISAV-B™ if it is licensed is: “HEPLISAV-B™ vaccine may be used for adults ≥18 years of age on a 2-dose schedule over 1 month.”

The WG summary is that HEPLISAV-B™ results in high levels of seroprotection, including among populations with reduced immunogenicity to HepB vaccination. The HEPLISAV-B™ vaccine series consisting of 2 doses administered over 1 month will likely improve coverage for series completion. Most safety outcomes are balanced between HEPLISAV-B™ and the comparator vaccine. In the HBV-23 study, acute MI was reported in a higher proportion of HEPLISAV-B™ than Engerix-B® recipients. Safety will be monitored in post-marketing studies.

Discussion Points

Referring to Dr. Janssen's Slide 16, Dr. Riley noted that everything is reported except race/ethnicity. This was brought up in the demographics, so clearly there are data. She requested that he comment on why this was not included, and whether there are any data on pregnancies or inadvertent pregnancies.

Dr. Janssen replied that they did not present the race/ethnicity data because race was not pre-specified, given that race has not been associated with reduced responsiveness to HepB vaccine. There are similar results among blacks, whites, and Hispanics/Latinos. In Asians, Native Americans, and Pacific Islanders, there were much smaller numbers. HEPLISAV-B™ was non-inferior, but was not statistically significantly higher in these groups. There was very little pregnancy data, given that women were not supposed to be pregnant. There were 40 pregnancies in the HEPLISAV-B™ group and 20 in the Engerix-B®, and the outcomes were very similar.

Dr. Atmar noted that Dr. Janssen showed that the seroprotection rates continued to increase in the HEPLISAV-B™ group beyond Week 12 and the peak was at Week 24. Some of the geometric mean concentration (GMC) data that have been published show a steady increase to that point. He asked Dr. Janssen to explain why this happens. This pertains to the issue of timing for safety events. If something is going on related to the vaccination and ongoing immune responses, it makes it tougher to judge later events that occur, though the balance is reassuring.

Dr. Janssen replied that this is challenging, and they do not honestly know. They do not have data to explain it. Most of the increase occurs within 4 to 8 weeks, as would be expected and is seen with most vaccines. Dynavax is unable to explain why that continues to increase. They did conduct a systems biology study in which the immune modules assessed were increased clearly through 28 days after the second dose, so through 56 days, and they all had returned to baseline by 28 days after that. The only long-term outcome is antibody development to HBsAg. There is no evidence that there is ongoing immune activation.

Dr. Plotkin (Vaccine Consultant) reported a COI in that he is a member of the Dynavax board. He indicated that he joined the board because this is an adjuvanted vaccine with TLR9 agonist. More broadly, he recently attended a meeting on the immunology of vaccines in the future. Adjuvants are the future, and they are facing the development of vaccines that are difficult because of the biology of the disease. It will be necessary to use more adjuvants in order to develop effective vaccines. There is a TLR4 agonist license for HPV. The AS01B is in a way a more complicated TLR4 and lipid adjuvant. HEPLISAV-B™ has a TLR9 adjuvant. The numbers are up to 10 and, in the future, ACIP is going to have to deal with more adjuvanted

vaccines because they are clearly going to be needed for high effectiveness as in the case of hepatitis. HEPLISAV-B™, for obvious reasons, is designated for adults who respond poorly. But there may be an application beyond the US in infants born to mothers who are HepB positive. Unfortunately, there are failures in that group. This vaccine might actually be a good vaccine to solve that problem.

It was not clear to Dr. Duchin, in the unexpected acute MI patients, what the age range was of people who experienced that complication. It appeared to be as low as the 30s, and he wondered if there was an unusual distribution of young patients. He also inquired as to whether this vaccine has been used in people who failed to respond to Enderix-B® in one or two series previously.

Dr. Janssen responded that there was one 39-year-old who actually had a previous stroke in the same region as a vascular malformation, not an MI. All of the people who had an MI had at least one risk factor, and many of them had three or more risk factors. The vaccine has not been used in patients who failed to respond to Enderix-B® in numbers Dr. Janssen was willing to talk about (N=19).

Given that thrombosis plays a role in MI, Dr. Belongia asked whether there is any biological reason to expect that the TLR9 adjuvant has an effect on platelets, and related to that whether they assessed other evidence of coagulation or clotting disorder and if there was imbalance there.

Dr. Janssen responded that there was in previous studies. The reasons they conducted the antiphospholipid study in HBV-23 is that in HBV-10 and HBV-16, there were 5 pulmonary embolisms in the HEPLISAV-B™ group and none in the Enderix-B® group. But it is important to remember that those were randomized 4:1 and 3:1. Because of that, they assessed antiphospholipid antibodies thinking that if there is a likely explanation, it potentially would be autoimmune. In toxicology studies, at 60-fold the dose that is used in humans, 1018 does not cause thrombosis. It would cause the opposite. They looked at thrombosis very carefully specifically because of the MI concern, and they did not see anything to suggest that that's true.

Dr. Schaffner (NFID) reminded everyone that for many years, he has been trying to persuade ACIP to be more assertive in expanding the recommendations for the use of HepB vaccine in order to achieve the goal of the interruption of the transmission of this virus in the population. Apropos of the anticipated licensure of this vaccine, looking back at some of the recommendations, people with diabetes are recommended routinely to receive this vaccine up to age 60. Beyond age 60, it is at the discretion of the physician. That was really driven because the vaccines available then were less effective in that older population. HEPLISAV-B™ appears to be quite effective in that population. He asked whether the WG had begun to consider broadening and making that recommendation stronger for the immunization of people with diabetes older than 60 years of age with this vaccine. In that context, given the nice data Dr. Nelson showed regarding the occurrence of HepB in the US population and the recent increases in populations, he wondered if the WG had considered increasing the universal recommendation to some other age, such as age 40 or age 50.

Dr. Nelson replied that the WG has had preliminary discussions on the topic of universal HepB vaccination based on the discussions that came out of the ACIP meeting a year ago when the HepB statement was presented. However, those discussions have not progressed to the point of discussing diabetes any further in terms of a more aggressive vaccine recommendation.

Referring to Dr. Nelson's slides regarding the completion of first and second doses as it applies to a more general recommendation of a vaccine for adults, Dr. Hunter said his understanding from slide 7 is that these were not free-ranging adults who were waiting to be selected by clinicians to be recommended for any particular vaccine. Instead, it seemed that they were in other programs, were already selected out due to high-risk situations, and had some case management perhaps by public health nurses. If ACIP was going to consider recommendations for clinicians taking care of diabetics 30 to 70 years of age, the completion rates would not necessarily apply to that group because the study was in high-risk settings such as drug treatment centers, correctional facilities, special pilot programs with follow-up, et cetera.

Dr. Weinbaum (ISD) responded that in this project, vaccine was provided to a variety of venues that saw people who were at behavioral risk for HepB. The programs did not have any additional infrastructure with which to implement this project, so they did not have dedicated public health nurses or any additional resources to follow-up with doses 2 and 3. It is true that these rates of receipt of doses 2 and 3 do not represent the general population. They certainly would not represent the follow-up that would be expected for somebody in routine medical care with a primary care physician (PCP) following them on a regular basis.

Dr. Romero asked Dr. Janssen whether consideration had been given to what would happen if someone received HEPLISAV-B™ followed by or concomitantly with influenza or some other vaccine in terms of a boost in their immune response at some later date of another vaccine.

Dr. Janssen responded that they are considering a study looking at co-administration with another vaccine.

Dr. Lee thought it would be great as they think about TLR agonists as adjuvants to have a long-term view on monitoring the safety of vaccines that use these adjuvants. It might be helpful for ACIP to understand where the opportunities are to learn and think about the existing systems that could study this more broadly. Even though Dynavax is conducting a large trial to monitor efficacy and safety, it still may not be large enough.

Dr. Janssen said they feel that the size of the 13-month follow-up study they are now conducting is probably feasible for them. To him, the next step is the VSD.

Dr. Bennett thought this was an excellent suggestion, which aligned with what Dr. Plotkin stated as well.

As one of the states that participated in the local and state health department study, Dr. Moore said that the patients involved in the study are among the most difficult to get immunized. Many of them are in jail, so there were jail-based programs or STD services within public health where there is not routine follow-up expected. In fact, these individuals would be the most at-risk behaviorally and also facing the most challenges for follow-up over a 6-month period of time. She agreed that they are not representative of the general population. There was no additional follow-up to track them down and the numbers reflect the challenges of those vulnerable populations. As a member of the WG, she expressed her hope that as there are different vaccines with different performance and opportunities to do better at preventing disease in this age group, they re-examine the recommendations and consider age-based recommendations.

As a member of the NAS committee that issued the report on elimination of HepB and C in the US, Dr. Reingold indicated that they certainly urged that much greater efforts be made to vaccinate high-risk population. To the extent that this new vaccine can be helpful with that, it would certainly help advance the goals of that IOM report.

Dr. Sun (FDA) noted that Dr. Nelson reported that the current rate of new onset HepB in the US in the young adult population is the highest in the 30 to 39-year age group. He asked what is known about those cases and how many of them are actually vaccine failures versus never vaccinated.

Dr. Nelson responded that they do not have information on vaccine failures, but do know that universal vaccine will reach adults in their 20s, but not necessarily up to ages 30 to 39 or 40 to 49. They are probably unvaccinated, and the increasing intravenous (IV) drug use cases may explain part of that.

Dr. Ward (SME) added that based on the literature, breakthrough infections with HepB among vaccinated populations that lead to clinical disease are extremely rare. There are breakthroughs and core antibody positivity, but hardly ever clinical disease. The rise in acute HepB is among unvaccinated persons.

Hepatitis A Outbreaks

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Dr. Nelson reported that 5 of the 6 largest US HAV outbreaks in the post-vaccine era have occurred in the last 5 years, including 4 since July 2016. CDC has provided technical assistance in 5 large HAV outbreaks since last summer, sending Epidemic Intelligence Service (EIS) officers and staff to the field for 3 of these, most recently to San Diego in the spring. Of the outbreaks, 2 were foodborne associated with foods imported from HAV endemic countries, and 3 were person-to-person transmission. The Division of Viral Hepatitis (DVH) also has been assisting in outbreaks among MSM associated with the current outbreak occurring in Europe. Over 1600 outbreak cases have been reported to CDC in the last 15 months, with the DVH laboratory sequencing over 1400 specimens. To put this in perspective, 459 outbreak cases were reported in the 10 years between 2005 through 2015.

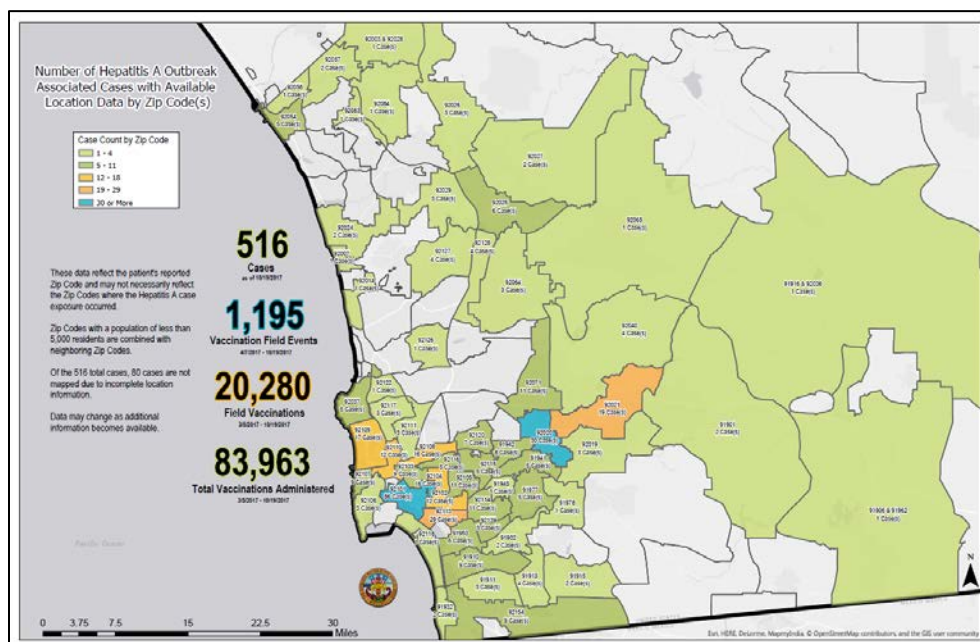
California is currently experiencing the largest person-to-person HepA outbreak not related to a common source or contaminated food product in the US since the HepA vaccine became available in 1996. The number of cases, hospitalizations, and deaths as of October 13, 2017 from the California Department of Health (CDPH) website is shown here:

Table. Outbreak Associated Hepatitis A infections by California Jurisdiction

Jurisdiction	Cases	Hospitalizations	Deaths
San Diego	507	351	19
Santa Cruz	73	33	0
Los Angeles	9	6	0
Other	11	5	0
Total	600	395	19

The majority of the cases are in San Diego with 507 cases, 351 hospitalizations, and 19 deaths. The populations primarily affected have been homeless and/or persons who use injection or non-injection drugs. The HAV genotype in this outbreak is 1B. Since early 2017, the Public Health Services Division in the County of San Diego Health and Human Services Agency (HHSA) has been investigating a local HepA outbreak. On 9/1/2017, San Diego County declared a local public health emergency. As of 10/19/2017, there have been 516 cases, 357 (69.2%) hospitalizations, and 19 (3.7%) deaths. Of the 325 cases with test results available for review, 64 (20%) have chronic HepC infection and 17 (5%) have chronic HepB infection. Based on data available as of 9/1/2017, the epidemic curve is considered stable at this point. San Diego has reported fewer new cases per week over the past two weeks than reported previously, but it is too early to say that this indicates a downward trend in the overall outbreak. The combination of the long incubation period and difficulty contacting much of the case population results in delays in reporting.

The following map shows HAV outbreak cases by Zip Codes as of 10/19/2017 and illustrates the large public health response that has gone into this outbreak:



There have been almost 1200 vaccination field events; over 20,000 field vaccinations, and a total of almost 84,000 vaccines administered.

Cases linked to the California outbreak have also been reported in Utah, Arizona, and Colorado. The outbreak is ongoing in Utah. In Utah, there have been 45 outbreak-associated cases among persons 23 through 69 years of age. Of these, 27 (60%) have been hospitalized and there have been no deaths. The primary risk factors have been homelessness and drug use. In addition, about 15% have been HBV co-infection, 33% have been HCV co-infection, and 13.3% have both.

A completely separate outbreak not linked to the California outbreak is ongoing in Michigan. This outbreak involves transmission by direct person-to-person spread. It is also predominantly genotype 1B. Greater risk of infection is thought to be associated with injection and non-injection drug use, homelessness or transient housing, and incarceration. Data as of 10/18/2017 report 431 cases, including 348 primary cases and 25 secondary cases. Of the primary cases, 348 (~86%) have been hospitalized and 17 (4.2%) have died. The number of deaths in the Michigan and San Diego outbreaks are quite high compared to what has occurred in past outbreaks. Based on the epidemic curve from 8/1/2017 through 10/18/2017, there was an increase in cases. This illustrates an ongoing outbreak of person-to-person spread [http://www.michigan.gov/mdhhs/0,5885,7-339-71550_2955_2976_82305_82310-447907--,00.html].

A separate outbreak in New York City among MSM was recently published in the *Morbidity and Mortality Weekly Report (MMWR)*, with 51 cases reported from January to August 2017. This outbreak was genotype 1A. Of the serum specimens, 24/25 matched strains circulating in Europe among European MSM. Cases are still being reported in New York [Latash J, et al. *MMWR Morb Mortal Wkly Rep* 2017;66:999–1000].

HAV epidemiology has shifted over the years since vaccine introduction. Past outbreaks were associated with asymptomatic children infecting the adults who cared for them and then transmitting infection to other adults. Since vaccine introduction, more cases have occurred among adults who are more susceptible. A large population of adults are not immune to HAV. The prevalence anti-HAV based on National Health and Nutrition Examination Survey (NHANES) data from 2009 to 2010 show overall protection of 26.5%. This is lower in the 30 through 49 age range at about 13.5%, and higher in the age range of ≥ 60 at about 36.9%. Of note based on the same study, protection in children 6 through 11 years of age is at 47%. Therefore, susceptible adults with classic risk-factors who are exposed to contaminated foods or other sources of infections may become infected. Older individuals are more likely to experience severe disease and adverse outcomes as well [Collier M, et al. *Hepatology* 2015., Ly KN, Klevens RM. *J Infect Dis* 2015., Epton E, et al. *Public Health*, 2015., Murphy TV, et al. *MMWR Suppl* 2016. Williams W, et al. 2015. *MMWR Surveill Summ*. 2017 May 5;66(11):1-28.; NHANES, National Health and Nutrition Examination Survey].

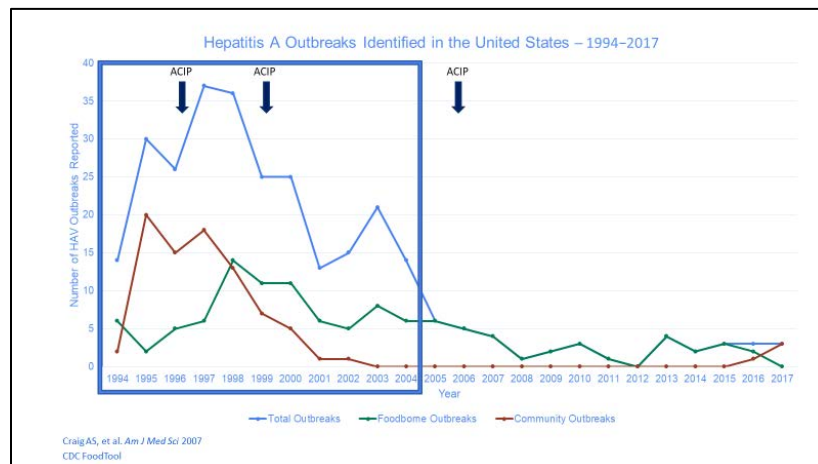
In addition, vaccination uptake among at-risk adults is low, with 2-dose coverage for persons 19 through 49 years of age being 12.3% overall in 2015 and 18.2% among persons with CLD in 2014 according to NHIS data. The overall coverage is about 9% and about 6% for those with CLD based on NHIS data for persons 19 years of age and above without an upper limit.

Another distinctive aspect about recent HepA outbreaks is an apparent shift to a HepA virus genotype previously rarely seen in the US. Historically, of the 7 HepA genotypes, the most common genotype that circulates in North and South America is genotype 1A. The majority of

outbreaks that have occurred in the last 5 years have been associated with genotype 1B. The current outbreak in San Diego is a genotype 1B, but consists of strains that are genetically different from outbreaks of genotype 1B currently seen in Michigan or previous foodborne outbreaks associated with frozen strawberries and frozen pomegranate arils from a few years ago. A 2% to 3% difference in the sequenced region indicates a significant difference in strain.

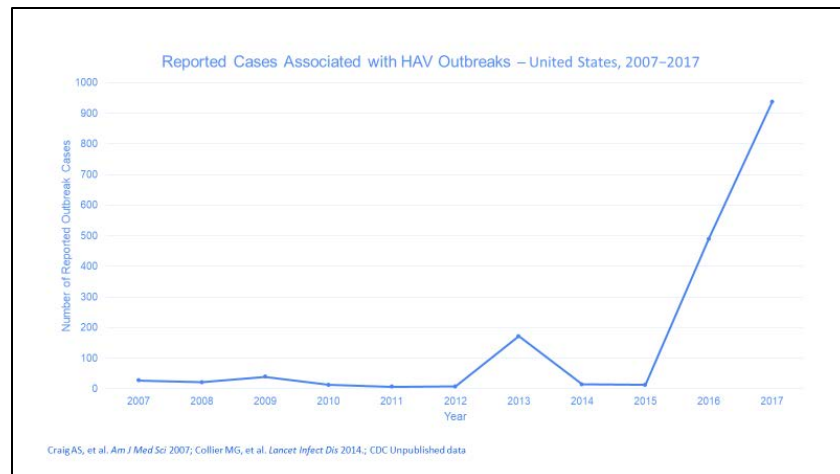
As a reminder, ACIP HepA vaccine recommendations were introduced incrementally. Targeted vaccination in 1996 included children at age 2 years in communities with high rates of disease, and children through teen years in outbreaks. Targeted vaccination in 1999 included 11 states with rates 2 times the national average, and consideration of vaccination in 6 states with rates above the national average. Universal childhood vaccination was recommended in 2006 for children 12 through 23 months of age in all states, with continuation of existing vaccination programs for children 2 through 18 years of age; consideration of catch-up vaccination in outbreaks and areas with increasing disease rates; and vaccination for any person wishing to obtain immunity [MMWR 1996;45(RR-15); MMWR 1999;48(RR-12); MMWR 2006;55(RR-7)].

This graphic shows HAV outbreaks identified in the US from 1994–2017, with arrow depicting ACIP recommendations:



During 1994 through 2004, prior to the universal childhood HepA recommendation, there were 256 HepA outbreaks identified in the US. The number of HepA outbreaks are reported on the vertical axis, years on the horizontal, and total number per year represented by the blue line. When the incremental ACIP recommendation were made are represented by the arrows. During this time, an average of 23 outbreaks per year were recorded, primarily consisting of large community-wide outbreaks associated with person-to-person transmission, shown in red. Over the following decade, 2005 through 2015, only 31 outbreaks were reported. These were mainly associated with contaminated food, an infected food handler, or other foodservice outbreaks, shown in green [Craig AS, et al. Am J Med Sci 2007; CDC FoodTool].

Taking a closer look at the last 10 years, there has been a significant change in the values of the y-axis, which represents the number of individuals infected as part of an outbreak. The x-axis is still years:



2013 was considered a “busy” year with 4 HAV outbreaks reported, with the largest involving over 160 individuals associated with contaminated pomegranate arils from Turkey. A striking increase started last year. Uncertainty exists in the 2016-2017 numbers, but there are probably approximately 200 cases unaccounted for based on the current line. There continues to be an increase in cases.

In light of the ongoing outbreaks of HepA among adults in the US, the demand for adult HepA vaccine has increased substantially over the past 6 months and vaccine supply to meet this unexpected demand in the US has become constrained. Both manufacturers, GSK and Merck, are exploring options to increase domestic supply to address increased demand for the vaccine. Both manufacturers are working collaboratively with CDC to monitor and manage public and private vaccine orders to make the best use of adult HepA vaccine during this period of unexpected increased demand. To address constrained supplies, CDC staff are working directly with public health officials to provide guidance about how best to target vaccine distribution. It is important to note that these constraints do not apply to the pediatric HepA vaccine supply in the US.

In terms of current product availability, Merck’s supply of available HepA vaccine will be intermittent through 2017. Following an outage during part of October, orders are anticipated to ship beginning the week of 10/30/2017. GSK’s pre-filled syringes are currently out of stock, but a limited number of vials are available to order with ordering controls in place. In addition, GSK is maintaining a limited medical reserve and continues to consult with public health officials to help support urgent public health needs. GSK anticipates that a limited resupply of pre-filled syringes will be available in early/mid November 2017. Twinrix®, GSK’s combination HepA/HepB vaccine is currently available for order.

Given the ongoing outbreaks and constrained vaccine supply, Dr. Nelson further discussed the homeless population. Little is known about HepA immunity among homeless populations in the US. Homelessness is not considered an independent risk factor for HAV infection. Older age, duration of homelessness, and injection drug use may indicate HAV immunity [Hennessey KA, et al. *Public Health Reports*. 2009].

The WG has recently considered the question: “Should homeless be included as a HAV risk group for vaccination either for routine vaccination or in outbreak settings?” The WG considered that there is a higher risk for high morbidity and death among homeless, who often have associated co-morbidities and additional risk factors (malnutrition, alcoholism, injection and non-injection drug use) and live in poor hygienic settings, which can result in increased transmission. Routine vaccination in shelters or during emergency department (ED) visits over time may be feasible where implementation is easier compared to outbreaks when vaccine supply is constrained. In addition, the WG has discussed catch-up vaccine and universal HepA vaccination.

Discussion Points

Dr. Stephens asked Dr. Nelson to comment further on the mortality associated with these outbreaks in terms of hepatic failure, age relationships, co-morbidities, et cetera.

Dr. Nelson replied that age, co-morbidities, poor nutrition, injection and non-injection drug use, and other issues may be factors in the high mortality.

Dr. Ward (SME) added that in addition to those, acute chronic hepatitis and alcohol use play a role. Probably seeking medical care identifies and brings it together to result in this several-fold higher mortality rate than typically would be expected for adults with HepA.

Regarding the issue of homeless persons and HAV infection, Dr. Duchin (NACCHO) encouraged ACIP to make a recommendation that would add persons who are homeless to the list of others who are indicated to receive this vaccine. Seattle has been trying to vaccinate its homeless population. Across the country, the number of homeless persons is rising. They are living in conditions that are often very unhygienic and unsanitary, with limited opportunities for toilet use and handwashing. This is a perfect set-up for the spread of viral hepatitis. Because of the constraints of limited vaccine supply, Seattle is limited in what it can do. But, they thought it would be a better idea to immunize its population before an outbreak occurred. These people are subject to a large amount of health disparities and poor outcomes, making them particularly vulnerable to hepatitis. He acknowledged that the data are limited on the seroprevalence of anti-HAV among homeless populations, but the limited data that are available suggest very high levels of anti-HAV seroprevalence upwards of 50%. He thanked ACIP for considering adding homeless persons to the list of indicated populations.

Dr. Nelson mentioned that while the WG has engaged only in preliminary discussions thus far, in general, the members are favorable to adding homeless persons as a risk group. However, ongoing discussion is needed to continue those deliberations.

Regarding the San Diego situation, Dr. Maldonado (AAP) pointed out that as a precursor to the homeless issue, there was quite a large effort to move the homeless away from the center of town and tourist areas. Many homeless persons were forced to move into even worse conditions than they were living in while in the center of town where they had more access to facilities. These were not only homeless, but also displaced homeless persons living in worse conditions, which is when the current outbreak took off. It would be beneficial for EIS officers to collect information about why people are living where they are.

Influenza

Introduction

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

Dr. Walter reminded everyone that during the June ACIP meeting there were updates on US influenza surveillance, vaccine effectiveness, and vaccine safety; as well as a discussion of and vote on the proposed 2017-2018 recommendations, which were subsequently published on August 25, 2017.

Since the June 2017 ACIP meeting, the WG has engaged in calls twice a month during which members heard updates on: 1) LAIV4 FluMist® Quadrivalent by MedImmune; and 2) A VSD study of spontaneous abortion and inactivated influenza vaccine (IIV) previously presented during the June 2015 ACIP meeting, and recently published in *Vaccine*.

The agenda for this session included the following topics:

- Influenza Surveillance Update
- Influenza Vaccine Coverage Update
- LAIV Efficacy/Effectiveness for the 2016-2017 Season and Strain Selection Update
- Evaluating Risk of Spontaneous Abortion Following Administration of Influenza Vaccine
- Summary and WG Considerations

Influenza Surveillance Update

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

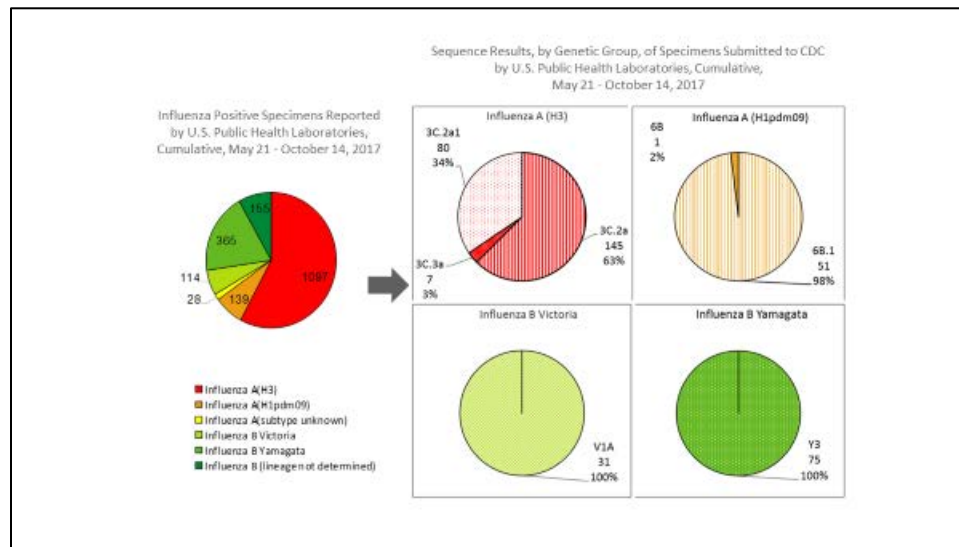
Ms. Brammer provided an update on international influenza activity, recent US activity, and the vaccine composition recommendations made in September 2017 for the Southern Hemisphere.

In terms of international influenza activity, based on the World Health Organization (WHO) reports received from national influenza centers around the world, influenza activity occurred at the times expected and the predominant virus in both the Northern and Southern Hemispheres was influenza A(H3N2) viruses, followed by influenza B activity. While there were some differences in Southern Hemisphere influenza activity, H3N2 predominated in Australia, South Africa, Argentina, and Chile. Some areas of the world are still seeing H1N1 activity. H1N1 appears to have been the predominant virus in Southern and Southeast Asia, but in more recent weeks they appear to be converting over to H3N2.

Regarding influenza positive specimens reported to CDC by clinical laboratories across the country from October 2, 2016 through October 14, 2017, relative to last winter, there is still very low influenza activity. Though recent activity is up-trending slightly, it remains low. As of the weekend ending October 14th, only 2.2% of the specimens tested by clinical laboratories were positive for influenza. More detailed information from US public health laboratories for the same

time period shows very low activity level compared to what occurs in the winter. However, activity has been increasing in recent weeks. For the first two weeks of this season ending with October 14th, 87% of the viruses seen by Public Health Laboratories (PHLs) have been influenza As. Of those that are subtyped, which is almost all of them, 92% have been H3N2 viruses.

CDC performs additional genetic and antigenic characterization of a subset of the viruses submitted by the PHLs, the results of which are shown in the following pie charts for the period May 21, 2017 through October 14, 2017:



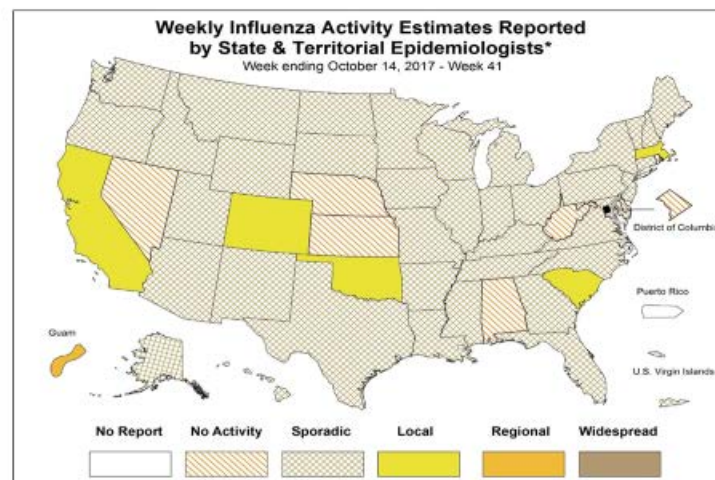
The pie chart on the left is the relative proportions of viruses reported by PHLs, while the pie charts on the right show the more detailed information for each subtype. For the H3N2 viruses, 3C.2a and 3C.2a1 genetic groups and subgroups are predominant in the US and worldwide overall. There are very little of the 3C.3a viruses. All of the H1N1 viruses belong to the 6B.1 genetic group, with the exception of one belonging to the 6B genetic group. All of the B Victoria viruses in the US belong to the V1A genetic group. This group includes a subgroup with a 2 amino acid deletion in the HA. This subgroup has not been designated an official named designation by the WHO Collaborating Centers yet, so for now CDC refers to them as B/Victoria double deletion variants. At this time, the majority of the B/Victoria double deletion variants viruses seen worldwide are in the US. All B Yamagata viruses are within the Y3 genetic group.

Antigenic characterization is performed using post-infection ferret antisera produced against the current cell grown vaccine-like reference viruses. The majority of viruses are tested using a hemagglutination inhibition (HI) assay, but for a subset of H3 viruses that do not have sufficient HA titers to perform HI testing, neutralization assays are used. For A(H1N1)pdm09, all 43 viruses antigenically characterized using ferret post-infection antisera are A/Michigan/45/2015-like. For A(H3N2), 113 of 117 (96.6%) influenza A(H3N2) viruses were antigenically characterized as A/Hong Kong/4801/2014-like by HI testing or neutralization testing. For B/Victoria lineage, 18 of 28 (64.3%) B/Victoria-lineage viruses were antigenically characterized as B/Brisbane/60/2008-like. Of the B/Yamagata lineage, all 40 were antigenically characterized as B/Phuket/3073/2013-like. Among the H3 viruses that reacted poorly with ferret antisera raised against A/Hong Kong/4801/2014-like viruses, all belong to genetic group 3C.3a. Among

the viruses that reacted poorly with ferret antisera raised against B/Brisbane/60/2008-like viruses, all were double deletion viruses.

In terms of the epidemiologic data for this season based on outpatient visits for influenza-like illness reported by the Influenza-like Illness Surveillance Network (ILINet) providers, 1.3% of patient visits were for ILI. That is well below the 2.2% baseline. Compared to other recent years, the influenza season is progressing typically for this time of year. Based on data from the National Center for Health Statistics (NCHS) Mortality Surveillance System for pneumonia or influenza listed somewhere on the death certificate, deaths for pneumonia or influenza are still well below the epidemic threshold. Of the deaths occurring through the most recent week for which there are data (September 30, 2018), 5.3% of deaths had pneumonia or influenza listed somewhere on the death certificate. That is compared to the epidemic threshold of 6.0% for that week.

Overall, there has been low influenza activity as illustrated by the following map:



* This map indicates geographic spread & does not measure the severity of influenza activity

However, looking at the geographic spread of influenza reported to CDC by state and territorial epidemiologists, 5 states already were reporting local activity by the week ending October 14, 2017. This means that these states are seeing outbreaks or increases in ILI with laboratory evidence of influenza in at least one region of the state. The majority of states (N=38) are reporting sporadic activity.

The WHO recommendations for influenza vaccine composition for the 2018 Southern Hemisphere season were made during the WHO Vaccine Consultation meeting September 25-27, 2017 in Melbourne, Australia. The recommended components for the 2018 Southern Hemisphere influenza trivalent vaccines are an A/Michigan/45/2015 (H1N1)pdm09-like virus, an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus, and a B/Phuket/3073/2013-like (B/Yamagata lineage) virus (8). Quadrivalent vaccines include the above three components as well as B/Brisbane/60/2008-like (B/Victoria lineage) virus.

Relative to the current Northern Hemisphere vaccine viruses, this represents a change in the H3N2 component. The decision to update the H3 component was based on global data presented at the WHO vaccine composition meeting in September. This data showed that most recent H3N2 viruses were well-inhibited by ferret antisera produced against cell-propagated A/Hong Kong/4801/2014-like reference viruses, indicating that the viruses have not undergone antigenic drift. However, the proportion of viruses that were well-inhibited by ferret antisera

raised against the egg-propagated reference virus was significantly lower. Recent H3N2 viruses were better inhibited by ferret antiserum raised against the egg-propagated A/Singapore virus compared to ferret antisera raised against other egg-propagated viruses. The change to an A/Singapore-like virus represents an incremental improvement in the vaccine strain. It was made not because of significant antigenic drift in the viruses, but because an egg-based virus and corresponding candidate vaccine virus were identified that are more similar to currently circulating wild-type viruses than Hong Kong/4801/2014. The final change that was made is that for trivalent vaccines, B/Phuket/3073/2013-like virus (Yamagata lineage) replaced B/Brisbane/60/2008-like virus (Victoria lineage) to reflect the predominance of B/Yamagata viruses globally. This has little practical implications for the US because the majority of vaccine is quadrivalent.

In summary, influenza A(H3N2) viruses have predominated in the US and worldwide since July. Influenza H1 and B viruses are also still being detected. So far in the US, influenza activity has been low. The majority of circulating stains are similar to those contained in the 2017-2018 Northern Hemisphere vaccine.

Discussion Points

Regarding pneumonia and influenza mortality, Dr. Hunter requested clarity regarding whether the threshold seemed to be decreasing slightly each year.

Ms. Brammer confirmed that the threshold has trended down pretty strongly over the years, and it seems to be due to a reduction in the proportion of death certificates that have pneumonia listed rather than the proportion of deaths due to influenza being lower. Though it is not clear why this is, it is what is driving the downward trend.

Coverage Update

Carla Black, PhD
Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Black provided an update on influenza vaccination coverage for the 2016-2017 season. CDC uses several data sources to estimate coverage in different populations. The data source used to estimate influenza vaccination coverage among children are from the National Immunization Survey-Flu (NIS-Flu). NIS-Flu is an on-going national list-assisted random-digit-dial (RSS) landline and cellular telephone survey of households with children. It is comprised of 3 components: NIS-Child for children 19 to 35 months old, NIS Teen for children 13 to 17 years old, and NIS Child Influenza Module to capture children 6 to 18 months and 3 to 12 years old. NIS-Flu data used to assess influenza vaccination coverage among children are based solely on parental report. Participants are asked if their child has received an influenza vaccination since July 1, 2016 and in which month and year. NIS-Flu interviews included in the analysis were conducted October 2016 through June 2017.

The data source for adults is the Behavioral Risk Factor Surveillance System (BRFSS). The BRFSS is an on-going state-based telephone survey of randomly selected persons ≥ 18 years among the non-institutionalized, US population on health conditions and risk behaviors. These data are based on self-report. Participants are asked if they had an influenza vaccination in the

past 12 months and in which month and year. BRFSS interviews conducted September 2016 through June 2017 were included in the analysis.

From both data sources, Kaplan-Meier survival analysis was used to determine cumulative monthly influenza vaccination coverage of at least one dose received from July 2016 through May 2017. Coverage estimates were calculated for children 6 months through 17 years of age from the NIS-Flu and for adults from the BRFSS, and these estimates were then combined to produce estimates for all persons 6 months and older. Imputations were performed where month and year of vaccination were missing. Weighted estimates were calculated in SUDAAN to account for complex survey design. T-tests ($p < 0.05$) were performed to determine significant differences between groups, and between the 2016-2017 and 2015-2016 seasons.

In terms of overall seasonal influenza vaccination coverage among children and adults from 2010 through 2017, there was an increase in coverage among all persons in 2016-2017 compared with the 2015-2016 season from 45.6% to 46.8% and among adults from 41.7% to 43.3%. There was an increase in coverage among children in the 2013-2014 season. Coverage among children has since plateaued at approximately 59%. In the 2016-2017 season, coverage among children decreased with increasing age, and was 76.3% among children 6 to 23 months old, which is higher than the Healthy People 2020 target of 70%. Coverage was 66.2% among children 2 to 4 years of age, 59.9% among children 5 to 12 years of age, and 48.8% among children 13 to 17 years of age. Again, overall coverage among children in 2016-2017 was similar to coverage in 2015-2016, and this was despite the ACIP recommendation not to administer LAIV during the 2016-2017 season. Compared with the 2015-2016 season, coverage decreased among children 5 to 12 years by 1.9 percentage points, and increased among children 13 to 17 years by 2 percentage points. Coverage was similar among children 6 to 23 months and among children 2 to 4 years.

A study that CDC published in 2015 found that younger children were more likely to receive LAIV than older children. Another study that is currently in CDC clearance found that overall, only 23% of parents of vaccinated children preferred LAIV for their children in the 2014-2015 season. This percentage differed by child age group, with the highest percentage among parents of children 9 through 12 years at 26.4% expressing a preference for LAIV and the lowest among parents of the oldest children 13 through 17 years with only 15.3% expressing a preference for LAIV. So, it is possible that the decrease in coverage among children 5 to 12 years could be due to the recommendation not to use LAIV. However, it is notable that overall coverage did not change among children, which is likely due to the fact that most parents did not report having a preference for LAIV.

For children, coverage was similar in 2016-2017 compared to 2015-2016 for all race-ethnicity groups. However, differences were observed in the 2016 season by race/ethnicity. For example, non-Hispanic white children had lower coverage than children of all other race/ethnicity groups.

In terms of the trend of influenza vaccination coverage among children by age group from 2010 through 2017, younger children 6 months to 4 years of age have consistently had the highest vaccination coverage trending from 63.6% in the 2010-2011 season to 70% in the 2016-2017 season. This is followed by children 5 to 12 years of age trending from 54.7% in the 2010-2011 season to 59.9% in the 2016-2017 season. Coverage for children 13 through 17 years of age trended from 34.5% in the 2010-2011 season to 48.8% in the 2016-2017 season.

Full and partial vaccination coverage among children 6 months to 8 years is based on data from six Immunization Information Systems (IIS) sentinel sites. Full vaccination coverage is defined as having received the complete number of doses, 1 or 2, that the child needed based on the ACIP recommendations for that influenza season. Children who received only 1 dose when they were recommended to receive 2 doses are considered to be partially vaccinated. In the 2016-2017 influenza season, full influenza vaccination coverage was 47.4% in the 6- through 23-month group, 36.7% in the 2- through 4-year group, and 32.0% in the 5- through 8-year group. From the 2015-2016 to the 2016-2017 influenza season, full vaccination coverage increased 2.4 percentage points in the 6- through 23-month group, but declined slightly in the 2- through 4-year group by 1.0 percentage point and the 5- through 8-year group by 1.1 percentage point.

In terms of the trends in coverage among adults from 2010 through 2017, adults 65 years of age and older have consistently had the highest coverage. In the 2015-2016 season, there was a decrease compared with 2014-2015 in adults 65 years of age and older and 50 through 64 years of age. This season, there was an increase in both of these age groups. However, this was simply an increase back up to the baseline seen prior to the 2015-2016 season. Unlike children, coverage for adults increases with increasing age, and was 33.6% among adults 18 through 49 years of age, 45.4% among adults 50 through 64 years of age, and 65.3% among adults 65 years of age and older. Overall, there was an increase of 1.6 percentage points in coverage among all adults 18 years of age and older from the previous season. That was driven primarily by an increase of 1.8 percentage points in adults 50 through 64 years of age, and a 1.9 percentage point increase in adults 65 years of age and older.

Regarding vaccination coverage by race/ethnicity among adults, coverage increased for non-Hispanic white adults in the 2016-2017 season by 1.4 percentage points compared with last season. For all other race-ethnicity groups, coverage was similar to 2015-2016. With the 2016-2017 season, differences are seen by race/ethnicity. Unlike children, non-Hispanic white adults had higher coverage than adults of all other race/ethnicity groups with the exception of Asian adults who have coverage similar to white adults.

Vaccination coverage estimates were also collected from two special populations, pregnant women and health care personnel. Estimates for both of these groups come from non-probability internet panel surveys that were conducted at the end of March and early April of 2017. For pregnant women, an opt-in web-based internet panel survey was conducted from March 28, 2017 through April 7, 2017. Women were recruited from general population internet panels operated by Survey Sampling International (SSI). The survey included 2,319 women who were pregnant during October 2016 through January 2017. For HCP, an opt-in web-based internet panel survey was conducted from March 28, 2017 through April 19, 2017. For this survey, 2,438 HCP were recruited from two internet sources: 1) Professional HCP recruited from the membership of WebMD; and 2) Assistants/aides and non-clinical support staff recruited from general population internet panels operated by SSI.

In the 2016-2017 season, coverage among pregnant women was 53.6%. Since these data come from a non-probability survey, CDC does not do statistical tests but instead uses a 5-percentage point difference as the cutoff for a “notable” difference. Using this criterion, coverage was similar to the previous four seasons and has been stable at about 50% since the 2012-2013 season. Influenza vaccination coverage among HCP in the 2016-2017 season measured from the internet panel survey was 78.6%. Coverage has increased over time since the 2009-2010 season, but has not increased since the 2013-2014 season according to the 5 percentage point criterion.

In conclusion, seasonal influenza vaccination coverage among children overall in 2016-2017 was similar when compared with the previous season. This season, there was a 2 percentage point increase for children 13 through 17 years of age. However, that was offset by a similar decrease among children 5 through 12 years of age. Among adults, there was an overall increase of 1.6 percentage points. For all age groups except children 6 through 23 months of age, coverage remained well below the Healthy People 2020 target of 70%. Coverage among pregnant women (53.6%) and health care personnel (78.6%) in the 2016-2017 season was similar to previous seasons.

These data have several limitations, including that most of the data were based on parental or self-report, which could lead to recall bias. It is known that coverage is overestimated, given that CDC estimated that 149.2 million people were vaccinated, but know that only 145.9 million doses of influenza vaccine were distributed. Overall response rates were low in NIS-Flu and BRFSS, which can potentially lead to nonresponse bias. NIS-Flu and BRFSS estimates were combined for overall estimates, although there are differences in survey methodology. Full vaccination coverage (2 doses) among children <9 years was not assessed in the NIS-Flu. The data from the IIS sentinel sites might not be representative of the US population. The data for HCP and pregnant women coverage were based on non-probability samples, so these also might not be representative of the US populations of these groups. In addition, no statistical tests were performed on the estimates for these two groups.

Discussion Points

Dr. Szilagyi emphasized that the fact that vaccine estimates have not decreased in children except for a very small number among children 5 through 12 years of age is a real tribute to the immunization delivery system, given that LAIV no longer exists and now it has been two seasons in a row. Many people thought that the rates would decrease. He was puzzled by why white non-Hispanic children have lower rates, but adults have higher rates, and wondered whether that is also somehow a reflection of the immunization delivery system. The delivery systems that take care of poor children are actually doing quite well or potentially better in immunizing children. Given that school-located vaccination is one area in which removal of LAIV might have an influence, he asked whether Dr. Black had any information on that.

Dr. Black responded that she does not have any information on whether removal of school-located LAIV vaccination might have an influence on coverage.

Dr. Reingold indicated that the Bay Area has a school-based immunization program currently funded by a private donor, and they did not observe a decline this year with the removal of LAIV from the program.

Dr. Cohn reminded everyone that there was a letter in the ACIP folder for the June 2017 meeting that described a county in Florida that experienced a decline, so this likely varies by location.

Dr. Kempe has been involved in an influenza project that has demonstrated that their IIS rates consistently are substantially lower at estimating influenza rates among children than what is observed in the NIS-Flu, even in mandated reporting states. Given CDC's rates that showed that the sentinel sites are significantly lower, she wondered whether consideration had been given to using a different method. Self-report in the NIS-Flu may not be the best method for doing this.

Dr. Black said she thought the estimates from the sentinel sites, the estimates are pretty close to the NIS-Flu estimates. They have assessed NIS-Flu estimates. For children 19 through 35 months of age and 13 to 17 years of age, they can get provider-reported estimates for influenza and they are somewhat lower than the parental-reported estimates. But relying on that, they cannot get estimates for those children not covered in the other NIS surveys, so they would not have estimates for children between 35 months and 13 years. The provider-reported estimates have some issues as well, because patients have many records and many providers. They do not all report, so the true estimate is probably somewhere in the middle.

Michelle Lin agreed with the comment that they are also seeing low coverage in the IIS sentinel site data. It is not clear which source should be used in the future.

Dr. Messonnier pointed out that in the NIS childhood data for routine childhood vaccines, there are discrepancies in lower socioeconomic status (SES) and racial/ethnic minorities, suggesting that the safety net of VFC is not working perfectly in those populations. She is not sure what to make of the data Dr. Black presented in comparison to that, but it is an interesting question. Regarding the broader question about influenza vaccination coverage, for many reasons CDC is trying to think through the best way to continue to estimate vaccination coverage in all groups. NIS is an incredibly robust system, but it depends upon people answering the phone and tracking backwards and validating immunization status. In the current environment, all of the systems that CDC relies on that rely on phone contact are much more difficult. CDC is engaged in a broader conversation about how to approach providing incredibly important data on vaccination coverage.

Dr. Duchin (NACCHO) asked whether they could see some of these data reported with SES as one of the variables, along with the racial/ethnic breakdown. They have some evidence locally that people of lower SES have higher immunization coverage rates for a number of vaccines than people of higher SES. For example, children who utilize their school-based health centers have higher vaccination coverage than children who receive their vaccines exclusively in the private sector.

Dr. Ezeanolue thought all of the states now have IISs, which he thought would be a more reliable resource to assess coverage. In his state, everyone has to report.

Dr. Bennett replied that this varies by states. Some states have very robust IISs, while others do not.

Dr. Messonnier noted that an *MMWR* will be published in November 2017 that examines this question, which they will make sure is distributed to ACIP members.

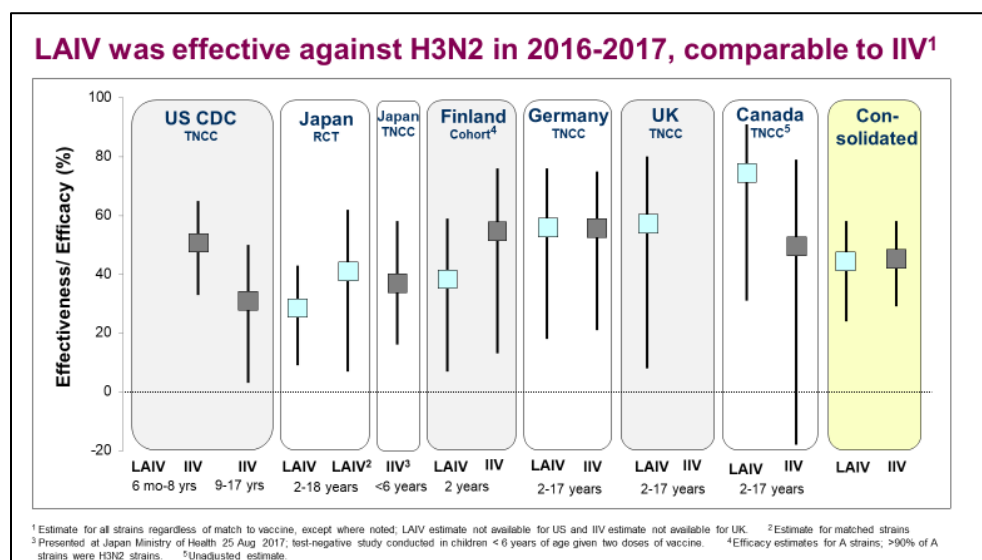
LAIV Efficacy/Effectiveness 2016-2017 Update

Raburn Mallory, MD
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Dr. Mallory provided an update on *in vitro*, *in vivo*, and clinical investigations to improve H1N1pdm09 effectiveness of LAIV. LAIV showed reduced effectiveness against H1N1pdm09 strains in the 2013-2014 and 2015-2016 seasons, resulting in the ACIP recommendation not to use the vaccine in the US. In 2016-2017, LAIV effectiveness for H3N2 strains was moderate and comparable to IIV, though there was some variation for both vaccines by country. *In vitro*

investigations identified reduced replicative fitness of post-pandemic H1N1 strains as the likely root cause of reduced effectiveness. This information was presented during the February 2017 ACIP meeting. An A/Slovenia strain with improved replicative fitness was selected for the 2017-2018 LAIV formulation. Since February 2017, an improved ferret efficacy model has been developed. In this new model, the A/Slovenia strain provided greater protection than recent H1N1pdm09 LAIV strains, similar to a previous clinically highly efficacious H1N1 strain. Data will be available in December 2017 from a randomized study in US children comparing A/Slovenia and 2015-2016 H1N1pdm09 LAIV strain (A/Bolivia). It is anticipated that study results, combined with improvements made to the strain selection process, will help inform ACIP recommendations on future use of LAIV in the US within the next 4 months.

As depicted by the data for 5 countries and the United Kingdom (UK) and Canada in the following graphic, LAIV was effective against H3N2 in 2016-2017 comparable to IIV:



H3N2 was the strain that dominated in all of the countries. In terms of study design, there were two studies from Japan. For LAIV, an RCT was conducted in children 2 through 18 years of age. In this study, all subjects received a single dose of vaccine. A test-negative study was conducted for IIV among children under the age of 6, all of whom received 2 doses of vaccine. A cohort study was conducted in Finland among children 2 years of age. The remaining 3 studies were all test-negative studies conducted in children 2 through 17 years of age. Also included in this graphic as a reference are the effectiveness data for IIV in the US for this past season and, in yellow on the right, consolidated estimates for effectiveness across all of these studies for both LAIV and IIV. LAIV demonstrated statistically significant effectiveness for H3N2 strains this past season, ranging from 28% to 74%. Effectiveness for IIV ranged from 34% to 56%. Based on the consolidated estimates in yellow, both vaccines appear to have had comparable effectiveness, with consolidated estimates of 45%.

Returning to the issue of H1N1 effectiveness, Dr. Mallory discussed some of the changes made to the ferret model used to assess the efficacy of these strains. Ferrets have been used previously to assess the efficacy of LAIV strains; however, the model has not been particularly good at distinguishing between more and less effective strains. This is likely due to the fact that ferrets previously received 2 doses of vaccine at a fairly high human dose of 10^7 virus particles. In order to better differentiate between the LAIV strains, the dose was reduced to 10^4 virus

particles, which is probably a more appropriate dose for ferrets. Ferrets now receive a single dose of the vaccine. Ferrets also were previously vaccinated with a monovalent formulation to the vaccine, but are now vaccinated with more relevant quadrivalent formulations. In addition, some minor changes were made to the endpoints of the study. Titers are now assessed using the same methods used in the clinical studies, fever is monitored continuously using telemetry, and neutralizing antibodies were added to the assessments of immunogenicity.

Three H1N1 strains were evaluated in this ferret model: 1) NC99 TLAIV 2004/5 (H1N1 A/New Caledonia/20/99); 2) CAL09 QLAIV 2013-14 (pdm09 H1N1 A/California/07/09); and 3) BOL13 QLAIV 2015/16 (pdm09 H1N1 A/Bolivia/559/2013). Some ferrets received the pre-pandemic H1N1 A/New Caledonia/20/99 strain, which has been shown in a number of pediatric RCTs to have high levels of efficacy. Other ferrets received either the recent A/California/07/09 or the A/Bolivia/559/2013 strain. B strains have been shown to have reduced effectiveness in recent clinical observational studies. Following vaccination, ferrets were challenged with a wildtype homologous strain. For example, ferrets who were vaccinated with the New Caledonia strain were then challenged with the wildtype New Caledonia strain and final titers were collected over the 3 days following challenge. The New Caledonia strain was highly effective in protecting ferrets from challenge, which corresponds to the clinical efficacy seen for this strain. The California and Bolivia strains showed reduced levels of protection in the ferret models, which again correspond to the reduced levels of effectiveness seen in the clinical observational studies [Internal Data, MedImmune. Speke UK, Sep 2017].

Having looked at both the California and Bolivia strains, the new A/Slovenia strain included in the vaccine for the upcoming season was examined. The A/Slovenia strain also showed high levels of protection in ferrets, reducing the level of shed titers to less than 2 logs, a level of protection that is seen in the previous highly efficacious A/New Caledonia strain. Because the Slovenia multi-challenge virus was shed somewhat less by the unvaccinated ferrets, the study is being repeated. In summary of the characterization data for the new A/Slovenia strain, A/Slovenia has improved replication in primary human nasal epithelium cells compared to the previous A/Bolivia strain, and is able to sustain multiple cycles of viral replication compared to both the A/California and A/Bolivia strains. These *in vitro* characteristics correspond with improved effectiveness in the modified ferret models. An ongoing clinical study in US children is evaluating how the *in vitro* ferret findings correspond with shedding and immune responses to the strain.

A pediatric study is underway to compare new A/Slovenia strain with previous A/Bolivia strain that was in the vaccine. This randomized, double-blind, study is being conducted in 200 children 24 to <48 months of age, half of whom have no history of being previously vaccinated for influenza. This study is being conducted in these subjects because it is known that for LAIV, immune responses and shedding are higher in younger and sero-naive subjects. The 200 subjects were randomized who then received 2 doses of vaccine. The subjects were randomized to one of three groups. One group received the current LAIV4 2017-2018 vaccine formulation that contains the new A/H1N1 Slovenia strain. Another group received the previous LAIV4 2015-2016 vaccine formulation that contains the A/H1N1 Bolivia strain. The third group received the LAIV3 2015-2016 vaccine formulation that contains a single B strain and the A/H1N1 Bolivia strain. The primary endpoint for the study is HAI antibody seroconversion rates after each dose. The secondary endpoints include neutralizing antibody seroconversion rates after each dose, mucosal IgA increases after each dose, shedding after each dose, and safety.

The primary objective of the pediatric study is to compare the shedding and immunogenicity of the new A/Slovenia strain to the previous A/Bolivia H1N1 strain as given in the relevant quadrivalent formulations. The study does have some limitations. Due to anticipated difficulties in enrolling young children, especially those with no history of influenza vaccination, the study is small and is only powered to detect 20% to 25% differences in the percentage of subjects with seroconversion and shedding of vaccine virus. The LAIV formulations chosen are based on those for which there are real-world effectiveness data, so these are the commercial formulations that were distributed in each of the countries. As a result, the strains of the formulations differ in their H1N1 strains of main interest. They also differ in their H3N2 strains, which potentially could affect the results. In seropositive subjects, shedding and seroconversion are somewhat insensitive measures of LAIV efficacy.

To summarize, data from five clinical studies indicate that LAIV was effective for H3N2 strains in the past season with a consolidated estimate of 45%, which is comparable to that seen for IIV. *In vitro* investigations identified reduced replicative fitness of post-pandemic H1N1 strains as the most likely root cause of reduced effectiveness, as presented during the February 2017 ACIP meeting. The A/Slovenia strain selected for the 2017-2018 LAIV formulation has improved replicative fitness. The improved ferret efficacy model supports the inclusion of the A/Slovenia strain in the vaccine. A/Slovenia provided greater protection than recent H1N1pdm09 LAIV strains, A/Bolivia and A/California. The protection appears to be similar to a previous clinically efficacious H1N1 strain in New Caledonia. To further characterize the A/Slovenia strain, MedImmune is wrapping up a clinical study comparing it to the A/Bolivia strain. It is anticipated that study results, combined with improvements made to the strain selection process, will help inform ACIP recommendation on future use of LAIV in US within the next 4 months.

VSD Pregnancy Study

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Dr. Donahue reported on a recently published study for which the objective was to determine whether there is an association between influenza vaccine and miscarriage in pregnant women. There are a lot of data to support the safety of the vaccine in pregnant women, especially in the second and third trimesters and increasingly for early pregnancy as well. In a VSD matched case-control study published in 2013 by Stephanie Irving, women were pregnant either in 2006-2006 or 2006-2007 before the 2009 pandemic. This study found that spontaneous abortion (SAB) was not associated with influenza vaccination in a 28-day exposure window [Obstetrics & Gynecology 2013; 121:159-65].

CDC was interested in making sure that the safety profile observed now with vaccines containing antigens from the pandemic H1N1 is the same as the safety profile observed then, which was recently published [Donahue et al, Vaccine 35 (2017) 5314-5322]. The two studies are largely the same in terms of design and implementation, with the only difference between them being the time period. Of the 8 integrated healthcare plans in the VSD, all but 2 provided data for this study.

Potential cases were initially identified electronically using International Classification of Diseases (ICD)-9 codes for SAB. All cases included in the study underwent medical record review. For the study, SAB was defined as from 5 to <20 weeks gestation. All cases were adjudicated to confirm SAB and estimate SAB date. The date used for a case was considered the reference date for each case-control pair. Controls were selected similarly starting out electronically using ICD-9 codes for live births and stillbirths. All controls also underwent chart review. Controls who had a last menstrual period (LMP) within 7 days of a case were selected and sorted by proximity to the case LMP. Most were much closer than that. The mean pairwise difference was about half a day, and the median pairwise difference was zero days. Controls were reviewed from this list until a match was found.

Vaccine exposures were identified by receipt of seasonal IIV documented in medical record. The primary exposure window of interest was 28 days before the reference date. Two other exposure windows also were examined: 29 through 56 and >56 days. All other vaccinations administered during pregnancy were abstracted, with few other than tetanus, diphtheria, and acellular pertussis (Tdap) given.

This was a matched case-control study that matched on age groups of <30 years of age or ≥ 30 years, LMP, and site. Because it was a matched study, a conditional logistic regression was done. The covariates included in the model were maternal age (quadratic spline), smoking during pregnancy, diabetes mellitus (history of type 1 or 2—not gestational), concomitant Tdap vaccination, pre-pregnancy body mass index (quadratic spline), previous health care utilization (quadratic spline), and number of days with a health care encounter during 12 months before LMP.

Selected characteristics of SAB cases and controls are shown in the following table:

	Cases (n=485)	Controls (n=485)	P
Maternal age (median, years)	31.8	31.6	0.02
Smoked during pregnancy, N (%)	52 (11)	34 (7)	0.05
BMI (median)	25.7	24.9	0.08
Same season influenza vaccination before reference date among vaccinated in previous season, N (%)*	56 (56.0)	53 (41.7)	
1-28 days before reference date	17 (17.0)	4 (3.1)	
29-56 days before reference date	5 (5.0)	5 (3.9)	
>56 days before reference date	34 (34.0)	44 (34.6)	
Same season influenza vaccination before reference date among not vaccinated in previous season, N (%)*	71 (18.6)	70 (19.7)	
1-28 days before reference date	21 (5.5)	20 (5.6)	
29-56 days before reference date	12 (3.1)	11 (3.1)	
>56 days before reference date	38 (10.0)	39 (11.0)	

*Statistical tests in prior season flu vac strata are not presented; the tests restrict the analyses to matched pairs concordant on prior season vac status and exclude substantial data. % computed using stratum-specific denominators.

In addition to the other variables, how the cases and controls broke out in terms of their exposure windows is also shown. Among women who were vaccinated in the previous season, 17% of cases and 4% of controls were vaccinated in the 1 to 28 days before their reference date. The other two exposure windows were similar between cases and controls in terms of distribution. Among women who were vaccinated in the same season, 21% of cases and 20%

of controls were vaccinated in the 1 to 28 days before their reference date. The other two exposure windows also were similar between cases and controls.

Regarding the odds of influenza vaccination in SAB cases compared to controls by timing of vaccination, the odds of influenza vaccination in the 1 to 28 days before the reference date was about 2.0 with a significant 95% confidence interval of 1.1-3.6. In the 29 to 56 days and >56 days windows, the odds ratios are essentially null. This was unexpected based on the investigators' previous work, as well as based on what was in the literature. One of the first questions they had regarded whether this was consistent across seasons, so they examined the 2010-2011 and 2011-2012 influenza seasons. Among women who were vaccinated in the 2010-2011 season in the 1 to 28 days before their reference data, the adjusted odds ratio was 3.7 with a 95% confidence interval of 1.4-9.4. The exposure window of 29 to 56 days was modestly elevated at 1.8 (0.06-5.1), but not significantly so. The exposure window of >56 was essentially null. Contrast that with the 2011-2012 season in which there was not much elevation at all in the 1- to 28-day exposure window at 1.4 (0.6-3.3), which is not significant. There is a protective odds ratio in the 29-56 days window, although the numbers are small and the confidence intervals are pretty wide. The >56 days window is essentially null.

Since a seasonal difference was observed, the next question regarded whether there was a possibility that having been vaccinated in the previous season somehow influenced the association between vaccine in the current season and SAB. For women who were vaccinated in the previous season, the odds ratio in the 1- to 28-day exposure window was 7.7 (2.2-27.3). The odds ratio for women not vaccinated in the previous season was close to null and not significant at 1.3 (0.7-2.7). Nothing was observed to be going on in the exposure windows of 29-56 or >56 days.

This led to the question regarding whether there was a possibility that seasonal differences were being observed with respect to the effect modification analysis. Women in the 2010-2011 study who were vaccinated in the previous season could have been vaccinated with the monovalent H1N1 vaccine, the seasonal vaccine, both vaccines, or neither. Women who were vaccinated with the monovalent H1N1 vaccine in the previous season, regardless of whether they had vaccination with the seasonal vaccine, had an odds ratio in the 1- to 28-day window of 32.5 (2.9-359), but with very broad confidence intervals. The other two exposure windows were elevated somewhat, but not significantly so for the 29- to 56-day window at 4.1 (0.3-63) and just marginally significant for the >56-day window with an odds ratio of 3.2 (1.0-10.5). For women who were vaccinated with both the monovalent and seasonal vaccines, the odds ratio was 31.5 (2.3-425) in the 1- to 28-day window. There was modest elevation in the other two exposure windows. The odds ratios for women vaccinated with seasonal only or unvaccinated were about the same and not significant in the 1- to 28-day window at 3.3, (0.5-20.1) and 3.4, (0.8-14.2), respectively. Nothing was occurring in the other two windows.

In the 2011-2012 season, women in the study who were vaccinated in the previous season would have been vaccinated with seasonal vaccine, which would have included pH1N1 antigen. The odds ratio in the 1- to 28-day window for women who were vaccinated in the previous season was 6.4 (1.0-41.2), which was marginally significant. If not vaccinated in the prior season, the odds ratio on the 1- to 28-day window was 0.7 (0.3-2.2). A protective odds ratio is observed among unvaccinated women in the 29- to 56-day window of 0.04 (0.0-0.8), and essentially null results in the .56-day window for both women who were vaccinated and unvaccinated in the prior season.

A number of additional questions arose based on these results. An obvious question pertains to whether women with early pregnancy loss were different from controls. More specifically, were cases more likely than controls to be vaccinated because they presented with early signs and symptoms of SAB? The investigators returned to the data and identified all of the outpatient diagnoses that were assigned on the date of influenza vaccination for cases and controls. They found that cases (58%) were, indeed, more likely than controls (52%) to have at least one diagnosis on the date of vaccination. That is not a significantly larger difference. Cases also were somewhat more likely to have a mean number of diagnoses at 1.7 versus 1.6. Again, that is not significantly different. Most diagnoses were V codes (e.g., routine pregnancy visits). There were 3 cases with diagnoses of specific SAB symptoms (e.g., pain, bleeding, spotting, cramping, et cetera) in the 1- to 28-day exposure window. When these 3 pairs were excluded and the overall effect modification analysis was run, the odds ratio in the 1- to 28-day window was 7.0 (1.9-25.2) among women vaccinated in the previous season.

The following table summarizes some of the additional post-hoc analyses performed:

Summary of additional post-hoc analyses			
Association between SAB and IIV receipt in the 1-28 days before the reference date by receipt of pH1N1-containing vaccine in the previous season (2010-11 and 2011-12 seasons combined)			
Study population	Matched pairs	Vaccinated in previous season?	
		Yes	No
Complete (original analysis)	451	7.7 (2.2-27.3)	1.3 (0.7-2.7)
Exclude pairs for 3 cases with early SAB signs/symptoms at time of vaccination	448	7.0 (1.9-25.2)	1.3 (0.6-2.6)
Exclude those with history of ≥ 2 SABs	387	6.5 (1.7-24.3)	1.1 (0.5-2.4)
Exclude unknown vax manufacturer	419	5.9 (1.6-21.5)	1.2 (0.6-2.5)
Women with ≥ 1 pregnancy ultrasound	398	6.9 (1.7-28.0)	1.3 (0.6-2.9)
Adjusted for current year influenza diagnosis code before reference date	451	7.9 (2.2-28.0)	1.3 (0.7-2.7)

OR adjusted for age, BMI, smoking, diabetes, concomitant Tdap-TIV vaccination, and health care utilization.
Referent exposure group for OR calculations: women unvaccinated as of the reference date.

The first two rows were described earlier. When women were excluded who had a history of ≥ 2 SABs, the odds ratio was 6.5 (1.7-24.3) for women vaccinated in the previous season and 1.1 (0.5-2.4) for women who were not vaccinated. When cases were excluded due to unknown vaccine manufacturer, the odds ratio was 5.9 (1.6-21.5) for women vaccinated in the previous season and 1.2 (0.6-2.5) for women not vaccinated in the previous season. When the analysis was restricted to women who had at least 1 pregnancy ultrasound, the odds ratio was 6.9 (1.7-28.0) for women vaccinated in the previous season and 1.3 (0.6-2.9) for women who were not vaccinated in the previous season. An attempt also was made to assess women who were infected with influenza, adjusting for current year influenza diagnosis code before the reference date, but this did not change much.

To summarize the key findings, SAB was significantly associated with IIV receipt in the 28-day exposure window. This finding differs from the results of a similar study conducted before the 2009 pandemic. Association between IIV and SAB was significant in the 2010-2011 overall, but not in the 2011-2012 season. In both seasons, the association was elevated only in the 28-day

window and only in women who had received pH1N1-containing vaccine in the prior influenza season.

This study has received a number of criticisms, one of which is the lack of biologic plausibility. This is true, given that there is no established way to explain the findings. However, multiple examples of vaccine- and drug-related AEs have been identified without known biologic plausibility *a priori*. It also is true that 50% to 60% of early SABs are likely due to chromosomal abnormalities, but misclassification in that case should be nondifferential and not related to vaccine and bias in that would be towards the null in most instances. Another criticism that also is very accurate is the small sample size in some of the analyses. The overall planned analysis is pretty stable, and the analysis with the overall effect modification is fairly stable. However, the sub-analyses are less solid. There was also crude matching and some inadequate adjustment for age, because matching was done in groups. Age was adjusted in all analyses as an analysis factor. No adjustment was made for history of SAB, which is based on prior work showing the possibility of introducing bias. As noted earlier, women with a history of ≥ 2 SABs were excluded, and the odds ratio was somewhat reduced but similar.

This all led to some additional questions and concerns, which the investigators hope to address with a follow-up IIV-SAB study in VSD. This study will evaluate the risk of SAB following seasonal IIV administered during the 2012-2013, 2013-2014, and 2014-2015 influenza seasons. Some similarities between the previous and follow-up study are that the design for both is matched case-control and the age range is 18 through 44 years. Other eligibility criteria include identification of LMP in the medical record and confirmed outcomes, with a plan to try to acquire additional information. Exclusions include ectopic pregnancy, elective abortion, and SAB at < 5 weeks gestational age. Case-control ascertainment, exposure ascertainment, and medical record review will be the same for the follow-up study. There also will be adjudication of gestational age and date of SAB. The following table depicts the differences between the previous study and the follow-up study:

Differences between previous study and follow-up study		
Feature	Previous study	Follow-up study
Objectives	Estimate overall IIV-SAB association	Estimate assn. in women vaccinated in prev. season
Study period	2010-11, 2011-12	2012-13, 2013-14, 2014-15
Study size	485 matched pairs	1500 matched pairs
Power	80% for OR=2.2, overall	80% for OR=2.2, each season
Matching	Age (2 groups- $< \geq 30$ yr), LMP, site	Age (3 groups-18-24, 25-34, ≥ 35 yr), vax in prev. season , LMP, site
Controls	Women with stillbirths/live births	Women with live births

The follow-up case-control study is underway, with preliminary results anticipated by late 2018 or early 2019.

Discussion Points

Dr. Reingold said he would have thought that influenza vaccine use in this age group among women who were not pregnant would be rather infrequent, so he wondered how correlated vaccination in the previous season is with gravidity and parity in terms of having been pregnant in the previous year. He asked whether Dr. Donahue could tell them something about why these women were getting vaccinated in the previous year. While odds ratios are great, for something like this, it might be beneficial to calculate excess risk and population attributable risk to offer some perspective on just how much of a problem this would be if it is real.

Dr. Donahue replied that gravidity and parity are controlled for in the analyses for the current season in which they were vaccinated. They do not have any information about specifically why women were getting vaccinated the previous year, but this is one of the things they want to try to capture in the follow-up study. In terms of calculating excess and population attributable risk, this is an observational study, so these are odds ratios. If the outcome is rare, then odds ratios often are a pretty good representative of relative risk. They cannot get at excess risk and population attributable risk with a case-control study like this (though Dr. Reingold said he was not sure this was right). One thing that makes this different from a lot of case-control studies is that the outcome is common, which makes it difficult to make comparisons between odds ratios and relative risk.

Dr. Riley said this begs the question regarding whether this is the right study design to examine SABs, because it is incredibly common and there are a million reasons why SABs occur. While 50% to 60% may be chromosomal abnormalities, this also makes the biologic plausibility even harder to understand. She is concerned that there is a signal, which will be followed up with perhaps not the ideal study design to actually answer the question in a way that people need. What she would want to know as a clinician and patient would be the attributable risk to getting an influenza vaccine.

Dr. Donahue emphasized that the follow-up study would not be able to determine attributable risk. There are a number of tradeoffs with different study designs. They had a meeting within VSD among all of the investigators to try to figure out the best study design. Taking all things into consideration, practically and scientifically, the matched case-control was determined to be the best study design.

Dr. Belongia completely agreed that they would like to know the excess risk associated with influenza vaccination in a setting where there is already a risk for many other issues. The excess risk may be very low, even if the odds ratio appears to be relatively high and may account for a tiny proportion. Unfortunately, this design does not get at this. Through all of the discussions in VSD, they have not come up with any other options other than a very large, multi-year cohort study, which does not seem very feasible and would take a long time to implement. The more immediate question regards whether what they observed in those two seasons is an anomaly or not. If they at least replicate the study and do not find it again, though they still will not know what happened, but at least they can be confident that there is no reason to be concerned. If they do find it, it does raise a question because the excess risk is not known.

Dr. Kempe said she did not quite understand what Dr. Donahue presented about the timing of the vaccine versus presentation for SAB. She asked whether they were able to discern how many of those women got the vaccine on the same visit.

Dr. Donahue indicated that if they knew the data of vaccination, they simply went back and got all of the diagnoses that were assigned on that date. Essentially, it was the outcome driving the exposure.

Dr. Kempe asked what percent of very early SABs present for care, and might there not be some ascertainment bias in women who knew they got a shot and were worried about it.

Dr. Riley said she thought that was the concern. Many women do not know they have had a miscarriage. In addition, it is not standard to get an ultrasound in the first trimester for absolutely everybody, especially this early. Prenatal diagnoses are being done at 10 and 12 weeks. Women are not being offered an ultrasound at 5.5 and 6 weeks. For many women, a pregnancy is not even established. For the 20% of women who did not have an ultrasound where the pregnancy is known to be established, it is still questionable.

Ms. Pellegrini noted that her day job is at the March of Dimes where the mission is “Healthy pregnancies and healthy babies.” This study provoked a great deal of conversation. While 50% to 60% of early SABs are due to chromosomal abnormalities, another roughly 30% have normal chromosomes but morphological abnormalities. So, the percentage of cases that are even potentially being affected by influenza vaccination is very small. When combined with the small N in this study and the lack of some other key data, this raises a lot of questions and uncertainty. For example, one of the other data elements that would be useful to have is the date of the most recent pregnancy before the one that was lost. It is known that rapid repeat pregnancies in less than 18 months are much more susceptible to adverse birth outcomes, including miscarriage. Given the small numbers, it is not clear that this is the full picture.

Dr. Plotkin (Vaccine Consultant) asked whether there is any information about respiratory illnesses in these women. It has been demonstrated fairly clearly that people who have serial vaccinations 1 year after the next and the strain does not change between years have a lower efficacy of influenza vaccine and, therefore, less protection against influenza. This is one of the reasons one vaccinates pregnant women. He emphasized that infection with influenza is an important variable in looking at this situation in terms of whether women have illnesses themselves that could precipitate SAB.

Dr. Donahue replied that they tried to address this question by going back to the data to capture all diagnoses for influenza, but did not capture all diagnoses for respiratory illness in general or acute respiratory illness (ARI). They did not identify too many, and do not have good capability to do so. He said it would be nice to identify women who actually were infected with influenza, but this is difficult to do unless a prospective study is conducted.

Dr. Lee acknowledged that this is one of the toughest topics to study in all of vaccine safety. She thinks the question of average gestational age in terms of the timing of the SAB is important. Related to that, she wondered if it would be possible to perform some type of sensitivity analysis on whether the LMP dating is accurate. That can be challenging depending on how it was validated.

Dr. Donahue responded that they did not perform a sensitivity analysis for the study he presented, but do plan one for the follow-up study. The median gestational age for cases in their study was 7 weeks. There is a pretty steep curve at 6 to 8 weeks, and then the vast majority (~99%) are by 10 weeks gestational age.

Regarding Dr. Plotkin's comment, Dr. Belongia recalled that they did assess febrile illnesses during the period prior to the miscarriage and that was relatively uncommon.

Dr. Donahue added that they assessed febrile illness in the first 3 months as well as the first 2 weeks preceding the actual SAB. There were only 3 or 4 cases that had febrile illness in that interval, at least in the 2 weeks before.

WG Considerations: Influenza Vaccines

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

Dr. Grohskopf indicated that the 2017-2018 ACIP influenza recommendations were published in the *MMWR* on August 25, 2017. Since publication, there has been one influenza vaccine licensure change. Afluria® Quadrivalent, which is an IIV4 manufactured by Seqirus, previously licensed for ages ≥18 years is now licensed for ages ≥5 years. The *MMWR* will not be reprinted; however, this information has been updated on the Table of Vaccines on the CDC web pages and on the brief summary of the recommendations on the ACIP website.

Regarding FluMist® Quadrivalent (LAIV4), the WG received a presentation of the same information presented during this session. Some of the WG discussion topics included various aspects of design and analysis of various studies, including the non-US observational studies, and the adequacy of shedding as a correlate of protection in terms of LAIV. No policy change was proposed with regard to LAIV for this meeting. The WG is looking forward to hearing the pediatric shedding study results in the near future. Anticipated for discussion during the February 2018 ACIP meeting are the analysis of combined LAIV effectiveness data from US observational studies, and discussion of a systematic review of post-pandemic LAIV effectiveness.

With regard to the SAB study presented by Dr. Donahue during this session, this study was presented initially to the WG and also to ACIP during the June 2015 meeting. The WG had another opportunity to hear the data post-publication. Some of the discussion included early median gestational age of SAB events which is characteristic of SAB events in general, the difficulty of studying this topic, biologic plausibility, and the decrease in magnitude of association from 2010-2011 to 2011-2012. It is important to note that the confidence intervals are fairly wide and the numbers relatively small. Nevertheless, the decrease in magnitude of the association was noted and discussed. One thing that was under discussion regarded what might be unique about H1N1pdm09 in particular, especially given that this was not seen with the earlier study with a similar design. There is a discussion of this work in the background materials for the current season 2017-2018 statement that was not yet published at the time of publication, so the information referenced is still the ACIP presentation from June 2015. However, this information has been referenced in the ACIP guidance for the current season and for the 2016-2017 season. The various other studies conducted previously to this one that did not note an association between SAB and receipt of influenza vaccine are discussed. No policy change was proposed for this meeting. Current language states that "Influenza vaccine can be given at any time during pregnancy, before and during the influenza season." Age-appropriate inactivated or recombinant vaccine is recommended. As noted earlier, results of the follow-up study described by Dr. Donahue are anticipated in 2018 or 2019.

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 related to that are focused on: 1) Reviewing the epidemiology of mumps in the 2-dose vaccine era, including the international experience; 2) Reviewing available evidence on duration of immunity for mumps after 2 doses of measles, mumps, rubella (MMR) and other risk factors for vaccine failure; 3) Reviewing the available evidence on the benefit provided by a third dose of MMR for mumps outbreak control; and 4) Evaluating programmatic implications and cost of various policy options for a third dose of MMR to prevent or control mumps outbreaks.

The Mumps WG has been very active over the last few months. Although evidence is not abundant for a third dose of an MMR vaccine for mumps outbreak control, the WG has sought it wherever it could be found. The WG members have a wide variety of areas of expertise (infectious diseases, mumps, immunology, vaccine policy, epidemiology, disease modeling, disease control); as well as organizations represented from state public health, academia, federal agencies (CDC, FDA, IHS), professional medical societies (AAP, AAFP, IDSA), college health, and consumer protection. The WG has reviewed published and unpublished data, including results of surveys conducted at the request of the WG to try to assess opinions from students and parents, as well as getting feedback from health departments and universities and mumps outbreak data for 2016-June 2017 from health departments across the US.

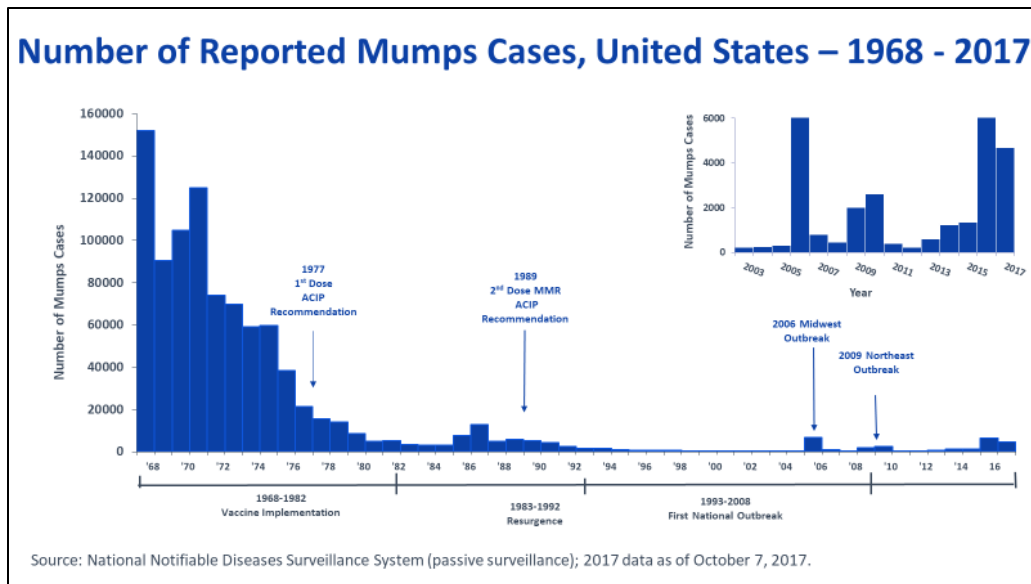
After reviewing all of this evidence, the WG assessment is that the scientific evidence is limited and insufficient at this time to fully characterize the impact of a third dose of MMR vaccine on reducing the size or duration of mumps outbreaks. However, the WG agrees that there is evidence available for a proposed recommendation to decrease the risk for mumps disease in persons at increased risk because of an outbreak.

This session included three presentations leading up to a vote: 1) an update on mumps epidemiology in the US, 2017; 2) GRADE evaluation of the evidence on the third dose of MMR vaccine; and 3) WG considerations and proposed recommendations.

Update on Mumps Epidemiology in the US

Mona Marin, MD
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Centers for Disease Control and Prevention

For this presentation, Dr. Marin provided an update on mumps epidemiology in the US. This figure shows the number of reported mumps cases in the US during the vaccine era:



Since introduction of the vaccine program in 1977, the number of mumps cases has declined by approximately 99%. However, mumps outbreaks have been reported since 2006 resulting in the increased number of cases in certain years, as shown in the inset.

Since 2012, there has been an increasing trend in the mumps case count, incidence, number of outbreak cases, proportion of outbreak-related cases among all reported cases, and number of jurisdictions reporting outbreak cases. 2016 had the highest number of cases overall, outbreak-related cases, and jurisdictions reporting outbreaks in a decade. Although preliminary, this trend appears to continue in 2017. As of October, the case count has reached more than 4600, incidence is lower than in 2016 but higher than any other year before 2016, and outbreak-related cases represent two-thirds of all cases, with 33 US jurisdictions reporting outbreaks. In 2017, the highest incidence continues to be in young adults 18 through 22 years of age, similar to previous years. The median age among mumps case-patients is 21 years, of which 75% with known vaccination history have had at least 2 doses of MMR vaccine.

Next, Dr. Marin presented data on epidemiologic characteristics of mumps outbreaks and outbreak-associated cases that occurred between January 2016 and June 2017, CDC obtains information on mumps outbreaks in three ways: by media reports, through direct phone call notification by jurisdictions, or through NNDSS. While NNDSS uses case-based surveillance to monitor disease activity nationally, it is not always possible to determine the number or size of outbreaks that occur within or across jurisdictions. Considering these limitations, in July 2017 CDC requested that jurisdictions support enhanced surveillance and submit aggregate-level outbreak data for mumps to better characterize the burden of outbreaks nationally.

CDC developed a mumps outbreak data collection tool that was sent to all 50 states and 2 jurisdictions that transmit data to NNDSS. Jurisdictions were asked to report aggregate data from all individual outbreaks that met the Council of State and Territorial Epidemiologists (CSTE) case definition of 3 or more cases linked by space and time and occurred between January 1, 2016 and June 30, 2017. Outbreaks that began in 2015 but went through 2016 also were included in the data collection. The data collection tool consisted of 3 sections: description of each outbreak, characteristics of case-patients, and control measures implemented during

each outbreak, including use of an outbreak or 3rd dose of MMR vaccine, which will hereafter be referred to as MMR3.

The response rate to CDC request was 98%, with only one jurisdiction not responding. From January 2016 through June 2017, 150 mumps outbreaks were reported, accounting for 9200 mumps cases, with 39 (76%) of jurisdictions reporting at least one outbreak. The median number of cases per outbreak was 10 and the median age of case-patients in these outbreaks was 21 years. Jurisdictions reported that an outbreak or 3rd dose of MMR vaccine was used in 35 (23%) outbreaks.

By setting, 75 (50%) outbreaks occurred in university settings, including outbreaks limited to sports teams and Greek organizations. Outbreaks in university settings accounted for 3664 (40%) cases. Community settings accounted for 32% of all outbreaks with organized groups such as churches, work settings, parties, and fitness centers accounting for 25% of all outbreak settings. Outbreaks in community settings accounted for 5238 (57%) cases. Schools, including elementary, middle, and high school accounted for 13% of all outbreak settings and household outbreaks accounted for only 5%. Of the outbreaks reported, 50% consisted of 3 to 9 cases, while 13% had 50 cases or more. These larger outbreaks accounted for 83% of all outbreak-related cases. The median duration increased with increase in the size of the outbreak, with outbreaks with 20 cases or more lasting more than 3 months. Regardless of size, the median age range was similar for each group, and ranged between 17 through 21 years of age.

In terms of the distribution of outbreak setting by size of outbreak, university outbreaks were the most common setting regardless of outbreak size and ranged from 40% to 78%. Overall, of the 35 outbreaks where an outbreak or 3rd dose of MMR vaccine was used, 24 (69%) occurred in universities. By setting, an outbreak or 3rd dose of MMR vaccine was administered in 32% of outbreaks that occurred in universities, 19% of community outbreaks, 11% of other school outbreaks, and none in outbreaks in household settings.

Regarding case-patient level information for outbreak-associated cases, examining the number and rate of complications by vaccination status, 350 case-patients were vaccinated with 3 doses of MMR vaccine at the time of infection, with only 2 complications reported in this group (less than 1%) while among the 5015 case-patients who had 2 doses of MMR vaccine 139 complications were reported (approximately 2.8%). In total, 270 complications occurred among 9200 case-patients, for a rate of 2.9%.

Comparing complication rates between the pre-vaccine era, published reports from 2006 to 2015, and data collected from these more recent outbreaks, in the pre-vaccine era, morbidity from complications was high. Published results showed that the proportion of complications was much lower in the vaccine era than in the pre-vaccine era. The 2016-2017 mumps outbreak data further support the conclusion that complications from mumps infection are much lower in the vaccine era.

To conclude, mumps outbreaks continue to be a public health burden. Young adults between the ages of 17 through 21 are at highest risk of disease. Half of all outbreaks reported occurred in university settings. Also, although half of outbreaks were less than 10 cases, 13% had 50 cases or more and accounted for over 80% of all outbreak-associated cases. While complications do still occur, the rates of complications in vaccinated persons remain low.

Discussion Points

Dr. Reingold asked whether there is any way to use the data CDC has to answer the question regarding whether vaccination in response to an outbreak has any impact.

Dr. Marin responded that the data have been collected regarding this issue and this assessment is ongoing.

Dr. Messonnier added that CDC will continue to examine the impact of vaccine on outbreaks, but it is anticipated that this analysis will be conducted over a longer period of time as additional evidence is accumulated. Because every outbreak is so different, it is very difficult to provide a precise answer.

GRADE: Third Dose of MMR Vaccine

Mariel Marlow, PhD, MPH

Division of Viral Diseases

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Centers for Disease Control and Prevention

Dr. Marlow presented the results of the GRADE evaluation of evidence on a third dose of MMR vaccine for the following GRADE steps: develop policy questions, consider critical outcomes, review and summarize evidence of benefits and harms, and evaluate the quality of evidence. The policy question for consideration is, "Should a third dose of MMR vaccine be administered to persons at increased risk for mumps because of an outbreak?" The population of interest is persons at increased risk for mumps because of an outbreak, the intervention is a third dose of MMR vaccine, and the comparison is two doses of MMR vaccine.

The outcomes the WG considered most important were: mumps disease, complications of mumps disease, duration of protection, immune response, SAEs, and reactogenicity (considered here as non-serious local and systemic AEs). Outcomes included in the evidence profile are divided into benefits and harms and each given an importance level of critical or important. The WG deemed the benefits outcomes to prevent mumps disease and prevent complications of mumps disease as critical, and duration of protection and immune response as important. The WG deemed the harms outcome SAEs as critical and reactogenicity as important.

The WG conducted a systematic review of studies in any language from PubMed, Embase, CIHNAL, Cochrane, Scopus, and clinicaltrials.gov databases. Efforts were made to obtain unpublished or other relevant data. The search string used to obtain all articles potentially related to a third dose of MMR included the following:

- "mumps" or "parotitis"
- and "vaccine" or "immunization" or "MMR"
- and "third" or "three" or "outbreak" or "additional" or "booster" and "dose"
 - or ("booster" and ("outbreak" or "epidemic")) or "military"

Included articles presented primary data on a third dose of MMR vaccine as the intervention, at least one outcome of interest, and were not animal studies. Working with an expert in library sciences, the WG identified 394 references via database searches, 81 references from clinical trials.gov, and 3 unpublished articles or datasets. Based on review of the titles and abstracts,

478 articles were pre-screened for exclusion and 53 were identified for full text screening. Of these latter articles further excluded were 34 that did not report data on a third dose as the intervention, 4 that did not report on the outcomes of interest, 1 study that was conducted only in immunocompromised children, and 3 studies with results not yet reported or not found. Ultimately, 11 studies were considered in the GRADE analysis.

For the GRADE analysis, the body of evidence is first assigned an initial evidence type based on the study design of included studies and ranked from 1 being the highest (for RCTs or overwhelming evidence from observational studies) to 4 being the lowest (clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations). Following GRADE methodology, all observational studies start as evidence type 3, the second lowest evidence type. It is worth noting that RCTs are challenging to conduct during mumps outbreaks due to ethical considerations.

In terms of the GRADE evidence for outcomes related to benefits of a third dose, the first outcome is VE against mumps in third dose vs two dose vaccinees. Three cohort studies reported on this outcome: Cardemil (2017), Nelson (2013), and Ogbuanu (2012) which included university students and school children, aged 11 to 17 years and 9 to 14 years, respectively. All studies were conducted in outbreak settings among populations with high 2-dose MMR coverage. One study, Fiebelkorn et al. from 2013, reported an attack rate but used a third dose for PEP among household contacts and was not included as part of the body of evidence for this outcome. All studies reported a lower attack rate in third-dose vaccinees compared with two-dose vaccinees. VE at 21 to 28 days post-vaccination was 61%, 78%, and 88%, but only the VE estimate of 78% for university students was significant with a p value less than .001. This estimate of effect was calculated using the hazard ratio and adjusted for 28 days post-vaccination and time since second MMR vaccination. The evidence type for third dose VE against mumps is 4. The 3 cohort studies were downgraded for serious risk of bias that included selection bias. The evidence also was downgraded for serious imprecision, given that the estimates had large confidence intervals of which some included no effect.

For outcomes two (VE against mumps complications) and three (duration of protection), no studies reported on VE against mumps complications and no clinical studies reported on duration of protection. Therefore, the WG was not able to determine the evidence type for these two outcomes.

For the fourth outcome, immune response, three repeated measures studies were evaluated: Latner (Unpublished), Fiebelkorn (2014), and Date (2008). These studies compared pre-third dose antibody titers with post-third dose antibody titers at multiple time points. The Latner and Fiebelkorn studies used serum samples from the same cohort, but different antibody detection methods. For immune response estimates of effect, the studies used 4 antibody detection methods, that included whole virus, nucleoprotein, and hemagglutinin-neuraminidase enzyme-linked immunosorbent assays (ELISAs), and plaque reduction neutralization assays (PRNTs). All studies showed a reduction in the proportion of persons with negative titers at 1 month post-third dose vaccination. Antibody levels also were significantly higher at 1 month, but then decreased to near baseline levels by 1 year. Since there is no correlate of protection for mumps, seronegative cutoffs were defined by each author. The evidence type for the outcome immune response is 4. The 3 repeated measures studies were downgraded for serious risk of bias that included potential selection bias. The studies also were downgraded for serious indirectness given there is no correlate of protection for mumps, immunogenicity was used as a proxy for effectiveness, samples were tested against vaccine strain versus circulating strain antigens, and studies were conducted in non-outbreak settings.

Regarding the evidence for outcomes of potential harms, for the fifth outcome, SAEs, 1 pre- and post-study and 4 case series studies reported on SAEs of a third dose of MMR vaccine: Routh (unpublished), Albertson (2016), Aasheim (2014), Nelson (2013), and Abedi (2012) and Ogbuanu (2012). The latter 2 studies, Abedi and Ogbuanu, reported the same survey data and were considered as one study for this analysis. Abedi/Ogbuanu and Nelson were cohort studies, but were considered case series for this outcome because the outcome was only reported for third dose vaccinees (no 2-dose MMR comparison group). An SAE is defined as death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability. No SAEs were reported in 14,368 children and young adults vaccinated with a third dose. Of the studies, 2 were based on passive reporting (Albertson and Aasheim) and 3 (Routh, Nelson, Abedi/Ogbuanu) actively surveyed vaccine recipients. In addition, no healthcare visits for vaccination-related symptoms were reported in any of the studies. No serious criteria for downgrading were identified among the 1 pre- and post- study and the 4 case series studies. The evidence type for the pre- and post- study remained a 3. When considered together, the case series studies were upgraded (to evidence type 2) for strong strength of association, given that no cases were found among over 13,000 actively and passively surveyed third dose vaccinees. Together, the highest evidence type, 2, is the overall evidence type for this outcome.

Three of the studies that reported SAEs also reported on the sixth outcome, reactogenicity (Routh, Nelson, Abedi/Ogbuanu). The pre- and post- study was conducted among young adults and the two case series studies were conducted among school children aged 9 to 14 years and 11 to 17 years, respectively. Regarding the estimates of effect for reactogenicity among young adults from the pre- and post- study that prospectively monitored adults aged 18 to 28 years (Routh), episodes of 14 symptoms were solicited using daily diaries from 2 weeks before third dose vaccination (baseline) to 4 weeks after third dose vaccination. Of these, 4 symptoms (joint problems, headache, diarrhea, swollen glands) were significantly elevated among subjects after vaccination with a third dose compared with baseline. The estimated net percent of vaccinees with 1 or more episodes attributable to third dose vaccination were 6% for joint problems, 7% for headache, 9% for diarrhea, and 12% for swollen glands. Median duration of these symptoms was about two days.

In terms of reactogenicity estimates of effect for children who were observed in the two case series studies, parents of children were retrospectively surveyed on symptoms their child experienced within two weeks post-third dose vaccination. The surveys were conducted 2 to 4 months after the third dose vaccination campaigns. Among children aged 11 to 17 and 9 to 14 years, 6% to 7% experienced at least one symptom. The most frequently reported symptoms were pain, redness, or swelling at injection site, joint ache, and dizziness, all of which occurred in 2% to 4% of vaccinees. For the outcome of reactogenicity, the pre- and post- study was downgraded for serious risk of bias from potential observer effect, and the 2 case series studies were downgraded for serious risk of recall bias. Together, the overall evidence type for this outcome is 4.

In summary of the GRADE evidence for a third dose of MMR vaccine versus two MMR doses for persons at increased risk for mumps disease because of an outbreak, the critical outcome of preventing mumps was supported by 3 cohort studies. Results from all studies suggested that a third dose was effective at preventing mumps, with one study demonstrating a significant effect. No studies assessed the effectiveness of a third dose to prevent mumps complications and an evidence type was not determined for this outcome. No SAEs were observed in 1 pre- and post- study and 4 large case series studies. The evidence types supporting these critical

outcomes are 4 for preventing mumps, not determined for preventing mumps complications, and 2 for SAEs.

Considerations, Proposed Recommendations, Vote

Mona Marin, MD

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Centers for Disease Control and Prevention

Dr. Marin began by providing the context for this presentation. Numerous mumps outbreaks have been reported in the US since late 2015, with the majority occurring in university settings and young adults being at highest risk for mumps. CDC guidance for health departments for use of MMR3 vaccine in outbreak settings has been available since 2012. However, CDC has heard from various stakeholders that an ACIP recommendation would provide better clarity. Evidence is limited and insufficient at this time to fully characterize the impact of MMR3 on reducing the size or duration of mumps outbreaks, though studies are ongoing to address this question. However, the mumps WG agrees that evidence is available for a potential recommendation to decrease risk for mumps disease in persons at increased risk because of an outbreak.

From this perspective, in this presentation Dr. Marin covered the remaining steps of the GRADE process for the policy question, “Should a 3rd dose of MMR vaccine be administered to persons at increased risk for mumps because of an outbreak?” The steps she addressed included the following: assess population benefit, evaluate values and preferences, considerations for formulating recommendations, and the WG’s proposed recommendation and GRADE category. Health economic data were not presented during this session. The WG used the format of the draft ACIP Evidence to Recommendation Framework to select factors important for developing recommendations and questions used to guide the WG’s discussions. These factors include: problem, benefits and harms, values, acceptability, and implementation. For each of these factors, Dr. Marin first presented a summary of the evidence reviewed by the WG, followed by the WG’s interpretation.

Starting with the problem, the burden of disease was reviewed during the earlier presentation. Therefore, for the problem Dr. Marin provided a brief summary of the evidence. The 2-dose MMR childhood vaccination program led to a significant decline in reported mumps cases in the US. Mumps can occur in persons vaccinated with 2-doses of MMR vaccine (or MMR2) but incidence is significantly lower in the 2-dose era compared with pre-vaccine and 1 dose eras. An increase in the number of cases and outbreaks has been observed since 2006. Outbreaks were reported in settings with high MMR2 coverage and most occurred in populations with high contact rates that facilitate transmission, mainly universities. Mumps outbreaks are occurring in more US jurisdictions in recent years. Outbreak control measures are resource-intensive for institutions and public health. Severity of mumps among MMR2 vaccinated persons is reduced. Considering the evidence on burden of disease, the WG interpretation of the evidence is that outbreaks, as opposed to sporadic disease, are a public health priority for the mumps vaccination program.

The WG then reviewed several lines of evidence to understand why this burden is occurring. Regarding 2-dose MMR vaccine effectiveness for prevention of mumps, the summary of the evidence reviewed by the WG is that the median 2-dose mumps vaccine effectiveness is 88%, with the range of estimates of 31% to 95%. Most studies included persons with the second

dose of MMR received less than 10 years prior. The 31% estimate is from the IA study in which students were vaccinated with MMR2 at least 13 years since the start of the outbreak. Of the studies, 7 were conducted in young adults and the median vaccine effectiveness was 84%. There is increased risk for mumps¹ and decreased VE with time since the second dose of MMR². The risk for mumps complications is lower among cases vaccinated with 2 doses of MMR compared with unvaccinated³. Most outbreaks occurred in residential or educational settings with high population density. Spread to the broader community was limited. The WG interpretation of the evidence on 2-dose VE is that the 2-dose program is acceptably effective at preventing mumps disease and complications in the general population, but not sufficiently effective at preventing mumps outbreaks in all close contact settings, although protection against severe disease is maintained [¹Cortese et al. *Clin Infect Dis* 2008; Vygen et al. *EuroSurveill* 2016; Cardemil et al. *N Engl J Med* 2017; ²Cohen et al. *Emerg Infect Dis* 2007; Cardemil et al. *N Engl J Med* 2017; ³Sane et al. *Emerg Infect Dis* 2014; Yung et al. *Emerg Infect Dis* 2011; Zamir et al. *Hum Vaccin Immunother* 2015].

Regarding the immune response to mumps virus, the summary of evidence, which is based on limited laboratory data and compared to measles and rubella immune responses, shows lower antibody levels after mumps natural infection or vaccination¹, as well as lower quality of antibodies in terms of avidity and failure to generate strong memory B cell responses². Neutralizing antibodies are important for protection and persons with lower neutralization titers had increased risk for disease³; however, there is no defined immunologic correlate of protection. Mean mumps antibody titers, both neutralizing and non-neutralizing, decline over time in MMR2 vaccine recipients⁴. The WG's interpretation of the evidence is that the immune response to mumps virus is less robust compared with the response to measles and rubella viruses and that vaccine-induced mumps virus-specific antibodies wane over time, potentially leading to inadequate protection against mumps for populations in conditions of highest risk [¹Lerman et al. *Pediatrics* 1981; Gans et al. *J Infect Dis* 2001; ²Kontio et al. *J Infect Dis* 2012; Latner et al. *Clin Vaccine Immunol* 2011; ³Cortese et al. *J Infect Dis* 2011; Gouma et al. *Open Forum Infect Dis* 2014; and ⁴Davidkin et al. *J Infect Dis* 2008; LeBaron et al. *J Infect Dis* 2009; Rubin et al. *J Infect Dis* 2008; Date et al. *J Infect Dis* 2008; Kontio et al. *J Infect Dis* 2012].

Lastly, the WG reviewed the evidence on changes in the molecular epidemiology of wild-type mumps virus which is summarized as vaccine contains genotype A virus; since 2006, genotype G has been predominantly circulating in the US though other genotypes were occasionally introduced by importation. There is no evidence to date that circulating mumps strains escape vaccine-induced immunity. MMR2 vaccine recipients all had neutralizing antibody against genetically diverse mumps strains when studied soon and 10 years after vaccination¹. However, studies found MMR2 vaccine recipients had lower (about one-half) neutralizing antibody GMTs to non-vaccine strains compared to the Jeryl Lynn vaccine strain. The significance of this finding is difficult to interpret in the absence of a known level of neutralizing antibody that predicts protection. The WG concluded that there is insufficient evidence to support that antigenic differences between vaccine and circulating mumps strains are a major contributor to the current burden of mumps [¹Rubin et al. *J Infect Dis* 2008; Rubin et al. *J Virol* 2012].

In summary, for the problem, the WG's interpretation is that persons at increased risk for mumps because of an outbreak are a public health priority for the mumps vaccination program and that waning immunity from vaccination in the setting of increased force of infection typical of outbreaks contributes to this risk.

Next, Dr. Marin presented the evidence for the second factor examined, benefits and harms of the intervention, which is the 3rd dose of MMR vaccine. As a reminder, the WG identified prevention of mumps disease, prevention of complications of mumps disease, duration of protection, and immune response to MMR3 as benefits and SAEs and reactogenicity after MMR3 as harms. Since the previous presentation described the evidence on benefits and harms, Dr. Marin only briefly summarized it in her talk. For prevention of mumps, 3 studies reported a lower attack rate in MMR3 versus MMR2 vaccinated recipients. VE ranged from 61% to 88%, with one estimate reported as significant at 78%. The summary of the study that provides the strongest evidence to date on benefit of the 3rd dose of MMR for prevention of mumps includes: there was a lower attack rate for mumps in students vaccinated with MMR3 versus MMR2 ($p < 0.001$); there was increased risk for mumps with increased time since MMR2; and receipt of MMR3 was associated with a 78% lower risk for mumps than receipt of MMR2 before the outbreak with a 95% confidence interval of 61% to 88%.

For prevention of mumps complications, no clinical studies were conducted. However, by preventing disease in 3rd dose vaccinated persons, complications that would have occurred had these persons had disease are also prevented. For duration of protection, no clinical studies were available. For immune response, studies showed an increase in the proportion of seropositive persons and antibody titers at 1 month post-MMR3 with a trend toward decline in both the proportion of seropositive persons and antibody titers at 12 months post-MMR3. For harms, the evidence reviewed showed there were no SAEs or vaccine-related health care visits in more than 14,000 MMR3 vaccine recipients evaluated. For reactogenicity overall, local and systemic non-serious AEs post-MMR3 were mild and reported at low rates. Among young adults, headache, joint pain, diarrhea, and swollen glands were reported at higher rates post-MMR3 compared with pre-MMR3. Duration was short, with a median of 1 to 3 days.

Based on this evidence, the WG interpreted the balance of benefits and harms to be that the benefits of MMR3 outweigh the risks. Data demonstrated a short-term benefit of MMR3 vaccine for persons in outbreak settings. There are no concerns for SAEs after MMR3. Injection site reactions and non-serious systemic AEs were mild and reported at low rates. The evidence type is 4 for benefits and 2 for harms.

Dr. Marin next presented the evidence on values of the target population, acceptability, and implementation from the stakeholders' perspective. To provide evidence for the WG's assessment of these factors, CDC conducted surveys of identified stakeholders. Students and parents were surveyed to learn more about their values and acceptability of a third dose, and health departments and universities and colleges were surveyed to learn more about the acceptability and implementation of a third dose in an outbreak setting. Because these data had not yet been presented to ACIP, Dr. Marin presented the main results from these surveys.

Regarding the students' and parents' opinions, CDC contacted several universities that experienced mumps outbreaks in 2016 and 2017 and only 1 of 5 agreed to participate. For the university that participated, the response rate was low and therefore data were not presented. The university survey was distributed through the American College Health Association (ACHA). 26% or 251-member student health service administrators responded. This included universities and colleges (referred to hereafter as universities) from 47 states. Of universities, 31% had mumps cases reported on campus since August 2014, of which 41% had a mumps outbreak. Of universities with mumps cases or outbreaks, 22% recommended an outbreak or third MMR vaccine dose. From the universities' experience, most respondents ranked student and parent attitudes toward a 3rd dose of MMR to protect the student during an outbreak as positive (more than 5). On a scale from strongly negative (0) to indifferent (5) to strongly

positive (10), 83% ranked students' attitudes toward the recommendation and 67% ranked students' attitudes toward attending a campaign as higher than 5. Of the respondents, 80% ranked parents' attitudes toward the recommendation as higher than 5. The median ranking was between 6 and 7. Of note, very limited numbers were negative.

Although no formal cost-benefit analysis was conducted, based on their experience using an outbreak or third MMR vaccine dose and compared with other outbreak control measures, on a scale from least to most, 60% of respondents felt the intervention was effective to some extent (better than neutral) and 53% regarded favorably the benefit of the intervention relative to its cost, both with a median of 6. Of the respondents, 75% were likely to recommend an outbreak or third dose again and 38% would recommend it without hesitation, with a median of 8 overall. On a scale from not disruptive (0) to extremely disruptive (10), almost all respondents indicated outbreaks resulted in some degree of disruption on campus, with half placing the intensity of disruption in the upper half of the scale (more than 5). Of the universities, 57% ranked disruption of mumps outbreaks to student life higher than 5, while 67% ranked disruption to staff and administrative activities greater than 5. Both had a median rank of 6.

The health department survey was distributed through CSTE to 62 state and territorial and 23 city or large urban health departments. Of the health department jurisdictions, 72% responded. Of these, 75% or 46 reported having 1 or more mumps outbreaks since January 1, 2016. Of those, 47% reported recommending an outbreak or third dose of MMR vaccine during at least one outbreak. Among health departments that used an outbreak or third dose, on a scale from not effective (0) to most effective (10), 42% felt that the intervention had an effectiveness score higher than 5 (more than somewhat effective), with a median of 5. Of the health departments, 53% regarded favorably the benefit of the intervention relative to its cost (score higher than 5, more than somewhat effective), with a median of 7.

The WG's interpretation for values of the target population is based on expert opinion. The WG considered that students and parents are concerned about mumps complications and the potential for loss of productivity, but not concerned with SAEs following the 3rd dose of MMR. For acceptability, stakeholders who implemented an outbreak/MMR3 recommendation had a positive experience overall, including a positive assessment of students' and parents' attitudes. For implementation, the WG agreed that an ACIP recommendation would allow health departments to make more rapid decisions regarding use of MMR3 and increase access to MMR3 for persons identified at increased risk because of an outbreak. The WG also considered that additional implementation guidance from CDC for the 3rd dose will be needed.

To address this need, CDC will update the guidance for use of a 3rd dose of MMR vaccine during mumps outbreaks with input from the WG and other stakeholders. Among the factors to be considered in the development of the new guidance are size of the target population, mumps incidence/number of cases, 3rd dose MMR vaccine coverage needed to impact an outbreak, timing of vaccination with MMR3, social networks, and intensity and duration of close contact of the target population.

CDC has several ongoing or planned priority activities to inform the development of this guidance and increase the understanding of the impact of a 3rd dose of MMR, which include development of transmission models to examine the factors that impact size and duration of an outbreak, examination of the contribution of antigenic differences between vaccine and circulating mumps strains on burden of mumps, evaluation of the quality of antibodies (namely avidity) after the third dose of MMR compared with after the second dose, and monitoring the

burden of disease over time among MMR3 vaccine recipients to better characterize the duration of enhanced protection after MMR3.

To conclude, to answer the policy question on whether a 3rd dose of MMR vaccine should be administered to persons at increased risk for mumps because of an outbreak, the WG's interpretation of the evidence reviewed is that for the problem, persons at increased risk for mumps because of an outbreak are a public health priority for the mumps vaccination program. Waning immunity in the setting of increased force of infection typical of outbreaks contributes to this risk. For benefits and harms, benefits outweigh the risks. The evidence type is 4 for effectiveness and 2 for safety. For values, the WG considered that persons in outbreak settings value prevention of mumps, mumps complications, and of loss of productivity. For acceptability, MMR3 vaccination was considered acceptable to students, parents, universities/schools, and health departments. For implementation, providers and the target population have experience with MMR vaccination. Public health should be involved in identifying groups at increased risk for mumps during an outbreak. In summary, there was WG agreement that a 3rd dose of MMR vaccine would improve protection for persons at increased risk for mumps because of an outbreak.

Before presenting the WG's proposed recommendation, Dr. Marin summarized the WG deliberations. There was unanimity among WG members that there is sufficient evidence to propose a recommendation to decrease risk for mumps disease in persons at increased risk because of an outbreak. The WG considered that public health should have a role in designating or identifying groups at increased risk, for several reasons: public health is routinely involved in declaring and responding to outbreaks and determining groups at increased risk; and, this will be helpful for providers who are not directly associated with the outbreak setting.

As far as the proposed recommendation's wording, the majority of WG members favored a wording indicating that persons previously vaccinated with two doses of MMR vaccine who are identified by public health as at increased risk for mumps because of an outbreak should receive a third dose of MMR vaccine to protect against mumps disease and its complications. A small minority of WG members preferred "may" instead of "should" in the wording - "may receive a third dose of MMR vaccine to protect against mumps disease and its complications." The main reasons expressed in support of "may" were: acknowledgement that there is a benefit, but the additional benefit is modest and disease is generally mild; the GRADE evidence type is low and evidence comes largely from one study; and a "may" recommendation would not obligate immunization campaigns by organizations and public health in response to outbreaks. The main reasons expressed in support of "should" were: evidence demonstrate a benefit of MMR3 for individuals; a single well-conducted vaccine effectiveness study during an outbreak on a college campus is sufficient—it is unlikely the evidence type will improve as biases are difficult to control in observational studies, particularly when conducted during outbreaks; a "should" recommendation is clear, much easier to communicate and promote, and is preferred by providers.

Lastly, looking at the implications of the proposed recommendation in the context of the existing recommendations for mumps vaccination, the impact would be only for persons previously vaccinated with 2-doses of MMR vaccine who are in an outbreak setting. All other combinations of vaccination status are covered by the existing recommendation. There would be no recommendation at this time for persons who have already received 3 or more doses of MMR vaccine.

For the policy question “Should a 3rd dose of MMR vaccine be administered to persons at increased risk for mumps because of an outbreak?” the WG proposed the following recommendation:

Persons previously vaccinated with two doses of a mumps-containing vaccine* who are identified by public health as at increased risk for mumps because of an outbreak should receive a third dose of a mumps-containing vaccine to improve protection against mumps disease and related complications.

*As stated in Prevention of Measles, Rubella, Congenital Rubella Syndrome, and Mumps, 2013: Summary Recommendations of the Advisory Committee on Immunization Practices (ACIP); wording includes MMR and MMRV.

Discussion Points

Dr. Atmar asked whether the timing from MMR2 to MMR3 would be identified by public health as an increased risk, because this recommendation does not give any guidance for the individual who received MMR2 a month ago, 6 months ago, a year ago. The data presented in June showed that it had been a number of years since the majority of people had gotten MMR2, at least in the Iowa outbreak. He expressed an interest in understanding how the WG thought that should be factored into the guidance that goes out.

Dr. Marin replied that this was considered to be part of the CDC guidance. Public health representatives in the WG are not so much in favor of checking every single record and determining time since vaccination. It was left for CDC guidance regarding whether for all persons who received 2 doses before an outbreak there is an intervention that would improve their protection.

Dr. Messonnier responded that CDC would commit to providing direction in the clinical guidance regarding how to think about time since last vaccination.

Regarding the health department survey, Dr. Belongia was struck by the fact that there was a lot less enthusiasm than he would have predicted for MMR3. He wondered whether there were any insights into that. Regarding “may” versus “should,” he asked whether there was any concern in the WG that by making it a “should” recommendation, that might be a disincentive to declare an outbreak if a health department is strapped for resources.

Dr. Marin said that they noticed that there was more variability on the scale of responses. When health departments deal with outbreak situations, it is hard to mount a campaign while responding to an outbreak in terms of finding resources.

Regarding the potential not to declare an outbreak, Dr. Cohn pointed out that for other vaccines such as meningococcal and Tdap, “you *should* get vaccinated in the setting of an outbreak” is used. But, that does not necessarily mean that a health department has to mount a campaign. They could send letters home, increase awareness, et cetera. There are a variety of approaches. While this is speculation, it may be that without a recommendation, it actually did require more focus, resources, and intensity than it may with a recommendation.

Dr. Duchin (NACCHO) commented that campaigns are very resource-intensive. For a large university, this is an extremely big undertaking. He thinks this recommendation will have a lot of implications in practice if it is “should” rather than “may.” On the other hand, it would be useful to be very clear about whether this recommendation is being made for outbreak control or to reduce clinical manifestations in the individual student. That has very different implications for who does the vaccinating.

Dr. Messonnier indicated that CDC had the opportunity to compare across, so the language in this is very similar to the language of other outbreak response vaccines. While she understood the issue, they can point to other similar language across other outbreak vaccines in which the language is “should” and university and health department implementation of those varies widely. CDC can say from a long experience that they do not feel that the proposed language locks in health departments or universities regarding what they have to do in terms of mounting a campaign versus educating. The issue regarding whether they are trying to stop an outbreak versus individual protection, is the issue the WG was trying to address.

Dr. Duchin (NACCHO) asked whether the level of evidence for the other recommendations is comparable to this.

Dr. Cohn responded that the meningococcal evidence is very similar in that it protects individuals. Whether vaccination campaigns can reduce the size or scope of an outbreak is highly variable on the timing of when the campaign is implemented, how quickly coverage can be increased, and many other parameters. There are so many programmatic issues, gaining enough evidence is going to be challenging.

Dr. Moore reported that the WG’s focus was on individual protection where there is evidence. Coming from a state that has dealt with outbreaks, she emphasized that one of the strains and stresses was that these states were left on their own to figure out what they wanted to do. Different states chose different degrees of “heavy lifting” as was evident from the responses of the states. By giving clear guidance and with CDC and other support to explain that given the mildness of disease, it may not be the place to mount a huge campaign. Instead, students or affected persons can be recommended to get the vaccine to reduce their risk of mumps. This will make it much clearer and more straightforward for respondents. The other thing that is evident is the heterogeneity of the outbreaks, 13% of which accounted for a huge proportion of the actual cases. Most of the outbreaks were actually quite small and may not be appropriate for a vaccination outreach effort. There is so much involved with outbreak management, the WG felt that it was not an area they wanted to get into, so they stuck with individual protection where they felt they were on solid ground.

Dr. Plotkin (Vaccine Consultant) said he thought the recommendation was illogical in the sense that no one doubts that immunity wanes. It has been shown definitely that B-cell memory wanes. That means that everyone with 2 doses is at risk of having lost immunity. As was said, this is a phenomenon that operates in communities where there is close contact. According to the data, if he calculated correctly, something like 12% of universities report that they have had a problem. To him, the logical course is to recommend a third dose of MMR for boys and girls entering colleges. That is straightforward, and it prevents disease. Preventing disease is why they are there—not to respond to outbreaks once they have started.

Dr. Schaffner (NFID) was curious that the rationale to improve protection against mumps disease and related complications appeared to be entirely clinical, and seemed to ignore its contribution to the curtailment of an outbreak.

As a member of the WG and as a host university for a mumps outbreak, Dr. Even (ACHA) pointed out that had there been guidance, they might not have had as widespread an outbreak because it started as a smaller subset. Addressing an outbreak early for those at highest risk (a sports team, fraternity, et cetera), might not involve a huge number of immunizations and would make it a clear-cut and prompt response.

Dr. Lee thought Dr. Plotkin's comment was something to consider. Now that ACIP have started to pilot this framework (ACIP Evidence to Recommendation framework), it is helpful. She thought it would be beneficial to complete a cost-effectiveness analysis for that particular part of it before making a decision. The way the recommendation was described seemed to be for both individual and outbreak control. It is an interesting question about who is responsible in that situation. This gives the flexibility, which may or may not be wanted, so that in an implementation situation it can be a partnership and at the discretion of that partnership to decide how to run it.

Dr. Maldonado (AAP) indicated that the Red Book Committee has reviewed this issue and spoke about this issue before the ACIP meeting. Given what is not known about T-cell immunity or reasons for the current increase in cases, for the time being, the Red Book Committee thought this would be a reasonable way to approach vaccination for providers and to give them guidance in dealing with the unpredictable nature of what may happen. It is not known where the outbreak situation may head in the future. It may be reasonable in the future to think about a third dose, but this is a good compromise for the general provider who will be fielding questions from families with college-bound children. Universities on their own may decide that they want to institute a third dose, but that is up to them. She thinks that the proposed recommendation gives people a lot of leeway to at least address individual risk, and the Red Book Committee feels that way as well.

Regarding the epidemiological data presented, Dr. Atmar noted that only half of the outbreaks and 40% of the cases were in university students. He thought Dr. Plotkin's suggestion was worth taking back to the WG.

Dr. Moore indicated that the WG did discuss this question, but there are no data on duration of protection at all. In the absence of any duration evidence and with no immunologic correlate of protection that can be used to extrapolate what that protection would be, the WG did not feel they had any evidence to support a decision about a routine dose outside of an actual exposure situation where there was not an immediate need for that vaccine. If people get vaccinated as an incoming freshman the majority may not be on a campus with an outbreak or maybe they are a senior when an outbreak occurs, and at that point would they need another dose? Would that dose work as well? All these unanswered questions left the WG unable to address the particular question of routine use at this time.

Dr. Savoy (AAFP) pointed out that as a physician sitting in her office, she may or may not receive an email from a public health department to inform her that there is an outbreak. While she understood why the recommendation was written to indicate identification by public health of persons at increased risk would be helpful in some instances, she also could understand why it could be limiting. If someone presented to her without evidence of increased risk of exposure, she was not clear that she could lean on this recommendation to explain why she would be giving that vaccine.

Dr. Moore indicated that the role of public health in these outbreaks is to communicate the message to clinicians, not just the university setting. There are methods for reaching clinicians in communities for any kind of public health concerns, and those mechanisms can be used to get the word out for this just as is done for any other community outbreak of any kind. The WG felt that it was particularly important for clinicians not to be stuck on their own without guidance trying to figure out whether a child needed an additional dose of vaccine, because of the heterogeneity of these outbreaks.

Dr. Lee said she would advocate that ACIP is focused on where the evidence base is for the recommendation, and then use the guidance to help with implementation.

Motion/Vote: Administration of a 3rd Dose of MMR Vaccine to Persons Previously Vaccinated with 2 Doses of a Mumps-Containing Vaccine Identified to be at Increased Risk for Mumps Because of an Outbreak

Dr. Romero moved to recommend that persons previously vaccinated with two doses of a mumps-containing vaccine, who are identified by public health as at increased risk for mumps because of an outbreak, receive a third dose of a mumps-containing vaccine to improve protection against mumps disease and related complications. Dr. Belongia seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Atmar, Belongia, Bennett, Ezeanolue, Hunter, Kempe, Lee, Moore, Pellegrini, Reingold, Riley, Romero, Stephens, Szilagyi, Walter
0 Opposed: N/A
0 Abstained: N/A

Vaccines for Children (VFC) Vote

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

Dr. Santoli indicated that the purpose of this resolution is to add guidance about the use of mumps-containing vaccines in the context of an outbreak and to update the links in this resolution, given that it has been about 8 years since this resolution was updated.

The first component is the MMR component of the resolution. The eligible groups section is completely unchanged and reads, "Children 12 months through 18 years of age (may be as young as 6 months of age in an outbreak or prior to international travel)." The link for the recommended schedule for MMR vaccines has been updated to reflect the 2013 ACIP recommendation and can be found at:

<https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6204a1.htm>.

In addition, language has been added about persons previously vaccinated with two doses of a mumps-containing vaccine* who are identified by public health as at increased risk for mumps because of an outbreak should receive a third dose of a mumps-containing vaccine to improve protection against mumps disease and related complications.

*As stated in Prevention of Measles, Rubella, Congenital Rubella Syndrome, and Mumps, 2013: Summary Recommendations of the Advisory Committee on Immunization Practices (ACIP), includes MMR and MMR-V.

Dosage Intervals for Measles, Mumps and Rubella Vaccines link also has been updated to reflect the 2013 ACIP recommendation and can be found at:

<https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6204a1.htm>

The recommended dosage section has been updated to refer to product package inserts, and the contraindications and precautions section has been updated to reflect the 2013 ACIP recommendations and can be found at:

<https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6204a1.htm>

No changes were proposed to the varicella component of the VFC resolution. For the MMR-V component of the VFC resolution, the eligible groups remain the same, "Children at least 12 months through 12 years of age." The link in the recommended schedule for combined MMR-V vaccine section has been updated to reflect the 2010 ACIP recommendations:

<https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5903a1.htm>

Language also has been updated in that section so that it mirrors the language in the 2010 ACIP recommendations, with the underlined language having been slightly reworded to be more true to the 2010 recommendations:

- ❑ For the first dose of measles, mumps, rubella, and varicella vaccines given at 12-47 months of age, either MMRV vaccine or separate MMR and varicella vaccines can be used. The potential benefits and risks of both vaccination options should be discussed with the parents or caregivers. Unless the parent or caregiver expresses a preference for combined MMR-V vaccine, CDC recommends that MMR vaccine and varicella vaccines be administered for the first dose in this age group.
- ❑ For the first and second doses of measles, mumps, rubella, and varicella vaccines given at 4 years of age or older, use of MMRV vaccine generally is preferred over separate injections of its equivalent component vaccines (i.e., MMR vaccine and varicella vaccine). Considerations should include provider assessment*, patient preference, and the potential for adverse events.

*Provider assessment should include the number of injections, vaccine availability, likelihood of improved coverage, likelihood of patient return, and storage and cost consideration.

The dosage intervals for combined MMR-V section has been updated to reflect the 2010 link:

<https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5903a1.htm>

The recommended dosage section has been updated to refer to product package inserts, and the contraindication and precautions section has been updated to reflect the 2010 ACIP recommendations:

<https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5903a1.htm>

This is the statement indicating that the next publication within 12 months would be incorporated into this VFC resolution by reference:

[If an ACIP recommendation or notice regarding measles, mumps, rubella, and/or varicella vaccination is published within 12 months following this resolution, the relevant language above (except in the eligible groups sections) will be replaced with the language in the recommendation and incorporated by reference to the publication URL.]

Motion/Vote: VFC Resolution

Ms. Pellegrini made a motion to approve the VFC Resolution as presented. Dr. Hunter seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Atmar, Belongia, Bennett, Ezeanolue, Hunter, Kempe, Lee, Moore, Pellegrini, Reingold, Riley, Romero, Stephens, Szilagyi, Walter
0 Opposed: N/A
0 Abstained: N/A

Vaccine Safety: Shoulder Injury After Vaccination

Introduction

Andrew Kroger MD, MPH
Medical Officer
Immunization Services Division
Centers for Disease Control and Prevention

Dr. Kroger reported that on September 19, 2017, CDC launched a campaign that is ongoing to promote safe intramuscular (IM) vaccination in adults. One of the goals of this campaign is to prevent shoulder injury after vaccination. He indicated that during this session, they would hear about the impetus behind this campaign in terms of Health Resources and Services Administration (HRSA) National Vaccine Injury Compensation Program (VICP) claims data pertaining to shoulder injury, a review of VAERS data reports of AEs related to the shoulder, and a discussion of the campaign and CDC resources.

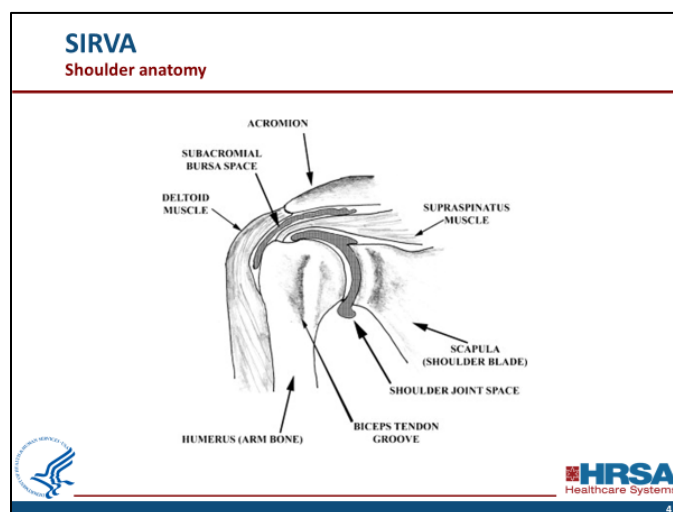
Data from HRSA VICP Claims

Narayan Nair, MD
Division Director/Chief Medical Officer
Division of Injury Compensation Programs
Healthcare Systems Bureau
Health Resources and Services Administration

Dr. Nair provided some background on shoulder injury related to vaccine administration (SIRVA) and shared some compensation data from the VICP. SIRVA is thought to result from the unintentional injection of a vaccine into the tissues and structures that lie underneath the deltoid muscle of the shoulder. The IOM reviewed the scientific and medical literature, and found that the evidence convincingly supported a causal relationship between vaccine administration and what they referred to as “deltoid bursitis.” One of the pieces of evidence that they considered was a paper by Dr. Atanasoff et al., who is a Medical Team Leader with the Division of Injury Compensation Programs (DICP), who published a case series reporting the experience of the VICP with regard to shoulder injuries following vaccination. The IOM reviewed this article and commented that the cases were consistent with deltoid bursitis.

This was a small case series of 13 claims, all of whom were from adults. They all had shoulder pain, with 93% reporting that the pain started within 24 hours after vaccination. Over half said that they had significant pain immediately after vaccination, and nearly half of them had concern at the time of administration that the vaccine was given too high in the shoulder compared to previous vaccinations. The most common findings in this case series were pain and limited range of motion (ROM). It was very uncommon for these individuals to report any type of neurologic symptoms, 31% required some type of surgical intervention, and over half required a corticosteroid injection for their shoulder pain.

To review the shoulder anatomy, this is an anterior view of the right shoulder:



Underlying the acromion and deltoid muscle, is the subacromial bursa space. There are additional reports of shoulder injury related to vaccine administration. Most notably, a paper was published by Marko Bodor in *Vaccine* in 2006 that reported on 2 cases of shoulder pain after vaccination that occurred within 2 days of vaccination. They used ultrasound on both

patients and on 21 controls, and they found that the bursa can extend 3 to 6 centimeters beyond the acromion and can lie anywhere between 0.8 centimeters to 1.6 centimeters below the surface of the skin. That is roughly about a third to .67 inch. Given that a standard adult needle is an inch, they proposed a theory that the vaccine was given high in the shoulder and the contents of the vaccine were injected into the subacromial bursa space, which triggered a robust local inflammatory response that led to bursitis, tendonitis, and inflammation of the shoulder capsule. In this paper, the authors proposed that injections should not be performed in the upper third of the deltoid muscle to avoid these types of injuries Marko Bodor, Enoch Montalvo; *Vaccination-related shoulder dysfunction; Vaccine 25 (2007) 585–587*].

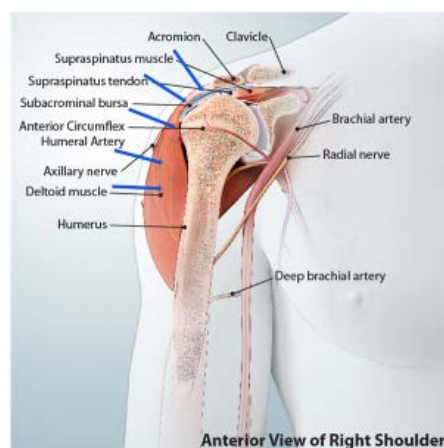
In terms of compensation data, Dr. Atanasoff's paper was published in 2010 and the IOM published its findings in 2011. From 2011-2014, there were 59 claims alleging shoulder injuries. Those individuals received approximately \$9.7 million. In 2015, those numbers had increased to 98 cases and approximately \$12.4 million. In 2016, there were 202 claims alleging SIRVA and compensation was approximately \$29 million. In 2017, there were 163 claims and compensation was approximately \$19.9 million. That does not include attorneys' fees or legal costs.

SIRVA was added to the Vaccine Injury Table earlier this year. While many injuries are compensated that are not found on the Vaccine Injury Table, the benefit of being on the table is that it does streamline the process and allows for a lookback period wherein individuals have a longer period of time to file, in this case, a SIRVA claim. A significant number of claims are anticipated in the future.

Data from the Vaccine Adverse Event Reporting System (VAERS)

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

Dr. Shimabukuro presented reports of shoulder dysfunction following IIV in the VAERS system. Looking at this anterior view of the right shoulder, he asked everyone to imagine that the arrows are injection sites and that they were tracking up the arm away from the thickest most centrally located portion of the deltoid muscle where the injection should be given:



Moving up the arm, the opportunity increases to inject into structures like the bursa or the rotator cuff tendons where injection should not be done because it could cause a shoulder injury.

As a reminder, SIRVA was added to the VICP Vaccine Injury Table in February 2017 [National Vaccine Injury Compensation Program: Revisions to the Vaccine Injury Table. A Rule by the Health and Human Services Department. 82 FR 6294. Effective date February 21, 2017. <https://www.federalregister.gov/documents/2017/01/19/2017-00701/national-vaccine-injury-compensation-program-revisions-to-the-vaccine-injury-table>].

By definition, SIRVA is caused by an injury to the musculoskeletal structures of the shoulder (e.g. tendons, ligaments, bursae, et cetera). SIRVA is not a neurological injury. The question remains, “Is there an epidemic of shoulder injuries related to vaccine administration? If so, how would you address that question?” The objective of the assessment of VAERS data was to describe reports submitted to VAERS of shoulder dysfunction following IIV. As a reminder, VAERS is CDC’s spontaneous reporting system. It is subject to the limitations of spontaneous reporting. Most importantly, causality generally cannot be determined using VAERS data alone.

The outcome is shoulder dysfunction following immunization, which implies a temporally associated AE of shoulder dysfunction in contrast to shoulder injury related to vaccine administration, which implies a causal association. The definition for this assessment includes shoulder pain and restricted range of motion (ROM) following injection of IIV into the upper arm¹. The affected shoulder must be of same arm in which IIV was administered alone. Reports are excluded where more than one vaccination, in addition to IIV, was given in the arm with the affected shoulder (e.g., IIV and PPSV23, Tdap/Td, et cetera). Onset is within 48 hours after IIV vaccination, and reports of neurological injuries are excluded (e.g., brachial neuritis, which is a separate VICP table injury). Symptoms had to last longer than one week to differentiate from injection site reactions². This is a key difference between the definition used for this study and the definition for SIRVA as it relates to injury compensation. Generally for SIRVA, symptoms must last longer than 6 months. Because of the way reports are submitted to VAERS and because of some of the limitations of VAERS and follow-up on VAERS reports, that is not possible. Therefore, they made a decision that if a patient was having symptoms for longer than 1 week, that was likely to be something more than a simple injection site reaction [Adapted from the VICP definition for SIRVA with modification; Modified from VICP requirement of >6 months of residual effects due to limitations on follow-up in VAERS].

In terms of the methods, the VAERS database was searched for reports of shoulder dysfunction following IIV from July 2010 through June 2016. MedDRA terms were used that potentially described shoulder dysfunction and selected vaccine administration error terms, and text string search of reports for “arm” or “shoulder.” All reports identified in the initial search were reviewed and classified into three categories: “Not a case,” “Indeterminate case,” or “Possible case.” Key information from reports was entered into an electronic database using a standardized extraction form in MS Access. For reference, here are some of the MedDRA terms used in the search for should dysfunction:

Acute osteomyelitis involving shoulder region	Capsulitis of shoulder	Osteoarthritis, localised, primary, involving shoulder region
Acute synovitis	Cervicobrachialgia	Osteoarthritis, localised, secondary, involving shoulder region
Adhesive capsulitis of shoulder	Cervicobrachial syndrome	Osteoarthritis, localized, not specified whether primary or secondary, involving shoulder region
Administration site joint discomfort	drug administration error	Osteoarthritis, unspecified whether generalized or localized, involving shoulder region
Administration site joint effusion	Effusion of joint of shoulder region	Other affections of shoulder region, not elsewhere classified
Administration site joint erythema	Effusion of upper arm joint	Other and unspecified injury to shoulder and upper arm
Administration site joint infection	Injected limb mobility decreased	Other and unspecified superficial injury of shoulder and upper arm, infected
Administration site joint inflammation	Injection site joint discomfort	Other and unspecified superficial injury of shoulder and upper arm, without mention of infection
Administration site joint movement impairment	Injection site joint erythema	Other specified arthropathy involving shoulder region
Administration site joint pain	Injection site joint infection	Other specified arthropathy involving upper arm
Allergic arthritis involving shoulder region	Injection site joint inflammation	Other specified crystal arthropathies involving shoulder region
arthralgia	Injection site joint movement impairment	Other specified disorders of bursae and tendons in shoulder region
Arthropathy involving shoulder region	Injection site joint pain	Other specified disorders of joint of shoulder region
Arthropathy unspecified, involving upper arm	Injury to other specified nerve(s) of shoulder girdle and upper limb	Other symptoms referable to joint of shoulder region
Arthropathy, unspecified, involving shoulder region	Injury to peripheral nerve(s) of shoulder girdle and upper limb	Other symptoms referable to upper arm joint
Brachialgia	Joint injury	
Bursa calcification	Joint range of motion decreased	
Bursa disorder	Joint swelling inflammatory	
Bursa injury	Late effect of injury to peripheral nerve of shoulder girdle and upper limb	
Bursal fluid accumulation	Loose body in joint of shoulder region	
Bursal synovitis	Neck, shoulder and arm syndrome	
Bursitis		

Pain in [l] shoulder	Shoulder osteoarthritis	Traumatic arthrosis
Pain in [r] shoulder	Shoulder pain	Unspecified disorder of joint of shoulder region
Pain in joint involving shoulder region	Shoulder pain (due joint disorder)	Unspecified disorder of upper arm joint
Pain in joint involving upper arm	Shoulder region stiffness of joint, not elsewhere classified, involving upper arm	Unspecified infective arthritis involving shoulder region
Pain in upper extremities	skeletal injury	Unspecified monoarthritis involving shoulder region
Palindromic rheumatism involving shoulder region	Stiffness shoulder	Unspecified monoarthritis involving upper arm
Periarthritis scapulohumeralis	Subacromial bursitis	Unspecified osteomyelitis involving shoulder region
Purulent synovitis	Synovial cyst	Unspecified polyarthropathy or polyarthritis involving shoulder region
Pyogenic arthritis involving shoulder region	Synovial disorder	Vaccination site joint discomfort
Rotator cuff syndrome	Synovial rupture	Vaccination site joint effusion
Rotator cuff syndrome of shoulder and allied disorders	Synovitis	Vaccination site joint erythema
Scapula pain	Synovitis of shoulder	Vaccination site joint infection
Shoulder bursitis	Tendon injury	Vaccination site joint inflammation
Shoulder discomfort	Tendon rupture	Vaccination site joint movement impairment
Shoulder dystocia	Transient arthropathy involving shoulder region	Vaccination site joint pain
Shoulder hand syndrome	Transient arthropathy involving upper arm	Vaccination site joint swelling
Shoulder joint pain associated with	Traumatic arthritis	Villonodular synovitis involving shoulder region
Shoulder ligament rupture	Traumatic arthropathy involving shoulder region	Villonodular synovitis involving upper arm
Shoulder muscle stiffness	Traumatic arthropathy involving upper arm	

Regarding the results, 2198 VAERS reports met the initial search criteria for shoulder dysfunction following IIV. Of these, 1006 (46%) were classified as possible cases and were included in the preliminary analysis. In terms of reports by influenza season for the analytic period, it may appear that there has been a slight increase in the number of reports moving through the analytic period with 128 (1.5%) reports in 2010-2011, 149 (2.0%) in 2011-2012, 148 (1.8%) in 2012-2013, 184 (2.0%) in 2013-2014, 223 (2.4%) in 2014-2015, and 174 (2.0%) in 2015-2016. However, if shoulder dysfunction reports are considered as a percent of all IIV reports, it is pretty constant at around 2% of all reports.

This table offers a side by side comparison of shoulder dysfunction reports following IIV compared to non-shoulder dysfunction reports and reflects some differences:

	Shoulder Dysfunction Following IIV, n (%)	Non- Shoulder Dysfunction Following IIV, n (%)
Total reports	1,006	50,247
Non-serious	933 (93)	46,707 (93)
Female	829 (82)	34,421 (69)
Median age in years	51 (range 14-94 years)	50 (range 0-102 years)
Age groups		
0-18	3 (<1)	8,541 (17)
19-59	702 (70)	23,709 (47)
60+	289 (29)	16,934 (34)
Unknown	12 (1)	1063 (2)
Type of reporter		
Patient	528 (52)	10,999 (22)
Vaccine provider	273 (27)	23,416 (47)
Manufacturer	36 (4)	4,613 (9)
Other/unknown	169 (17)	11,219 (22)

The first difference is sex. Of the shoulder dysfunction reports, 82% were among females compared to 69% of non-shoulder dysfunction reports. Less than 1% were in individuals 0 through 18 years of age compared to 17% for non-shoulder dysfunction reports. Most of the reports were in individuals 19 through 59 years of age. Of the shoulder dysfunction reports, 52% were submitted by patients compared to 22% for the non-shoulder dysfunction reports. That is a pretty substantial difference and differs from VAERS reports in general for which about 15% to 20% of reports are from patients or parents.

Onset had to occur within 48 hours by definition. However, in 75% of these reports, symptoms occurred on the day of vaccination. In 85% of the reports, the pain had not resolved at the time the report was made to VAERS. In 49% of reports, the patient was seen by an HCP for shoulder dysfunction. Referral to a specialist was not commonly documented in reports, but when it was, the patients were most commonly referred to an orthopedist.

This table depicts the characteristics of commonly reported shoulder dysfunction-related AEs following IIV. It is important to note that that these are not mutually exclusive, so these numbers add up to more than 1006:

Most Commonly Reported Shoulder Dysfunction-Related Adverse Events (N=1,006 total reports)	n (%)
Shoulder pain	442 (44)
Injected limb mobility decreased	407 (41)
Joint range of motion decreased	191 (19)
Drug administered at inappropriate site	156 (16)
Bursitis	94 (9)
Arthralgia	92 (9)
Rotator cuff syndrome	90 (9)
Frozen shoulder	57 (6)
Shoulder bursitis	30 (3)

The most common AEs are the broad, relatively non-specific events of shoulder pain, injected limb mobility decrease, or joint ROM decrease. Less commonly reported are the more specific events such as bursitis, rotator cuff syndrome, or frozen shoulder. In the interest of time, Dr. Shimabukuro skipped impact on activities of daily living (ADL) among shoulder dysfunction reports.

In 222 of the 1006 reports, there was documentation of a contributing factor described in the narrative. Of these, most commonly described was vaccination given too high on the arm. Improper/poor administration technique is a “grab bag.” Uneven position between the vaccinator and patient is usually the vaccinator standing above the patient while the patient is sitting down.

In terms of place of vaccination, in 40% of the reports the vaccination was given in a pharmacy or a drug store and in 32% it was a doctor’s office or hospital. Those two venues account for 72% of all shoulder dysfunction reports, and 12% were in the workplace.

To summarize, reports to VAERS of shoulder dysfunction following IIV ranged from 128 to 223 during the six influenza seasons assessed from 2010-2011 to 2015-2016. During that period, around 130 million doses of IIV were distributed each influenza season in the US. There was a higher percentage of reports of shoulder dysfunction following IIV among females when compared to non-shoulder dysfunction reports. Most (70%) of the reports were in the age group 19 through 59 years, while few were in individuals 0 through 18 years of age (<1%). When possible contributing factors were described, vaccination given too high on the arm was most commonly reported. The most common place of vaccination documented in reports was in pharmacies/drug stores and doctor’s offices/hospitals.

In conclusion, improperly placed IIV or any injectable vaccination has the potential to cause shoulder injury. However, reports to VAERS of shoulder dysfunction following IIV appear to be rare, given the amount of IIV distributed in the US each influenza season. There does not appear to be an increase in shoulder dysfunction reports following IIV submitted to VAERS

during recent seasons. Shoulder dysfunction accounted for approximately 2% of all IIV reports during the 2010-2011 through 2015-2016 seasons. Proper administration technique is important.

Communication and Education Campaign

Andrew Kroger MD, MPH
Medical Officer
Immunization Services Division
Centers for Disease Control and Prevention

Dr. Kroger shared some highlights of the CDC/NCIRD campaign, and provided information about the resources available for safe IM vaccination in adults. As just mentioned, a substantial percentage of the adult VAERS reports came from either pharmacies or stores, so before anything was rolled out on web pages and the like, CDC/NCIRD engaged in a couple of phone calls with the American Pharmacists Association (APhA), National Association of Chain Drug Stores (NACDS), National Community Pharmacists Association (NCPA), and its awardees to share what was coming with regard to the web site rollout. CDC/NCIRD also updated its Vaccine Administration webpage, and posted an online tool for vaccine administration. This is basically an online training tool that includes imbedded videos. In this case, the videos highlight administration techniques. These tools are the product of over a year's worth of work.

CDC/NCIRD did do some promotion of these tools in advance of the official start of the campaign. For instance, the "Current Issues in Immunization Netconference Webinar on Influenza" shared some information on September 13, 2017 about shoulder injury and highlighted the e-Learn. As part of the campaign initiation, the agency released an infographic and newsletter article template, which appeared in several pharmacist journals in September 2017. The is the infographic, which Dr. Kroger shared in hard copy with the ACIP members and liaisons:

YOU CALL THE SHOTS

Shoulder injuries related to vaccine administration
 Improper vaccine administration could result in shoulder injuries such as shoulder bursitis and tendinitis.

Make sure vaccination is safe.
KNOW THE SITE. GET IT RIGHT!

When administering vaccine by an intramuscular (IM) injection to an adult:

Use the correct syringe and needle

- Vaccine may be administered using either a 1-mL or 3-mL syringe
- Use a 22 to 25 gauge needle
- Use the correct needle size based on your patient's size

Injection site: Deltoid muscle of upper arm

1 in (25 mm)	1.5 in (38 mm) OR 1 in (25 mm)	1.5 in (38 mm)
Medol syringe (101-0052)	Titus (9-58 kg/22-50 lbs)	Titus syringe (101-0052)
Medol syringe (101-0052)	Titus (9-58 kg/22-50 lbs)	Titus syringe (101-0052)
Medol syringe (101-0052)	Titus (9-58 kg/22-50 lbs)	Titus syringe (101-0052)

*Some reports recommend a 5/8-inch needle for men and women who weigh less than 60 kg (130 lbs).

Identify the injection site

- Locate the deltoid muscle of the upper arm
- Use anatomical landmarks to determine the injection site
- In adults, the midpoint of the deltoid is about 2 inches (or 2 to 3 fingers' breadth) below the acromion process (bony prominence) and above the armpit in the middle of the upper arm

Acromion Process, Scapula, Deltoid Muscle, Humerus, Axillary Fold/Armpit

Administer the vaccine correctly

- Inject the vaccine into the middle and thickest part of the deltoid muscle
- Insert the needle at a 90° angle and inject all of the vaccine into the muscle tissue

Always follow safe injection practices

- Maintain aseptic technique
- Perform hand hygiene before preparing and administering vaccines
- Use a new needle and new syringe for each injection
- If using a single-dose vial (SDV) discard after use. *A SDV should be used for one patient only!*

IM injection best practices

- Administering the injection too high on the upper arm may cause shoulder injury
- If administering additional vaccines into the same arm, separate the injection sites by 1 inch if possible

Report any clinically significant adverse event after vaccination to the Vaccine Adverse Event Reporting System (VAERS) at vaers.hhs.gov/

For additional information on proper vaccine administration, visit the CDC vaccine administration web page at www.cdc.gov/vaccines/imz/downloads/immunization-practices.html

U.S. Department of Health and Human Services
 Centers for Disease Control and Prevention

Remember—recall the 3Cs when it comes to proper vaccine administration!

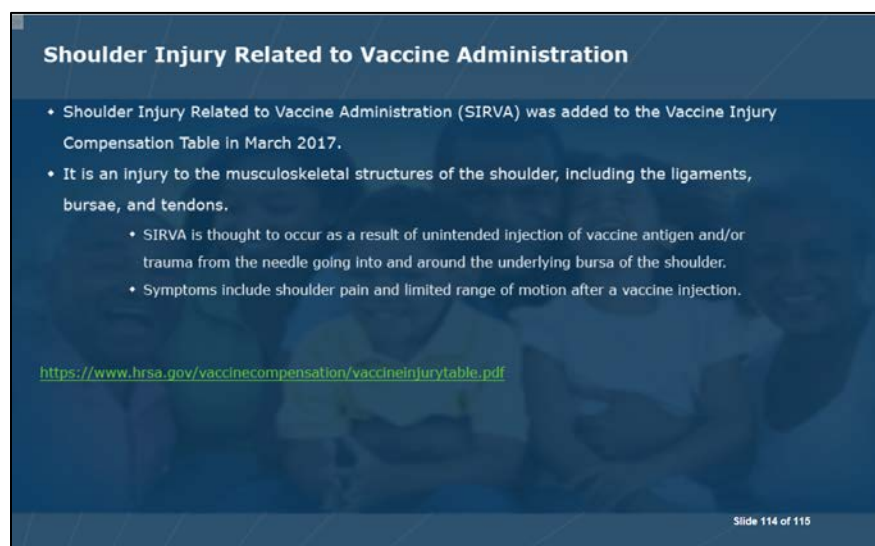
The infographic highlights the campaign message, which headlines the message “KNOW THE SITE. GET IT RIGHT!” and appropriately promotes current educational tools as well as the outcome to be prevented. The first row highlights the importance of selecting the correct needle lengths, which is critical to ensuring that immunizations are delivered by the correct IM route. Needle length is based on age, gender, and site-selection. Proper IM placement of vaccine is based on technique. The second row focuses on correct site selection, which is believed to be the essence of correcting these administration errors. The correct site is the deltoid muscle, visualized by the inverted triangle, the base of which is located some distance from the acromion process. For adults, 2 inches is thought to be an appropriate distance. In children, it may be more useful to measure this in terms of finger breadth. The key point is that the picture is shown on the infographic. The third row highlights some aspects of proper technique, such as the injection angle of 90 degrees and also attention to other safe injection practices. In the lower right-hand corner is a link to CDC’s recently revised Vaccine Administration webpage. The infographic can be found at: <https://www.cdc.gov/vaccines/hcp/infographics/call-the-shots.html>

The focus of the newsletter article template was to highlight that shoulder injuries are preventable with correct IM administration. The newsletter highlights specific shoulder injuries throughout, including bursitis and tendinitis. The article also highlights the following resources:

- ❑ Vaccine Administration e-Learn: Posted June 21, 2017
- ❑ Revised Vaccine Administration Webpage: Posted September 1, 2017

The revised Vaccine Administration webpage is a direct link from the Immunization Provider web page and is located at: <https://www.cdc.gov/vaccines/hcp/admin/admin-protocols.html>

Here is a sample page from the vaccine administration e-Learn, which is a self-paced education tool with links to videos and resources, contains knowledge checks, and is available for continuing education credits (CEUs):



This sample page is focused on shoulder injury related to vaccine administration, and the e-Learning course can be found at: <https://www.cdc.gov/vaccines/ed/courses.html>

With respect to preliminary campaign statistics, there have been 3411 clicks to the CDC website since the campaign began. Of these, 3108 came directly from the emails CDC sent. The remaining 303 clicks were most likely clicks received from other emails in which CDC's links were pasted, and 3204 of the total clicks came from the US. The IM video on the YouTube page has received 1235 clicks, and the Vaccine Administration resources page has received 762 clicks. These data come from the first three weeks of the campaign.

Discussion Points

Dr. Szilagyi observed that there were almost no children, though children do get bursitis. He also asked what percentage of IIV is given in pharmacies in adults.

Dr. Shimabukuro replied that up to a certain age, children are not at risk because they receive vaccine in the quadricep. Nevertheless, this is a good question and they could assess other vaccines that are given in children and adolescents in addition to influenza vaccines. The 3 individuals under 18 years of age were older children of 13, 14, and 17 years old. Based on the National Internet Flu Survey for the 2016-2016 season through November, there is a mismatch between reports of shoulder dysfunction and place of vaccination. From this, it appears that about 25% of influenza vaccine in that season was given in pharmacies. That is consistent with other data indicating that about a quarter of vaccines are given in pharmacies and drug stores.

With that in mind, Dr. Bennett asked whether CDC is targeting pharmacies for this information and education campaign.

Dr. Shimabukuro emphasized that the VAERS data are passively reported, and there are a number of reporting biases in VAERS data. Therefore, CDC is not making any assumptions regarding place of vaccination.

Dr. Kroger added that the focus of the campaign is adults, and they are targeting all providers who provide vaccines to adults. There have been discussions with pharmacist groups because of this, but it is an adult IM administration campaign.

Dr. Walter asked whether they looked at other antigens to determine whether reporting was comparable with influenza.

Dr. Shimabukuro indicated that they have not yet assessed other antigens. They knew that most of the SIRVA claims in VICP were for influenza vaccine, so they started out looking at that information. They also wanted to keep this clean, so one vaccine given in the shoulder. There were some potential issues with tetanus-containing vaccines being more reactogenic and painful, with the pain lasting longer and perhaps people are getting tetanus vaccines for other reasons. Certainly, this can be expanded to examine other vaccines as well.

Dr. Messonnier asked Dr. Shimabukuro to mention CDC's first ever Epi-Aid to HRSA.

Dr. Shimabukuro indicated that ISO would be conducting an Epi-Aid investigation, with an EIS officer going to HRSA to assist them in reviewing some of these cases. This will not be for the purpose of adjudicating claims. Instead, it will be for scientific purposes to help HRSA with their review and publication of the review of claims submitted to the VICP.

Dr. Lee suggested that it might be helpful to dive deeper into the pharmacy and whether it is retail-based clinics, nurse practitioners, or pharmacists. It seems like it would be great to partner with national organizations to develop toolkits, training, and competencies to support this. Much like everything else in the world, the higher the volume, the better things are in terms of procedures or immunizations. It may be that there already is competency in physicians' and pediatricians' offices where the volume is huge; whereas, in a pharmacy that may not see a lot of children, so they are not as comfortable with vaccine administration.

Dr. Weinbaum (SME) indicated that CDC has been working with APhA and NACDS in order to get the messages out through their constituencies. They do have immunization curricula for their vaccinators in stores. Currently, CDC does not have the level of data to determine whether this is occurring in a clinic within a pharmacy or among pharmacists.

Human Papillomavirus (HPV) Vaccines

Introduction

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

Dr. Szilagyi introduced the session by pointing out that the last ACIP HPV vaccine session was during the October 2016 ACIP meeting. As a reminder, during every meeting in 2016, the HPV Vaccines WG had presented to ACIP issues related to a 2-dose schedule. In October 2016, ACIP voted to recommend a 2-dose schedule for persons initiating the vaccination series before 15 years of age. A Policy Note was published two months later in December 2016.

While the WG has not presented to ACIP since October 2016, there have continued to be WG conference calls. Since that time, Dr. Kempe's term on ACIP ended and Dr. Szilagyi became the new HPV Vaccines WG chair. Dr. Szilagyi commended Dr. Kempe for her scholarly, passionate, and very careful leadership of the HPV Vaccines WG.

The WG has convened monthly conference calls during which some potential policy issues were discussed, including: 1) the routine target age group wording 9-12 years vs 11-12 years, with a statement that the vaccination series can be started at age 9 years; and 2) harmonization of the upper age for male and female vaccination. The WG also reviewed other topics and data, including: 1) footnotes for child/adolescent and adult schedules; and 2) 9-valent HPV vaccine safety data.

Update

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

During this session, Dr. Markowitz discussed selected CDC and other activities after 2-dose recommendation, provided an overview of ACIP HPV Vaccines WG calls and discussions over the last year, and summarized HPV vaccination coverage and impact in the US.

As mentioned, in October 2016 ACIP voted to recommend a 2-dose schedule and the *MMWR* Policy Note was published two months later in December 2016. Following that, there were a variety of education and communication efforts to clarify and increase awareness of the new schedule. This included webinars and presentations at scientific conferences; updating of CDC websites and fact sheets; and a CDC communication campaign to raise awareness, including digital media outreach to parents and clinicians.

The 2017 Healthcare Effectiveness Data and Information Set (HEDIS), which covers the performance period for calendar year 2016 during which time the recommendation was for 3 doses, will not change. The HEDIS 2018 measure, which covers calendar year 2017, has been updated to reflect the new 2-dose schedule. The Clinical Decision Support for Immunization (CDSi) Resources, which supports electronic processes to determine the recommended immunizations needed for patient health information systems, has been updated for the 2-dose schedule. For vaccine coverage data in the National Immunization Survey (NIS)-Teen, 2-dose coverage criteria for NIS-Teen 2016 were added to the measure for up-to-date coverage, and that will be used going forward [<http://www.ncqa.org/hedis-quality-measurement/hedis-measures/hedis-2018>; <https://www.cdc.gov/vaccines/programs/iis/cdsi.htm>].

The policy issues discussed by the HPV Vaccines WG included the wording for routine target age group recommendation, and harmonization of the upper age for male and female vaccination. Both of these were mentioned briefly a year ago at the last ACIP HPV session. Regarding wording for the routine target age group, the current recommendation is that ACIP recommends routine HPV vaccination at age 11 or 12 years, and vaccination can be given starting at age 9 years. This has been the recommendation since the beginning of the US vaccination program in 2006. The potential alternative wording that was discussed was routine vaccination at 9 through 12 years of age, which some WG members felt would facilitate vaccine initiation and completion.

The WG deliberations have included review of the very limited data available on this topic and discussion with WG liaison and others from AAP. Most WG members favored retaining the current wording of the routine recommendation. The decision of the WG is not to bring forward any change for consideration by ACIP. ACIP and CDC will ensure that the option for starting the series at age 9 years will be evident on current schedules and in other materials, as it is now. Deliberations also occurred within AAP and COID, and their recommendations will remain consistent with ACIP. However, in the 2018 Red Book, AAP will recommend starting the series between 9 and 12 years of age, at an age that the provider deems optimal for acceptance and completion of the vaccination series.

The second policy being discussed by the WG is harmonization of the upper age for male and female HPV vaccination. As a reminder, the current recommendation is that ACIP recommends vaccination for females through age 26 years and for males through age 21 years who were not previously adequately vaccinated. The vaccine is licensed through age 26 for both males and females. Males aged 22 through 26 years may be vaccinated. There also are recommendations for specific groups to receive HPV vaccine through age 26 years. This includes MSM, transgender persons, and males with immunocompromising conditions. The alternative policy that was proposed was harmonization of the upper age for males and females through age 26 years. This would simplify the HPV vaccine schedule, eliminate the need to mention specific groups that should be vaccinated at age 22 and 26 years, and might also facilitate reaching higher risk groups. Many WG members favor simplification of the immunization schedule through extension of the male age recommendation through age 26 years.

For some history, ACIP recommended routine vaccination of males in 2011. Vaccination of males was included in the immunization schedule and, at that time, GRADE was used for consideration of the evidence and recommendations which included cost-effectiveness data. The recommendation for catch-up through age 21 years for males has been in place since that time. Over the past year, the ACIP HPV Vaccines WG while considering this potential policy issue has reviewed updated cost-effectiveness data, vaccine coverage among males in general and among MSM. The WG plans to continue to review this issue, to use the new Evidence to Recommendations framework, and to present this to ACIP in 2018. Other issues discussed by the WG over the past year included simplification of the footnotes for child/adolescent and adult schedules, and 9-valent HPV vaccine safety. Specifically, the WG heard an update of an ongoing analysis from the VSD on 9-valent vaccine showing no safety concerns. The Immunization Safety Office (ISO) plans to present data to ACIP in February 2018.

Regarding HPV vaccination coverage and impact in the US, data from NIS-Teen from 2006 to 2016 for three vaccines recommended for adolescents, vaccination coverage in females is increasing but more slowly than for other vaccines delivered to adolescents. In 2016, at least 1-dose coverage for HPV was 65% and 3-dose coverage was 43%. Coverage among males began to increase in 2011 after the routine recommendation for males, and reached 56% for at least 1 dose in 2016 and 32% for 3 doses. There has been a steeper increase in coverage in males compared to females for the last few years. Between 2015 and 2016, at least 1-dose coverage increased 6.2 percentage points for males and 2.3 percentage points for females. Because of the more rapid rise in coverage among males in recent years, the gap between female and male coverage is narrowing. While the gap in at least 1-dose coverage was 33 percentage points in 2012, it was only 9 percentage points in 2016.

Although coverage is still significantly higher in females than males, this year CDC calculated overall HPV vaccination coverage among all adolescents, which was 60.4% for at least 1 dose, 49.2% for at least 2 doses, and 37.1% for 3 or more doses. Another new measure that was added this year for adolescents was that adolescents are considered to be up to date (UTD) based on at least 3 doses, or 2 doses according to the new recommendations. Although it is too early to assess the direct impact of the 2-dose recommendation on practices because the 2-dose recommendation was just made at the end of 2016, when applied retrospectively, UTD coverage increased 6.3 percentage points compared to 3 or more doses, which was 43.4% in 2016.

Several monitoring efforts are ongoing in the US. The WG has presented some of these to ACIP before and hopes to be able to present further information to ACIP in the future. Dr. Markowitz mentioned data from prevalence monitoring in NHANES, which CDC has been using since the beginning of the vaccination program to evaluate impact of the vaccination because declines in prevalence will be one of the first impacts appreciated. In terms of vaccine type prevalence in female participants in NHANES, there was a 56% decrease within the first 4 years of the vaccination program in females 14 through 19 years of age. The most recent data through 2014 show further decreases among females with a 71% decrease in females 14 through 19 years of age and a 61% decrease in vaccine type prevalence in females 20 through 24 years of age, and no evidence of type replacement.

The WG's plans for 2018 are to continue reviewing and considering harmonization of the upper age for male and female vaccination recommendations, present to ACIP 9vHPV safety from post-licensure monitoring, and the impact of HPV vaccination in the US.

Discussion Points

Dr. Hunter said he was not sure he followed the WG's reasoning on not simplifying the 9- to 12-year-old age range recommendation, and if the WG was okay with the AAP saying the same thing in a different way.

Dr. Markowitz replied that ACIP just made a major change in the recommendation for the 2-dose schedule. The routine recommendation at age 11 to 12 is the age when other vaccines are recommended in the adolescent platform. The WG felt that right now, the recommendation does allow vaccination at age 9 years, so there would not really be any advantage to changing the wording since it is not really changing the recommendation. There also is substantial information and an entire program focusing on 11- to 12-year olds.

Dr. Maldonado (AAP) added the reason that AAP has made that recommendation and also alluded to the issue regarding catch-up vaccination because those are the two concerns they hear most frequently from among their 66,000 members. AAP thought it could address at least one of those issues in the Red Book itself.

Dr. Szilagyi noted that there are pros and cons like any other decision. He requested that Dr. Kempe talk about a provider survey, because the WG did have some data regarding what providers think about 9- to 12-year old versus 11- to 12-year old. The data presented from the provider survey suggested that there was not a major push from pediatric providers for the earlier age group. The WG has not presented those data to the full ACIP yet.

Dr. Kempe indicated that it was a rapidly conducted survey to determine if they could get a quick idea about this issue. In fact, most providers favored keeping things as they are. However, this is in the context of providers doing what they do and they worry, she thinks, about parents who are already concerned about 11- to 12-year olds and starting vaccination even younger. She thinks the responses would be very different if it were now the norm to administer this vaccine at 9 and 10 years of age. Those were the only data available.

Day 1: Public Comment

No public comments were provided during this session.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Messonnier indicated that since the last ACIP meeting, CDC has welcomed a new Director, Dr. Brenda Fitzgerald. Though Dr. Fitzgerald was in Uganda during this meeting, Dr. Messonnier was hopeful that she would be able to attend the February 2018 meeting. 2018 marks the centennial of the 1918 influenza pandemic. CDC and its partners are working on a variety of events to commemorate that, including a multi-faceted communication campaign. During a previous ACIP meeting, there was discussion about the Ebola vaccine trials. The CDC-led Ebola vaccine trial in Sierra Leone has been completed. Nearly 8000 participants

were vaccinated from April through November 2015. Thankfully, there were no cases of Ebola. Though there are no vaccine efficacy data as a result, this is the largest safety database regarding Ebola vaccines. There were no SAEs, the AE profile was similar to Phase I and II studies, and post-vaccine reactogenicity was mild with quick recovery. A Clinical Study Report was submitted to the FDA, and a variety of manuscripts are in development that will be published in a *Journal of Infectious Diseases (JID)* supplement. Immunogenicity study specimens are being tested by Merck. CDC is excited that if perchance there is another Ebola outbreak, there would be a better tool for response. November 12th is World Pneumonia Day, which began in 2009 and marks the incredible toll of pneumonia to raise awareness. Pneumonia is a leading killer of children throughout the world, and this event is an opportunity globally to mark and raise awareness.

Centers for Medicare and Medicaid Services (CMS)

Ms. Hance reported that the Centers for Medicare and Medicaid (CMS) is once again working with pharmacies and other stakeholders to encourage Medicare/Medicaid beneficiaries to get their influenza vaccines. Specifically, they have worked with community pharmacies to provide influenza vaccines for Medicare beneficiaries and report data. As in past years, CMS has worked with HRSA and the National Vaccine Program Office (NVPO) to post Medicare influenza vaccination information for those in fee-for-service (FFS) plans on the NVPO website. That website is updated weekly.

Department of Defense (DoD)

Dr. Deussing indicated that for the 2017-2018 Department of Defense (DoD) Seasonal Influenza Program, the influenza vaccine remains mandatory for all uniformed personnel, including Active Duty, Coast Guard, Reserve, and National Guard members. The immunization goal is 90% vaccination compliance by mid-December. As a reminder, the influenza vaccine is also mandatory for HCP who provide direct patient care in military treatment facilities and is recommended for all other HCP within the Military Health System (MHS). The DoD began administering this season's influenza vaccine the last week of August, and anticipates that approximately 3.5 million beneficiaries will be covered this season. The DoD continues to closely monitor the limited Yellow Fever Vaccine[®] (YF-Vax[®]) supply within the MHS. The Defense Health Agency's (DHA) Immunization Healthcare Branch (IHB) utilizes an approval validation process for YF-Vax[®] requests by military treatment facilities. DoD's Global Immunization Healthcare Specialists also communicate frequently with immunization providers and redistribute YF-Vax[®] based on expiration data and demand to ensure that vaccine doses are optimally used and not wasted. Of note, this redistribution program applies to all vaccines within the MHA and it is an extremely successful program. DoD will continue to monitor and judiciously use its YF-Vax[®] during the supply constrained period.

Food and Drug Administration (FDA)

Dr. Sun reported that since the last ACIP meeting in June 2017, FDA has approved a new seasonal influenza vaccine, Afluria[®] Quadrivalent for children 5 through 17 years of age. This is noteworthy because due to a campaign in Australia several years in which Afluria[®] Trivalent showed an increase in febrile seizures, the indication was changed to 5 years of age and above. ACIP recommended Afluria[®] Trivalent for 9 years of age and above. The company, Seqirus[™], as made some manufacturing changes for Afluria[®] Quadrivalent. Afluria[®] Quadrivalent was approved based on non-inferiority comparison with a licensed quadrivalent, and has been shown to be safe and effective. Shingrix, which contains AS01 adjuvant, was recently

approved. A Vaccine Advisory Committee will be convened on November 7, 2017 to discuss the clinical development of a *Staphylococcus aureus* (*S. aureus*) vaccine by Pfizer for use as a pre-surgical prophylaxis in elective orthopedic surgeries.

Health Resources and Services Administration (HRSA)

Dr. Nair reported that HRSA continues to be busy in the VICP. For this fiscal year (FY), over 1176 claims were received in this program. As of September 25, 2017, the amounts awarded include \$250 million to petitioners and \$29.7 for attorneys' fees/costs and dismissed claims. More data can be obtained on the HRSA website. HRSA continues its outreach efforts to ensure that providers and the public are aware of the program and how to file a claim.

Indian Health Service (IHS)

Ms. Groom indicated that this would be the Indian Health Service's (IHS) second year with a full mandatory influenza vaccination policy for its HCP. IHS achieved the Healthy People 2020 goal last year of 90%, and are hopeful that they will achieve this goal again this year. They also rolled out a reminder for HepA and HepB vaccines for its patients with CLD and HepC in an attempt to focus efforts on some of the high-risk populations. This is in addition to the reminder for people with diabetes. IHS will use its adult composite measure as a performance measure for the agency, which considers up-to-date coverage among adults with all age-appropriate recommended vaccines to include Td, Tdap, Zoster (which will be updated to include Shingrix), and both pneumococcal vaccines. This will be the performance measure for the agency for FY18. IHS is pleased to announce that two of its sites were selected as the winners of the CDC/American Cancer Society (ACS) *HPV Vaccine Is Cancer Prevention Champion* award. A facility or healthcare system was selected in each of the 10 HHS regions that achieved at least 70% up-to-date coverage with HPV vaccine in males and females.

National Institutes of Health (NIH)

Dr. Mulach reported that the US Government expressed an interest in developing a couple of H7N9 vaccines. NIH's National Institute of Allergy and Infectious Diseases (NIAID) is part of that process and will be conducting a series of Phase II clinical trials, including 2 dose-ranging studies with product produced by different manufacturers and using the adjuvant AS03 to evaluate dose and a few other Phase II studies. In June, NIAID convened a universal influenza vaccine meeting titled "Pathway to a Universal Influenza Vaccine" on June 28-29, 2017 in Rockville, Maryland to discuss key considerations for developing a universal influenza vaccine. The meeting report is available in October 17, 2017 issue of *Immunity* [Cl Paules et al. The Pathway to a Universal Influenza Vaccine. *Immunity* DOI: 10.1016/j.immuni.2017.09.007 (2017)]. Dr. Fauci supports the development of a broadly protective, universal influenza vaccine. Norman E. "Ned" Sharpless, MD was officially sworn in as the 15th Director of the National Cancer Institute (NCI) on October 17, 2017. Previous to this, Dr. Sharpless served as the Director of the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center, a position he held since January 2014. His research focus is on understanding the biology of the aging process that promotes the conversion of normal self-renewing cells into dysfunctional cancer cells. There are a couple of meeting reports available for meetings that occurred last year, "The Impact of *Mycobacterium tuberculosis* Immune Evasion on Protective Immunity: Implications for TB Vaccine Design" [Cesar Boggiano, et al., *Vaccine*, Volume 35, Issue 27, 14 June 2017, Pages 3433-3440] and "Waning Immunity and Microbial Vaccines – Workshop of the National Institute of Allergy and Infectious Diseases" [Gu X-X, Plotkin SA, Edwards KM, Sette A, Mills KHG, Levy O, Sant AJ, Mo A, Alexander W, Lu KT, Taylor CE.

2017. Waning immunity and microbial vaccines—workshop of the National Institute of Allergy and Infectious Diseases. *Clin Vaccine Immunol* 24:e00034-17].

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

Dr. Wharton reported that NVPO is working with other HHS agencies to complete the report requested by the [21st Century Cures Act](#), which will outline the status of vaccine development, barriers, and potential solutions. There was no National Vaccine Advisory Committee (NVAC) meeting in September 2017, given that the HHS Assistant Secretary for Health (ASH) position was vacant. However, a meeting is in the planning stages for February 7-8, 2018. NVPO and Emory University co-hosted a meeting on vaccine confidence in the summer, a summary report of which will be available on the NVPO website once completed.

US Department of Veterans Affairs (VA)

Dr. Cohn conveyed the US Department of Veterans Affairs' (VA) apologies for not having a representative available for this meeting and read their report into the record:

The VA partnered with Walgreen's for the 2016-2017 influenza season, promoting access to seasonal influenza vaccines for veterans receiving care from the VA. This partnership resulted in over 70,000 vaccinations paid for by the VA. This partnership will continue for the 2017-2018 season. VA recently released an electronic decision support tool, also called a clinical reminder, for meningococcal immunization in August 2017. This clinical reminder can be used in VistA, the VA EMR. VA is exploring electronic measures to align with HEDIS.

Adult Immunization Schedule

Introduction

Laura E. Riley, MD
Chair, Adult Immunization Work Group
Advisory Committee on Immunization Practices

Dr. Riley reminded everyone that ACIP updates the adult immunization schedule each year. The schedule represents current ACIP policy and is designed for implementation of those policies. The updates are approved by the following:

- American College of Physicians (ACP)
- American Academy of Family Physicians (AAFP)
- American Congress of Obstetricians and Gynecologists (ACOG)
- American College of Nurse Midwives (ACNM)

The adult immunization schedule is published in the *MMWR* as an announcement and in the *Annals of Internal Medicine* in its entirety.

Updates to the 2018 Adult Immunization Schedule include the following:

- ❑ Zoster vaccination recommendations, which were approved the day before
- ❑ Measles, mumps, and rubella vaccination recommendations, also reflecting the previous day's discussion and vote
- ❑ Adult immunization schedule format and content changes

Adult Immunization Schedule

Dr. David Kim

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Centers for Disease Control and Prevention

Dr. Kim reported that the Adult Immunization WG drafted the proposed 2018 Adult Immunization Schedule to include the recommended use of HZ/su vaccine and mumps-containing vaccine in mumps outbreak settings. To recap the vote taken the previous day, HZ/su vaccine: 1) is recommended for adults age 50 years or older; 2) is recommended for adults who previously received ZVL; and 3) for adults age 60 years or older, HZ/su or ZVL can be administered (but HZ/su is preferred over ZVL). ACIP also recommended a third dose of mumps-containing vaccine in mumps outbreak settings, as determined by public health authorities.

During this session, Dr. Kim reviewed the changes in the Adult Immunization schedule, including format changes. The schedule is still 6 pages, including the cover page, Figures 1 and 2, 2 pages of footnotes, and the table of contraindications and precautions. This is the proposed cover page:

Recommended Immunization Schedule for Adults Age 19 Years or Older, United States, 2018

In February 2018, the Recommended Immunization Schedule for Adults Age 19 Years or Older, United States, 2018 became effective, as recommended by the Advisory Committee on Immunization Practices (ACIP) and approved by the Centers for Disease Control and Prevention (CDC). The 2018 adult immunization schedule was also reviewed and approved by the American College of Physicians, the American Academy of Family Physicians, the American College of Obstetricians and Gynecologists, and the American College of Nurse-Midwives.

CDC announced the availability of the 2018 adult immunization schedule in the *Morbidity and Mortality Weekly Report* (MMWR).¹ The schedule is published in its entirety in the *Annals of Internal Medicine*.²

The 2018 adult immunization schedule consists of figures that summarize routinely recommended vaccines for adults by age groups and medical conditions and other indications, footnotes for the figures, and a table of vaccine contraindications and precautions. Consider the following information when reviewing the adult immunization schedule:

- The figures in the adult immunization schedule should be reviewed with the accompanying footnotes.
- The figures and footnotes display indications for which vaccines, if not previously administered, should be administered unless noted otherwise.
- The table of contraindications and precautions identify populations and situations for which vaccines should not be used or should be used with caution.
- When indicated, administer recommended vaccines to adults whose vaccination history is incomplete or unknown.
- Increased interval between doses of a multi-dose vaccine series does not diminish vaccine effectiveness; it is not necessary to restart the vaccine series or add doses to the series because of an extended interval between doses.
- Combination vaccines may be used when any component of the combination is indicated and when the other components of the combination are not contraindicated.
- The use of trade names in the adult immunization schedule is for identification purposes only and does not imply endorsement by ACIP or CDC.

The 2018 adult immunization schedule footnotes that accompany the figures identify special populations for whom additional considerations have been described, including:

- Pregnant women. Pregnant women should receive the tetanus, diphtheria, and pertussis vaccine during pregnancy and the influenza vaccine during or before pregnancy. Live vaccines (e.g., measles, mumps, and rubella vaccine) are contraindicated.
- Asplenia. Adults with asplenia have specific vaccination recommendations because of their increased risk for infection by encapsulated bacteria. Asplenia or functional asplenia includes congenital or acquired asplenia, splenic dysfunction, sickle cell disease and other hemoglobinopathies, and splenectomy.
- Immunocompromising conditions. Adults with immunosuppression should generally avoid live vaccines. Inactivated vaccines (e.g., pneumococcal vaccines) are generally acceptable. High-level immunosuppression includes HIV infection with a CD4+T lymphocyte count <200 cells/ μ L, receipt of daily corticosteroid therapy with a 20 mg of prednisone or equivalent for a 14 day, primary immunodeficiency disorder (e.g., severe combined immunodeficiency or complement component deficiency), hematological malignancy or transplantation, and receipt of cancer chemotherapy. Other immunocompromising conditions and immunosuppressive medications to consider when vaccinating adults can be found in *ADA Clinical Practice Guidelines for Vaccination of the Immunocompromised Host*.³ Additional information on vaccinating immunocompromised adults are in *General Best Practice Guidelines for Immunization*.⁴

Additional resources for health care providers include:

- Details on vaccines recommended for adults and complete ACIP statements at www.cdc.gov/vaccines/hq/immunization/acip/
- Vaccine Information Statements that explain benefits and risks of vaccines at www.cdc.gov/vaccines/hq/vis/index.html
- Information and resources on vaccinating pregnant women at www.cdc.gov/vaccines/adults/hec-vac/gpreg.html
- Information on travel vaccine requirements and recommendations at www.cdc.gov/travel/
- CDC Vaccine Schedule App for immunization service providers to download at www.cdc.gov/vaccines/hq/vis/hqvis/hqvis-checkup-app.html
- Adult Vaccination Quiz for self-assessment of vaccination needs based on age, health conditions, and other indications at www.cdc.gov/hq/vis/adultinched/default.asp
- Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger at www.cdc.gov/vaccines/hq/vis/hqvis/hqvis-child-adolescent.html

Report suspected cases of reportable vaccine-preventable diseases to the local or state health department, and report all clinically significant post-vaccination events to the Vaccine Adverse Event Reporting System at www.cdc.gov/vaers/ or by telephone 800-822-7967. All vaccines included in the 2018 adult immunization schedule except 23-valent pneumococcal polysaccharide and zoster vaccines are covered by the Vaccine Injury Compensation Program. Information on how to file a vaccine injury claim is available at www.hrsa.gov/vaccinecompensation/ or by telephone 800-338-2882.

Submit questions and comments to CDC through www.cdc.gov/ask-cdc/ or by telephone 800-CDC-INFO (800-232-4636), in English and Spanish, 8:00am-8:00pm ET, Monday-Friday, excluding holidays.

The following abbreviations, in the order of their appearance in the 2018 adult immunization schedule, are used for vaccines recommended for adults:

IPV	inactivated influenza vaccine
RV	recombinant influenza vaccine
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
TD	tetanus and diphtheria toxoids
MMR	measles, mumps, and rubella vaccine
MMRV	measles, mumps, and rubella vaccine with varicella vaccine
ZVL	zoster vaccine live
HPV vaccine	human papillomavirus vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PPV23	23-valent pneumococcal polysaccharide vaccine
HepA	hepatitis A vaccine
HepA-HepB	hepatitis A vaccine and hepatitis B vaccine
HepB	hepatitis B vaccine
MenACWY	serogroups A, C, W, and Y meningococcal vaccine
MenB	serogroup B meningococcal vaccine
HP	Haemophilus influenzae type b vaccine

1. MMWR Morbidity and Mortality Weekly Report. 2018;65(7):e1-10. Available at www.cdc.gov/mmwr/preview/mmwrhtml/6507a1.htm.

2. Ann Intern Med. 2018;168(7):e1-10. Available at www.annals.org/lookup/forward?doi=10.12691/aim.168.7.e1.

3. Rubin et al. *CDC 2011 ASSESS* 144-155. Available at www.cdc.org/immunization/content.aspx?ci=222375011.

4. Kogler et al. Available at www.cdc.gov/vaccines/hq/vis/hqvis/gbest/index.html.


 U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

The cover page now contains additional information on special populations (pregnancy, asplenia, immunocompromising conditions). The intent was to consolidate this information so that the details are not repeated multiple times in the footnotes. Also revised are the abbreviations for vaccines. The list is now organized by the order of the vaccines' appearance on the schedule to keep vaccines for similar indications together.

This is the working Figure 1. Recommended immunization schedule for adults age 19 years or older by age group, United States, 2018:

Figure 1. Recommended immunization schedule for adults age 19 years or older by age group, United States, 2018.
This figure should be reviewed with the accompanying footnotes. This figure and the footnotes describe indications for which vaccines, if not previously administered, should be administered unless noted otherwise.

Vaccine	19–21 years	22–26 years	27–49 years	50–64 years	≥65 years
Influenza ¹	1 dose annually				
Tdap/Td ²	1 dose Tdap, then Td booster every 10 yrs				
MMR ³	1 or 2 doses depending on indication (if born in 1937 or later)				
VAR ⁴	2 doses				
ZVL ⁵					1 dose
pending					
HPV–Female ⁶	2 or 3 doses depending on age at series initiation				
HPV–Male ⁶	2 or 3 doses depending on age at series initiation				
PCV13 ⁷					1 dose
PPSV23 ⁷			1 or 2 doses depending on indication		1 dose
HepA ⁸	2 or 3 doses depending on vaccine				
HepB ⁸	3 doses				
MenACWY ¹⁰	1 or 2 doses depending on indication, then booster every 5 yrs if risk remains				
MenB ⁹	2 or 3 doses depending on vaccine				
Hib ¹¹	1 or 3 doses depending on indication				

Recommended for adults who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection
 Recommended for adults with other indications
 No recommendation

The major change in Figure 1 is with zoster vaccine. Instead of the ZVL row for age 60 and older, a row each for HZ/su and ZVL was created for individuals 50 years of age and older. The indication bar will have the text “2 doses HZ/su (or 1 dose ZVL if age ≥60 yrs).” There are other minor changes. Last year, ACIP recommended a 2-dose HPV vaccination series for adolescents and young adults based on their age at first dose. To reflect that recommendation, the text in the indication bar for HPV has been changed from “3 doses” to “2 or 3 doses depending on age at series initiation.” Moving down to the MenACWY row, meningococcal polysaccharide vaccine (MPSV4) was removed because it is no longer on the market. In the indication bar for MenACWY, the text has been revised from “1 or more doses depending on indication” to “1 or 2 doses depending on indication, then booster every 5 yrs if risk remains” to reflect ACIP recommendations more accurately. Also on Figure 1, the order of “Td/Tdap” has been reversed to state “Tdap or Td” to emphasize Tdap in adult immunization. In addition, the indication bar for Tdap or Td has been revised to “1 dose Tdap, then Td booster every 10 yrs.” The previous text, “Substitute Tdap for Td once, then Td booster every 10 yrs” was not quite accurate as the dose of Tdap for adults was meant to be given at the first opportunity rather than waiting until a Td booster is needed.

This is a working draft of Figure 2: Recommended immunization schedule for adults age 19 years or older by medical condition and other indications, United States, 2018:

Figure 2. Recommended immunization schedule for adults age 19 years or older by medical condition and other indications, United States, 2018
 The figure should be reviewed with the accompanying footnotes. This figure and the footnotes describe indications for which vaccines, if not previously administered, should be administered unless noted otherwise.

Vaccine	Pregnancy ^{a,b}	Immunocompromised (excluding HIV infection) ^{c,d,e}	HIV infection CD4+ count (cells/ μ L) ^{f,g}	Asplenia, complement deficiencies ^{h,i,j}	End-stage renal hemodialysis ^k	Heart or lung disease, alcoholism ^l	Chronic liver disease ^m	Diabetes ⁿ	Health care personnel ^o	Men who have sex with men ^p
Influenza ¹			<200							
Tdap/Td ²	1 dose Tdap each pregnancy									
MMR ³		contraindicated								
VAR ⁴		contraindicated								
ZVL ⁵		contraindicated								
Pending										
HPV-Female ⁶										
HPV-Male ⁶										
PCV13 ⁷										
PPSV23 ⁷										
HepA ⁸										
HepB ⁸										
MenACWY ⁹										
MenB ⁹										
Hib ¹¹										

Recommended for adults who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection
 Recommended for adults with other indications
 Contraindicated
 No recommendation

As in Figure 1, Figure 2 incorporates the HZ/su vaccine. At the moment, the indications and contraindications for HZ/su vaccine will mirror the indications and contraindications for ZVL. The row for zoster vaccination is subject to change as more is learned about HZ/su.

These are the working drafts of page 1 and 2 of the footnotes:

Footnotes. Recommended immunization schedule for adults age 19 years or older, United States, 2018

1. Influenza vaccination
www.cdc.gov/vaccines/imz/downloads/pdf/13-001a.pdf
 General information
 • Administer 1 dose of age-appropriate inactivated influenza vaccine (IV) or recombinant influenza vaccine (RV) annually
 • Available options for adults include:
 – High-dose or adjuvanted IV for adults age 65 years or older
 – Intradermal IV for adults age 18 through 64 years
 • Live attenuated influenza vaccine (LAIV) is not recommended for the 2017–2018 influenza season
 • A list of currently available influenza vaccines is available at www.cdc.gov/flu/protect/vaccine/vaccines.htm
 Special populations
 • Administer age-appropriate IV or RV to:
 – Pregnant women
 – Adults with latex-only egg allergy
 – Adults with egg allergy other than hives (e.g., angioedema or respiratory distress): Administer IV or RV in a medical setting under supervision of a health care provider who can recognize and manage severe allergic conditions

2. Tetanus, diphtheria, and pertussis vaccination
www.cdc.gov/vaccines/imz/downloads/pdf/13-001a.pdf
 General information
 • Administer to adults with no previous dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) as an adult or child 1 dose of Tdap, followed by a dose of tetanus and diphtheria toxoids (Td) booster every 10 years
 • Infection on the use of Tdap or Td as tetanus prophylaxis in wound management is available at www.cdc.gov/mmwr/preview/mmwrft031517a1.htm
 Special populations
 • Pregnant women: Administer 1 dose of Tdap during each pregnancy, preferably in the early part of gestational weeks 27–36

3. Measles, mumps, and rubella vaccination (revision pending ACIP recommendation)
www.cdc.gov/vaccines/imz/downloads/pdf/13-001a.pdf
 General information
 • Administer to adults without evidence of immunity to measles, mumps, or rubella 1 dose of measles, mumps, and rubella vaccine (MMR)
 • Evidence of immunity is:
 – Born before 1957 (except for health care personnel; see below)
 – Documentation of receipt of MMR
 – Laboratory evidence of immunity or disease
 • Documentation of a health care provider-diagnosed disease without laboratory confirmation is not considered evidence of immunity
 Special populations
 • Administer 1 dose of MMR to:
 – Pregnant women without evidence of immunity to rubella: Administer before pregnancy and before discharge from health care facility
 – Non-pregnant women of childbearing age without evidence of immunity to rubella
 • Administer 2 doses of MMR at least 28 days apart to adults with HIV infection and CD4 cell count ≥ 200 cells/ μ L for at least 6 months
 • Administer 2 doses of MMR at least 28 days apart if no evidence of immunity or 1 dose of MMR if received 1 dose previously to:
 – Students in postsecondary educational institutions
 – International travelers
 – Health care personnel born in 1957 or later (if born before 1957, consider MMR vaccination)
 – Household contacts of immunocompromised persons
 • MMR is contraindicated for pregnant women and adults with severe immunodeficiency

4. Varicella vaccination
www.cdc.gov/vaccines/imz/downloads/pdf/13-001a.pdf
 General information
 • Administer to adults without evidence of immunity to varicella 2 doses of varicella vaccine (VAR) 4–6 weeks apart if previously received no varicella-containing vaccine, or 1 dose of VAR if previously received 1 dose of varicella-containing vaccine (at least 4 weeks after the first dose)
 • Evidence of immunity to varicella is:
 – U.S.-born before 1980 (except for pregnant women and health care personnel; see below)
 – Documentation of receipt of 2 doses of varicella or varicella-containing vaccine at least 4 weeks apart
 – Diagnostic or verification of history of varicella or herpes zoster by a health care provider
 • Laboratory evidence of immunity or disease
 Special populations
 • Administer 2 doses (series of VAR) 4–6 weeks apart if previously received no varicella-containing vaccine, or 1 dose of VAR if previously received 1 dose of varicella-containing vaccine (at least 4 weeks after the first dose) to:
 – Pregnant women without evidence of immunity: Administer the first of the 2 doses or the second dose after pregnancy and before discharge from health care facility
 – Health care personnel without evidence of immunity
 • Adults with HIV infection and CD4 cell count ≥ 200 cells/ μ L. May administer, based on individual clinical decision, 2 doses of VAR 3 months apart
 • VAR is contraindicated for pregnant women and adults with severe immunodeficiency

5. Zoster vaccination (revision pending ACIP recommendation)
www.cdc.gov/vaccines/imz/downloads/pdf/13-001a.pdf
 General information
 • Administer to adults age 60 years or older should receive 1 dose of zoster vaccine live (ZVL), regardless of whether they had a prior episode of herpes zoster.
 Special populations
 • Adults age 60 years or older with chronic medical conditions may receive ZVL unless they have a medical contraindication, e.g., pregnancy or severe immunodeficiency
 • Adults with malignant conditions, including those that affect the bone marrow or lymphatic system or who receive systemic immunosuppressive therapy, should not receive ZVL

6. Human papillomavirus vaccination
www.cdc.gov/vaccines/imz/downloads/pdf/13-001a.pdf
 General information
 • Administer human papillomavirus (HPV) vaccine to females through age 26 years and males through age 21 years (male age 21 through 26 years may be vaccinated based on individual clinical decision)
 • The number of doses of HPV to be administered depends on age at initial HPV vaccination
 • No previous dose of HPV vaccine: Administer 3-dose series (0, 1–2, and 6 months minimum intervals; 4 weeks between first and second doses, 12 weeks between second and third doses, and 5 months between first and third doses (upset doses if given too soon))
 • Age 9–14 years at vaccine series initiation and received 1 dose or 2 doses less than 5 months apart: Administer 1 dose
 • Age 9–14 years at vaccine series initiation and received 2 doses at least 5 months apart: No additional dose is needed
 Special populations
 • Adults with immunocompromising conditions (including HIV) through age 26 years: Administer 3-dose series at 0, 1–2, and 6 months
 • Men who have sex with men through age 26 years: Administer 2- or 3-dose series depending on age at initial vaccination (see above); if no history of HPV vaccine, administer 3-dose series at 0, 1–2, and 6 months
 • Pregnant women through age 26 years: HPV vaccination is not recommended during pregnancy, but there is no evidence that the vaccine is harmful and no intervention needed for women who inadvertently receive HPV vaccine while pregnant; delay remaining doses until after pregnancy; pregnancy testing is not needed before vaccination

7. Pneumococcal vaccination
www.cdc.gov/vaccines/imz/downloads/pdf/13-001a.pdf
 General information
 • Administer to immunocompetent adults age 65 years or older 1 dose of 13-valent pneumococcal conjugate vaccine (PCV13) followed by 1 dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23) at least 1 year after PCV13
 • When both PCV13 and PPSV23 are indicated, administer PCV13 first (PCV13 and PPSV23 should not be administered during the same visit; additional information on vaccine timing is available at www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf)

<p>Special populations</p> <ul style="list-style-type: none"> Administer to adults age 19 through 64 years with the following chronic conditions: 1 dose of PPV23 (at age 65 years or older; administer 1 dose of PCV13, if not previously received, and another dose of PPV23 at least 1 year after PCV13 and at least 5 years after PPV23); Chronic heart disease (including hypertension) Chronic lung disease Chronic liver disease Alcoholism Diabetes mellitus Cigarette smoking <p>Administer to adults age 19 years or older with the following indications: 1 dose of PCV13 followed by 1 dose of PPV23 at least 8 weeks after PCV13, and a second dose of PPV23 at least 5 years after the first dose of PPV23 (administer a second dose of PPV23 at least 5 years after the first dose of PPV23, if the most recent dose of PPV23 was administered before age 65 years; at age 65 years or older, administer another dose of PPV23 at least 5 years after the last dose of PPV23):</p> <ul style="list-style-type: none"> Immunodeficiency disorders including B- and T-lymphocyte deficiency, complement deficiencies, and phagocytic disorders HIV infection Anatomical or functional asplenia Chronic renal failure and nephrotic syndrome <p>Administer to adults age 19 years or older with the following indication: 1 dose of PCV13 followed by 1 dose of PPV23 at least 8 weeks after PCV13 (if the dose of PPV23 was administered before age 65 years, at age 65 years or older, administer another dose of PPV23 at least 5 years after the last dose of PPV23)</p> <ul style="list-style-type: none"> Cerebrospinal fluid leak Cochlear implant <p>B. Hepatitis A vaccination www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepa.html</p> <p>General information</p> <ul style="list-style-type: none"> Administer to adults who have a specific risk (see below), or lack a risk factor but want protection, 3-dose series of single antigen hepatitis A vaccine (HepA, Haver) at 0 and 6-12 months or Vagta at 0 and 6-18 months; minimum interval: 6 months for combined hepatitis A and hepatitis B vaccine (HepA-HepB) at 0, 1, and 6 months; minimum intervals: 4 weeks between first and second dose, 5 months between second and third doses <p>Special populations</p> <ul style="list-style-type: none"> Administer HepA or HepA-HepB to adults with the following indications: <ul style="list-style-type: none"> Travel to or work in countries with high or intermediate hepatitis A endemicity Men who have sex with men Injection or non-injection drug use Work with hepatitis A virus in a research laboratory or with non-human primates infected with hepatitis A virus Clotting factor disorders 	<p>Chronic liver disease</p> <ul style="list-style-type: none"> Close, personal contact with an international adoptee (e.g., household or regular babysitting) during the first 60 days after arrival in the United States from a country with high or intermediate endemicity (administer the first dose as soon as the adoption is planned) Healthy adults up to age 40 years who have recently been exposed to hepatitis A virus; adults older than age 40 years may receive HepA or HepA-HepB if hepatitis A immunoglobulin cannot be obtained <p>9. Hepatitis B vaccination www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepb.html</p> <p>General information</p> <ul style="list-style-type: none"> Administer to adults who have a specific risk (see below), or lack a risk factor but want protection, 3-dose series of single antigen hepatitis B vaccine (HepB) or combined hepatitis A and hepatitis B vaccine (HepA-HepB) at 0, 1, and 6 months (minimum intervals: 4 weeks between first and second dose, 5 months between second and third doses) <p>Special populations</p> <ul style="list-style-type: none"> Administer HepB or HepA-HepB to adults with the following indications: <ul style="list-style-type: none"> Chronic liver disease (e.g., hepatitis C infection, cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice the upper limit of normal) HIV infection Percutaneous or mucosal risk to blood (e.g., household contacts of hepatitis B surface antigen [HBsAg] positive persons; persons younger than age 40 years with diabetes mellitus or age 40 years or older with diabetes mellitus based on individual clinical decision; persons in predialysis care or receiving hemodialysis or peritoneal dialysis; recent or current injection drug users; health care and public safety workers at risk for exposure to blood or blood-contaminated body fluids) Sexual exposure risk (e.g., sex partners of HBsAg-positive persons; sexually active persons not in a mutually monogamous relationship; persons seeking evaluation or treatment for a sexually transmitted infection; and men who have sex with men [MSM]) Deer or cave rat settings with a high proportion of adults have risks for hepatitis B infection (e.g., facilities providing sexually transmitted disease treatment, drug-abuse treatment and prevention services, hemodialysis and end-stage renal disease programs, institutions for developmentally disabled persons, health care settings targeting services to injection-drug users or men who have sex with men, HIV testing and treatment facilities, and correctional facilities) Travel to countries with high or intermediate hepatitis B endemicity <p>10. Meningococcal vaccination www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html</p> <p>Special populations: Serogroups A, C, W, and Y meningococcal vaccine (MenACWY)</p> <ul style="list-style-type: none"> Administer 2 doses of MenACWY at least 8 weeks apart and boosters with 1 dose of MenACWY every 5 years, if the risk remains, to adults with the following indications: <ul style="list-style-type: none"> Anatomical or functional asplenia including sickle cell disease HIV infection Persistent complement component deficiency Eculizumab use Administer 1 dose of MenACWY and revaccinate with 1 dose of MenACWY every 5 years, if the risk remains, to adults with the following indications: <ul style="list-style-type: none"> Travel to or live in countries where meningococcal disease is hyperendemic or epidemic, including countries in the African meningitis belt or during the Hajj At risk from a meningococcal disease outbreak attributed to serogroup A, C, W, or Y Micrобиologists routinely exposed to <i>Neisseria meningitidis</i> Military recruits First-year college students age 21 years or younger who live in residential housing (if did not receive MenACWY at age 16 years or older) <p>General Information: Serogroup B meningococcal vaccine (MenB)</p> <ul style="list-style-type: none"> May administer, based on individual clinical decision, to young adults and adolescents age 16-23 years (preferred age is 16-18 years) who are not at increased risk MenB (2-dose series of MenB-4C [Bexsero] at least 1 month apart or 2-dose series of MenB-FHbp [Trumenb] at least 6 months apart) MenB-4C and MenB-FHbp are not interchangeable <p>Special populations: MenB</p> <ul style="list-style-type: none"> Administer 2-dose series of MenB-4C at least 1 month apart or 3-dose series of MenB-FHbp at 0, 1-2, and 6 months to adults with the following indications: <ul style="list-style-type: none"> Anatomical or functional asplenia (including sickle cell disease) Persistent complement component deficiency Eculizumab use At risk from a meningococcal disease outbreak attributed to serogroup B Micrобиologists routinely exposed to <i>Neisseria meningitidis</i>
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Each footnote is presented in more of a bulleted format as opposed to a paragraph format. The WG worked very hard to consolidate the information, remove outdated or less pertinent information, and keep the footnotes brief and concise. Overall, the length of the footnotes for 2018 decreased by about 25% and there is a lot more white space compared to the 2017 version. Moreover, the WG compared the Adult schedule side-by-side with the Child and Adolescent schedule to make the transition as smooth as possible. The proposed revised zoster and MMR vaccination footnotes are shown in the following table compared to the existing footnote:

2017	Proposed 2018
<p>Herpes zoster vaccination</p> <p>General information</p> <ul style="list-style-type: none"> Adults aged 60 years or older should receive 1 dose of herpes zoster vaccine (HZV), regardless of whether they had a prior episode of herpes zoster. <p>Special populations</p> <ul style="list-style-type: none"> Adults aged 60 years or older with chronic medical conditions may receive HZV unless they have a medical contraindication, e.g., pregnancy or severe immunodeficiency. Adults with malignant conditions, including those that affect the bone marrow or lymphatic system or who receive systemic immunosuppressive therapy, should not receive HZV. Adults with human immunodeficiency virus (HIV) infection and CD4+ T-lymphocyte count <200 cells/μl should not receive HZV. 	<p>Zoster vaccination www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/shingles.html</p> <p>General information</p> <ul style="list-style-type: none"> Administer 2 doses of herpes zoster subunit vaccine (HZ/su) 8 weeks apart to adults age 50 years or older regardless of past episode of herpes zoster or past history of zoster vaccine live (ZVL) Adults age 50 years or older who previously received ZVL should receive 2 doses of HZ/su 8 weeks apart at least 8 weeks after ZVL ZVL continues to be an option for adults age 60 years or older; however, HZ/su is preferred in this age group <p>Special populations</p> <ul style="list-style-type: none"> Pregnant women and adults with immunocompromising conditions, including those with HIV and CD4 cell count <200 cells/μL, should not receive HZ/su or ZVL

<p>Measles, mumps, and rubella vaccination</p> <p>General information</p> <ul style="list-style-type: none"> Adults born in 1957 or later without acceptable evidence of immunity to measles, mumps, or rubella (defined below) should receive 1 dose of measles, mumps, and rubella vaccine (MMR) unless they have a medical contraindication to the vaccine, e.g., pregnancy or severe immunodeficiency. Notes: Acceptable evidence of immunity to measles, mumps, or rubella in adults is: born before 1957, documentation of receipt of MMR, or laboratory evidence of immunity or disease. Documentation of healthcare provider-diagnosed disease without laboratory confirmation is not acceptable evidence of immunity. <p>Special populations</p> <ul style="list-style-type: none"> Pregnant women who do not have evidence of immunity to rubella should receive 1 dose of MMR upon completion or termination of pregnancy and before discharge from the healthcare facility; nonpregnant women of childbearing age without evidence of rubella immunity should receive 1 dose of MMR. Adults with primary or acquired immunodeficiency including malignant conditions affecting the bone marrow or lymphatic system, systemic immunosuppressive therapy, or cellular immunodeficiency should not receive MMR. Adults with human immunodeficiency virus (HIV) infection and CD4+ T-lymphocyte count ≥ 200 cells/μl for at least 6 months who do not have evidence of measles, mumps, or rubella immunity should receive 2 doses of MMR at least 28 days apart. Adults with HIV infection and CD4+ T-lymphocyte count < 200 cells/μl should not receive MMR. Adults who work in healthcare facilities should receive 2 doses of MMR at least 28 days apart; healthcare personnel born before 1957 who are unvaccinated or lack laboratory evidence of measles, mumps, or rubella immunity, or laboratory confirmation of disease should be considered for vaccination with 2 doses of MMR at least 28 days apart for measles or mumps, or 1 dose of MMR for rubella. Adults who are students in postsecondary educational institutions or plan to travel internationally should receive 2 doses of MMR at least 28 days apart. Adults who received inactivated (killed) measles vaccine or measles vaccine of unknown type during years 1963–1967 should be revaccinated with 1 or 2 doses of MMR. Adults who were vaccinated before 1979 with either inactivated mumps vaccine or mumps vaccine of unknown type who are at high risk for mumps infection, e.g., work in a healthcare facility, should be considered for revaccination with 2 doses of MMR at least 28 days apart. 	<p>Measles, mumps, and rubella vaccination www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mmr.html</p> <p>General information</p> <ul style="list-style-type: none"> Administer to adults without evidence of immunity to measles, mumps, or rubella 1 dose of measles, mumps, and rubella vaccine (MMR) Evidence of immunity is: <ul style="list-style-type: none"> Born before 1957 (except for health care personnel, see below) Documentation of receipt of MMR Laboratory evidence of immunity or disease Documentation of a health care provider-diagnosed disease without laboratory confirmation is not considered evidence of immunity <p>Special populations</p> <ul style="list-style-type: none"> Administer 1 dose of MMR to: <ul style="list-style-type: none"> Pregnant women without evidence of immunity to rubella: Administer after pregnancy and before discharge from health care facility Non-pregnant women of childbearing age without evidence of immunity to rubella Administer 2 doses of MMR at least 28 days apart to adults with HIV infection and CD4 cell count ≥ 200 cells/μL for at least 6 months Administer 2 doses of MMR at least 28 days apart if no evidence of immunity or 1 dose of MMR if received 1 dose previously to: <ul style="list-style-type: none"> Students in postsecondary educational institutions International travelers Health care personnel born in 1957 or later (if born before 1957, consider MMR vaccination) Household contacts of immunocompromised persons <u>Administer 1 dose of MMR to adults who previously received 2 doses of measles-containing vaccine who are identified by public health as at increased risk for mumps in an outbreak</u> MMR is contraindicated for pregnant women and adults with severe immunodeficiency
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Note that the WG proposed the underlined simplified language “Administer 1 dose of MMR to adults who previously received 2 doses of measles-containing vaccine who are identified by public health as at increased risk for mumps in an outbreak” to address the language voted on by ACIP the previous day reading “Persons previously vaccinated with two doses of a mumps-containing vaccine who are identified by public health as at increased risk for mumps because of an outbreak should receive a third dose of a mumps-containing vaccine to improve protection against mumps disease and related complications.”

Other than the zoster and MMR vaccination footnotes, there are no other footnote content changes. As mentioned earlier, the WG tries to harmonize the footnotes in the adult schedule and the child and adolescent schedule when possible. A good example is the HPV vaccination footnote. This was important because the number of doses of HPV vaccine that an adult should receive depends upon what he or she did or did not receive as a child. The format and information are similar in the adult and child and adolescent schedules:

2017	Proposed 2018
<p>Human papillomavirus vaccination</p> <p>General information</p> <ul style="list-style-type: none"> Adult females through age 26 years and adult males through age 21 years who have not received any human papillomavirus (HPV) vaccine should receive a 3-dose series of HPV vaccine at 0, 1-2, and 6 months. Males aged 22 through 26 years may be vaccinated with a 3-dose series of HPV vaccine at 0, 1–2, and 6 months. Adult females through age 26 years and adult males through age 21 years (and males aged 22 through 26 years who may receive HPV vaccination) who initiated the HPV vaccination series before age 15 years and received 2 doses at least 5 months apart are considered adequately vaccinated and do not need an additional dose of HPV vaccine. Adult females through age 26 years and adult males through age 21 years (and males aged 22 through 26 years who may receive HPV vaccination) who initiated the HPV vaccination series before age 15 years and received only 1 dose, or 2 doses less than 5 months apart, are not considered adequately vaccinated and should receive 1 additional dose of HPV vaccine. Notes: HPV vaccination is routinely recommended for children at age 11 or 12 years. For adults who had initiated but did not complete the HPV vaccination series, consider their age at first HPV vaccination (described above) and other factors (described below) to determine if they have been adequately vaccinated. <p>Special populations</p> <ul style="list-style-type: none"> Men who have sex with men through age 26 years who have not received any HPV vaccine should receive a 3-dose series of HPV vaccine at 0, 1-2, and 6 months. Adult females and males through age 26 years with immunocompromising conditions (described below), including those with human immunodeficiency virus (HIV) infection, should receive a 3-dose series of HPV vaccine at 0, 1–2, and 6 months. Pregnant women are not recommended to receive HPV vaccine, although there is no evidence that the vaccine poses harm. If a woman is found to be pregnant after initiating the HPV vaccination series, delay the remaining doses until after the pregnancy. No other intervention is needed. Pregnancy testing is not needed before administering HPV vaccine. Notes: Immunocompromising conditions for which a 3-dose series of HPV vaccine is indicated are primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity, e.g., B-lymphocyte antibody deficiencies, complete or partial T-lymphocyte defects, HIV infection, malignant neoplasm, transplantation, autoimmune disease, and immunosuppressive therapy. 	<p>Human papillomavirus vaccination www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html</p> <p>General information</p> <ul style="list-style-type: none"> Administer human papillomavirus (HPV) vaccine to females through age 26 years and males through age 21 years (males age 22 through 26 years may be vaccinated based on individual clinical decision) The number of doses of HPV to be administered depends on age at initial HPV vaccination <ul style="list-style-type: none"> No previous dose of HPV vaccine: Administer 3-dose series at 0, 1–2, and 6 months (minimum intervals: 4 weeks between first and second doses, 12 weeks between second and third doses, and 5 months between first and third doses (repeat doses if given too soon)) Age 9–14 years at vaccine series initiation and received 1 dose or 2 doses less than 5 months apart: Administer 1 dose Age 9–14 years at vaccine series initiation and received 2 doses at least 5 months apart: No additional dose is needed <p>Special populations</p> <ul style="list-style-type: none"> Adults with immunocompromising conditions (including HIV) through age 26 years: Administer 3-dose series at 0, 1–2, and 6 months Men who have sex with men through age 26 years: Administer 2- or 3-dose series depending on age at initial vaccination (see above); if no history of HPV vaccine, administer 3-dose series at 0, 1–2, and 6 months Pregnant women through age 26 years: HPV vaccination is not recommended during pregnancy, but there is no evidence that the vaccine is harmful and no intervention needed for women who inadvertently receive HPV vaccine while pregnant; delay remaining doses until after pregnancy; pregnancy testing is not needed before vaccination

For 2018, the footnotes for meningococcal vaccination have been reorganized to present MenACWY and MenB separately. Doing so allowed the content to be shortened and easier to follow, as shown here:

2017	Proposed 2018
<p>Meningococcal vaccination</p> <p>Special populations</p> <ul style="list-style-type: none"> Adults with anatomical or functional asplenia or persistent complement component deficiencies should receive a 2-dose primary series of serogroups A, C, W, and Y meningococcal conjugate vaccine (MenACWY) at least 2 months apart and revaccinate every 5 years. They should also receive a series of serogroup B meningococcal vaccine (MenB) with either a 2-dose series of MenB-4C (Bexsero) at least 1 month apart or a 3-dose series of MenB-FHbp (Trumenba) at 0, 1–2, and 6 months. Adults with human immunodeficiency virus (HIV) infection who have not been previously vaccinated should receive a 2-dose primary series of MenACWY at least 2 months apart and revaccinate every 5 years. Those who previously received 1 dose of MenACWY should receive a second dose at least 2 months after the first dose. Adults with HIV infection are not routinely recommended to receive MenB because meningococcal disease in this population is caused primarily by serogroups C, W, and Y. Microbiologists who are routinely exposed to isolates of <i>Neisseria meningitidis</i> should receive 1 dose of MenACWY and revaccinate every 5 years if the risk for infection remains, and either a 2-dose series of MenB-4C at least 1 month apart or a 3-dose series of MenB-FHbp at 0, 1–2, and 6 months. Adults at risk because of a meningococcal disease outbreak should receive 1 dose of MenACWY if the outbreak is attributable to serogroup A, C, W, or Y, or either a 2-dose series of MenB-4C at least 1 month apart or a 3-dose series of MenB-FHbp at 0, 1–2, and 6 months if the outbreak is attributable to serogroup B. Adults who travel to or live in countries with hyperendemic or epidemic meningococcal disease should receive 1 dose of MenACWY and revaccinate every 5 years if the risk for infection remains. MenB is not routinely indicated because meningococcal disease in these countries is generally not caused by serogroup B. Military recruits should receive 1 dose of MenACWY and revaccinate every 5 years if the increased risk for infection remains. First-year college students aged 21 years or younger who live in residence halls should receive 1 dose of MenACWY if they have not received MenACWY at age 16 years or older. Young adults aged 16 through 23 years (preferred age range is 16 through 18 years) who are healthy and not at increased risk for serogroup B meningococcal disease (described above) may receive either a 2-dose series of MenB-4C at least 1 month apart or a 2-dose series of MenBFHbp at 0 and 6 months for short-term protection against most strains of serogroup B meningococcal disease. For adults aged 56 years or older who have not previously received serogroups A, C, W, and Y meningococcal vaccine and need only 1 dose, meningococcal polysaccharide serogroups A, C, W, and Y vaccine (MPSV4) is preferred. For adults who previously received MenACWY or anticipate receiving multiple doses of serogroups A, C, W, and Y meningococcal vaccine, MenACWY is preferred. Notes: MenB-4C and MenB-FHbp are not interchangeable, i.e., the same vaccine should be used for all doses to complete the series. There is no recommendation for MenB revaccination at this time. MenB may be administered at the same time as MenACWY but at a different anatomic site, if feasible. 	<p>Meningococcal vaccination www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html</p> <p>Special populations: Serogroups A, C, W, and Y meningococcal vaccine (MenACWY)</p> <ul style="list-style-type: none"> Administer 2 doses of MenACWY at least 8 weeks apart and revaccinate with 1 dose of MenACWY every 5 years, if the risk remains, to adults with the following indications: <ul style="list-style-type: none"> Anatomical or functional asplenia including sickle cell disease HIV infection Persistent complement component deficiency Eculizumab use Administer 1 dose of MenACWY and revaccinate with 1 dose of MenACWY every 5 years, if the risk remains, to adults with the following indications: <ul style="list-style-type: none"> Travel to or live in countries where meningococcal disease is hyperendemic or epidemic, including countries in the African meningitis belt or during the Hajj At risk from a meningococcal disease outbreak attributed to serogroup A, C, W, or Y Microbiologists routinely exposed to <i>Neisseria meningitidis</i> Military recruits First-year college students age 21 years or younger who live in residential housing (if did not receive MenACWY at age 16 years or older) <p>General Information: Serogroup B meningococcal vaccine (MenB)</p> <ul style="list-style-type: none"> May administer, based on individual clinical decision, to young adults and adolescents age 16–23 years (preferred age is 16–18 years) who are not at increased risk MenB (2-dose series of MenB-4C [Bexsero] at least 1 month apart or 2-dose series of MenB-FHbp [Trumenba] at least 6 months apart) MenB-4C and MenB-FHbp are not interchangeable <p>Special populations: MenB</p> <ul style="list-style-type: none"> Administer 2-dose series of MenB-4C at least 1 month apart or 3-dose series of MenB-FHbp at 0, 1–2, and 6 months to adults with the following indications: <ul style="list-style-type: none"> Anatomical or functional asplenia (including sickle cell disease) Persistent complement component deficiency Eculizumab use At risk from a meningococcal disease outbreak attributed to serogroup B Microbiologists routinely exposed to <i>Neisseria meningitidis</i>

The last page of the proposed 2018 Adult Immunization Schedule is the table of contraindications and precautions. There are no substantive changes in this table.

In terms of next steps, the 2018 Adult Immunization Schedule draft will be revised based on ACIP's comments and suggestions. If voted to move forward, the schedule will be submitted for approval by the CDC Director. Approval will then be obtained from the partner professional organizations mentioned earlier (ACP, AAFP, ACOG, and ACNM). The schedule will be submitted for CDC clearance for *MMWR* announcement and publication in *Annals of Internal Medicine* in February 2018.

Discussion Points

Dr. Bennett congratulated the WG for making good strides toward simplifying the Adult Immunization Schedule.

Dr. Kempe asked how the new preferential recommendation for HZ/su would be indicated in the figure, given the concern that many people will not look beyond the figure.

Dr. Kim replied that the left column titled "Vaccine" on Figure 1 will read "HZ/su or ZVL" and there will be a yellow bar beginning at age 50 indicating that the vaccine is routinely recommended. The text within the yellow bar will read "2 doses HZ/su (or 1 dose ZVL if age ≥ 60 yrs)." For Figure 2, the left-hand column under "Vaccine" also will read "HZ/su or ZVL" versus "ZVL" alone and the rest of the line will remain the same.

Dr. Messonnier clarified that the line did not express the intent of ACIP, which was to express a preference for HZ/su. The line as presented made the vaccines appear to be equivalent.

Dr. Riley suggested adding "preferred" in parentheses beside of HZ/su in the "Vaccine" column. Dr. Kempe agreed that this would be sufficient.

Dr. Belongia suggested in the yellow bar stated "2 doses HZ/su (preferred) or 1 dose ZVL if ≥ 60 yrs" which would not be in parentheses.

Dr. Friedland (GSK) indicated that in the prescribing information for Shingrix, the only contraindication is people who have had an allergic reaction to ingredients in the vaccine or the first dose of the vaccine. Pregnancy and immunocompromising conditions are not identified as contraindications and have no warnings or precautions.

Dr. Belongia indicated that immunocompromising conditions have not yet been addressed, but the WG will address these in the future as more data become available. Given that the current FDA licensing indication does not have a contraindication, it seems that the schedule should be consistent with that.

Dr. Moore emphasized that all ACIP could say is that they have not made a recommendation for pregnancy.

Dr. Reingold pointed out that while there will not be many pregnant women over the age of 50, there are likely to be a few.

Dr. Baker (IDSA) recalled that live vaccines in the pregnancy age group are included in precautions rather than contraindications, and suggested that the same language should be included for zoster. She agreed that while there are not many pregnant women over the age of 50, there are some.

Dr. Offit (The Children's Hospital of Philadelphia) pointed out that immunocompromised individuals are at higher risk of having shingles. It seemed to him that while the vaccine might not be as effective in immunocompromised persons, safety is not as great an issue. If anything, its use should be encouraged in immunocompromised individuals.

Dr. Middleman (SAHM) suggested that these two vaccines needed separate lines in order to indicate what is truly appropriate for each vaccine.

Dr. Sun (FDA) clarified that unless there is a study of a vaccine in pregnant women, regardless of the age indication, use in pregnant women would still be considered off-label.

Dr. Messonnier expressed concern in that the WG was grappling with this issue and was planning to bring it back during the next ACIP meeting.

Dr. Belongia agreed that more time is needed to address this. There is a difference between the pregnancy and immunocompromised individuals. It seemed clear to state that the vaccine is not recommended in pregnancy, but the WG could come back with some recommendations for immunocompromised individuals. However, they were not prepared to do that at this time.

Dr. Bennett stressed that they must move forward with the schedule due to the timeline, so they must have a solution of some sort at this time.

Dr. Duchin (NACCHO) agreed that HZ/su and ZVL should be dealt with separately in the schedule. Perhaps a statement could be included such as, "HZ/su is not currently recommended in pregnancy and immunocompromised individuals."

Dr. Schaffner (NFID) emphasized that there are many immunocompromised individuals older than 50 years of age. Many providers have followed the development of this vaccine closely and will wish to start immunizing their patients, even though there is no information regarding exactly how effective under what circumstances the vaccine will be. They will regard it as harmless in the sense that there are few if any safety issues, but the benefit is potentially large.

Dr. Fryhofer (ACP) pointed out that the previous day when the vote was taken, specifically ACIP voted for immunocompetent patients. There is a white box for "no recommendation," so perhaps the line for HZ/su could be white for "no recommendation" until the WG has had time to address that.

Dr. Moore indicated that in general, the WG agreed with Dr. Fryhofer's suggestion to leave a white space specifically for HZ/su. ZVL is contraindicated in immunocompromised people and that indication needs to be maintained. Given that ACIP voted on the word "immunocompetent" in the recommendation the previous day, they could not include "immunocompromised" because of the way they voted. They have split a bar in half in the childhood schedule because there were two different comments in the same bar. She suggested doing the same in this case.

Dr. Messonnier recapped that in the HZ/su line for immunocompromised patients, there would be two bars, and the HZ/su bar would be blank because there has not been discussion of immunocompromised populations regardless of the fact that some ACIP members feel strongly that this is a group for whom this vaccine is specifically targeted. Therefore, regardless of whether there are data, this issue should be revisited during the February 2018 ACIP meeting. This may mean that it would not get on the schedule, but guidance would be provided clearly

regarding those for whom the vaccine is recommended. However, it was not clear to her whether the bar should remain blank for pregnant women or if they are considered to be immunocompromised.

Dr. Riley responded that for other vaccines for which there are no data but there are concerns, they have left the box white. She thought they could do the same for pregnancy in this case.

Dr. Belongia noted that there is a contraindication for Zostavax[®] in pregnancy. The white box for HZ/su makes sense and is consistent.

Dr. Weber (SHEA) observed that the wording of the footnote for Tdap states, “Administer to adults with no previous dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine as an adult or child.” That would mean that since Tdap is given to those 11 to 12 years of age and potentially those as young as 7 years of age, HCP for whom Tdap is recommended would not be given the vaccine when they become a medical or dental student if they had Tdap as a child per the schedule. However, the recommendation in the HCP guideline states that “HCP regardless of age receive a single Tdap as soon as feasible if they have not received a previous Tdap.” That means that once an individual receives Tdap between the ages of 7 to 12, even if they are an HCP, they would never need a Tdap as an adult according to the schedule.

Dr. Messonnier clarified that the language in the pertussis statement indicates that HCP need a dose regardless, so the schedule does not reflect the actual ACIP statement on Tdap. Dr. Weber’s request was to update the schedule based on what ACIP had already voted on. The vaccine is not licensed for more than one dose; however, because HCP are at especially high risk, ACIP previously recommended that they should receive a dose regardless of their Tdap vaccine history.

Dr. Hunter noted that the correction would be made under the “Special Populations” rather than the “General Information” section of Tdap.

Dr. Whitley-Williams (NMA) pointed out that for providers who do not read the footnotes, this can be very confusing. Perhaps the footnote number for Tdap should be added beside “1 dose of Tdap” in the bar in the figures. Looking at the schedule, she would interpret that everybody should receive a second dose even if they received it at 9 to 12 years.

Dr. Kimberlin (AAP) asked whether they were saying that there are two groups of people in the world who are recommended to receive more than one dose of Tdap, pregnant women and HCP who previously received Tdap. He did not recall this vote, but it seemed like it needed one.

Dr. Cohn clarified that the issue was that the vote for HCP to receive one dose occurred, all HCP were adults and Tdap had not been in use long enough for those adolescents to age into adulthood. They technically have now aged into adulthood, but ACIP technically has not addressed the issue of HCP who already received a dose, but there is a recommendation for all HCP to receive a dose.

Dr. Bennett added that ACIP has not taken up specifically whether HCP should receive a second dose of Tdap, but this was because of the way it occurred. At the time ACIP made the Tdap recommendation for HCP, most HCP had not had a previous Tdap. Now that they have, she agreed with Dr. Kimberlin that perhaps ACIP needs to address that issue specifically. However, she thought the schedule should continue to show that HCP should receive a dose

because that was the historic decision. She emphasized that there was a limit to what they could do, but they were trying to make the schedule reflect what ACIP thinks the best recommendations are at this time. They could not review each one of the recommendations.

Dr. Messonnier stressed that the goal of the Adult Immunization Schedule WG is to make the schedule reflect the existing recommendations, though she agreed that at times this points out loopholes they need to think about.

Dr. Cohn suggested that the WG take some time to revise zoster vaccine on the schedule based on the discussion.

Adult Immunization Schedule Revised

Dr. David Kim
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

After taking a few minutes to incorporate the suggestions made during the previous discussion, Dr. Hill revisited three topics: Zoster, MMR in outbreak settings, and Tdap. The WG revised Figure 1, the recommended schedule by age group:

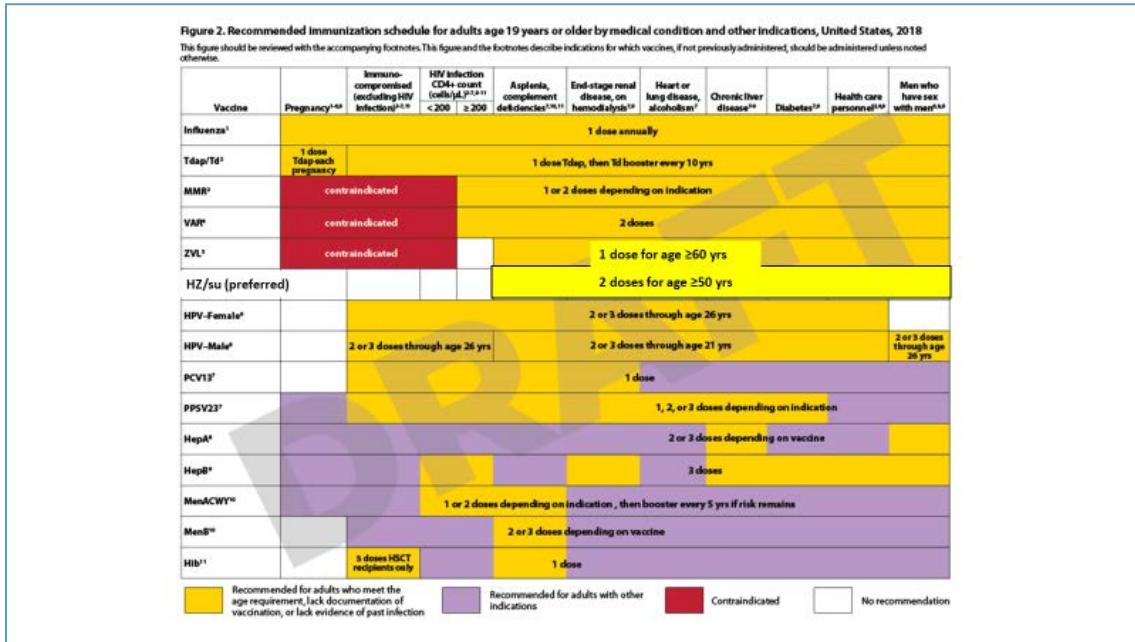
Figure 1. Recommended immunization schedule for adults age 19 years or older by age group, United States, 2018.
 This figure should be reviewed with the accompanying footnotes. This figure and the footnotes describe indications for which vaccines, if not previously administered, should be administered unless noted otherwise.

Vaccine	19–21 years	22–26 years	27–49 years	50–64 years	≥65 years
Influenza ¹	1 dose annually				
Tdap/Td ²	1 dose Tdap, then Td booster every 10 yrs				
MMR ³	1 or 2 doses depending on indication (if born in 1937 or later)				
VAR ⁴	2 doses				
ZVL ⁵					1 dose
HZ/su (preferred)				2 doses	
HPV–Female ⁶	2 or 3 doses depending on age at series initiation				
HPV–Male ⁶	2 or 3 doses depending on age at series initiation				
PCV13 ⁷	1 dose				
PPSV23 ⁷	1 or 2 doses depending on indication				1 dose
HepA ⁸	2 or 3 doses depending on vaccine				
HepB ⁸	3 doses				
MenACWY ^{9a}	1 or 2 doses depending on indication, then booster every 5 yrs if risk remains				
MenB ^{9b}	2 or 3 doses depending on vaccine				
Hib ¹¹	1 or 2 doses depending on indication				

Recommended for adults who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection
 Recommended for adults with other indications
 No recommendation

In the left-hand column under “Vaccine” there is now a row for ZVL and a separate row for HZ/su. The order will be reversed because the preferred vaccine is HZ/su. While the ZVL line will remain the same, the HZ/su line will include (preferred) and the indication bar for 50 years of age and older will contain “2 doses.”

The WG also revised Figure 2, the recommended schedule by medical condition and other indications:



In the left-hand column under "Vaccine" ZVL and HZ/su will have separate lines and as in Figure 1, those lines will be reversed. For ZVL, there will be a change in the indications bar to state that 1 dose is recommended for persons ≥ 60 years. HZ/su will say (preferred) the indication column will state that 2 doses are recommended for persons ≥ 50 years.

Shown superimposed over the footnotes in the blue box is what ACIP voted on the previous day regarding mumps-containing vaccines in outbreak settings, while the red bubble highlights the language that will be included in the footnote:

Footnotes. Recommended immunization schedule for adults age 19 years or older, United States, 2018

1. Influenza vaccination
www.cdc.gov/vaccines/imz/ad/acip-recs-vac-specific/flu.html
 General information
 • Administer 1 dose of age-appropriate inactivated influenza vaccine (IIV) or recombinant influenza vaccine (RIV) annually
 • Available options for adults include:
 – High-dose or adjuvanted IIV for adults age 65 years or older
 – Intradermal IIV for adults age 18 through 64 years

2. Measles, mumps, and rubella vaccination (revision pending ACIP recommendation)
 General information
 • Administer to adults without evidence of immunity to measles, mumps, or rubella 1 dose of measles, mumps, and rubella vaccine (MMR)
 • Evidence of immunity is:
 – Born before 1957 (except for health care personnel; see below)
 – Documentation of receipt of MMR
 – Laboratory evidence of immunity or disease
 – Documentation of a health care provider-diagnosed disease without laboratory confirmation is not considered evidence of immunity
 Special populations
 • Administer 1 dose of MMR to:
 – Pregnant women without evidence of immunity to measles, mumps, and rubella vaccination
 – Men, mumps, and rubella vaccination
 – Adults born in 1957 or later without acceptable evidence of immunity to measles, mumps, or rubella (defined below) should receive 1 dose of measles, mumps, and rubella vaccine (MMR), unless they have a medical contraindication to the vaccine.
 • Adults who were vaccinated before 1979 with either mumps vaccine of unknown type who are at high risk for work in a healthcare facility, should be considered for MMR at least 28 days apart.
 • Adults who received inactivated (non-replicating) mumps vaccine during years 1963–1967 should receive MMR.
 • Adults who were vaccinated before 1979 with either mumps vaccine of unknown type who are at high risk for work in a healthcare facility, should be considered for MMR at least 28 days apart.

3. Measles, mumps, and rubella vaccination (revision pending ACIP recommendation)
 General information
 • Administer 1 dose of MMR to:
 – Pregnant women without evidence of immunity to measles, mumps, and rubella vaccination
 – Men, mumps, and rubella vaccination
 • Adults born in 1957 or later without acceptable evidence of immunity to measles, mumps, or rubella (defined below) should receive 1 dose of measles, mumps, and rubella vaccine (MMR), unless they have a medical contraindication to the vaccine.
 • Adults who were vaccinated before 1979 with either mumps vaccine of unknown type who are at high risk for work in a healthcare facility, should be considered for MMR at least 28 days apart.
 • Adults who received inactivated (non-replicating) mumps vaccine during years 1963–1967 should receive MMR.
 • Adults who were vaccinated before 1979 with either mumps vaccine of unknown type who are at high risk for work in a healthcare facility, should be considered for MMR at least 28 days apart.

4. Measles, mumps, and rubella vaccination (revision pending ACIP recommendation)
 General information
 • Administer 1 dose of MMR to:
 – Pregnant women without evidence of immunity to measles, mumps, and rubella vaccination
 – Men, mumps, and rubella vaccination
 • Adults born in 1957 or later without acceptable evidence of immunity to measles, mumps, or rubella (defined below) should receive 1 dose of measles, mumps, and rubella vaccine (MMR), unless they have a medical contraindication to the vaccine.
 • Adults who were vaccinated before 1979 with either mumps vaccine of unknown type who are at high risk for work in a healthcare facility, should be considered for MMR at least 28 days apart.
 • Adults who received inactivated (non-replicating) mumps vaccine during years 1963–1967 should receive MMR.
 • Adults who were vaccinated before 1979 with either mumps vaccine of unknown type who are at high risk for work in a healthcare facility, should be considered for MMR at least 28 days apart.

5. Measles, mumps, and rubella vaccination (revision pending ACIP recommendation)
 General information
 • Administer 1 dose of MMR to:
 – Pregnant women without evidence of immunity to measles, mumps, and rubella vaccination
 – Men, mumps, and rubella vaccination
 • Adults born in 1957 or later without acceptable evidence of immunity to measles, mumps, or rubella (defined below) should receive 1 dose of measles, mumps, and rubella vaccine (MMR), unless they have a medical contraindication to the vaccine.
 • Adults who were vaccinated before 1979 with either mumps vaccine of unknown type who are at high risk for work in a healthcare facility, should be considered for MMR at least 28 days apart.
 • Adults who received inactivated (non-replicating) mumps vaccine during years 1963–1967 should receive MMR.
 • Adults who were vaccinated before 1979 with either mumps vaccine of unknown type who are at high risk for work in a healthcare facility, should be considered for MMR at least 28 days apart.

Special populations
 • Administer 1 dose of MMR to:
 – Pregnant women without evidence of immunity to measles, mumps, and rubella vaccination
 – Men, mumps, and rubella vaccination
 • Adults born in 1957 or later without acceptable evidence of immunity to measles, mumps, or rubella (defined below) should receive 1 dose of measles, mumps, and rubella vaccine (MMR), unless they have a medical contraindication to the vaccine.
 • Adults who were vaccinated before 1979 with either mumps vaccine of unknown type who are at high risk for work in a healthcare facility, should be considered for MMR at least 28 days apart.
 • Adults who received inactivated (non-replicating) mumps vaccine during years 1963–1967 should receive MMR.
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 • Adults who were vaccinated before 1979 with either mumps vaccine of unknown type who are at high risk for work in a healthcare facility, should be considered for MMR at least 28 days apart.
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 • Adults who were vaccinated before 1979 with either mumps vaccine of unknown type who are at high risk for work in a healthcare facility, should be considered for MMR at least 28 days apart.
 • Adults who received inactivated (non-replicating) mumps vaccine during years 1963–1967 should receive MMR.
 • Adults who were vaccinated before 1979 with either mumps vaccine of unknown type who are at high risk for work in a healthcare facility, should be considered for MMR at least 28 days apart.

Special populations
 • Administer 1 dose of MMR to:
 – Pregnant women without evidence of immunity to measles, mumps, and rubella vaccination
 – Men, mumps, and rubella vaccination
 • Adults born in 1957 or later without acceptable evidence of immunity to measles, mumps, or rubella (defined below) should receive 1 dose of measles, mumps, and rubella vaccine (MMR), unless they have a medical contraindication to the vaccine.
 • Adults who were vaccinated before 1979 with either mumps vaccine of unknown type who are at high risk for work in a healthcare facility, should be considered for MMR at least 28 days apart.
 • Adults who received inactivated (non-replicating) mumps vaccine during years 1963–1967 should receive MMR.
 • Adults who were vaccinated before 1979 with either mumps vaccine of unknown type who are at high risk for work in a healthcare facility, should be considered for MMR at least 28 days apart.

The ACIP policy guideline for Tdap simply states that 1 dose of Tdap is indicated for adolescents and adults, except for pregnant women. The guidance reads as follows:

ACIP recommends that adults aged 65 years and older (e.g., grandparents, child-care providers, and health-care practitioners) who have or who anticipate having close contact with an infant less than 12 months of age and who previously have not received Tdap should receive a single dose of Tdap to protect against pertussis and reduce the likelihood of transmission.

Discussion Points

Dr. Messonnier pointed out that due to the solid line, ZVL and HZ/su appeared to be two separate vaccines, both of which need to be given. This should be formatted such that it reflects a choice between two vaccines rather than that both should be given. This could be done by dividing the zoster row with a dotted line to make clear that these are two types of zoster vaccine, only one of which should be administered.

Dr. Duchin (NACCHO) suggested being consistent with pneumococcal and meningococcal as well, which have multiple vaccines for the same disease.

Dr. Bennett pointed out that both pneumococcal and meningococcal vaccines are given, so these are different.

Wayne Hachey (Protein Sciences; now a Sanofi Pasteur Company) noted that the influenza general comments section lists a number of vaccines for adults, but does not include RIV, which is also a vaccine limited to the adult population. Data on recombinant influenza vaccine (RIV) were presented to ACIP that showed increased effectiveness in adults 50 years of age and older.

Dr. Kim indicated that RIV is not included in the figures, but it is included in the footnotes.

Dr. Cohn requested that Dr. Hachey send an email to ACIP at cdc.gov to ensure that this is clear.

In terms of the footnote language regarding mump-containing vaccines, Dr. Moore stressed that they should not give the impression that those with zero doses should not also get a dose.

Dr. Hunter said he was still not clear regarding whether an adult should receive a second dose of Tdap if he or she received a dose as an adolescent.

Dr. Cohn clarified that all individuals are recommended to receive a single dose of Tdap, including HCP, adults, and older adults. Pregnant women are recommended to receive a dose with each pregnancy.

Dr. Weber (SHEA) pointed out that whether ACIP should recommend that the adolescent group now becoming HCP should receive a second dose has not been addressed and should be explicitly discussed by the WG. Dr. Bennett deferred this topic to the “parking lot.”

Dr. Fryhofer (AMA/ACP) observed that the Tdap guidance reads adults 65 and older with the descriptive language in parentheses, meaning that grandparents, child-care providers and HCP over 65 should receive a single dose.

Dr. Hunter noted that the wording of the footnote for MMR for mumps outbreak states “1 or 2 doses,” but should state ≤ 2 doses to receive the 0, 1, and 2 doses.

Public Comment

Andrea Woodruff Concerned Citizen

For healthcare workers, how are they going to prove evidence of a past infection of chicken pox? Are they going to get titers beforehand? Is that recommended? I also am getting a lot feedback about pregnancy and Tdap and influenza. A lot of the pregnant women who have contacted her are very concerned because when they go to the CDC webpage, they only see a couple of studies that only show that the baby survived the pregnancy. It doesn't go on to show if there are long-term disabilities. I'm just generally getting a lot of pushback from this. I just want to let you guys know, because it really puts everyone in a bad spot when the public is pushing back.

Laurel Wood Immunization Action Coalition (IAC)

The Immunization Action Coalition (IAC) is very aware, as all of us in this room are, about the difficulty of adult immunizations and the challenges that we're all seeing with that. Because of that, I wanted to let you know about a wonderful new resource that we've just published titled “Vaccinating Adults: A Step-by-Step Guide.” We were able to do this with support from CDC, and we're really grateful for that. CDC also reviewed early sections and early versions of the guide. This book is available. It is an update of our 2004 version, of which we had over half a million downloads off of our website of various chapters. Clearly, there is still lots of confusion about adult immunizations. We've updated this to a great resource and easy-to-use “How To” guide for providers who are either already giving adults vaccinations or who would like to enhance their services. The practical steps in the guide include:

- Setting up vaccination services
- Storing and handling vaccines
- Deciding who should receive which vaccines
- Administering vaccines
- Documenting vaccinations
- Understanding financial considerations and billing information

It also includes many, many web addresses to help people stay up-to-date with current information. So, I wanted to let you know that the ACIP members and liaison members will be receiving a complimentary guide in their offices so that you would not have to carry them with you today. Also for everyone else, within the next 1 to 2 weeks, we will have a website available at <http://immunize.org/guide> where people will either be able to order a hard copy of the book like this, or they will be able to download for free all of the pages to print, do with them what they would like, and share them with others. We hope this will be helpful edition to what is clearly a lot of confusion about adult immunizations. We thank CDC and we thank you for your attention and hopefully your ability to help us share this with providers around the country. Thank you.

Motion/Vote: Adult Immunization Schedule

Dr. Belongia made a motion to approve the Adult Immunization Schedule with the suggested revisions. Dr. Romero seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Atmar, Belongia, Bennett, Ezeanolue, Hunter, Kempe, Lee, Moore, Pellegrini, Reingold, Riley, Romero, Stephens, Szilagyi, Walter
0 Opposed: N/A
0 Abstained: N/A

Child and Adolescent Immunization Schedule**Introduction**

Dr. José R Romero
Chair, Child and Adolescent Immunization Work Group

Dr. Romero introduced this session on behalf of the Child and Adolescent Immunization Schedule WG. He reminded everyone that the schedule is presented for a vote every fall, given that the ACIP's approval is necessary prior to publication of the schedule in the *MMWR* in January or February of the following year. ACIP's approval is also necessary before its partners (AAP, AAFP, and ACOG) review and approve the schedule. He emphasized that no new policy is established by the schedule. It simply reflects the recommendations already approved by ACIP. Dr. Romero indicated that for the remainder of this presentation, Dr. Robinson would discuss proposed edits to Figure 2 (catch-up) and Figure 3 (high-risk) and introduce a proposed simplified format for all of the footnotes. These edits are intended to improve readability and utility of the schedule, and hence translate the respective ACIP recommendations into language that is easy to interpret for the busy provider. In addition to the simplification, content changes were proposed for the HepB, influenza, and polio footnotes.

Child and Adolescent Immunization Schedule 2018

Candice L. Robinson, MD, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Robinson indicated that the manufacturing of MenHibrix[®] (Hib-MenCY) has been discontinued and all doses expired mid-September 2017. Mention of MenHibrix[®] has been removed from Figure 1, Figure 2, and relevant footnotes for *Haemophilus influenzae type b* (Hib) and meningococcal vaccines. A table has been added to the cover page that delineates vaccine types, abbreviations, and brand names for respective vaccines:

Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger, UNITED STATES, 2018

The table below shows vaccine acronyms, and brand names for vaccines routinely recommended for children and adolescents. The use of trade names in this immunization schedule is for identification purposes only and does not imply endorsement by the ACIP or CDC.

Vaccine	Abbreviation	Trade Name
Diphtheria, tetanus, and acellular pertussis vaccine	DTaP	Boostrix Infanrix
Diphtheria, tetanus vaccine	DT	No Trade Name
Haemophilus influenzae type B vaccine	4b (IPV) 4b (IPV-COMP)	Act-Sole Hibex Hib (IPV-COMP)
Hepatitis A vaccine	HeptA	Varivax Vaqta
Hepatitis B vaccine	HeptB	Engerix-B Recombivax HB
Human papillomavirus vaccine	HPV	Cervarix Gardasil-9
Influenza vaccine (inactivated)	IV	Multigrip
Measles, mumps, and rubella vaccine	MMR	M-M-R-II
Meningococcal serogroups A, C, W, Y vaccine	MenACWY	Menactra MenQuadri
Meningococcal serogroup B vaccine	MenB-4C MenB-2Hep	Bexsero Trumenb
Meningococcal 13-valent conjugate vaccine	PCV13	Prevnar 13
Pneumococcal 23-valent polysaccharide vaccine	PPSV23	Pneumovax
Poliovirus vaccine (inactivated)	IPV	IPOL
Rotavirus vaccines	RV1 RV2	Rotarix RotaTeq
Tetanus, diphtheria, and acellular pertussis vaccine	Tdap	Adacel Boostrix
Tetanus and diphtheria vaccine	Td	Tandax No Trade Name
Varicella vaccine	VAR	Varivax

Combination Vaccines	Trade Name
DTaP, hepatitis B and inactivated poliovirus vaccine	DTaP-Hept-IPV
DTaP, inactivated poliovirus and Haemophilus influenzae type B vaccine	DTaP-IPV/Hib
DTaP and inactivated poliovirus vaccine	DTaP-IPV
Measles, mumps, rubella and varicella vaccines	MMRV

Approved by the
Advisory Committee on Immunization Practices
www.cdc.gov/vaccines/acip/
American Academy of Pediatrics
www.aap.org
American Academy of Family Physicians
www.aafp.org
American College of Obstetricians and Gynecologists
www.acog.org

This schedule includes recommendations in effect as of January 1, 2018.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

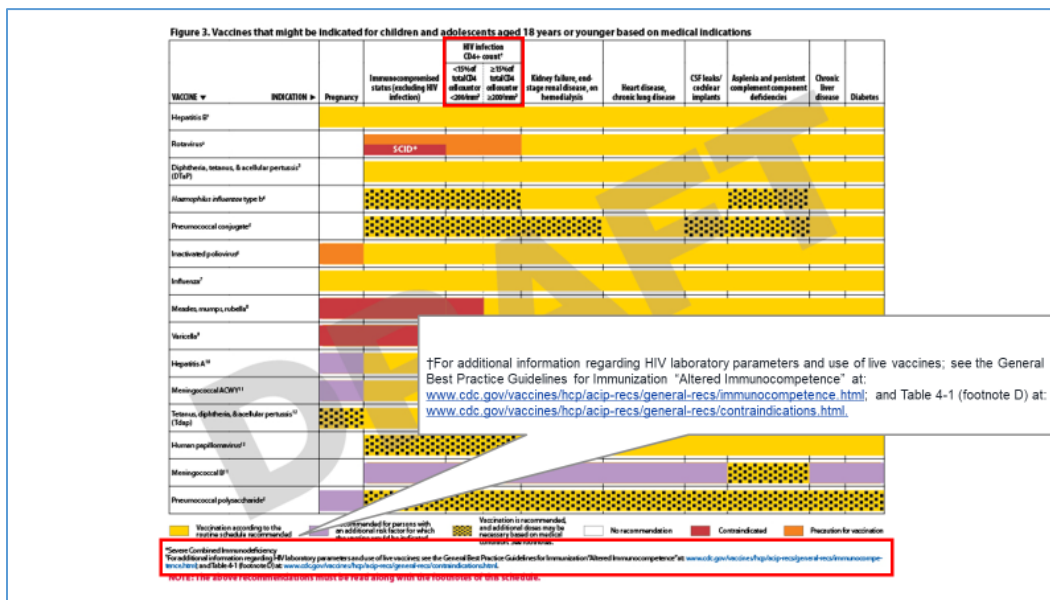
No substantive changes were proposed to Figure 1, the routine immunization schedule. For Figure 2, the catch-up figure, the maximum age for administration of the first dose of rotavirus vaccine (14 weeks, 6 days) and the maximum age for the final dose (8 months, 0 days) have been added to the catch-up figure. This information is also present within the footnote. Additionally, clarification has been made for the catch-up regarding inactivated poliovirus vaccine specifically for catch-up vaccinations for persons ≥ 4 years of age. Also added to poliovirus in the Dose 2 to Dose 3 column is that the minimal interval is 4 weeks if the current age is < 4 years and 6 months (as a final dose) if the current age is ≥ 4 years of age. Clarification has also been made regarding catch-up vaccination of children 7 through 18 years of age. The Dose 2 to Dose 3 column indicates that the minimal interval between Doses 2 and 3 is 6 months, and a 4th dose is not necessary if the 3rd dose was administered at ≥ 4 years of age and at least 6 months after the previous dose. Language was added in the Dose 3 to Dose 4 column that a fourth dose of IPV is indicated if all previous doses were administered at < 4 years or if the third dose was administered < 6 months after the second dose:

FIGURE 2. Catch-up immunization schedule for persons aged 4 months–18 years who start late or who are more than 1 month behind—United States, 2018.
 The figure below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. Always use this table in conjunction with Figure 1 and the footnotes that follow.

Vaccine	Minimum Age for Dose 1	Children ages 4 months through 18 years				
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5	
Hepatitis B ¹	Birth	4 weeks	4 weeks and at least 16 weeks after first dose. Minimum age for the final dose is 2 weeks.			
Rotavirus ²	6 weeks (Maximum age for first dose is 14 weeks, 6 days)	4 weeks	4 weeks ³ Maximum age for final dose is 8 months, 0 days.			
Diphtheria, tetanus, and acellular pertussis ⁴	6 weeks	4 weeks	4 weeks	6 months	6 months ⁵	
Haemophilus influenzae type B ⁶	6 weeks	4 weeks If first dose was administered before the 1 st birthday, 8 weeks for final dose. If first dose was administered at age 12 through 18 months, no further doses needed if first dose was administered at age 15 months or older.	4 weeks ⁷ If current age is younger than 12 months and first dose was administered at younger than age 7 months, and at least 1 previous dose was PRP-4 (Act-Hib, Pentacel, Hibex) or unknown, 8 weeks and age 12 through 18 months for final dose. OR - if current age is younger than 12 months and first dose was administered at age 7 through 11 months; - if current age is 12 through 18 months and first dose was administered before the 1 st birthday, and second dose administered at younger than 15 months; OR - if both doses were PRP-COMP (PediVaxIM, Comvax) and were administered before the 1 st birthday. No further doses needed if previous dose was administered at age 15 months or older.	6 months (see final dose)	6 months (see final dose) This dose only necessary for children age 12 through 18 months who received 3 doses before age 15 months or for children ≥ 18 months who received 3 doses at any age.	
Pneumococcal ⁸	6 weeks	4 weeks If first dose administered before the 1 st birthday, 8 weeks (see final dose for healthy children). If first dose was administered at the 1 st birthday or after, no further doses needed for healthy children. If first dose was administered at age 24 months or older.	4 weeks If current age is younger than 12 months and previous dose given at < 7 months old, 8 weeks (see final dose for healthy children). If previous doses given between 7–11 months (week until at least 12 months old), 6 months. OR If current age is 12 months or older and at least 1 dose was given before age 12 months, no further doses needed for healthy children. If previous dose administered at age 24 months or older.	6 months	6 months (see final dose) This dose only necessary for children age 12 through 18 months who received 3 doses before age 15 months or for children ≥ 18 months who received 3 doses at any age.	
Inactivated poliovirus ⁹	6 weeks	4 weeks ¹⁰	4 weeks ¹¹ (see final dose) If current age is < 4 years, 6 months (see final dose) If current age is 4 years or older, 6 months (see final dose)	6 months	6 months (see final dose) This dose only necessary for children age 4 years or older who received 3 doses before age 12 months or for children ≥ 12 months who received 3 doses at any age.	
Measles, mumps, rubella ¹²	12 months	4 weeks	4 weeks	6 months	6 months	
Measles, mumps, rubella ¹³	12 months	4 weeks	4 weeks	6 months	6 months	
Measles, mumps, rubella ¹⁴	12 months	4 weeks	4 weeks	6 months	6 months	
Meningococcal (MenACWY) or mnc, MenACWY-CRM, or mnc	9 months	4 weeks	4 weeks	6 months	6 months	
Meningococcal (MenB-4C) or mnc, MenB-2Hep, or mnc	9 months	4 weeks	4 weeks	6 months	6 months	
Meningococcal (MenACWY-CRM, or mnc, MenACWY-CRM, or mnc)	Not Applicable (N/A)	Not Applicable (N/A)	Not Applicable (N/A)	Not Applicable (N/A)	Not Applicable (N/A)	
Tetanus, diphtheria, tetanus, diphtheria, and acellular pertussis ¹⁵	7 years ¹⁶	4 weeks	4 weeks If first dose of DTaP/DT or Tdap/Td was administered before the 1 st birthday, 6 months (see final dose). If first dose of DTaP/DT or Tdap/Td was administered at or after the 1 st birthday, 6 months (see final dose). Boostrix (Boostrix) is not recommended.	6 months	6 months (see final dose) If first dose of DTaP/DT was administered before the 1 st birthday.	
Human papillomavirus ¹⁷	9 years	6 months	6 months	6 months	6 months	
Hepatitis A ¹⁸	N/A	6 months	6 months	6 months	6 months	
Hepatitis B ¹⁹	N/A	6 months	6 months	6 months	6 months	
Inactivated poliovirus ²⁰	N/A	4 weeks	4 weeks	6 months	6 months A fourth dose of IPV is indicated if all previous doses were administered at < 4 years or if the third dose was administered < 6 months after the second dose.	
Measles, mumps, rubella ²¹	N/A	4 weeks	4 weeks	6 months	6 months	
Varicella ²²	N/A	4 weeks	4 weeks	6 months	6 months	

NOTE: The above recommendations must be read along with the footnotes of this schedule.

Within Figure 3, the high-risk figure, an asterisk has been added to the HIV Infection column, which refers the provider to a footnote added to the bottom of the figure. This figure directs providers to additional information regarding laboratory values under consideration when providing live vaccine to HIV-infected children. This guidance is found in the *General Recommendations Best Practice Guidelines for Immunization* and directs providers to two separate areas where they can find relevant information:



In addition to the figure changes, the WG introduced a change to a simplified format of the footnotes. The goal was to remove unnecessary text while preserving all pertinent information and maintaining clarity. This was accomplished by a transition from complete sentences to bullets, removal of unnecessary or redundant language, and formatting changes. In most cases, the simplification resulted in a shorter footnote such as with the rotavirus footnote:

2017 Rotavirus and MMR Footnotes	Proposed 2018 Rotavirus and MMR Footnotes
<p>Rotavirus (RV) vaccines. (Minimum age: 6 weeks for both RV1 [Rotarix] and RV5 [RotaTeq])</p> <p>Routine vaccination: Administer a series of RV vaccine to all infants as follows:</p> <ol style="list-style-type: none"> If Rotarix is used, administer a 2-dose series at ages 2 and 4 months. If RotaTeq is used, administer a 3-dose series at ages 2, 4, and 6 months. If any dose in the series was RotaTeq or vaccine product is unknown for any dose in the series, a total of 3 doses of RV vaccine should be administered. <p>Catch-up vaccination:</p> <ul style="list-style-type: none"> The maximum age for the first dose in the series is 14 weeks, 6 days; vaccination should not be initiated for infants aged 15 weeks, 0 days, or older. The maximum age for the final dose in the series is 8 months, 0 days. For other catch-up guidance, see Figure 2. 	<p>Rotavirus vaccines. (minimum age: 6 weeks)</p> <p>Routine vaccination: Rotarix: 2-dose series at 2 and 4 months. RotaTeq: 3-dose series at 2, 4, and 6 months. If any dose in the series is either RotaTeq or unknown, default to 3-dose series.</p> <p>Catch-up vaccination:</p> <ul style="list-style-type: none"> Do not start the series on or after age 15 weeks, 0 days. The maximum age for the final dose is 8 months, 0 days. For other catch-up guidance, see Figure 2.

In other cases, such as the HepB footnote seen here, the simplified version is not shorter. However, the reformatting and use of bold text will allow providers to easily find the information they are looking for:

2017 Hepatitis B (HepB) Footnote	Proposed 2018 Hepatitis B (HepB) Footnote
<p>Hepatitis B (HepB) vaccine. (Minimum age: birth) Routine vaccination: At birth</p> <ul style="list-style-type: none"> Administer monovalent HepB vaccine to all newborns within 24 hours of birth. For infants born to hepatitis B surface antigen (HBsAg)-positive mothers, administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) at age 9 through 12 months (preferably at the next well-child visit) or 1 to 2 months after completion of the HepB series if the series was delayed. If mother's HBsAg status is unknown, within 12 hours of birth administer HepB vaccine regardless of birth weight. For infants weighing less than 2,000 grams, administer HBIG in addition to HepB vaccine within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if mother is HBsAg-positive, also administer HBIG for infants weighing 2,000 grams or more as soon as possible, but no later than age 7 days. <p>Doses following the birth dose</p> <ul style="list-style-type: none"> The second dose should be administered at age 1 or 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks. Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine on a schedule of 0, 1 to 2 months, and 6 months starting as soon as feasible (see Figure 2). Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks), administer the third dose at least 8 weeks after the second dose AND at least 16 weeks after the first dose. The final (third or fourth) dose in the HepB vaccine series should be administered no earlier than age 24 weeks. Administration of a total of 4 doses of HepB vaccine is permitted when a combination vaccine containing HepB is administered after the birth dose. <p>Catch-up vaccination:</p> <ul style="list-style-type: none"> Unvaccinated persons should complete a 3-dose series. A 2-dose series (doses separated by at least 4 months) of adult formulation Recombivax HB is licensed for use in children aged 11 through 15 years. For other catch-up guidance, see Figure 2. 	<p>Hepatitis B (HepB) vaccine. (minimum age: birth) Birth Dose (Monovalent HepB vaccine only):</p> <ul style="list-style-type: none"> Mother is HBsAg-Negative: 1 dose within 24 hours of birth for medically stable infants >2,000 grams. Infants <2,000 grams: administer 1 dose at chronological age 1 month or hospital discharge. Mother is HBsAg-Positive: <ul style="list-style-type: none"> Give HepB vaccine and 0.5 mL of HBIG (at separate anatomic sites) within 12 hours of birth, regardless of birth weight. Test for HBsAg and anti-HBs at age 9 through 12 months. If HepB series is delayed, test 1-2 months after final dose. Mother's HBsAg status is unknown: <ul style="list-style-type: none"> Give HepB vaccine within 12 hours of birth, regardless of birth weight. For infants <2,000 grams, give HBIG in addition to HepB vaccine within 12 hours of birth. Determine mother's HBsAg status as soon as possible. If mother is HBsAg-positive, give HBIG to infants >2,000 grams as soon as possible, but no later than 7 days of age. <p>Routine Series:</p> <ul style="list-style-type: none"> A complete series is 3 doses at 0, 1-2, and 6 months. (Monovalent HepB vaccine should be used for doses given before age 6 weeks.) Infants who did not get a birth dose should begin the series as soon as feasible (see Figure 2). Administration of 4 doses is permitted when a combination vaccine containing HepB is used after the birth dose. Minimum age for the final (third or fourth) dose: 24 weeks. Minimum Intervals: Dose 1 to Dose 2: 4 weeks / Dose 2 to Dose 3: 8 weeks / Dose 1 to Dose 3: 16 weeks. (When 4 doses are given, substitute "Dose 4" for "Dose 3" in these calculations.) <p>Catch-up vaccination:</p> <ul style="list-style-type: none"> Unvaccinated persons should complete a 3-dose series at 0, 1-2, and 6 months. Adolescents 11 through 15 years of age may use an alternative 2-dose series, with at least 4 months between doses (adult formulation Recombivax HB only). For other catch-up guidance, see Figure 2.

The following colorful table shows the 2017 HPV footnote and the proposed 2018 footnote. This graphic demonstrates that all of the information provided in the 2017 footnote is maintained in the 2018 footnote:

2017 HPV Footnote	Proposed 2018 HPV Footnote
<p>Human papillomavirus (HPV) vaccine. (Minimum age: 9 years)</p> <p>Routine and catch-up vaccination:</p> <ul style="list-style-type: none"> Administer a 2-dose series of HPV vaccine on a schedule of 0, 6-12 months to all adolescents aged 11 or 12 years. The vaccination series can start at age 9 years. Administer HPV vaccine to all adolescents through age 18 years who were not previously adequately vaccinated. The number of recommended doses is based on age at administration of the first dose. For persons initiating vaccination before age 15, the recommended immunization schedule is 2 doses of HPV vaccine at 0, 6-12 months. For persons initiating vaccination at age 15 years or older, the recommended immunization schedule is 3 doses of HPV vaccine at 0, 1-2, 6 months. A vaccine dose administered at a shorter interval should be readministered at the recommended interval. <ul style="list-style-type: none"> In a 2-dose schedule of HPV vaccine, the minimum interval is 5 months between the first and second dose. If the second dose is administered at a shorter interval, a third dose should be administered a minimum of 12 weeks after the second dose and a minimum of 5 months after the first dose. In a 3-dose schedule of HPV vaccine, the minimum intervals are 4 weeks between the first and second dose, 12 weeks between the second and third dose, and 5 months between the first and third dose. If a vaccine dose is administered at a shorter interval, it should be readministered after another minimum interval has been met since the most recent dose. Persons who have completed an age-appropriate HPV vaccine series (i.e., either 2 or 3 doses of 2vHPV, 4vHPV, or 9vHPV at the recommended intervals) are considered adequately vaccinated. <p>Special populations:</p> <ul style="list-style-type: none"> For children with history of sexual abuse or assault, administer HPV vaccine beginning at age 9 years. Immunocompromised persons* aged 9-26 years, including those with human immunodeficiency virus (HIV) infection, should receive a 3-dose series at 0, 1-2, and 6 months. <p>Note: HPV vaccination is not recommended during pregnancy, although there is no evidence that the vaccine poses harm. If a woman is found to be pregnant after initiating the vaccination series, no intervention is needed; the remaining vaccine doses should be delayed until after the pregnancy. Pregnancy testing is not needed before HPV vaccination.</p> <p>*See MMWR December 16, 2016;65(49):1405-1408, available at www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6549a5.pdf.</p>	<p>Human papillomavirus (HPV) vaccine (minimum age: 9 years)</p> <p>Routine and catch-up vaccination:</p> <ul style="list-style-type: none"> Routine vaccination at 11-12 years (can start at age 9) and through age 18 if not previously adequately vaccinated. Number of doses dependent on age at initial vaccination: <ul style="list-style-type: none"> Age 9-14 years at initiation: 2-dose series at 0 and 6-12 months. Minimum interval: 5 months (repeat a dose given too soon at least 12 weeks after the invalid dose and at least 5 months after the 1st dose). Age 15 years or older at initiation: 3-dose series at 0, 1-2 months, and 6 months. Minimum intervals: 4 weeks between 1st and 2nd dose; 12 weeks between 2nd and 3rd dose; 5 months between 1st and 3rd dose (repeat dose/s given too soon). Persons who have completed a valid series with any HPV vaccine do not need any additional doses. <p>Special situations:</p> <ul style="list-style-type: none"> History of sexual abuse or assault: Begin series at age 9 years. Immunocompromised* (including human immunodeficiency virus [HIV]) aged 9-26 years: 3-dose series at 0, 1-2 months, and 6 months. Pregnancy: Vaccination not recommended, but there is no evidence the vaccine is harmful and no intervention needed for women who inadvertently received a dose of HPV vaccine while pregnant. Delay remaining doses until after pregnancy. Pregnancy testing not needed before vaccination. <p>*See MMWR, December 16, 2016;65(49):1405-1408, at www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6549a5.pdf.</p>

In addition to the overall simplification, there are a few content edits for the 2018 footnotes. Throughout the footnotes, the word “through” was replaced in an age range with an en-dash. Within the additional information section, text was added to describe this change as well as vaccine preference information:

- Within a number range (e.g., 12-18), a dash (–) should be read as “through.”
- ACIP does not express a preference for any vaccine product where 1 or more products may be appropriate and considered for use

In terms of the text regarding no preference by ACIP, the WG will revisit this text in light of the previous day’s vote to ensure that it is clear that this applies to the Child and Adolescent Immunization Schedule footnote specifically.

Within the HepB footnote, language was added to clarify the guidance for the birth dose administration that reads, “Mother is HBsAg-Negative: 1 dose within 24 hours of birth for medically stable infants >2,000 grams. Infants <2,000 grams: administer 1 dose at chronological age 1 month or hospital discharge.”

Within the poliovirus footnote, there is a change reflecting the recently published guidelines for vaccination of persons who previously received doses of oral polio vaccine (OPV), with the link provided in the footnote. The updated guidance follows:

Series Containing Oral Polio Vaccine (OPV), either mixed OPV-IPV or OPV-only series:

- Total number of doses needed to complete the series is the same as that recommended for the U.S. IPV schedule. See www.cdc.gov/mmwr/volumes/66/wr/mm6601a6.htm?s_cid=mm6601a6_w
- Only trivalent OPV (tOPV) counts toward the U.S. vaccination requirements. For guidance to assess doses documented as “OPV,” see www.cdc.gov/mmwr/volumes/66/wr/mm6606a7.htm?s_cid=mm6606a7_w
- For other catch-up guidance, see Figure 2

A placeholder has been added in the Measles, Mumps, and Rubella footnote for the language voted on the previous day with regard to use of mumps-containing vaccines in an outbreak setting, which reads:

Persons at risk due to a mumps outbreak:

- Previously vaccinated persons identified as being at risk should receive a 3rd dose of MMR vaccine

The WG will continue to work on this language with its SMEs to ensure that it meets the format of the revised footnotes and is true to the recommendation.

Within the influenza footnote, the guidance was updated to direct providers to the published 2017-2018 influenza season recommendations as follows:

- For additional guidance, see the 2017–18 ACIP influenza vaccine recommendations (MMWR August 26, 2016;65(5):1-54: www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6505.pdf).

In conclusion, Dr. Robinson opened the floor for discussion and asked whether ACIP approved of the proposed edits to the Child and Adolescent Immunization Schedule, including the simplified footnotes.

Discussion Points

Drs. Walter and Bennett applauded the WG for revising the footnotes to be much more readable.

Dr. Fryhofer (ACP) said that as a practicing physician, she thought that giving the brand names in the table was very helpful. While the table is not as streamlined as the adult schedule, she found it easier to read.

Regarding the footnote about not expressing a preference, Dr. O’Leary (PIDS) said his understanding was that ACIP did express a preference for combination vaccines. If so, the sentence should reflect that.

Dr. Moore inquired as to whether the mumps vaccine recommendation was reflected in the childhood schedule. Dr. Robinson confirmed that it was.

Dr. Meharry (ACNM) clarified that the statement about HepB should be > 2000 grams rather than \geq 2000 grams. Dr. Robinson confirmed that it should read > 2000 grams and that while a typo was present on the slide, the information was correct in the draft footnotes.

Regarding the mumps outbreak language, Ms. Pellegrini said she thought the phrase “identified by public health” should be included.

Dr. Kimberlin (AAP) observed that it appeared that the General Recommendations definition of “severe” versus “non-severe” immunologic deficiency in someone who is HIV-infected may differ from the Infectious Disease Society of America (IDSA) and Red Book recommendations. While it may not matter that much and there may not be definitive evidence, harmonizing all of these in future years may be something to think about going forward. With Dr. Rubin having been a former ACIP member and involved as well in the leadership of the ISDA document, Dr. Kimberlin suggested that he would be a very good person to reach out to about this.

Dr. Robinson replied that the WG discussed at length the differences between the guideline and recommendations, and deferred to the ACIP-related document for the schedule since the schedule is meant to reflect current ACIP policy. However, the new format of the *General Best Practice Guideline* permits editing of the text as evidence emerges and SMEs agree. The schedule will point to the updated text as well, and this is under consideration by the General Best Practice Guidelines WG as well.

Dr. Kroger (SME) reported that discussions are underway with NIH, the vaccine-specific ACIP SMEs, and HIV experts in terms of how to deal with the issue of the different types of tests that are used and the cutoff parameters. The goal is to harmonize all of this. The *General Best Practices Guideline* is currently harmonized with the *MMWR* ACIP-specific statement that discusses that issue, so there is harmony within those two documents. Efforts are underway to ensure that all are harmonized, understanding that HIV is focused on surveillance and categories are sometimes defined in perpetuity. When defining categories, NCIRD does not necessarily want to do this. If someone is immunocompetent after a point in time, the ACIP vaccine-specific statement reflects that they may be given a dose of vaccine.

Ms. Groom (IHS) reminded everyone that there is ACIP language addressing American Indian/Alaskan Native (AI/AN) children pertaining to Hib vaccine, and requested that the WG ensure that language is included in the statement about these special populations.

Vote: Child and Adolescent Immunization Schedule

Dr. Kempe made a motion to approve the Child and Adolescent Immunization Schedule. Dr. Walter seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Atmar, Belongia, Bennett, Ezeanolue, Hunter, Kempe, Lee, Moore, Pellegrini, Reingold, Riley, Romero, Stephens, Szilagyi, Walter
0 Opposed: N/A
0 Abstained: N/A

Japanese Encephalitis Vaccine

Introduction

Chip Walter, MD
Chair, ACIP Flavivirus Vaccines WG

Dr. Walter noted that the Flavivirus Vaccines WG activities have changed focus somewhat. They began work on Japanese encephalitis (JE) vaccine, but were derailed by additional issues such as Zika, dengue, and the yellow fever (YF) vaccine shortage.

The JE Vaccine WG's objectives, the first three of which have been completed, are to: 1) review newly available safety and immunogenicity data for JE vaccine; 2) review epidemiology and risk of JE in travelers; 3) review ACIP recommendations for use of JE vaccine in

consideration of updated safety, immunogenicity, and traveler risk data; and 4) update the *MMWR Recommendations and Reports* published in 2010.

Presentations during this session focused on JE among US travelers, JE vaccine post-marketing AE surveillance among US military personnel, AEs following JE vaccine reported to VAERS from 2012-2016, and the WG summary and plans.

Epidemiology and Risk of Japanese Encephalitis in US Travelers

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 reminded everyone that JE is caused by a mosquito-borne flavivirus. It occurs in most of Asia and the Western Pacific, with an estimated 68,000 cases annually. The highest incidence is in rural agricultural areas, and seasonality varies by region. Most infections are asymptomatic but when clinical disease occurs, it is often severe with a 20% to 30% case fatality rate and about 30% to 50% of survivors having sequelae. Inactivated Vero cell culture-derived JE vaccine (JE-VC; IXIARO®) is the only JE vaccine available in the US and is manufactured by Valneva. Inactivated mouse brain-derived JE vaccine (JE-MB; JE-VAX®) is no longer available in the US.

As a reminder about the timeline for recommendations for the use of JE-VC, in 2009 the FDA licensed JE-VC for use in adults and ACIP approved recommendations for a primary series in adults. In 2010, the *MMWR Recommendations and Reports* from 1993 was updated and published. In 2011, ACIP approved recommendations for use of a booster dose in adults and a *Policy Note* was published in the *MMWR*. In 2013, ACIP approved recommendations for use of a primary series in children and an additional *Policy Note* was published in the *MMWR*.

The JE Vaccine WG is currently reviewing recommendations for JE-VC use in consideration of updated safety, immunogenicity, and traveler risk data. While those considerations were not part of Dr. Hills' presentation during this session, before presenting information on the epidemiology and risk of JE among US travelers, she reminded ACIP members of the existing recommendations for prevention of JE among travelers. First, providers should discuss the risks of JE disease and the importance of personal protective measures to reduce the risk of mosquito bites with all travelers to JE-endemic countries. For some travelers who will be in a high-risk setting, JE vaccine can further reduce the risk for infection. Evaluation of an individual traveler's risk should take into account their planned itinerary including travel location, duration, season, and activities. In all cases when making recommendations regarding the use of JE-VC, providers should weigh the overall low risk for travel-associated JE, the high morbidity and mortality when JE does occur, the low probability of SAEs following vaccination, and vaccine cost.

The existing ACIP JE vaccine recommendations for travelers that were updated in 2010 are as follows:

- ❑ Recommended
 - Travelers who plan to spend ≥ 1 month in endemic areas during JE virus transmission season, including recurrent travelers or urban-based expatriates planning to visit rural areas

- ❑ Consider
 - Short-term travelers (<1 month) during JE virus transmission season if they plan to travel outside an urban area and have itinerary or activities that increase risk of JE virus exposure
 - Travelers to areas with an ongoing JE outbreak
 - Travelers to endemic areas who are uncertain of specific destinations, activities, or duration of travel

- ❑ Not Recommended
 - Short-term travelers whose visit is restricted to urban areas or outside of transmission season

In terms of JE epidemiology among travelers, the JE-MB vaccine was licensed in the US at the end of 1992. This made JE vaccine widely available for the first time. This review of the epidemiology among travelers focused on a 25-year period from 1993 through 2017. There were 58 cases of travel-associated JE among people from non-endemic countries published in the literature or in conference proceedings or reported to CDC from 1993 through 2017. A limited number of cases were reported annually, with a median of 2 cases and a range of 0 to 6 cases per year. There was a small increase in the annual number of reported cases over this period, which was likely related to an increase in overall traveler numbers and possibly related to increased awareness of and testing for the disease.

Among the 58 traveler cases among persons from non-endemic countries globally that have occurred since 1993, 12 cases have occurred among US travelers. All cases occurred in 2003 or later. There was a median of 0 cases per year, with a range of 0 to 2. As far as could be established, none of the travelers had received JE vaccine. Among the 12 cases, 8 (67%) were male and patients ranged in age from 5 weeks to 68 years of age, with 2 to 4 cases in each 20-year age group. Of the cases, 75% occurred from June to August. While JE risk exists year-round in some countries in tropical regions, the annual seasonal increase in JE in countries in temperate areas occurs over these summer months. Another possible factor contributing to the seasonality of cases might be that a greater number of US travelers may take overseas vacations to Asia during the summer. Among the 12 cases, 2 (17%) died, 3 (25%) survived but had sequelae, and 50% recovered fully. One infant spent 3 weeks in an Intensive Care Unit (ICU), but the outcome is unknown. The countries of probable acquisition for the 12 US travel-associated cases were 4 from the Philippines (33%), 2 from Thailand (17%), 2 from Vietnam (17%), 2 from South Korea (17%), 1 from China (8%), and 1 from Taiwan (8%).

Of the 12 cases, 8 (67%) occurred in tourists and 4 (33%) occurred in expatriates. The tourist category included 3 persons traveling to visit friends and relatives and 1 study abroad program student. The expatriate group included 1 college professor who worked in the US but had spent several months working in a JE-endemic country. Of the 12 travelers, 8 (67%) had traveled for 1 month or longer and should have received JE vaccine based on their longer-term travel, but had not. Among the remaining 4 shorter-term travelers, 3 (25%) traveled for 2 to less than 4 weeks and 1 (8%) traveled for 1 to less than 2 weeks. To consider exposure of these shorter-term travelers, the itineraries of the 4 shorter term travelers who traveled for less than 1 month were reviewed. Of these 4 travelers, 1 (8%) spent the majority of time in rural areas, 2 (17%) stayed in urban areas but made 1 or more overnight or day trips to rural areas, and 1 (8%) had no exposure-related information.

Information was provided to consider estimates of risk to US travelers to Asia. If risk is estimated based on reported US cases and traveler denominator data, there were 12 US travel-associated JE cases in the 25 years from 1993 to 2017 or less than 1 case per year. There were 4 to 5 million US citizen trips to Asia per year since 2004 based on data collected by the National Travel & Tourism Office ([NTTO](#)). Therefore, the overall risk is less than 1 case per million trips to Asia. The risk will vary based on season, destination, duration, and activities. However, this provides an overall estimate to consider the magnitude of risk. There are limitations to this estimate of risk. First, the figure for the denominator in the calculation is based on the number of trips to Asia as accurate data on the number of travelers are not available. Second, the rate of under-diagnosis and under-reporting of JE cases is unknown. If 10 times as many cases are assumed as occurred among US travelers and have been diagnosed or reported, which is however unlikely, the calculation would be that 120 US traveler cases have occurred over a 25-year period, or about 5 cases per year. There have been about 100 to 125 million US citizen trips to Asia based on an annual number of 4 to 5 million trips per year. For this scenario, the risk estimate is about 1 case of JE per million trips to Asia.

A final question that arises regards whether the risk estimate is low because the majority of travelers are vaccinated and not at risk. Two studies have been conducted that provide some data to address the question of vaccination rates among US travelers. The first was an airport survey conducted in 2007 that showed that only 11% of higher risk travelers reported receiving JE vaccine¹. The second was a Global TravEpiNet (GTEN) study conducted from 2009 to 2012 that showed only 28% of higher risk travelers were vaccinated during a clinic visit or had received JE vaccine within previous 2 years². For both studies, the number of lower risk travelers who had received JE vaccine was 2% to 4%. Therefore, even with low JE vaccination rates among US travelers, cases of disease are rare [1. Duffy et al. *J Travel Med*, 2013; 2. Deshpande et al, *Am J Trop Med Hyg* 2014].

JE-VC Post-Marketing Adverse Event Surveillance Among US Military Personnel

Dr. Christian Taucher
Head of Global Medical Affairs
Valneva

Dr. Taucher presented data on a surveillance study of AEs after immunization with IXIARO[®], which is the Vero cell culture-derived vaccine that is currently licensed in the US. This study was a post-marketing commitment to the FDA. As such, a list of pre-defined events of special interest was compiled when looking at the safety profile of both the Vero cell culture-derived vaccine as well as the previously available JE-MB due to some events that have been potentially associated with other vaccines. The primary objective of the study was to detect,

verify, and characterize rare potential SAEs such as neurological or hypersensitivity reactions among 20,000 IXIARO[®] vaccinated military personnel. The secondary objective was to identify unexpected or unanticipated AEs that were possibly associated with IXIARO[®] vaccination by performing data mining for events with significantly higher incidence after IXIARO[®] vaccination than in an IXIARO[®] non-exposed comparison group of JE-VAX[®] vaccinees and among these events, to identify medically significant events (i.e., two outpatient visits or one inpatient visit within 7 days after vaccination).

The Defense Medical Surveillance System (DMSS) database was utilized and the population included male and female Active Duty US military personnel (Army, Navy, Air Force, and Marines) ≥ 17 years of age who received at least one dose of either IXIARO[®] or the previously available JE-MB vaccine JE-VAX[®]. Enrollment agreed to with the FDA was that the first 20,000 subjects entered into the database who received one dose of IXIARO[®] would be included; between July 1, 2010 and May 27, 2011 21,347 subjects vaccinated with JE-VC were included. There were 49,441 subjects vaccinated with JE-VAX[®] between January 1, 2009 and May 27, 2011 who were the comparator group. There were two categories of AEs. Tier 1 events consisted of those on the list of pre-defined serious ICD-9 codes potentially associated with vaccines, while Tier 2 events included events with ICD-9 codes detected with a frequency of ≥ 5 and a significantly increased incidence rate in the IXIARO[®] group and 2 two outpatient visits or a hospitalization within 7 days after the primary ICD-9 code reporting date. In terms of the characteristics of this military population, not very surprisingly the mean age was relatively young at about 27 years in the JE-VAX[®] group and 25 years in the IXIARO[®] group. Also not very surprisingly, this was a predominantly male population with over 90% males in both the JE-VAX[®] and IXIARO[®] groups.

Regarding the Tier 1 events, the analysis began with 21,347 subjects in the database who had been vaccinated with at least one dose of IXIARO[®] and 49,441 subjects vaccinated with at least one dose of JE-VAX[®]. Active electronic surveillance was conducted for ICD-9-CM coded AEs within 42 days after each vaccination. That revealed 182 subjects with pre-defined Tier 1 ICD-9 codes detected, of whom 4 subjects were excluded as non-eligible, 5 subjects could not clearly be assigned to either IXIARO[®] or JE-VAX[®]. Among the remaining 173 subjects 45 subjects were assigned to IXIARO[®], and 128 subjects were assigned to JE-VAX[®]. The 45 subjects in the IXIARO[®] group and 128 subjects in the JE-VAX[®] group were included in the incident risk ratio analysis of Tier 1 events. In addition to this initial screening, a detailed study was conducted of EHRs, including verification of diagnosis, temporal association with vaccination, medical history, concomitant medications, and outcome of events and information was transferred into individual Case Report Forms (CRFs). That served as the basis of information for the DSMB to assess the causal relationship. The CRF review resulted in 2 subjects being reassigned to the IXIARO[®] group, and 1 subject being considered non-eligible as notes on CRF confirmed that the Tier 1 event had already occurred 4 months before the documented visit. Ultimately, 46 subjects were assignable to the IXIARO[®] eligible population for assessment.

Tier 1 AE incidence rates and ratios are delineated in the following table:

Tier 1 AE	JE-VAX [®]			IXIARO [®]			IRR	P-value
	Case N	Person Year	IR per 1000 py	Case N	Person Year	IR per 1000 py		
Ataxia	1	9206	0.11	0	3634	0	0	1
Bell's Palsy	3	9193	0.33	0	3632	0	0	1
Bronchospasm	2	9191	0.22	0	3628	0	0	1
Cerebrovascular accident	0	9210	0	0	3637	0	.	1
CNS Inflammation / Encephalitis	1	9205	0.11	0	3636	0	0	1
Encephalopathy	1	9208	0.11	0	3635	0	0	1
Guillain-Barré-Syndrome	0	9209	0	0	3637	0	.	1
Multiple sclerosis	0	9207	0	0	3636	0	.	1
Myelitis	1	9205	0.11	0	3636	0	0	1
Neuropathy	4	9195	0.44	0	3633	0	0	1
TIA	1	9204	0.11	0	3635	0	0	1
ADEM	0	9211	0	0	3637	0	.	1
Convulsion	9	9185	0.98	6	3627	1.65	1.69	0.27
Delayed hypersensitivity / Serum sickness ^a	5	9205	0.54	3a	3635	0.83	1.52	0.58
Anaphylactic shock	7	9188	0.76	2	3629	0.55	0.72	0.75
Angioedemaa	6	9183	0.65	2a	3629	0.55	0.84	0.96
Neuritis	84	8845	9.5	29	3525	8.23	0.87	0.84
Meningitis	1	9198	0.11	2	3634	0.55	5.06	0.23
Ptosisc	2	9200	0.22	1c	3632	0.28	1.27	0.83

^a Single additional subject assigned to IXIARO group after CRF review as documented JE-VAX vaccination was outside of the time window of 42 days after diagnosis of Tier One code.

^c considered non-eligible, as notes on the (CRF) revealed that the Tier One event had already occurred 4 months before the documented visit date, hence an exclusion criterion was met.

An incident risk ratio above 1 indicates that the AE occurred at a high incidence in the IXIARO[®] group, but if it is below 1 that means it happened at a high incidence in the JE-VAX[®] group. Looking at the far-right column, none of the differences were statistically significant. However, since a limited number of events of special interest were found and after a discussion with the WG, Dr. Taucher further detailed these findings.

Regarding the 6 cases of convulsion in the IXIARO[®] group, 5 had Code 780.39 (Other, Convulsions) and 1 had Code 345.9 (Epilepsy, Unspecified). The time of onset was between 4 days to over a month. Concomitant vaccinations were given in 4 cases including rabies, influenza, typhoid, and smallpox/anthrax. No causality was specified or suspected for any of the cases of convulsions. In at least 3 of the 6 cases, a second dose of IXIARO[®] was given after the event was recorded for which no further events were detected in the database.

All 4 cases of delayed hypersensitivity/serum sickness had Code 999.5 (Other, Serum Reaction). Onset was on the day of vaccination in 2 cases, 1 week after vaccination in 1 case, and 1 month after vaccination in 1 case. Anthrax vaccine was given concomitantly in 2 cases, 1 of which had a causality specification in the database. A second dose of IXIARO[®] was given in 3 of the cases.

In terms of the 2 cases of anaphylactic shock, one had Code 999.4 (Anaphylactic shock due to serum) and the other had Code 999.5 (Other anaphylactic shock). Onset in the first was 21 days after the second dose of IXIARO[®] vaccination and anthrax vaccine was given concomitantly. Onset in the second was 2 months after the first dose and 3 days before the second dose of IXIARO[®] vaccination. No concurrent vaccines were administered in that case, and there was some additional information about this case. The patient presented to the ED 2 months after the first dose of IXIARO[®] vaccination with dermatitis (full body rash, itchy, and shortness of breath). The patient denied exposure to new foods, soaps, or detergents. Prednisone, Benadryl[®] (diphenhydramine) and Zantac[®] (ranitidine) were prescribed and a diagnosis of anaphylaxis was made. Causality was not specified in the database for either of these 2 cases.

All 3 cases of angioedema had Code 995.1 (Angioneurotic edema, not elsewhere classified). Onset for 1 case was 15 days after the second IXIARO[®] vaccination. Rabies vaccination was given concomitantly in this case, and no causality was specified. Onset was 25 days in another case for which bee sting was specified as the causality, and a second dose of IXIARO[®] vaccination was given after the recorded event. In the third case, onset was 2 weeks after the first dose, there were no concurrent vaccines, no causality was specified, and a second dose was given after the recorded event.

In the eligible Tier 1 population, overall there were 46 identified cases. Of these, 12 (26.1%) were identified as possibly related:

ICD-9 CM Code	Medical Term / Diagnosis	Total (N=46) No. (%)*
723.4	Brachial neuritis or radiculitis NOS	4 (8.7)
780.39	Other convulsions	2 (4.3)
999.5	Other serum reaction not elsewhere classified	3 (6.5)
999.4	Anaphylactic reaction to serum	1 (2.2)
995.1	Angioneurotic edema, not elsewhere classified	2 (4.3)
Total number of subjects with AEs assessed as related		12 (26.1)
Total number of such AEs		17

Tier 2 events were those that occurred at a significantly higher incidence in the IXIARO[®] group, with at least 5 cases detected in the database. There were 9 cases in the JE-VAX group and 38 in the IXIARO[®] group with a Code 0229 (Anthrax Unspecified), which potentially is a coding error. There were 21 cases in the JE-VAX group and 15 in the IXIARO[®] group with a Code 470 (Deviated Nasal Septum), for which the DSMB failed to see a causal relationship.

In conclusion, in a population of 21,347 US military personnel receiving 36,358 doses of IXIARO[®], screening for pre-defined events that are potentially serious (i.e., AEs with evidence or suspicion of an association with JE vaccines or excipients and adjuvants) revealed no statistically significant increased incidence rates compared to a reference population of subjects vaccinated with JE-VAX (N= 49,441). Data mining for non-predefined events with statistically significant higher incidence rates in the IXIARO[®] population compared to the JE-VAX population revealed no events with causal relationship for vaccination with IXIARO[®]. No safety signals have been identified during the review of the 401 study data. Overall, this review of data on more than 20,000 military personnel vaccinated with IXIARO[®] strengthened IXIARO[®]'s good safety profile known from clinical development as well as from post-marketing experience since 2009. The benefit-risk evaluation for IXIARO[®] remains positive and unchanged compared to that at time of authorization.

Discussion Points

Dr. Lee asked how causality was determined for convulsion, noting that only 1 of the 6 had a medical history of convulsions. She found it very unusual that an adult would have a sudden onset of convulsions in any period after a vaccination. Regarding unanticipated AEs, it seemed that the Tier 2 criteria were fairly strict and had two requirements. This seemed very unlikely to pick up unanticipated AEs, and she wondered if the criteria could be loosened to be broader.

Dr. Taucher acknowledged that causality was clearly a limitation of the study, given that it was from the database and fairly limited information was available. The causality assessment was based heavily on the temporal association.

Adverse Events Following JE-VC[®] Reported to VAERS 2012-2016

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 presented findings from an analysis of AEs following JE-VC reported to VAERS from 2012-2016. As a reminder and to provide a context to this review, distribution of JE-VC began for adults aged ≥ 17 years in May 2009 and in mid-2013 for persons 2 months to < 17 years of age. In 2015, a review was completed of VAERS reports for adults who received JE-VC from May 2009 through April 2012*, covering the first three years post-licensure. The objective of Dr. Hills' presentation during this session was to summarize JE-VC VAERS reports from May 1, 2012 through April 30, 2016. This includes the period when the vaccine began to be used among children [*Rabe IB et al. Adverse events following vaccination with an inactivated, Vero cell culture-derived Japanese encephalitis vaccine in the United States, 2009-2012. *Vaccine* 2015; 33:708-12]. As a reminder, VAERS is a passive surveillance system for reporting of AEs following immunization. Manufacturers, healthcare providers, or vaccine recipients can submit reports using a standardized form which collects data on patient demographics, vaccination, and a description of the AE. Events are coded using MedDRA-preferred terms. The causal relationship between vaccination and reported events usually cannot be determined. Reports are classified as serious or non-serious according to the FDA regulatory definition, which defines a SAE as one that is life-threatening, that results in death, a persistent or significant disability, a congenital anomaly, hospitalization or prolongation of hospitalization, or another

medically important condition that requires medical or surgical intervention to prevent one of these outcomes.

An AE was excluded if it occurred more than 60 days after vaccination, it was a local reaction contralateral to the site of JE-VC administration, the vaccine was administered inappropriately with no AE, or the symptoms were clearly related and unique to another co-administered vaccine. An important factor for consideration of JE-VC AE data is that a high percentage of vaccine doses are distributed to the US military, which impacts the demographics of vaccine recipients and profile of co-administered vaccines, which in the military often includes vaccines such as smallpox and anthrax.

The following definitions were used to classify particular events. Hypersensitivity events were classified as anaphylaxis if they met Level 1 or Level 2 of diagnostic certainty using the Brighton Collaboration case definition¹ and occurred within 2 hours of vaccination. For non-anaphylaxis hypersensitivity events, a modified Brighton definition was used that was developed by expert consensus and used in a previous JE-VC VAERS analysis. Non-anaphylaxis reactions were divided by interval between vaccination and onset, designating events under 2 hours after vaccination as immediate and between 2 hours and 14 days after vaccination as delayed. Neurologic events were classified as central or peripheral. For central neurological events, Brighton Collaboration case definitions² were used for events such as aseptic meningitis, encephalitis, acute disseminated encephalomyelitis (ADEM), GBS, or generalized seizure. Reports consistent with paresthesia or peripheral neuritis were classified as peripheral neurological events. To enable calculation of incidence rates of AEs, Valneva provided total doses distributed by month. However, no data were available on doses administered by age and sex [Ruggeberg JU et al. *Vaccine* 2007;25:5675–84; Rabe IB et al. *Vaccine* 2015; 33:708-12].

In terms of AEs following vaccination with JE-VC, there were 119 AEs during the 4-year period of this analysis, including 9 (8%) serious events and 110 (92%) non-serious events. During this time, over 802,000 vaccine doses were distributed for an overall AE reporting rate of 14.8 events per 100,000 doses distributed. The rate of SAEs was 1.1/100,000 doses distributed, and for non-serious events was 13.7/100,000 doses distributed. Regarding the distribution of AEs by sex and age group, males accounted for 61% of the AE reports. Among age groups, the majority of reports were for persons 17 through 39 years of age (66%). The higher percentage of cases among males and the high number of cases in persons 17 through 39 years of age is likely in large part related to the administration of substantial numbers of JE-VC doses to young adult males in the military. There were 11 AE reports for children and adolescents under 17 years of age. As mentioned, there were no data on doses administered by age group available to calculate rates of AEs in children.

In considering whether AEs events occurred after the first, second, or a subsequent dose, the data showed 53% among persons receiving a first dose, 22% after a second dose, and 8% after subsequent doses. The dose number was unknown for 17%. AEs were considered among persons who received JE-VC alone or JE-VC concurrently with other vaccines, and whether the event was serious versus non-serious. The majority (67%) of all AEs occurred following JE-VC co-administered with other vaccines, including 8 serious events. One serious (1%) and 38 (32%) non-serious events occurred following administration of JE-VC alone.

Overall, 24 (20%) of all 119 AEs were classified as hypersensitivity events, including 2 (2%) serious events; 11 (9%) were classified as neurologic, including 1 serious event; and the majority (71%) were classified as other event types, with 6 (5%) events being serious. Among the hypersensitivity events, 1 (4%) was anaphylaxis, 7 (30%) were immediate, and 15 (65%) were delayed events. Of the 2 serious hypersensitivity reports, one was a report of anaphylaxis and the other of immediate hypersensitivity. The anaphylaxis event was in a 19-year old female and occurred approximately 25 minutes after receiving anthrax, typhoid, YF, and JE vaccines. The serious immediate hypersensitivity event was in a 23-year old male with onset 15 minutes following anthrax, typhoid, and JE vaccines. For the 11 neurologic AEs reported, 2 were central, both of which were seizures with 1 being serious and 1 being non-serious. There were 9 (82%) peripheral events, with 6 described as paresthesia, 2 as somatosensory events, and 1 as sensorineural hearing loss. The serious seizure was in a 15-year old male and occurred 7 days after receiving the second dose of JE-VC and third dose of rabies vaccine. Subsequent seizures also were reported.

There were 84 other non-hypersensitivity, non-neurologic events. Of these, 23 (27%) were local reactions and 61 (73%) non-local. The most frequent descriptors for these other events were rash, headache, dizziness, nausea, and fever. Among the non-local events, 6 (7%) were characterized as serious. The 6 serious other events included 1 case each of sudden cardiac death, cardiomyopathy, myocardial infarction and acute myocarditis, angina pectoris, systemic febrile reaction with acute vaccinia syndrome, and acute kidney injury and myopathy. Most of these occurred following co-administration with other vaccines. The only event that occurred following administration of JE-VC alone was in the sudden cardiac death patient, who was a 42-year old male who 8 days after vaccine administration suddenly collapsed while running. The final cause of death was recorded as sudden cardiac death due to ischemic heart disease.

The following table shows a comparison of reporting rates of AEs following JE-VC per 100,000 doses distributed between the first analysis of VAERS data and this analysis:

	2009–2012 ¹	2012–2016
All AEs	15.2	14.8
Hypersensitivity	4.4	3.0
Neurologic	2.2	1.4

¹Rabe IB et al. Adverse events following vaccination with an inactivated, Vero cell culture-derived Japanese encephalitis vaccine in the United States, 2009-2012. *Vaccine* 2015; 33:708-12

The rates found are similar to or lower than those found in the prior analysis. Overall rates of AEs were 15.2/100,000 doses distributed in the previous analysis and 14.8/100,000 in the current analysis. The hypersensitivity event rate of 3.0/100,000 doses and neurological event rate of 1.4/100,000 doses were lower than the previous analysis.

In conclusion, rates of total, hypersensitivity, and neurologic AEs have not increased compared with the previous VAERS analyses. Few AEs were reported in persons less than 17 years of age, but administration data by age group are not available to calculate age-specific rates and it is likely that low numbers of vaccines are administered to children. VAERS data suggest that hypersensitivity and neurologic AEs occur, but are uncommon. With over 800,000 doses distributed during this review period, the data support the good overall safety profile of JE-VC.

Discussion Points

Ms. Pellegrini asked whether any of the data were related to pregnancy. She pointed out that behind the last tab in the notebooks provided to ACIP members, a couple of letters were provided and commented on this and another letter seemed to be missing.

Dr. Hills indicated that there was one report of administration during pregnancy, but no AEs were reported.

Dr. Cohn confirmed that one of the letters was from the American Society of Tropical Medicine and Hygiene (ASTMH). ASTMH send letters to ACIP in 2013, 2015, and a couple of weeks before this meeting [*Post Script: This statement accurately reflects the comment made during the meeting, but is not correct. The letter is from the Expert Advisory Group on Japanese Encephalitis Prevention that first convened at an annual meeting of the American Society of Tropical Medicine and Hygiene (ASTMH), but the group is not associated with ASTMH. Also, the group sent the 3 letters in 2015, April 2017, and October 2017. The letter submitted for this meeting may be found in Appendix A*].

JE Vaccine WG Summary and Plans

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 data presented during this session and updated ACIP on the future plans of the JE Vaccine WG. As a reminder, when the JE Vaccine WG was reformed in March 2015, the objectives were to:

- Review newly available safety and immunogenicity data for JE-VC
- Review updated data on the epidemiology and risk of JE among travelers
- Review the ACIP recommendations for use of JE vaccine in consideration of the updated safety, immunogenicity, and traveler risk data
- Prepare a revised *MMWR Recommendations and Reports* to update the document that was published in 2010

To summarize the data presented during this session, Dr. Hills first presented the WG's conclusions on the epidemiology and risk of JE among US travelers. The WG review indicated that JE is a low risk disease for US travelers. Only 12 cases were reported in the 25 years from 1993 through 2017. Based on US citizen trips to Asia, the incidence is less than 1 case/1 million trips to Asia. The estimated risk remains low at about 1 case/1 million trips even if there is substantial under-diagnosis and 10 times as many cases occurred as were diagnosed and reported. The majority (67%) of US traveler cases occurred in longer-term (≥ 1 month) travelers, and the remainder for whom information was available had rural exposures. There has been no apparent change in the risk of JE for travelers compared with an assessment at the time JE-VC recommendations were considered previously in 2010, which also estimated a risk of less than 1 case/1 million travelers.

The second topic presented pertained to JE-VC AE surveillance data, including one post-marketing surveillance study and a review of recent VAERS surveillance data. The WG summary was that active surveillance among more than 21,000 US military personnel vaccinated with JE-VC showed no statistically significant increased incidence rates for selected neurologic or hypersensitivity events compared with the personnel vaccinated with the previously available JE-MB vaccine, JE-VAX[®].

An updated analysis of passive surveillance data collected through VAERS in the period 4 to 7 years post-licensure when over 800,000 vaccines were distributed showed that rates for total, hypersensitivity, and neurologic AEs were not higher than rates in the first 3 years post-licensure. There was a low number of reports among children, although age-specific rates could not be calculated. Therefore, overall, rare SAEs were reported, but recent data support the overall good safety profile of JE-VC and suggest rates of SAEs are not higher than rates for JE-MB.

To complete the remaining ACIP JE Vaccine WG objectives, the following topics will be addressed at upcoming ACIP meetings:

- A review of the ACIP recommendations for use of JE-VC in consideration of updated safety, immunogenicity, and traveler data that have been presented to ACIP during this and previous meetings
- A cost-effectiveness analysis of JE-VC vaccine for US travelers
- A GRADE analysis to update the analysis performed in 2013 when pediatric JE vaccine recommendations were considered
- Presentation of a draft of an updated *MMWR Recommendations and Reports*

Discussion Points

In consideration of future decision-making, Dr. Lee observed that comparative rates to the older vaccine did not appear to be very different based on passive surveillance data. However, because it seems like an under-estimate, she wondered if more robust safety data could be presented to reflect accurate AE rates following this vaccine as this is being considered in the GRADE and cost-effectiveness analyses. She suggested a more detailed review of the study coming out of the DoD population to be considered by the WG, and recognizing the under-estimation of the burden of disease due to lower detection, and trying to understand how that might influence decision-making as well on both ends.

Dr. Hills indicated that she could present data during a future ACIP meeting comparing AE rates of JE-MB and JE-VC, but results are based on VAERS reports as those are the data available. In addition, there are the data from the post-marketing surveillance study presented during this session and the initial data available prior to vaccine licensure.

Dr. Bennett seconded Dr. Lee's suggestions. AEs were more frequent than disease itself and SAEs were about 1/100,000 which is a fairly significant SAE rate.

As a clinician and local public health person who does not deal with travel medicine or this vaccine, Dr. Hunter wondered about the public health implications. It appears that a large number of people are traveling who might be at risk, a very small number of whom experience very serious consequences. To him, that looked somewhat like meningococcal meningitis. However, there are many implementation issues, vaccine performance, and AEs that are quite different.

Dr. Walter said that this observation was correct. JE disease is not good when contracted, but it rarely occurs in the traveler. The average person who acquires JE disease does not get very sick, but it is very bad for those who do become severely ill.

Dr. Bennett emphasized that this is why the AE rate is so important with this particular vaccine.

Dr. Atmar stressed that the vast majority of travelers are not at risk and the vaccine would not be indicated for them, so less than 1 case/1 million travelers to Asia does not accurately reflect the people for whom the vaccine might be indicated. There still will be a cost-benefit, and it will be interesting to see an economic analysis.

Dr. Kempe was struck that the vast majority of the AEs occurred with multiple vaccines, and she wondered about how to separate that out. To her, that made these data helpful but not clear.

Dr. Walter added that especially the cardiac events could be attributed largely to smallpox vaccines.

Dr. Reingold requested a reminder about the efficacy, duration of protection, and need for revaccination.

Dr. Hills indicated that for the 2-dose schedule of 0 and 28 days, there is an approximately 90% seroprotection rate at one month. The rates decrease through about 12 months, with variable rates in different studies of about 60% to 85% with those 2 doses. For booster doses, data are available through 6 years, which show good rates of seroprotection over that period.

Dr. Messonnier was struck that in the initial cases series, a lot of those individuals were in the category of "should have been vaccinated" or "should consider being vaccinated." She asked whether more was known about why they did not get vaccinated, and if in the "consider" category there was an offer of vaccine that was refused. That is, were those groups in which there should have been prevention based on the current recommendations.

Dr. Hills replied that unfortunately, they do not have these data. They have tried to follow-up the cases as much as possible with state or local health departments to ask those questions, but it is often difficult to get additional information.

Dr. Romero requested further comment about the smallpox vaccine association with cardiac disease.

Dr. Szilagyi requested a reminder about why they could not acquire rates among children, especially since many states require notification to registries.

Dr. Hills indicated that notification of JE-VC would not be part of registry reports. Doses distributed are known, but it is not known to whom they are administered and, therefore, the age and sex of recipients is unknown.

Dr. Walter added that a lot of travel vaccines are given in travel clinics and not by providers who would use a registry, so that information is oftentimes not available.

Dr. Sun (FDA) asked whether the numbers reported included civilian and military travelers.

Dr. Hills confirmed that the numbers reported are for both. It is known that a majority of doses of JE-VC, about 80%, are distributed to the military.

Dr. Belongia requested a reminder about the current DoD policy for JE-VC in terms of whether everybody deployed to Southeast Asia is vaccinated. He observed that the analysis of the safety surveillance study from the DoD database was through 2011, so there should be a lot of additional data potentially to assess in a larger follow-up. Since those were not part of the post-marketing commitment of the manufacturer to FDA, ACIP would not routinely have access to those data. There will not be additional safety data unless DoD wants ACIP to assess their data further. There is going to be receipt of multiple vaccines, including some fairly reactogenic vaccines, so it is going to be very hard to separate this out further.

Dr. Deussing (DoD) responded that the current policy is for Active Duty members from all services who are stationed on the Korean Peninsula and in Japan for 30 days or greater to receive JE-VC. It is also recommended to other beneficiaries, and is based on risk for the other endemic JE areas.

Dr. Lee asked whether the DoD database also includes spouses, children, and associated members in the military. If so, to follow up on Dr. Belongia's point, it would be great to suggest a collaboration in this instance to be able to review current data and capture information on both children and adults. The profile on children might be very different.

Dr. Deussing (DoD) indicated that if family members are vaccinated based on the recommendation within a military treatment facility, that would be captured within the military's EHR. A small number of doses are administered in children, but if they could sort that out, it could be beneficial.

Ms. Pellegrini noted that it should be cleaner because the children would not be receiving smallpox or anthrax vaccines.

Dr. Taucher indicated that they had discussions with the DoD to determine the vaccination rate of dependents and to establish some collaboration. The current status is that the information is not available, but they are pursuing this opportunity. If ACIP could support them in this effort, they would be happy to do it.

John Allen (Valneva) indicated that unpublished data from a study from the DoD in 2015 showed that 2% of the Air Force dependents are currently receiving JE-VC.

Pneumococcal Vaccines

Introduction

Arthur Reingold, MD
Pneumococcal Vaccines WG Chair
Advisory Committee on Immunization Practices

Dr. Reingold 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; and
- Revise or update recommendations for pneumococcal vaccine use, as needed.

As a reminder, ACIP recommended PCV13 for children in 2010, adults ≥ 19 years with immunocompromising or other conditions that increased their risk for invasive pneumococcal disease in 2012, and all adults ≥ 65 years of age in August 2014. The ACIP concluded in August 2014 that in the short-term, such a recommendation for universal PCV13 use in this age group was warranted. However, not everyone in the US agreed with this recommendation or thought it would be cost-effective based on the feedback received. The WG did realize that in the long-term, continued herd effects could limit the utility of such a universal recommendation. The magnitude of indirect effects was unknown, and there was uncertainty about the burden of vaccine-preventable non-bacteremic pneumonia and the difficulties of studying it.

At that time, ACIP recognized that there would be a need to reevaluate the recommendation for the routine use of PCV13 in adults ≥ 65 years of age and set the time for that as 2018. That reevaluation is going to rest on data from a number of sources, including monitoring of the impact of the new recommendation in the target population of adults ≥ 65 years old, assessing indirect vaccine effects on pneumococcal disease trends among PCV13-naïve adults 19 through 64 years of age without PCV13 indications, and updating ACIP routinely on direct and indirect effects and pneumococcal disease trends among adults leading up to discussions in 2018.

Dr. Reingold indicated that during this pneumococcal vaccine session, ACIP would hear presentations on the following:

- Pneumococcal colonization studies among children < 5 years of age and among adults ≥ 65 years old
- Changes in invasive pneumococcal disease in children, adults, and adults living with HIV
- Progress of research to inform potential policy reconsideration in 2018 for PCV13 use among adults

In conclusion, Dr. Reingold posed the following questions for ACIP's consideration:

- Is the proposed research agenda appropriate to help determine if a policy change is needed in 2018?
- What additional information will the committee need to help determine in 2018 whether continued PCV13 use in adults 65 years and older is warranted?

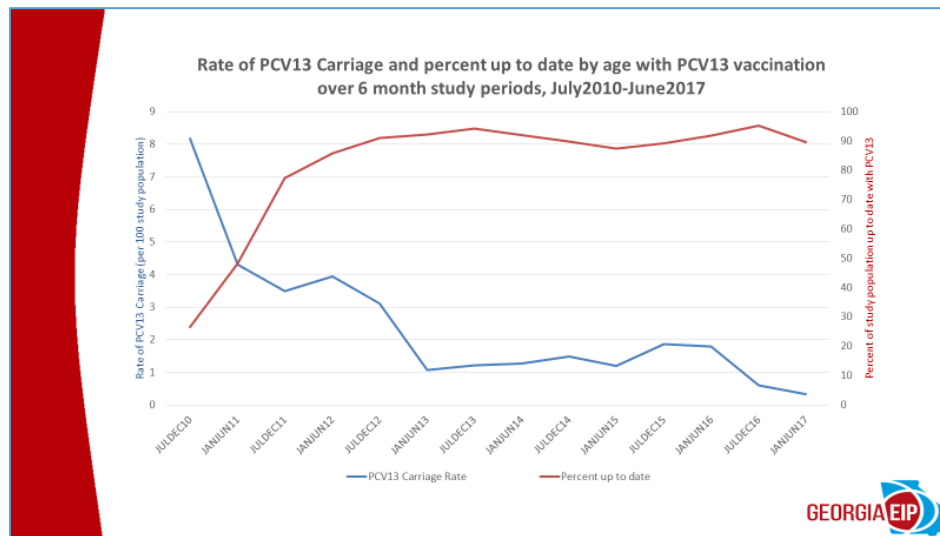
PCV13 Impact on Nasopharyngeal Carriage Among Children

Stephanie M. Thomas, MSPH
Co-Director, Georgia Emerging Infections Program (EIP)
Emory University School of Medicine

Ms. Thomas presented information on the Georgia EIP's Pediatric Pneumococcal Carriage Study. In terms of the study methods, nasopharyngeal (NP) swabs were collected from children 6 through 59 months of age presenting to the ED at a children's hospital in Atlanta, Georgia. Children presenting for any reason were eligible as long as they were deemed stable by their physician. During this presentation, Ms. Thomas discussed 2 time periods: The pre-13-valent pneumococcal conjugate vaccine (PCV13) era from January through August 2009 and the post-PCV13 era from July 2010 to June 2017. NP samples were collected on flock swabs, stored in transport media, and frozen at -80°C until processed in the Georgia EIP Laboratory. Specimens were then placed in enrichment broth for 4 hours, cultured, and identification of *Streptococcus pneumoniae* (*S. pneumoniae*) was confirmed. All lab-confirmed pneumococcal isolates were sent to the CDC *Streptococcal* laboratory where they were serotyped by the Quellung method and tested for antimicrobial susceptibilities by broth micro dilution. An interview including presenting symptoms, demographics, and potential risk factors was conducted with the parent. Vaccination history was collected from the Georgia vaccine registry. Vaccine status for PCV13 was determined using the child's age at enrollment, current ACIP vaccination recommendations, and pneumococcal vaccine history. Carriage data were compared to data collected through the Georgia EIPs Active Bacterial Core Surveillance (ABCs) for invasive pneumococcal disease (IPD), which was conducted in the same population during the same time period.

During the pre-PCV13 period, 451 children were enrolled. Of those, 31% were colonized with *S. pneumoniae* during this time period. Of the pneumococcal isolates, 22% were PCV13 serotypes, most of which were 19A (N=32; 7%). During the post-PCV13 period, 4765 children were enrolled. Of these children, 30.4% were colonized with *S. pneumoniae*. *However, there was a decline in the proportion of PCV13 serotypes.* In terms of the demographics and risk factors associated with pneumococcal carriage in the post-PCV13 period, the mean age of children who carried pneumococcus was 25 months compared to 28 months in those who did not ($P<0.001$). During the post-PCV13 period, carriage was significantly higher in children presenting with respiratory infections ($p<0.001$), otitis media ($p=0.03$), children attending daycare ($p<0.001$), children with a sibling in the household ($p=0.03$), and among children of black race ($p=0.04$). Overall, pneumococcal carriage rates were similar in children whose pneumococcal vaccine status was up-to-date (UTD) for their age for PCV13 vaccine compared to those who were not at 30% and 29%, respectively. However, children who were UTD for PCV13 had a significantly lower carriage rate of PCV13 serotypes at 1.8 cases per 100 study population compared to children who were not UTD who had a rate of 5.7. By late 2012, most children were UTD for PCV13 vaccination at more than 90%.

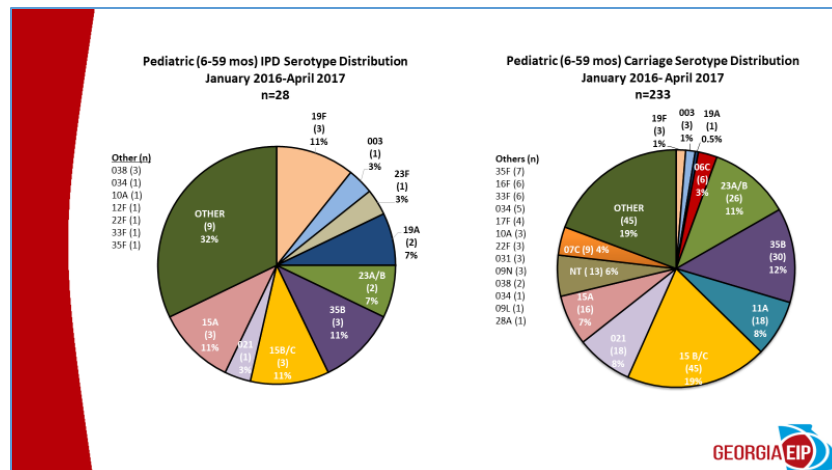
This graph shows the rate of PCV13 carriage and the percent UTD with PCV13 vaccine during the post-PCV13 period:



Shown in blue is the PCV13 carriage with rate per 100 study population on the left axis. The red line shows the proportion of children UTD with percent on the right axis. The X axis shows the time period in 6-month intervals. As shown in red, the study population had a rapid uptake of the PCV13 vaccine, with nearly 80% of children with UTD status by December 2011. The blue line demonstrates that PCV13 serotype carriage declined from 8/100 study population to less than 4 by December 2011 and was 0.33 in 2017. The graph demonstrates that a 2-fold decrease was seen in PCV13 serotype carriage by the time 50% of the children were UTD with PCV13 vaccination.

With regard to the difference in rates of pneumococcal carriage serotypes from the pre-PCV13 period compared to the post PCV13 time period, 19A decreased significantly while other PCV13 vaccine types did not. 6C also declined significantly while modest increases were seen in non-PCV13 serotypes. In terms of PCV13 serotype carriage during the post-PCV13 period by year for 2010 to 2017, the combined PCV13 rate significantly declined from 8/100 study population to 0.3/100 study population in 2017. 19A significantly declined, 3 and 19F remained relatively steady over this time period, and 6C rates also significantly declined. There is evidence of cross-protection against serotype 6C from vaccine serotype 6A in PCV13. After the initial increase in the non-PCV13 serotypes from 2010 to 2011, the rates have since remained stable. No one serotype has emerged as a dominant carriage serotype.

These pie charts show serotype distribution of pediatric invasive disease on the left compared with NP carriage in the same age group on the right for January 2016 through April 2017:



Note that IPD cases have significantly decreased to only 28 cases in this recent time period. Currently, children are carrying a broader diversity of serotypes than those causing invasive disease, as shown above. A subset of serotypes is commonly carried, but are not among those causing invasive disease. This includes 6C, 11A, 7C, and non-typeable strains.

In conclusion, overall pneumococcal carriage was stable throughout the Georgia EIP Pediatric Pneumococcal Carriage Study at 30%. Significant reductions of serotype 19A carriage occurred after introduction of PCV13. Carriage of 6C, a vaccine-related serotype, also significantly decreased. Very low-level carriage of PCV13 vaccine serotypes persists, including serotypes 19F, 3, and 19A. Carriage of the vaccine-related serotype 6C also persists. No single non-vaccine serotype has emerged as a dominant carriage serotype. IPD serotypes are generally similar to carriage serotypes with the exceptions of serotypes 11A, 7C, 6C, and non-typeable strains, which did not cause invasive disease.

Discussion Points

Dr. Reingold noted that carriage appeared to be stable in 2011 and carriage and coverage among children were stable following widescale uptake of the vaccine in children. He asked whether the data could be broken out pre- and post-introduction of the vaccine in the elderly to determine whether that has had any impact on carriage in children pre- and post-introduction of the vaccine in the elderly.

Ms. Thomas responded that they have a fair amount of data and probably could assess different time periods.

Dr. Kempe found it interesting that swabbing was being done in ED samples and wondered if any thought had been given to how the condition that children were presenting with that might affect carriage rates, and whether subgroups (by presenting complaint) have been assessed. She also asked whether there is a relationship between the sample of children being examined for carriage surveillance and those who are included in IPD surveillance.

Ms. Thomas indicated that they are examining samples from an ED in a children's hospital that acts as a tertiary care facility as well as a community ED in Atlanta, and the IPD surveillance is also conducted through Active Bacterial Core Surveillance in metropolitan Atlanta, so it is a very

similar population but not necessarily the same children. In terms of subgroups, the reason for admission is captured, so they could perform a subset analysis on different populations.

Dr. Kimberlin (AAP) asked whether the higher rate of carriage among black children has changed at all in the time since introduction of PCV13, or if the pre- and post-periods were combined.

Ms. Thomas indicated that for this analysis, the post-period was assessed for the entire timeframe from 2010 through 2017. They would be able to break this down into smaller time periods.

Dr. Stephens inquired as to whether density was assessed in terms of amount of organisms carried, which is an area of some interest now in terms of colonization.

Ms. Thomas responded that they did not assess density.

PCV13 Impact on Nasopharyngeal Carriage Among Adults

Fernanda Lessa, MD, MPH
Respiratory Diseases Branch
Division of Bacterial Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Lessa presented preliminary findings from the US Adult Pneumococcal Colonization Study. Although most times there is only asymptomatic colonization of pneumococcus in the upper respiratory tracts, colonization can lead to invasive and non-invasive pneumococcal disease. Pneumococcal colonization in US adults 65 years of age and older is not well-studied. A study conducted among HIV-infected adults from 2005 through 2007 found only 3.4% pneumococcal carriage¹, while another study in Native Americans among household members of children under 9 years of age found a pneumococcal carriage rate of 9.3% in adults 40 years of age and older². However, only 7 study participants were older than 65 years of age in that study. In the UK, a pneumococcal carriage survey among 599 adults aged 65 and older prior to PCV13 introduction into the infant immunization schedule found a 2.2% pneumococcal carriage³. It has been documented that pneumococcal conjugate vaccine decreased vaccine type (VT)-carriage and not pneumococcal colonization. In a study in Kenya, vaccination of children with PCV10 led to a decline in vaccine-type carriage from 33% to 14% in HIV-infected parents 18 months after vaccine introduction while pneumococcal carriage rate remained stable at 35%⁴ [Onwubiko. JCM 2008; ²Scott JR JID 2012; ³Hamaluba Medicine (Baltimore) 2015; ⁴Kim. L. 2016 ISPPD poster].

The initial study objectives for the US Adult Pneumococcal Colonization Study were to: 1) Conduct cross-sectional study of NP and oropharyngeal (OP) pneumococcal carriage to describe serotype distribution among adults 65 years of age and older in the US; 2) assess the risk factors for pneumococcal colonization; and 3) provide baseline carriage data prior to widespread PCV13 vaccination among older adults to assess the new vaccine recommendations. These objectives changed somewhat during the course of the study when the investigators began to perform some preliminary data analyses. The ABCs EIP infrastructure was used to conduct this study in four states: Georgia, Maryland, New York, and Tennessee. All four of these sites had clinical research units or databases with individuals in the target age groups. Sites also enrolled participants from senior residential communities,

senior day centers, and geriatric outpatient clinics. Enrollment began mostly in the summer of 2015 and ended at the end of 2016.

Participants were screened for eligibility using a standardized screening form and consented for participation. Participants were then asked a series of questions including history of recent illness, chronic conditions, and recent exposure to antimicrobials or healthcare settings. A series of questions also was asked about vaccination and health care exposures to help identify where an individual might have received vaccines since August 2014. Both an NP and OP specimen were collected and placed in two separate vials of skim milk tryptone, glucose, glycerol (STGG) media. After enrollment, study teams then followed up with providers indicated by the participant in the questionnaire to document vaccine history. No verbal reports of vaccine from participants were considered. Participants were included in the study if they were 65 years and older at the time of specimen collection, not severely immunocompromised based on 2012 PCV13 recommendations, agreed to participate in the study, and had both NP and OP specimens collected. Participants from nursing homes were excluded.

Two sample sizes were calculated. Initially assumed were a 2% baseline colonization rate with VT serotypes and a 50% reduction in those VT serotypes after PCV introduction to 1% VT colonization with a 65% vaccination coverage at follow-up survey. This resulted in a total sample size of 2970. However, the sample size had to be adjusted mid-study based on preliminary findings indicating very high vaccination coverage and low VT carriage. With the goal of assessing pneumococcal carriage and VT serotype, a point estimate of 0.5% was used for VT-carriage and upper/lower bound of +/-0.25%, resulting in a sample size of 3049.

Both culture and molecular methods were used for detection of pneumococcus. NP and OP specimens were processed separately. Pneumococci were identified by susceptibility to optochin and bile solubility. Pneumococcal isolates were serotyped by conventional Quellung. Antimicrobial susceptibility testing was also performed, though not presented during this session. For molecular detection, NP specimens were determined poor quality if no ribonuclease P (RNase P) gene was detected and those people were excluded from analysis. Pneumococci were identified by detection of the *N*-acetylmuramoyl-L-alanine amidase (*lytA*) gene by polymerase chain reaction (PCR) and multiplex-PCR for serotype identification was done for specimens that were *lytA* positive. Based on the paper published in *PeerJ*, molecular testing was not included for OP specimens based on concerns that other streptococci confound the serotype specific PCR assay. This confounding issue was primarily an issue with OP specimens [Carvalho MG, Pimenta FC, Moura I, Roundtree A, Gertz RE Jr, Li Z, Jagero G, Bigogo G, Junghae M, Conklin L, Feikin DR, Breiman RF, Whitney CG, Beall BW. Non-pneumococcal mitis-group streptococci confound detection of pneumococcal capsular serotype-specific loci in upper respiratory tract. *Peer J* 2013; 1:e97; PMID:23825797; <http://dx.doi.org/10.7717/peerj.97>].

A total of 3008 participants were enrolled in the study meeting 98.7% of the target enrollment. Georgia was the largest catchment area, so they had a larger enrollment target:

Study Site	Adults 65+ Enrolled
Georgia	1,119
Maryland	549
New York	769
Tennessee	571
Overall	3,008

Compared to the 2015 American Community Survey (ACS) from the US Census Bureau, the median age of the study population (74 years) and the percentage with health insurance (99.3%) was similar to the US population. However, a higher percentage of African Americans (23.8%) and females (64.3%) were enrolled. Most people reported living alone or with one other person, with a range of 1 to 10 persons per household. Participants were asked about whether young children lived in the household with the participant, but very few people reported any children. Approximately 7% of participants reported smoking, which is consistent with what CDC reports for this age group (~8%). About 40% of individuals reported having at least one of these chronic conditions: asthma, cardiovascular disease (CVD), stroke, diabetes, chronic obstructive pulmonary disease (COPD), and heart failure. CVD (19.4%) and diabetes (21%) were the most common. Among individuals 65 years of age and older, those enrolled seem to be pretty healthy. Participants were asked whether they had pneumonia and influenza in the 1 month prior to enrollment, and less than 1% reported either. Approximately 4% of individuals reported taking any antibiotic in the prior 2 weeks, 30% reported a runny nose, and 1.4% reported a fever.

Of participants with known vaccination histories, almost half had already received PCV13 at the time of enrollment. The study teams did a great job of following up on vaccination histories, and only 5.6% of those enrolled had an unknown vaccination status. Maryland participants had the highest vaccine coverage at 54.7%, while Georgia had the lowest at 41.9%. The pneumococcal polysaccharide vaccine (PPSV) vaccination rate is likely underestimated, because sites were not required to look back very far in medical records. Some sites did record PPSV from the late 1990s, but only if it was available. All sites were required to review back to August 2014, but some reviewed records prior to that.

Of the 3008 participants enrolled, 24 were excluded from laboratory analyses due to poor specimen quality. Among the remaining 2984 participants, 45 (1.5%) were culture-positive for pneumococcus. Of the 2939 participants without pneumococcus isolated, 10 were positive for the pneumococcal *lytA* gene, resulting on an overall pneumococcal colonization prevalence of 1.8%. Among the culture-positive cases, 7 were PCV13-type. None of the PCR-positive cases were VT, resulting in a VT-carriage prevalence of 0.2%. Among the 7 adults with VT pneumococcal carriage, the serotypes isolated were 3, 19A, and 19F. This is also the most common serotypes causing IPD disease in adults aged over 65 years from ABCs. Among non-vaccine types, 11A was the most common followed by 23A, 23B, and 33F/33A/37. Pneumococcal carriage rates did not differ by vaccination status. Among vaccinated individuals, pneumococcal colonization was 1.8% compared to 1.6% among non-vaccinated. Vaccine-type carriage was also similar among vaccinated and non-vaccinated participants.

In summary, the overall pneumococcal carriage prevalence was 1.8% in US adults 65 years of age and older. This prevalence is similar to what the UK observed in the same age groups after PCV7 introduction and before PCV13 introduction in persons 65 and older. PCV13-type pneumococcal carriage was 0.2% in the US Adult Pneumococcal Colonization Study. In the UK, five years after routine PCV7 use and prior to PCV13 introduction, PCV13-type carriage in persons aged 65 and older was 0.5%.

In conclusion, carriage of pneumococcus is rare in US adults 65 years of age and older who are not institutionalized in nursing homes. PCV13 serotypes account for only 13% of those with pneumococcus detected. Both vaccinated and unvaccinated individuals in the US Adult Pneumococcal Colonization Study had a less than half a percent VT carriage. Many years of PCV vaccination of children may have led to herd effects in adults. However, given the low VT-

carriage rates observed in an already high PCV13 adult coverage environment, it is very difficult to attribute these findings to the direct versus indirect effect of PCV13 on adult carriage.

Discussion Points

Dr. Reingold noted that Dr. Lessa did not show any data about what proportion of these free-living elderly have contact with young children, and wondered what was known about what proportion of elderly in the country have regular contact with young children.

Dr. Lessa replied that they simply asked the question about children in the household.

Dr. Hunter recalled that the rate of smokers was 6.8%, which seemed low.

Dr. Bennett replied that this was about the rate in the community surveys for older people, and is much higher for younger people.

Dr. Lessa added that the CDC data show about 8% for this age group.

Dr. Duchin (NACCHO) inquired about Dr. Lessa's thoughts on the implications of the carriage studies on invasive disease incidence in adults. The cross-sectional studies tell something about the prevalence of carriage strains, but it is not clear that those are the ones that are most responsible for IPD. It may be the recent acquisition of a new strain that is more related to the development of IPD. Seasonality might have something to do with carriage as well, and he wondered whether that was accounted for in the study.

Dr. Lessa responded that the three serotypes found in the carriage studies (3, 19A, and 19F) are also the most common found in IPD based on the ABCs data. The carriage rates are so low, it will be very difficult to assess seasonality.

Dr. Bennett added that Ann Falsey is conducting an ongoing study in which she is examining carriage over time. They are resampling people over the course of a couple of years. Her carriage rates per person are considerably higher because they are assessing it over time.

Dr. Whitney (SME) added that if they think of serotypes as people being exposed to them and then having them for some time, this suggested to her that older adults are not being exposed to the vaccine types very much relative to the other types.

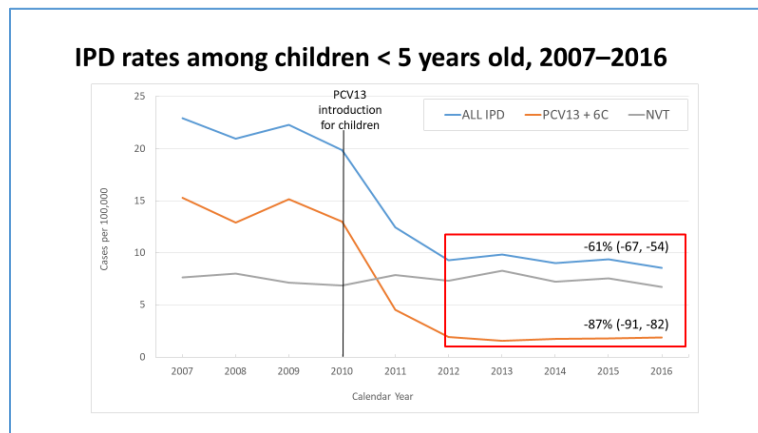
PCV13 Impact Invasive Pneumococcal Disease From Active Bacterial Core Surveillance (ABCs)

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

Dr. Matanock presented on IPD in the US. Recalling the timeline for PCV13 introduction in the US, she indicated that the aim of examining the ABCs data was to evaluate the impact of PCV13 on IPD in the general population of children and adults and among adults living with HIV. IPD cases were identified, defined as isolation of pneumococcus from a normally sterile site, through the ABCs, a laboratory and population-based surveillance system ongoing at 10 sites. The US Census was used for total population numbers. CDC's HIV surveillance, which

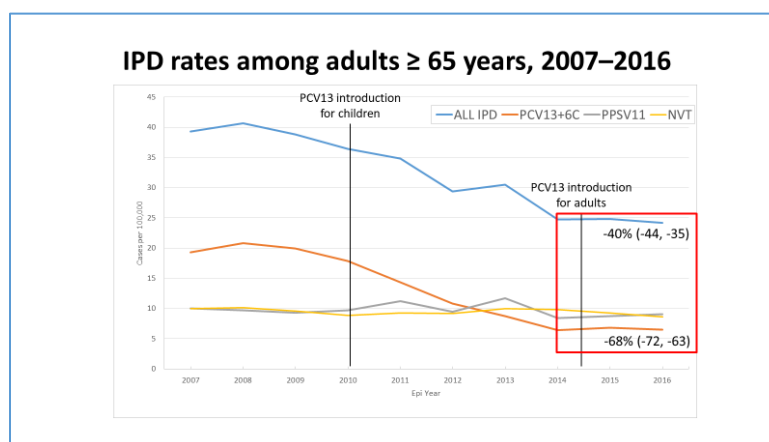
was implemented nationwide by 2008, was used for HIV population numbers. Isolates were serotyped by Quellung or PCR at reference laboratories and were grouped as PCV13 serotypes, which included 6C because of observed cross-protection; PPSV11, the additional unique serotypes in PPSV23; and all additional serotypes together as non-vaccine types (NVT). For this analysis, overall and serotype-specific IPD incidence were compared pre-and post-pediatric PCV13 introduction. Slightly different time frames were used for the analysis looking at IPD among adults with HIV, because the CDC HIV surveillance data are only available for 2008 through 2014. From the incidence, the percent reduction in disease incidence was calculated.

Pictured here are IPD rates among children less than 5 years old:



Comparing pre-PCV13 rates to post-PCV13 2016 rates, there is a 61% reduction in all IPD and an 87% reduction in PCV13-serotypes. This percent change was first noted in 2012 and has stayed relatively stable since that time. Looking just at PCV13 serotypes, which again included 6C, the largest declines have been in 19A followed by 7F.

Pictured here are IPD rates among adults 65 years and older:



Comparing before and after pediatric PCV13 introduction, there has been a 40% reduction in all IPD and a 68% reduction in PCV13-serotypes. Annual rates plateaued prior to the recommendation for PCV13 among adults 65 years and older. In the unique PPSV23 serotype

group, PPSV11, the grey line, there has been no significant change over this time period. Again, looking at PCV13 serotypes, the largest reductions were in 19A followed by 7F in adults 65 years of age and older. The burden of serotype 3 remained relatively stable over this timeframe.

These two tables show the rank order of non-PCV13 serotypes causing IPD among children and older adults in 2015-2016. Those highlighted in green are common to both age groups. Additionally, there is no one or even a set of a few non-PCV13 serotypes causing the majority of non-PCV13 serotype IPD:

**Rank order of non-PCV13 serotypes causing IPD,
2015-2016**

Children < 5 years		Adults ≥ 65 years	
TYPE	Cases/100,000	TYPE	Cases/100,000
23B	0.62	22F	2.57
22F	0.62	23A	1.33
33F	0.57	35B	1.31
15C	0.52	15A	1.16
15A	0.48	33F	0.97
35B	0.43	16F	0.88
10A	0.33	11A	0.82
12F	0.29	9N	0.72
15B	0.29	23B	0.67
3B	0.19	12F	0.61
other	1.67	other	4.66

Green denotes serotypes common to both age groups

In terms of pneumococcal meningitis incidence, one concern that has been raised is that perhaps there are less blood cultures obtained because of changes in clinical practice. Because it was thought that meningitis might be less sensitive to changes in culturing practice, it was assessed separately. The same reductions in PCV13 type and over all pneumococcal meningitis were observed as in overall IPD.

Regarding the characteristics of IPD among adults with HIV, in general, IPD cases with HIV were more likely to be younger, male, and of black race. IPD case fatality, defined as the proportion of IPD cases who died from IPD, were higher in older age groups, but the proportions were similar between those with and without HIV.

At baseline, defined as the 2008-2009 time-period for this analysis, the IPD incidence rate among adults with HIV was 299 per 100,000. In the years that followed, there was a significant reduction in the overall IPD rates by 27% in 2011-2012 and by 36% in 2013-2014. Despite reductions in overall IPD, adults with HIV had an 18 times higher risk for IPD than adults without HIV.

In terms of the reductions seen in overall IPD among adults with HIV, there was a 43% reduction in PCV13 IPD in 2011-2012, the period in which there were only indirect effects from the pediatric vaccine. After the October 2012 recommendation for PCV13 among adults with HIV, a 61% reduction in disease was observed. However, even with these reductions among adults with HIV, the risk of PCV13 type IPD still remained 18-fold higher. As in the general older adult population, no statistically significant changes were observed in unique PPSV23 serotypes over the time period of this study among adults with HIV.

In summary, there have been significant reductions in overall and PCV13 serotype IPD among children and adults since PCV13 was introduced in the US. These reductions have been driven primarily by decreases in 19A and 7F. Annual rates have plateaued in the past two years. No further reductions were observed in PCV13 serotype IPD among adults 65 years and older after the 2014 recommendations for PCV13 in this age group. Despite reductions, IPD rates, including PCV13 serotype rates, remain higher in adults with HIV compared to those without HIV. A better understanding of PCV13 coverage is needed to assess direct effects of PCV13 vaccination in adults with HIV. There have been relatively small changes in some non-PCV13 serotypes; however, there have been no large increases in any one non-PCV13 serotype among children or adults, including those with HIV. Similar trends are observed for pneumococcal meningitis as seen in overall IPD.

In conclusion, in the 6 years since PCV13 was first introduced, there have been sustained benefits in overall IPD and IPD caused by the PCV13 serotypes in children and adults. No evidence of serotype replacement has been observed. However, monitoring for changes in disease and serotype distribution continues in order to inform new vaccine policy.

Discussion Points

Dr. Reingold requested a reminder regarding what is known currently about PCV13 coverage among the elderly.

Dr. Matanock replied that coverage is between 30% to 50% among older adults. Coverage is not known for HIV+ adults, but is suspected to be lower because PCV13 coverage is known to be lower overall among those 19 through 64 years of age who have an indication.

Dr. Stephens asked whether Dr. Matanock could comment on serotype 3, which is persistent, and any issues regarding that particularly serotype and PCV13.

Dr. Whitney (SME) responded that these findings are consistent with what others are observing in that the benefits of PCV13 against this serotype are not showing through very clearly.

Regarding colonization and black race, Dr. Kimberlin (AAP) observed that for some of the graphics for adults, there was a correlation with black race and IPD. He asked whether they were exploring differences in outcomes and likelihood of invasive disease by race among children.

Dr. Matanock indicated that this is an analysis that is planned in younger and older age groups looking not only at race, but also SES.

Dr. Reingold added that the early studies show a marked decrease in racial disparities with the introduction of PCV.

Dr. Kimberlin (AAP) noted that he just wanted to make sure that this is being maintained, correlates with number of doses of PCV13, et cetera.

Dr. Ezeanolue asked whether there is a biologically plausible reason that blacks have a different outcome, or if it is primarily associated with SES. He wondered if SES data are being collected.

Dr. Bennett responded that this is a question many people are trying to tackle in terms of trying to parse out the impact of SES (housing, poverty, et cetera) versus what the other characteristics might be. SES is being collected by EIP and examined closely. She offered to share those data offline.

Observing that the changes in IPD incidence in adults with HIV and changes in IPD among adults over 65 years of age both declined through 2014, Dr. Lee inquired about the vaccination rates amongst adults infected with HIV in the 2012-2014 period and whether it is possible to determine how much is actually due to direct effects versus population-level effects.

Dr. Matanock indicated that there are some estimates of coverage in adults 19 through 64 years of age with immunocompromised conditions in the period ending in 2014 of about 5%, but this is likely not uniform amongst all of the immunocompromised conditions. There is good reason to believe that this may differ amongst adults with HIV who are of that age. It is known that the immunization rates are much higher for adults 65 years of age and older, which Dr. Pilishvili would further discuss in the next presentation.

Dr. Lee said it was hard for her to say that there was any evidence of direct effect in the post-2014 era.

Progress of the Research Agenda to Inform Potential Policy Change in 2018 for PCV13 Use Among Adults

Dr. Tamara Pilishvili
Respiratory Diseases Branch
National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Pilishvili reminded everyone that the WG thought that in order to have enough evidence to make a determination on the utility of the use of PCV13 in the elderly population, the following questions needed to be answered before the 2018 review:

- Is PCV13 use among adults ≥ 65 years old preventing disease?
- To what extent are the observed benefits driven by adult PCV13 use (direct effects) versus pediatric PCV13 use (indirect effects)?
- What benefits would be expected from continued PCV13 use among adults?

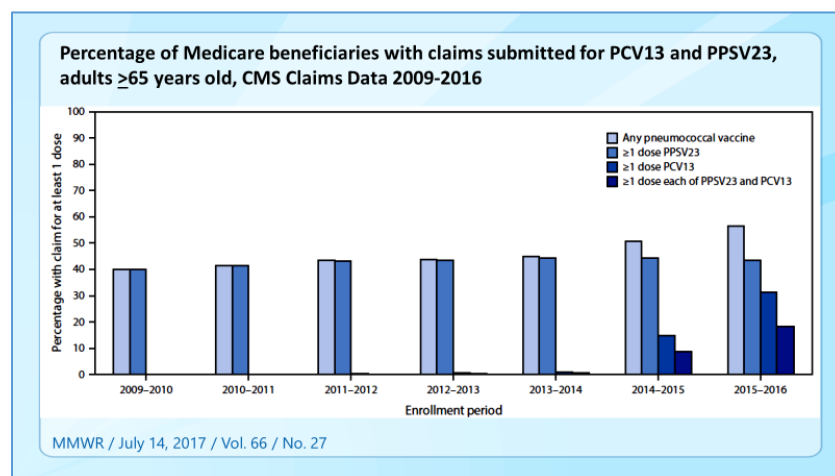
In terms of changes in PCV13-type IPD burden among adults ≥ 65 years old, PCV13-type IPD rates declined through 2014 due to indirect PCV13 effects. No additional declines in annual rates were observed in annual rates from 2015-2016. PCV13-types declined to 22% of IPD in 2016 compared to 43% pre-PCV13. Regarding changes in IPD among adults < 65 years old with and without indications for PCV13 use, PCV13-type IPD burden continues to decline among adults with and without current indications for PCV13 use. The largest disease burden for the PCV13 serotypes was due to three serotypes: 3, 7F, and 19A. The vaccine has been very effective in reducing 19A and 7F through indirect effects, with no direct or indirect impact observed on serotype 3. As noted earlier, this is consistent with other settings and was not surprising based on immunogenicity data pre-licensure and from post-licensure studies that assess effectiveness specifically against serotype 3. To continue to try to understand the direct and indirect effects, there is continuous monitoring of the impact of the vaccine on disease in

age groups (those younger than 65 years of age) currently not recommended for the vaccine among. The reductions are similar and comparable among adults with and without indications for this vaccine.

Carriage is a precursor for diseases and offers a good snapshot in time and understanding of the strains that are circulating in the population. As pointed out earlier, there is greater diversity in carriage serotypes than in IPV serotypes in terms of the impact of the vaccine observed in children and adults. What is seen with disease and carriage is very similar, so the same serotypes that declined in carriage are the same ones that decline in IPD and the same serotypes that still persist post-PCV13 in carriage are the ones seen in IPD as well. Regarding the impact on NP colonization changes among children <5 years old, there has been a significant reduction in PCV13-type carriage rates, mostly due to 19A and 6C. There has been no change in overall pneumococcal carriage rates. PCV13-types remaining in 2015-16 include 19A, 19F, and 3. Carriage among adults >65 years old are very low overall, making it difficult to tease apart among vaccinated and unvaccinated.

Monitoring vaccine uptake of PCV13 and PPSV23 in the target population of adults ≥ 65 years old is important in order to understand how much of this impact can be attributed to the direct versus indirect effects. Two data sources are currently used to monitor coverage of PCV13 and PPSV23. CDC has an ongoing collaboration with CMS for PCV13 and PPSV23 claims to estimate uptake among Medicare part B beneficiaries. Analysis of vaccine sales and IMS claims are used to estimate PCV13 coverage^{1,2} [¹QuintilesIMS, Anonymized Patient-Level Data (APLD), Oct 2016 (includes diagnostic and prescription utilization claims for PCV13); ²Pfizer, Inc. internal sales data for PCV13, Oct 2016].

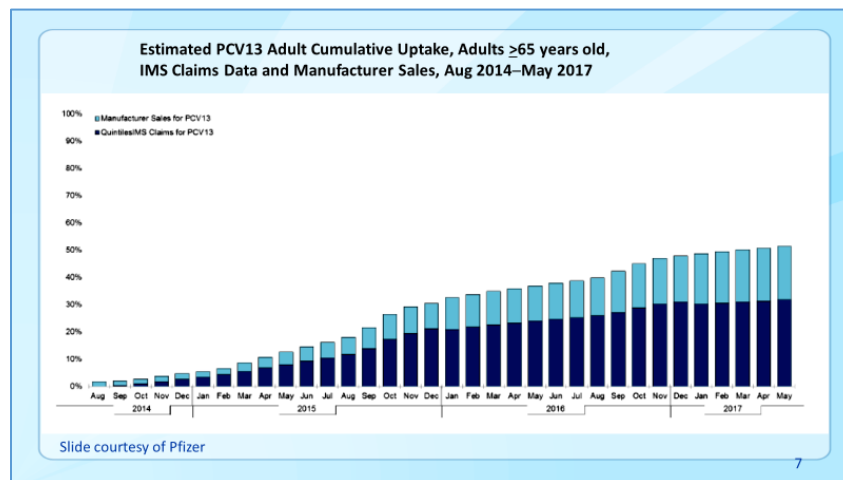
This graphic depicts the first method to determine the percentage of Medicare beneficiaries with claims submitted for PCV13 and PPSV23 among adults ≥ 65 years old from CMS claims data for 2009-2016:



In late 2014, ACIP voted to recommended PCV13 for adults, but CMS did not change their regulations until January 2015 such that the two vaccines in series were covered. This resulted in uptake beginning to increase in 2015. This analysis observed that for a single dose of PCV13 receipt, the coverage through September 2016 increased to 31.5%. This is any PCV dose regardless of polysaccharide receipt. For any polysaccharide receipt regardless of PCV receipt, coverage increased to 43.2%. For both PCV13 and PPSV23 received in a series, coverage increased to 18.3% during the same period. The light blue bar represents any pneumococcal

vaccine receipt, which was 56.4% in this population. This is somewhat lower than what is being reported through NHIS, in which the latest report for any coverage with pneumococcal vaccine was approximately 64%. But it is important to note that the analysis reflected in this graph covers only Part B beneficiaries.

This graphic depicts estimated PCV13 adult cumulative uptake among adults ≥ 65 years of age from the second data source, IMS claims data and manufacturer sales from August 2014 through May 2017:



Complex modeling was performed to estimate the uptake of the vaccine among adults 65 years of age and older based on IMS claims data and manufacturer sales. Based on the claims only, the dark blue portion, uptake was 31.7% through May 2017. If sales data are incorporated, coverage was 51.4%. Thus, sizeable uptake of the vaccine is being observed in the adult population 65 years of age and older.

In terms of what is upcoming, Dr. Pilishvili emphasized that the research agenda is not completed and there are ongoing studies. Two parallel studies focus on vaccine effectiveness (VE) among adults ≥ 65 years old against vaccine type (VT) IPD, for which two case-control evaluations are being performed. The first uses population-based non-IPD controls, utilizing IPD cases identified through ABCs. Vaccination histories are being updated through primary care providers in order to measure VE. The second is a study of Medicare Part B beneficiaries through a collaboration with CMS in which ABCs surveillance data are being linked with Medicare Part B beneficiaries, including an update of medical histories through the CMS database. These two studies are sample size-driven, so the investigators are waiting for a sufficient number of VT cases. The number of cases should be sufficient after another winter of enrollment.

Though they have been discussing IPD only, the recommendation in 2014 relied heavily on the burden of pneumonia. Therefore, it is important to examine the impact of PCV13 vaccine on community-acquired pneumonia (CAP). There are ongoing studies for which the WG hopes to present data during upcoming ACIP meetings. These studies examine different outcomes for pneumonia. One examines administrative data ICD-codes for all-cause CAP. Another is examining the impact on pneumococcal pneumonia looking at pneumococcal-positive urinary antigen test (UAT) using BinaxNOW[®] (Binax). There also are industry-led studies focused on assessing VT pneumococcal pneumonia through serotype-specific urinary antigen detection

(UAD), which examine the impact and effectiveness of pneumococcal vaccine against VT pneumococcal pneumonia.

To bring this all together to try to make sense of these various post-licensure studies, CDC will use a model to try to estimate the public health impact and cost-effectiveness of various policy options going forward. One of the policy options would be to maintain the observed impact of PCV use in children, with no age-based recommendation among adults 65 years of age and older. Another would be to model the results if the indications were expanded for adults less than 65 years of age to include those with chronic comorbid conditions, which are currently utilizing only PPSV. As seen with previous studies on IPD, no impact has been observed on PPSV unique serotypes over the same time period.

Discussion Points

Dr. Bennett said she thought this was a study in “looking for a needle in a haystack.” She commended the pneumococcal group for conducting these very difficult and important studies, which is also testimony to the value of ACIP for doing this. It would have been easy in 2014 to make a recommendation for those over 65 years of age because it makes sense and not do anything further. Instead, they have taken a long, hard look at impact.

Dr. Hunter inquired as to whether there would be enough time from the introduction of the pneumococcal conjugate vaccine for people over 65 years of age until a decision needs to be made in 2018 to see an effect on pneumococcal pneumonia and IPD.

Dr. Pilishvili replied that what is being observed currently in terms of the plateau of disease is very different from what was expected, but she thinks this has to do with the serotype composition and the remaining disease burden, at least for invasive disease. In terms of whether the number of years are sufficient to assess the impact, the number of cases being observed in some of the ongoing modeling studies, another winter’s worth of data is anticipated to provide a sufficient number of data points to say with confidence whether there is an impact.

To put this into some context, Dr. Bennett noted that 22% of disease is still caused by these serotypes and there is a vaccine rate of less than 40%.

Dr. Kempe noted that the first study (case-control VE among adults ≥ 65 years old) would offer some insight into the effectiveness of the vaccine versus carriage, because it will be known whether subjects were vaccinated or not.

Dr. Pilishvili confirmed this, noting that this study examines individual level effectiveness unlike the studies looking at the population-level in which vaccinated versus unvaccinated cannot be teased apart.

Dr. Walter asked whether there are any data from geographic regions where ABCs surveillance is conducted.

Dr. Pilishvili indicated that the CMS data she presented are national. The same *MMWR* where these data were published presents these estimates by state. The other analyses were conducted looking specifically at ABCs areas. There is some variation across the sites in terms of coverage.

Dr. Lessa added that the South has lower coverage than the North. The carriage survey showed the same, with Maryland and New York having higher coverage than Georgia and Tennessee.

Dr. Messonnier requested that for the upcoming ACIP meeting, vaccine safety data be reviewed for ACIP in a concerted fashion. Perhaps the framework that the EBRWG is developing might be beneficial in this case, because there may be difficulty in turning all of this evidence into a decision.

Dr. Bresnitz (Merck) pointed out that Merck has also used IMS claims to assess the issue of whether individuals have received both doses of the vaccine subsequent to the policy recommendation, and they are finding the same level of completion. He asked whether Dr. Pilishvili could comment on to what extent not getting PPSV23 is potentially a function of the individual not being eligible to receive it because they might have gotten it less than 5 years before they got PCV13. That would impact the percentage of who would be eligible, and the percentages being recorded.

Dr. Pilishvili said she did not think that the analysis for coverage for both doses presented during this session addressed this, because some people would not have been eligible to receive PPSV23 or might already have received a previous dose of PPSV23 and because of that had not yet received PCV13. This way of looking at the cohorts is probably not appropriate to assess to what degree receiving one impacts receipt of the other one. They will have the ability to examine this with other analyses being conducted.

Anthrax Vaccine

Introduction

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

Dr. Stephens reminded everyone that the Anthrax Vaccine WG has been reconstituted. The WG's terms of reference are to review new data on anthrax adsorbed vaccine (AVA) including the following:

- New safety studies
- Immunogenicity, reactogenicity and logistical considerations for administering AVA via the subcutaneous versus the intramuscular route for administration as PEP
- AVA plus CPG 7909 adjuvant data for use as PEP
- Efficacy and immunogenicity data on dose-sparing strategies for PEP during a mass casualty incident when AVA is a limited resource
- Data on reduced booster schedule for pre-exposure prophylaxis
- Advice on the use of AVA and antitoxin for PEP when no effective antimicrobials are available or there is an absolute contraindication

The WG reviewed data on the first two terms of reference, with WG discussions to be presented during this session on the following topics:

- Preparedness/operational concerns during an anthrax mass casualty event
- New safety data regarding AEs to intramuscular (IM) versus subcutaneous (SC) routes of administration
- Data on immunogenicity for IM versus SC route of administration

Preparedness/Operational Concerns

William Bower, MD, FIDSA

**National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention**

Dr. Bower emphasized that anthrax vaccine is different from most vaccines discussed by ACIP, as it is not part of the routine vaccine schedule. One of the licensed indications is for pre-exposure prophylaxis (PrEP) in certain groups who are at risk for exposure to *Bacillus anthracis* (*B. anthracis*). However, the PrEP indication is for very few groups of individuals. CDC's questions for ACIP mainly concern the use of anthrax vaccine as PEP following an intentional release of aerosolized spores. In this presentation, Dr. Bower discussed some of the operational concerns related to administering anthrax vaccine during a large anthrax event to help ACIP understand why these questions are being asked.

The main focus of this presentation pertained to operational concerns for providing post-exposure prophylaxis during a large anthrax event. But first, Dr. Bower provided some background on anthrax vaccine. This vaccine is quite old and has a long history. It was first developed at Ft. Detrick in the 1950s, and in the 1970s was licensed and manufactured by the Michigan Department of Health and Human Resources (MDHHR) for use in individuals at high risk of exposure to anthrax. Today the vaccine is known as AVA and is manufactured by Emergent Biosolutions under the tradename BioThrax[®]. The final product is a sterile, cell-free filtrate made from an avirulent strain of *B. anthracis* and contains aluminum and two preservatives. The primary immunogen is protective antigen released during the growth period. The vaccine contains no live or dead bacteria.

As a reminder, there were several changes in approved indications since ACIP published anthrax vaccine recommendations in 2010. In 2008, the route of administration was changed from SC to IM for PrEP and the priming dose at week 2 was eliminated. In 2012, the priming series was change to 0-, 1-, and 6-month injections as data indicated protection was achieved at 6 months. AVA was first approved in the European Union (EU) in 2013 as a 3-dose priming series with a booster dose every 3 years. AVA was given a PEP indication in 2015. Other important updates include additional safety studies and new data from studies used for the PEP indication and a planned Biologics License Application (BLA) for AVA plus a new adjuvant CPG 7909. Also, studies were conducted to support dose-sparing strategies if vaccine needs exceed supplies.

To summarize, here are the current AVA PrEP and PEP licensed indications for adults 18 through 65 years of age:

- PrEP:
 - IM route
 - 3-dose priming series at 0, 1 and 6 months
 - Booster doses at 12 and 18 months, then annually

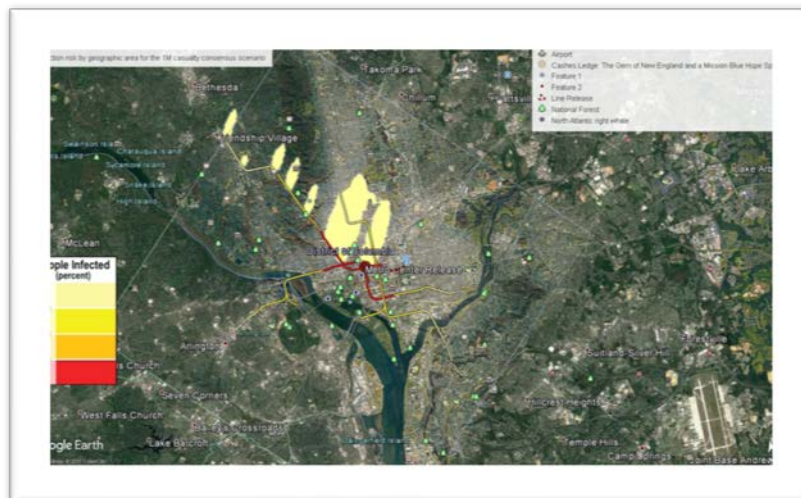
- ❑ PEP:
 - SC route
 - 3-dose series at 0, 2 and 4 weeks
 - Co-administration of antibiotics for 60 days

To set the stage for AVA use in a large anthrax event, Dr. Bower briefly discussed anthrax as a bioweapon. *B. anthracis* spores are considered one of the most likely bioweapons because they are relatively easy and cheap to produce, can be produced and stored in large amounts, are easy to disseminate covertly and, once disseminated, can remain a potential exposure risk for a long time. Anthrax has been used as a bioweapon and is also known to cause widespread illness and death in unprotected populations. This picture illustrates the plume that resulted from an accidental release of spores from a Soviet bioweapons facility in 1979:



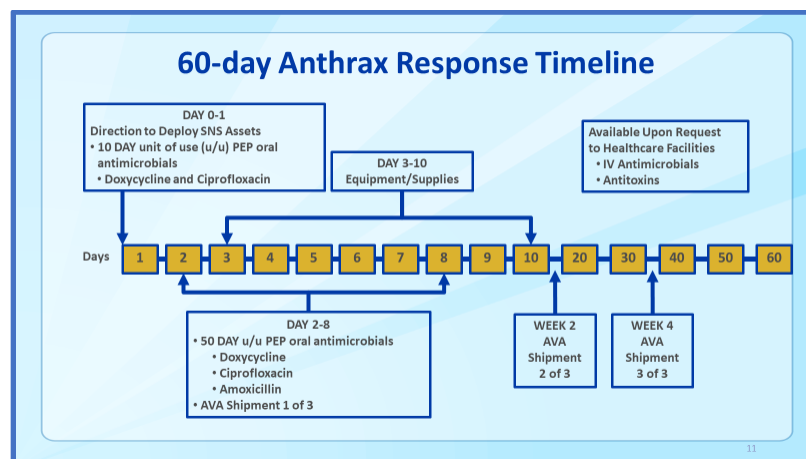
This incident resulted in at least 79 cases of anthrax with 68 deaths. More recently in 2001, there was an incident in the US where spores were sent through the US Mail. Direct exposure to letters and presumably to items that were cross-contaminated by letters resulted in 22 cases of anthrax and 5 deaths.

The US government preparedness plans include scenarios where a wide-area outdoor aerosol release in a densely populated area could expose millions to *B. anthracis* spores. This map depicts a hypothetical wide area release generated by an aerosolizing device on a DC Metro train:



In this hypothetical scenario, thousands of people would be exposed initially in the train stations, but when the train emerges to travel above ground, winds would carry the spores over densely populated areas exposing hundreds of thousands.

In terms of the US government's planned response for a large anthrax event, the federal government, through CDC's Strategic National Stockpile (SNS), will respond to a release of *B. anthracis* spores by deploying antimicrobials, antitoxins, vaccine, and other medical countermeasures. The current plan is to provide 60 days of oral antimicrobial drugs in conjunction with a 3-dose course of anthrax vaccine to those potentially exposed to aerosolized spores. For this PEP plan to be most effective, the prophylaxis should be administered as soon as possible. This graphic depicts the 60-day anthrax response timeline:



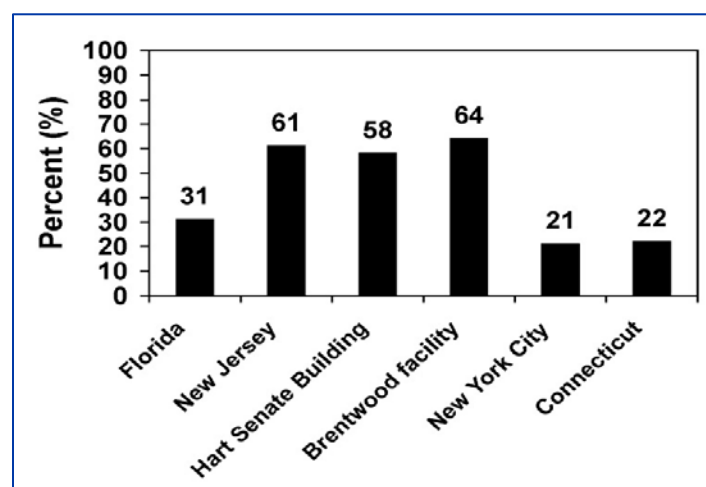
Immediately following the federal decision to deploy medical countermeasures from the SNS, CDC will begin delivery of 10-day supplies of oral ciprofloxacin and doxycycline for the potentially exposed populations. The goal is to dispense the PEP oral antimicrobial within 48 hours of the decision to deploy SNS assets. The deployment process for the 50-day supply and ancillary supplies begins immediately following shipment of the initial 10-day supply. The 50-day oral antimicrobial supplies will arrive no more than 8 days after the federal decision to deploy. The first dose of AVA will be shipped along with the 50-day supply of oral antimicrobials and administered when the 50-day supply of oral antimicrobials is dispensed. The second and third doses of AVA will be shipped separately and administered 2 and 4 weeks after the first dose. IV antimicrobials and antitoxin will also be available upon request by healthcare facilities.

There are some operational concerns related to a large anthrax event that prompted CDC to ask ACIP for advice on route of administration. As a reminder, AVA for PEP is currently licensed for administration only by the SC route. SC vaccinations are usually given with 5/8-inch needles, while IM vaccinations are given with either 1 or 1-½ inch needles. In a large event, CDC's supplies of 5/8-inch needles might be insufficient to administer vaccine by the SC route. The manufacturer supply chain does not have sufficient 5/8" needles either, so there also may not be enough available from commercial suppliers in the short-term to fulfill the needs either. CDC also stockpiles 1-inch needles for IM vaccine administration. In a large event, needle supplies may only be met through use of both 5/8-inch and 1-inch needles.

NuThrax[®] is the next generation human anthrax vaccine, which is currently in phase 2 trials. NuThrax[®] is expected to be licensed for IM administration only. CDC's SNS will start transitioning to NuThrax[®] in 2018 for use under an Emergency Use Authorization (EUA) while the company seeks licensure. During transition from AVA to NuThrax[®], which is expected to occur over 4 to 5 years, the stockpile will have two vaccines with two different routes of administration, which could lead to administration errors with both vaccines. Administration of vaccine to potentially millions of individuals relies on the most efficient method available. Most vaccines are given by the IM route. Thus, there is more experience in the healthcare community giving IM injections, and this route might be more efficient for vaccinating large numbers of individuals over a short period of time.

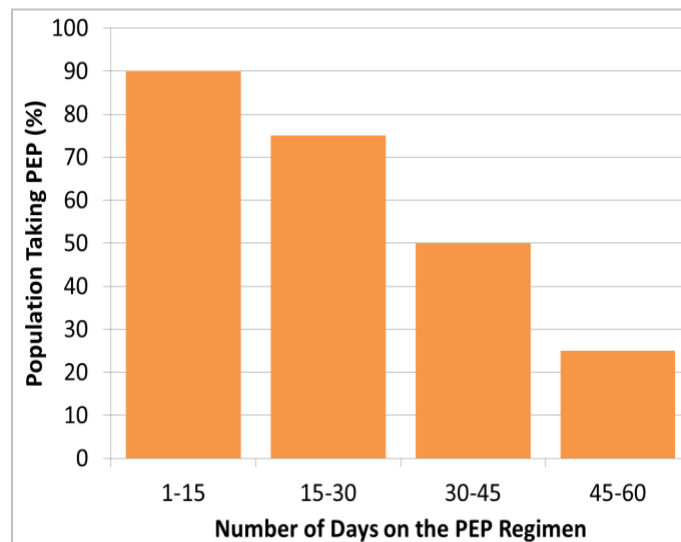
Adherence to antimicrobials is another concern. Post-exposure recommendations for individuals exposed to aerosolized spores are to take 60 days of oral antimicrobials in conjunction with a 3-dose course of anthrax vaccine. With this strategy, the antimicrobials provide protection against germinating spores until the vaccine elicits a protective immune response. For this strategy to work, adherence to taking oral antimicrobials as recommended is of critical importance. A paper from 2002 looked at adherence to PEP antimicrobials involving persons exposed at six US sites where letters containing *B. anthracis* spores were sent through the US Postal Service (USPS). Approximately 10,000 persons were advised to take at least 60 days of antimicrobial prophylaxis to prevent inhalational anthrax. Of these, 6178 were interviewed for AEs and adherence. Most respondents were aged 40 to 64 years and 60% were male. In this study, of the 6178 respondents, 13% either never collected antimicrobial supplies or if they collected initial supplies, then never initiated PEP. Only 44% of respondents reported taking antimicrobial prophylaxis for at least 60 days. Of the 2631 persons taking at least one dose of antimicrobial prophylaxis but stopping before 60 days, 43% stated that AEs were the most important reason they discontinued prophylaxis, 25% reported perception of a low risk for anthrax, and 7% identified fear of long-term side effects from antimicrobial prophylaxis [Shepard CW, Soriano-Gabarro M, Zell ER, Hayslett J, Lukacs S, Goldstein S, et al. Antimicrobial Postexposure Prophylaxis for Anthrax: Adverse Events and Adherence. *Emerg Infect Dis.* 2002;8(10):1124-1132].

This graph show adherence at the six sites. Adherence through 60 days was highest at the Brentwood facility at 64% and lowest at the New York City facility at 21%. The authors of this study concluded that risk perception was the strongest predictor of adherence across the six exposed cohorts:



In another survey looking at adherence following potential exposure to *B. anthracis* spores that happened at a laboratory at CDC, 42 individuals were contacted who were recommended 60 days of antimicrobials. This was a small study with only 29 responses at 30 days and 18 at 60 days. Of those surveyed, 97% initiated the antimicrobial portion of PEP. By day 30, 52% reported discontinuing PEP and by day 60, only 33% reported completing PEP. The main reason for discontinuing PEP early was low perceived risk of exposures at 64% followed by experiencing AEs at 35% [Nolen LD, Traxler RM, Kharod GA, Kache PA, Katharios-Lanwermyer S, Hendricks KA, et al. Postexposure Prophylaxis After Possible Anthrax Exposure: Adherence and Adverse Events. *Health Secur.* 2016 Nov/Dec;14(6):419-423].

The graph shows modeling assumptions for PEP adherence done by the HHS:



The modeling assumptions were loosely based on PEP adherence rates observed after the 2001 anthrax letter incident. The main source is the Shepard 2002 EID article presented earlier. The model predicts a drop of about 25% every 2 weeks. In this model, adherence is around 50% when the last dose of vaccine is given at Week 4.

Another potential obstacle to effective anthrax post-exposure prophylaxis is adherence to the 3-dose vaccine series. Predicting adherence to anthrax vaccine is challenging as there are few data on the effect of AEs and vaccine adherence in emergency situations. Dr. Hendricks will present data from the Anthrax Vaccine Research Program (AVRP) study used to evaluate an alternative administration route for pre-exposure vaccination, which was used as a surrogate for adherence to vaccine during an event. This study showed that IM administration of AVA elicits far fewer local reactions than SC administration. This raised a concern that a higher rate of AEs might lead to lower adherence to the vaccine component of PEP. However, a look at drop-out rates in this study showed that they were generally low and did not differ by route of administration.

To summarize the WG discussions, the WG felt that the different length needles would not be an impediment to administration of vaccine. The 1-inch needles in the stockpile that are generally used to administer vaccines IM could be used to administer vaccine SC without compromising the efficiency of the response. There are data to suggest that adherence to the

antimicrobial component of anthrax PEP wanes over time and could be as low as 50% by the 3rd dose of vaccine. This finding caused some concern within the WG, because the immune response at 4 weeks is significantly lower for the IM route of administration compared to the SC route. The higher rate of AEs for the SC route of administration was also a concern. However, data from the study describing AEs in groups receiving IM and SC administration failed to show any difference in drop-out rates by different routes of administration. The small survey that followed the laboratory incident at CDC showed a low adherence rate with vaccine, but it did not compare the IM versus the SC route.

Discussion Points

Dr. Kempe asked whether the three antimicrobials being used are equivalent in terms of effectiveness. They are very different in terms of tolerance. Amoxicillin is tolerated by almost everyone; whereas, there are more problems with the others. She wondered about prioritizing amoxicillin.

Dr. Bower replied that ciprofloxacin and doxycycline are considered to provide the same effectiveness as PEP. Amoxicillin is not FDA-approved as PEP, but efforts are underway to get that indication. There also is the issue of antimicrobial resistance. There are naturally occurring strains that are resistant to penicillin, so it is important to ensure that the strain being used is susceptible to penicillin before amoxicillin is used. The current plan is not to ship amoxicillin before the first 10 days, though this could change.

Dr. Messonnier noted that there are similar vaccines for which CDC is responsible, such as smallpox, where the general indication is laboratory workers and emergency response. She emphasized that she did not want to leave the impression that this was outside of the scope of what CDC asks ACIP to consider. It is important to ensure that the WG includes a sufficient number of individuals who would be implementing such a recommendation. In her mind, those are the state and local preparedness planners, so they need to give some thought to who is on the WG and that someone from that community also weighs in on the practicality of needle lengths.

Dr. Hunter indicated that he and Dr. Moore have been part of the point-of-dispensing demonstration.

Anthrax Vaccine (BioThrax[®]) New Safety and Reactogenicity Data

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Centers for Disease Control and Prevention

Dr. Hendrix indicated that this safety presentation takes up where the 2010 guidelines left off. During this session, she discussed published and recent unpublished VAERS information, as well as studies that relied on a variety of data sources other than VAERS. Most of the non-VAERS studies were performed in military populations. Of note, the post-licensure AVA data are based on PrEP uses. The mode of administration for PrEP changed from SC to IM in 2008.

As a reminder, VAERS is a national passive reporting system for AEs that occur following administration of US-licensed vaccines. It receives approximately 40,000 reports annually and accepts reports from a wide variety of reporting entities, including HCP, manufacturers, and the public. Signs and symptoms of AEs are coded using MedDRA terms and are entered into the database. VAERS is utilized primarily for signal detection and hypothesis generation. Since 1990, it has been jointly administered by CDC and FDA. The main objectives of VAERS are to detect new, unusual, or rare AEs; identify potential risk factors in recipients for particular types of AEs; monitor trends; and identify lots associated with increased numbers or types of AEs. It enables a rapid response to vaccine safety concerns or public health emergencies.

AEs are temporally associated events which might be caused by a vaccine or might be coincidental and not related to vaccination. VAERS data must be interpreted with caution and cannot generally be used to assess causality. In recent years, 2011 to 2014, for all vaccines there were about 30,000 VAERS reports per year. Of these, 7% were classified as serious. VAERS reports are classified as “serious” if they contain information that the AE resulted in death, hospitalization, prolongation of hospitalization, life-threatening illness, persistent or significant disability, or congenital anomalies. Ms. Hendrix noted that this list explained the basis for a number of the studies she would be discussing during this session. This table identifies VAERS’ strengths and limitations:

VAERS Strengths and Limitations	
Strengths	Limitations
<ul style="list-style-type: none"> <input type="checkbox"/> National data; accepts reports from anyone (HCP submitted 38% of reports, vaccine manufacturers 30%, and patients and parents 14%) <input type="checkbox"/> Rapid signal detection <input type="checkbox"/> Can detect rare AEs <input type="checkbox"/> Collects information about vaccine, characteristics of vaccinee, and AEs (some reports have no AEs) <input type="checkbox"/> Transparency; data available to public 	<ul style="list-style-type: none"> <input type="checkbox"/> Reporting bias; the problem is under-reporting <input type="checkbox"/> Inconsistent data quality and completeness; non-medical people reporting medical information <input type="checkbox"/> Lack of unvaccinated comparison group <input type="checkbox"/> Generally cannot assess whether a vaccine caused an AE <input type="checkbox"/> Pregnancy inconsistently reported

A 2009 study by Niu described VAERS reports following AVA receipt for a 17-month period from August 16, 2005 through January 2007. During this timeframe, 4753 reports were filed of which 4273 (90%) were non-serious, 455 (9.6%) were serious, and 25 (0.5%) were death reports. The authors also noted that “During March 1, 1998 to May 7, 2007 approximately 6 million AVA doses were administered to military personnel” (DoD unpublished). One-third or more of the complaints were for myalgia (39%), arthralgia (35%), pain (29%), and headache (28%). These are not mutually exclusive. One-fifth to one-fourth of the complaints were for depression (26%); asthenia (25%); rash, anxiety, insomnia (24%), and back pain (20%). The authors conclude that review of VAERS reports for this timeframe did not definitively link any unexpected SAE events to AVA vaccination other than injection site and some allergic reactions, and that no causal relationship is suggested for SAEs or deaths [Niu, MT. *Vaccine*. 2009].

A 2011 study by Woo reviewed reports of thrombocytopenia to VAERS for all vaccines to identify any that might warrant further study for possible causal associations. The review included all thrombocytopenia reports, defined as a platelet count of $<150 \times 10^9/L$ lacking a clear etiology for a 17 ½ -year time period ending in 2008. Using MedDRA codes for thrombocytopenia, just over 1500 reports were identified following exclusions for meningitis, cancer, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura, and 1440

reports remained. Of these, 14 had occurred following receipt of AVA. The investigators concluded that since acute and chronic thrombocytopenia commonly occur in the absence of recent immunizations, post-immunization thrombocytopenia may have been coincidental [Woo EJ. Vaccine. 2011].

The following data are unpublished CDC data. From January 1, 2009 through June 30, 2017, VAERS received 2439 non-duplicate reports from US sources following receipt of AVA, either alone or concurrently with other vaccines. Of these, 329 (13.5%) were considered serious events (i.e., events resulting in death, hospitalization, or permanent disability). The 5 deaths among AVA recipients were investigated; 3 had autopsies and 2 did not. Causes of death included a spectrum of cardiovascular disorders, unintentional or intentional injuries, and chronic illnesses. Approximately 80% (1975/2439) of all reported AEs that occurred after administration of AVA were in persons aged <40 years. About 25% (606/2439) occurred in women and 75% (1788/2439) in men. Most (54%) (1111/2439) received AVA concurrently with other vaccines, and 46% (1328/2439) received just AVA. About 91% (2225/2439) of AVA reports were documented as being administered or funded by the military. Approximately 1770 different MedDRA terms were reported in conjunction with AVA from 2009 through June 30, 2017. The 10 most common AEs that occurred following AVA receipt, either alone or concurrently with other vaccines, with each occurring in about 9% to 15% of the population were:

- Headache (n = 358, 14.7%)
- Injection-site erythema (n = 331, 13.6%)
- Pain (n=307, 12.6%)
- Fever (n = 282, 11.6%)
- Fatigue (281, 11.5%)
- Arthralgia (n=272, 11.2%)
- Erythema (n=272, 11.2%)
- Pain at the injection site (242, 9.9%)
- Injection site swelling (n=240, 9.8%)
- Rash (n=229, 9.4%)

In conclusion, there were no new safety concerns detected in VAERS monitoring [unpublished data]. The remainder of the studies presented are based on data sources other than VAERS.

Data were compiled from the following studies, some of which were dose reduction or schedule modification studies about AVA and some of which were immunogenicity or AE studies of other vaccines which included an AVA arm as a control:

Author	Year	~ AVA Doses (Recipients x Schedule)	Serious Adverse Events	Possibly Related to AVA
Hopkins	2014	600	2	None
Wright*	2014	8320	231	6 (no deaths)
King	2015	950	None	None
Hopkins	2016	70	None	None
Hopkins	2014	600	2	None
Wright*	2014	8320	231	6 (no deaths)
King	2015	950	None	None
Hopkins	2016	70	None	None

*AVRP

Although not all of these studies mentioned the number of doses administered, the doses were calculated by multiplying the number of study subjects in each arm times the number of vaccinations they were to receive. This denominator does not take into account dropout rates, which were usually small. Only 1 SAE was reported in this group of studies, and it was deemed to be unrelated to the vaccination. The remainder of the studies solicited both AEs and SAEs, and reported none. The denominator created (i.e., doses) also does not address length of follow-up, which varied from study to study, and likely accounts for the increased numbers of SAEs identified in the Wright study, which followed the more than 1000 recipients for years rather than months. For AVRP, there were 231 AEs in the approximately 8300 doses that were given. Of these, 6 AEs, all of which were non-fatal, were considered to be possibly related to the vaccine.

A study published in 2012 by Stewart evaluated quality of life of more than 1500 18- to 61-year old civilian participants from 5 AVRP study sites. The AVRP was a randomized double-blinded, placebo-controlled trial of immunogenicity and reactogenicity. A standardized survey instrument, the SF-36, was used to assess their health-related quality of life at baseline and at months 12, 18, and 42. A large number of health-related covariates (study group, dose number, study site, sex, smoking status, and age, race, and body mass index categories and interactions between each of these and dose number) were accounted for in the analysis. The mean physical and mental scores decreased over the 3 ½ years that the group was followed. However, there was no evidence that the score difference from baseline varied among the seven study groups, two of which were saline placebo. The authors concluded that the results do not favor an association between receipt of AVA and an altered health-related quality of life over a 42-month period [Stewart B. *Vaccine*. 2012].

In 2015, King et al published a re-analysis of existing datasets that compared 18- to 20-year olds to adults aged 21 to 29 years old who had participated in four previous US government-funded AVA studies. He found that rates of elicited AEs were not significantly different between younger and older age groups or either local or systemic events. Robust and similar proportions of seroresponses to vaccination were observed in both age groups. The authors concluded that AVA was safe and immunogenic in 18- to 20-year olds compared to 21- to 29-year olds [King JC. *Vaccine*. 2015].

The next 7 studies were conducted in military populations. A study published by Phillips et al in 2008 evaluated whether there was a relationship between squalene and chronic symptoms in a cohort of Gulf War veterans. This appears to be just one of many hypotheses that were being investigated to assess possible associations with chronic multisystem disease. However, it is important to understand some background information. Squalene is a naturally occurring substance produced by the liver to help metabolize cholesterol and combat physical injuries. Although squalene has never been added to AVA as an adjuvant, trace amounts have been found in 3 US vaccines, including AVA. About 500 deployed Gulf War veterans and just under 1000 non-deployed veterans were assessed by means of a questionnaire and laboratory tests. The following groups were demographically similar: participants and nonparticipants, squalene antibody-positive and squalene antibody-negative veterans, and ill and well veterans. Squalene antibodies were similar in deployed and non-deployed veterans and were not associated with chronic multisystem illness. The authors concluded that there was no association between squalene antibody status and chronic multi-symptom illness [Phillips CJ. *Vaccine*. 2009].

The next study, published by Sulsky in 2011, is a cohort study evaluating the potential for long-term or delayed health effects from anthrax vaccination. US Army personnel active during a 7+ year period from December 15, 1997 through February 15, 2005 were eligible study cohort members. After all exclusions, the cohort comprised just over 1 million soldiers, 43.8% (439,059) of whom had received at least one dose of AVA. A variety of military databases were used to identify the cohort and any disabilities that they might have. The organ systems listed were included in the assessment: Musculoskeletal, Neurological, Respiratory, Mental, Digestive, Cardiac, Endocrine, and Other. Just above 5% of the cohort (52,151) was evaluated for disability. Unadjusted rates show those receiving at least one dose of AVA were nearly 3 times less likely to have been evaluated for disability than unvaccinated personnel (177.7/100,000 vs. 60.4/100,000 person-months). The authors used multiple logistic regression models to investigate whether the odds of disease increased with more doses of AVA. Only among soldiers with 2 years of service who entered the army in 2000 or later was there a dose-related increase in odds of disability evaluation. In contrast, soldiers who enlisted before 2000 had a dose-related inverse trend in risk. As there were no changes in the formulation, dosing schedule, or mode of delivery of the AVA during the study period, the authors concluded that the difference in the direction of the dose-response association based on calendar year of enlistment suggests a statistical artifact rather than a true, biological difference in risk associated with vaccine doses. The authors concluded that there was no consistent pattern or statistically significant difference in risk of disability evaluation, disability determination, or reason for disability associated with anthrax vaccination [Sulsky SI. *Vaccine*. 2011].

The next study, also published by Sulsky, is a case-control study nested within the cohort of all Active Duty personnel known to have separated from the US Army during an 8-year time period ending in December 2005. Again, the data were pulled from a variety of military datasets. Cases had been determined to be at least 10% disabled either by the Army prior to separation (N = 5846) or by the Veterans Benefits Administration (VBA) after separation (N = 148,934). Controls had separated without disability and were not on VBA disability. The authors used logistic regression to adjust for a variety of demographic and work-related variables. After adjustment for covariates, veterans who had been vaccinated against anthrax had lower odds of later receiving VBA benefits than their unvaccinated counterparts. There was no association between prior vaccination against anthrax and odds of disability separation from the Army, overall. The author concluded that the risk of disability separation from the Army and receipt of disability compensation from the VA were not increased in association with prior exposure to AVA. This study provides evidence that vaccination against anthrax is not associated with long term disability [Sulsky SI. *Vaccine*. 2012].

The next study, published by Duderstadt in 2012, was a retrospective population-based cohort based on data from the Defense Medical Surveillance System (DMSS). In this study, the authors assessed whether vaccination with AVA increased the risk of type 1 diabetes mellitus. The population included 2.3 million active component US military personnel 17 through 35 years of age followed for 7.6 million person years over a 7-year time period ending in December 2008. Incident type 1 diabetes was identified from ICD-9 codes, and just over a thousand new cases of type I diabetes were identified. Multivariable modeling that adjusted for a variety of demographic, work-related variables and receipt of one or more of the study vaccines was used to examine the risk of diabetes following individual vaccines. The authors concluded that compared to their unvaccinated counterparts, AVA recipients were not at increased risk for type I diabetes [Duderstadt, SK. *Vaccine*. 2012].

The next study, published by Bardenheier in 2016, was a case-control study that evaluated the relationship of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) with AVA vaccination using the DMSS. The population included US military personnel on Active Duty during an 8-year timeframe ending December 2005. RA and SLE cases for both inpatient and outpatient settings were identified based on ICD-9 codes. After matching for sex, age, and service branch, conditional logistic regression models that controlled for deployment status were used to estimate matched odds ratios for AVA exposure during various time intervals ranging from 3 months to 3 years before disease onset. RA cases (N=133) were no more likely than controls to have received AVA in the previous 3 years; however, they were more likely to have received AVA in the previous 3 months. There were far fewer cases of SLE (N=81). There was no increased risk of SLE in AVA recipients compared to their unvaccinated counterparts. The authors concluded that AVA was associated with recent onset RA and may have acted as a trigger in predisposed individuals. However, AVA receipt did not increase long-term risk for either RA or SLE [Bardenheier, BH. *Military Medicine*. 2016].

The next two studies are both by Conlin et al. The first was a retrospective cohort that looked at pregnancy and infant health outcomes in women who were inadvertently given AVA while pregnant. Data regarding women who were exposed to AVA while pregnant were ascertained from the National Smallpox Vaccine in Pregnancy Registry and electronic healthcare data. There were 463 women in the primary analysis of whom 155 received only smallpox vaccine and were unexposed to AVA and 308 received both smallpox vaccine and AVA. A study limitation was the inability to control for potential confounding. Compared to military women exposed to neither vaccine, both the unexposed and exposed groups had similar fetal outcomes with regard to ectopics, elective and spontaneous abortions, and stillbirths. They also had similar infant health outcomes with regard to preterm births, low birth weight, mean birth weight, male sex, and major birth defects. The authors concluded that the similar rates between AVA-exposed and AVA-unexposed groups provided further confidence in the safety of AVA when given inadvertently to a relatively young and healthy population during pregnancy [Conlin, AM. *Vaccine*. 2015].

The next study, also published by Conlin et al, was a retrospective cohort study of infants born to military women from 2003 through 2010. The study population included 126,839 live born infants. Mothers were categorized by AVA vaccination exposure timing in relation to pregnancy. Infant medical records were assessed for birth defect diagnoses within the first year of life. Multivariable logistic regression was used to calculate odds ratios and 95% confidence intervals. Variables in the multivariable analysis included birth year, sex, and plurality for the infants and a variety of demographic and service-related variables for the mother (age at delivery, race/ethnicity, marital status, occupation, military service branch, rank, reserve status, deployment during pregnancy and amount of time deployed, and other potentially risky vaccinations in first trimester). When women who received AVA in their first trimester were compared to women who received AVA any other time (pre-pregnancy, post-pregnancy, or never), their risk of having a child with a birth defect was not increased as demonstrated by these odds ratios that hover near 1 and which all have confidence intervals that overlap 1:

Any Other Time	OR = 1.1 (95% CI, 0.93 – 1.29)
Pre-Pregnancy	OR = 1.05 (95% CI, 0.88 – 1.24)
Post-Pregnancy	OR = 1.17 (95% CI, 0.97 – 1.43)
Never	OR = 1.03 (95% CI, 0.86 – 1.23)


The authors concluded that there were no strong associations between inadvertent AVA vaccination during pregnancy and birth defects risk [Conlin AMS. *Vaccine*. 2017].

In 2014, Wright et al published the portion of the AVRP that evaluated alternative administration routes, reduced schedule priming series, and increased intervals between booster doses for AVA. Both immunogenicity and reactogenicity were assessed. This table shows the dosing schedule for the 7 study groups in the Wright paper:

Dosing Schedule for 2014 AVRP Study

Study Group	# Enrolled	# of AVA doses	Route	Month									
				0	0.5	1	6	12	18	30 (booster)	42 (booster)		
8-SC	259	8	SC	AVA	AVA	AVA	AVA	AVA	AVA	AVA	AVA	AVA	AVA
8-IM	262	8	IM	AVA	AVA	AVA	AVA	AVA	AVA	AVA	AVA	AVA	AVA
7-IM	256	7	IM	AVA	S	AVA	AVA	AVA	AVA	AVA	AVA	AVA	AVA
5-IM	258	5	IM	AVA	S	AVA	AVA	S	AVA	S	S	AVA	AVA
4-IM	268	4	IM	AVA	S	AVA	AVA	S	S	S	S	AVA	AVA
Placebo SC	133	0	SC	S	S	S	S	S	S	S	S	S	S
Placebo IM	127	0	IM	S	S	S	S	S	S	S	S	S	S

Wright JG, et al. *Vaccine*. 2014



As it was a double-blind study, everyone was dosed with saline when they did not receive AVA. AVA doses are shaded a maize color and saline doses are shaded light blue. The top two rows are the 8-SC and 8-IM groups which were dosed at 0, 0.5, 1, 6, 12, and 18 months and boosted at 30 and 42 months. All of the reduced schedules skipped the 0.5-month dose. At the bottom are the SC and IM placebo groups. The immunogenicity data from Wright will be presented next by Mr. Schiffer. One finding in Wright was the differences in injection site reactions between the IM and SC routes of administration for AVA. Itching, edema, and bruising were less likely overall in participants who were vaccinated by the IM rather than the SC route and warmth, erythema, induration, and nodules were less common in both males and females who were vaccinated by the IM rather than the SC route. For injection site reactions, only arm motion limitation was more common in recipients vaccinated by the IM rather than the SC route. For systemic reactions, muscle aches were more common in IM than SC recipients, with an OR of 1.59. A slight but nonsignificant decrease in fatigue was seen in IM recipients compared to SC recipients [Wright JG, et al. *Vaccine*. 2014].

In conclusion, no new safety concerns have arisen since December 2008 based on updated VAERS and review of the published literature. Injection site reactions were significantly less common with IM than the SC route of administration.

Immunogenicity Data for Anthrax Vaccine Licensure Changes

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Mr. Schiffer reviewed the immunogenicity data that supported the recent changes to the anthrax vaccine licensure. He reminded everyone that the current AVA PrEP and PEP licensed indications for adults 18 through 65 years of age are:

- ❑ PrEP:
 - IM route
 - Simplified regimen in 2012 reducing the primary series to 3 IM doses (0, 1, 6 months)
 - Resulting in protection being achieved in 6 months, and shortening the priming series by 12 months

- ❑ New PEP Indication 2015:
 - SC route
 - 3-dose series at 0, 2 and 4 weeks
 - Co-administration of antibiotics for 60 days

To review the progress of the disease, anthrax is a toxin-mediated disease. Anthrax toxin consists of three proteins: Lethal Factor (LF), Protective Antigen (PA), and Edema Factor (EF). LF and PA combine to form lethal toxin. When taken up by cells, lethal toxin can cause cell lysis and affects primarily immune response cells. LF and PA form edema toxin. When that is taken up by cells, it produces cAMP and edema. PA is a carrier protein, which has no toxic activity on its own but is required for the activity of LF and EF and is a primary antigen in the vaccine.

AVA vaccination produces antibodies against PA. Anti-PA antibodies that bind to free PA or the toxin complexes can block any of the intoxication steps. This protects host immune system cells from intoxication, allowing normal immune response to clear the bacteria. The immune response includes many other components (cellular responses, rapid increase in antibody levels in response to antigen detection, et cetera), but antibody level at time of challenge is an accurate correlate of protection in animal models.

Immune response is measured in two primary ways. The first is Anti-PA IgG ELISA, which measures total IgG against PA in mg/mL and uses species-specific reference standards and conjugate. The reference standards were calculated independently, so there is the potential for miscalculation between species. The second is Toxin Neutralization Activity assay (TNA), which measures the ability of antibodies to neutralize Lethal Toxin (LTx). It is not specific to antibody subtype or PA and is also species-independent.

The TNA units are reported in varying studies in two different units. One is the Effective Dose 50 (ED₅₀), which is the reciprocal of the serum dilution which neutralized 50% of the *in vitro* LTx cytotoxicity. The scale is generally from approximately 50 up to about 10,000. The Neutralization Factor 50 (NF₅₀) is the ED₅₀ of the sample divided by the ED₅₀ of the reference standard on the same run. This helps normalize run-to-run variation and makes the NF₅₀

specific to the reference standard used. All data presented here use the same reference standard, which is AVR801. That also changes the scale from approximately 0.1 up to about 10.

The Vaccine and Related Blood Products Advisory Committee (VRBPAC) meeting in November 2010 reviewed pathways to licensure using the animal rule for AVA. The final recommendations were that antibody levels are an appropriate marker to use to bridge between animal efficacy and human immunogenicity; bridging using the “Kohberger method” is an appropriate model for predicting human survival using animal challenge models; and using a PrEP animal model design is appropriate for use for the PEP licensure.

Fay et al conducted an inter-species bridging meta-analysis in which they analyzed all of the government-sponsored animal challenge trials that had been done since 1999. They covered two different non-human primate (NHP) species plus rabbits to determine what factors affected the bridging between animal species when the survival data are known in those species. They identified that genus and species were important; that bridging between different NHP species was more accurate than bridging between rabbits and NHP; and that vaccine formulation, vaccine schedule, time of immune response measurement, and time of challenge matter. That is, immune response changes over time. If the response is measured at a specific time as a predictor, the same time has to be used in the comparison group if bridging between humans and animals or between two different animals. Fay et al focused on the TNA assay because it is considered to be species-neutral [Fay et al., 2012 *Sci Transl Med.* 4(151): p. 151ra126].

The studies that support the recent AVA changes are the CDC AVRVP study and the Emergent Biosolutions pivotal PEP trial. The CDC AVRVP study was a Phase IV human clinical trial that compared IM and SC routes in the original PrEP schedule and evaluated reduced booster schedules in the IM route out to 42 months. It was also a matched NHP non-clinical challenge trial in which NHP were given the 3-dose priming schedule and subjected to anthrax lethal challenge to measure duration of protection at the extended times of 12, 30 and 52 months. The Emergent Biosolutions pivotal PEP trial was a Phase III human clinical trial that used the SC route only. The decision to use the SC route was based on data from the AVRVP. The study followed the PEP schedule of 0, 2 and 4 weeks and measured immunogenicity out to day 70, which is just at the end of the antibiotic prescription. It contained matched rabbit and NHP non-clinical challenge trials. The animals were vaccinated at 0 and 28 days and were subjected to high-dose anthrax lethal challenges at day 70.

The PrEP priming series change was based on the subset of AVRVP immunogenicity data looking at the human clinical trial data using the licensed IM route and schedule at 0, 1, 6, 12 and 18 months. The magnitude of the anamnestic response to the month 6 dose is comparable to the response at months 12 and 18. This indicates that priming is complete after the month 6 dose. As shown in this table, anti-PA IgG concentration and TNA ED₅₀ at month 7 are not significantly different than at month 19, indicating that priming is complete after dose at Month 6:

Month		Anti-PA IgG GMC ($\mu\text{g}/\text{mL}$)	TNA ED50 GMT
6	N	223	108
	GMC/GMT	4.17	21.83
	95% CI	(3.62 – 4.79)	(19.81 – 24.06)
7	N	214	102
	GMC/GMT	213.18	1465.27
	95% CI	(185.13 – 245.47)	(1208.4 – 1776.74)
12	N	211	99
	GMC/GMT	36.75	228.07
	95% CI	(31.90 – 42.33)	(173.38 – 300.02)
13	N	203	91
	GMC/GMT	243.11	1784.79
	95% CI	(210.79 – 280.39)	(1510.67 – 2108.64)
18	N	194	79
	GMC/GMT	45.93	325.27
	95% CI	(39.77 – 53.04)	(255.09 – 414.76)
19	N	192	100
	GMC/GMT	216.78	1343.22
	95% CI	(187.64 – 250.44)	(1120.81 – 1609.76)

Wright et al., 2014 *Vaccine*. 32(8): p. 1019-1028

FDA approved the AVA priming schedule in 2012, simplifying the dose series from 5 IM doses over 18 months to 3 IM doses over 6 months. Vaccine recipients are considered protected after the 6-month dose, so priming is completed 12 months sooner than previous licensure. The major impact is on time to deployment or approval to work for emergency responders and laboratory workers. Thus, there is a significant impact on response activities. The dosing schedule for the primary series will be updated in the revised recommendations.

Regarding the PEP licensure, the PEP studies were designed using the SC route for the human clinical trial. This was based on the CDC AVRP data in which the SC route was compared to the IM route for the PrEP licensure. While the IM route had reduced frequency, severity, and duration of injection site AEs compared to the SC route, the WG and FDA both felt that the rapid onset of immune response was prioritized over reduction in AEs for PEP indication. The SC route has a statistically significant higher immune response as measured by the total anti-PA IgG. At week 4 the IM response is lower than the SC and the difference is significant. By week 8 and for the rest of the study, they were not statistically significant. By TNA ED₅₀ assay they were still different, but not statistically significant. The confidence intervals were overlapping, but the SC route still appeared to be slightly higher than IM as shown in the following table:

Week		Subcutaneous	Intramuscular	Subcutaneous	Intramuscular
		Anti-PA IgG GMC ($\mu\text{g}/\text{mL}$) (95% CI)	Anti-PA IgG GMC ($\mu\text{g}/\text{mL}$) (95% CI)	TNA ED50 (95% CI)	TNA ED50 (95% CI)
0	N	259	262	111	112
	GMC/GMT	1.89	1.93	18	18
	95% CI	(1.85 – 1.92)	(1.87 – 1.99)	(–)	(–)
4	N	242	241	105	108
	GMC/GMT	49.79	30.81*	100.41	81.38
	95% CI	(43.38 – 57.14)	(26.90 – 35.29)	(77.91 – 129.41)	(63.74 – 103.88)
8	N	235	234	112	103
	GMC/GMT	94.43	84.58	229.07	240.84
	95% CI	(82.20 – 108.47)	(73.78 – 96.97)	(190.86 – 274.93)	(196.52 – 295.16)

* Statistically significantly different

The PrEP animal model was used for PEP licensure. PEP licensure is intended for use post-exposure with concomitant antibiotic treatment. However, it is difficult to develop an animal model for PEP. Even a very low vaccination dose with concomitant antibiotics resulted in close to 100% survival¹. It is not possible to generate correlates of protection and establish a protective required level if some animals do not die. Studies were conducted that showed that antibiotics do not interfere with vaccine immunogenicity, and vaccination provides significant improvement in protection versus antibiotics alone² [Leffel *et al.*, 2012 *Clin. Vaccine Immunol.* 19(8): p. 1158-1164; Vietri *et al.*, 2006 *PNAS.* 103(20):p. 7813-7916].

The PrEP animal model was used in rabbits or NHP vaccinated with graded vaccine doses at 0 and 4 weeks to generate a range of immune responses from highly protective to poorly protective. They were then subjected to a high dose of aerosolized *B. anthracis* spore challenge at Day 70. The model was designed to be very conservative. The high-dose challenge of 200 LD₅₀ should be far larger than residual spores left in the lungs at 70 days post-exposure. TNA NF₅₀ used as the reportable value for antibody response. Logistic regression was used on the animal models to generate a correlation between the antibody response and survival in the animals. The antibody level required to provide 70% protection (NF₅₀ = 0.56) was used as a protective threshold and applied to the human immunology results. More recent data added additional animals that shifted the threshold down, which will be presented at a later time, but these are the data that were used for licensure. There was a slightly different response in NHP. The NF₅₀ 0.56 threshold resulted in almost 90% survival in the NHP and an NF₅₀ 0.29 threshold resulted in 70% in NHP [Ionin *et al.*, 2013 *Clin. Vaccine Immunol.* 20(7): p. 1016-1026]. Again, Fay *et al* indicated that the more closely related the animal model is to humans, there is most likely better predictive accuracy.

The human clinical trial had participants vaccinated SC at 0, 2, and 4 weeks and the NF₅₀ was measured out to day 63 as reflected in the following table from the BioThrax[®] Product Insert:

PEP Schedule Elicits Protective Human Immune Response

Table 4: Proportion of Subjects Achieving TNA NF₅₀ Threshold^a in the Pivotal Clinical Study (PP Population^b)

Animal Model	Time Point Human/Animal	n	Human GMT TNA NF ₅₀ (SD)	Animal TNA NF ₅₀ Threshold ^c	Number of Subjects Meeting Threshold	Proportion of Subjects Meeting Threshold (%) ^d		
						Point Est. (%)	95% CI (%)	
							Lower Bound	Upper Bound
Rabbit ^e	Day 63/Day 69	184	0.86 (2.09)	0.56	131	71.2	64.1	77.6
Non-human Primate ^f	Day 63/Day 70	184	0.86 (2.09)	0.29	172	93.5	88.9	96.6

CI = confidence interval, NF₅₀ = 50% neutralization factor, PP = per protocol, SD = standard deviation, TNA = toxin neutralizing antibody.
 Note: Sample size (N) and denominators used for percentages are based on the number of subjects meeting the PP criteria at specified day(s).
^a TNA NF₅₀ threshold is defined as the TNA NF₅₀ value associated with 70% survival in the animal challenge studies.
^b Human data are from the pivotal clinical study (NCT01491607).
^c A logistic regression model with log10-transformed TNA NF₅₀ values as the predictor and survival as the response is used to derive the TNA NF₅₀ threshold associated with 70% probability of survival in rabbits and non-human primates, respectively.
^d 95% CI is calculated with the exact (Clopper-Pearson) method.
^e The proportion of subjects achieving a TNA NF₅₀ response at Day 63 that met or exceeded the TNA NF₅₀ threshold in the rabbit model at Day 69 comprised the primary immunogenicity endpoint.
^f Comparison of the human TNA NF₅₀ response at Day 63 with the NHP TNA NF₅₀ threshold at Day 70 was defined as an immunogenicity endpoint and was supportive of the bridging of human immunogenicity data to rabbit survival.

Biothrax Product Insert, Hopkins *et al.*, 2014 *Vaccine* 32: p. 2217-2224

The percentage of human subjects who achieved greater than 70% protection at day 63 was used to evaluate VE. Day 63 was selected because it was 3 days after the ceasing of antibiotics. Of note, this is a simplified bridging model, not the full Kohberger method that was recommended by VRBPAC. Based on the rabbit model threshold, 71% of the humans would be greater than 70% protected and 93% of the humans would be greater than 70% protected based on the NHP threshold.

In summary, there have been two changes to BioThrax[®] licensure since 2010. The PrEP priming series was simplified from 5 doses over 18 months to 3 doses over 6 months based on the magnitude of human anamnestic response to the month 6 dose compared to the month 18 dose. PEP licensure was granted with a 0-, 2-, 4-week SC schedule with concomitant antibiotics for 60 days. The SC route was chosen based on superior immune response at week 4, and licensure was based on the percentage of human response exceeding 70% protective levels established in both rabbit and NHP challenge models.

WG Discussion & Conclusions Summary

William Bower, MD, FIDSA
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Dr. Bower reported that WG felt that there were no new concerns based on VAERS review or data published since AVA was last reviewed in 2008. These data continue to support the safety of AVA for use as pre-exposure and post exposure prophylaxis, given the high mortality associated with anthrax. The WG felt that more data are needed to evaluate the safety of AVA in pediatric populations. However, although data are not available in children regarding the types and frequency of AEs after immunization, the benefits of AVA in children exposed to aerosolized *B. anthracis* spores are currently believed to outweigh these potential risks. In terms of the AVA pre-exposure indication change in 2012, in 2012 FDA approved a change in the priming series from 5 IM doses over 18 months to 3 IM doses over 6 months. This will be included in the revised recommendations.

After reviewing the data on intramuscular administration of AVA, the WG was not in favor of recommending it as an alternative route of administration during an anthrax event. The WG felt that the needles contained in the CDC stockpile could all be used to administer AVA by the SC route and would not be an impediment to administration of vaccine. The WG also felt that IM administration would not be more efficient than SC administration. The higher rate of AEs for the subcutaneous route of administration was a concern. However, this is a theoretical concern as there are no data to show that this translates to decreased adherence in an anthrax event. The issue that carried the most weight in the WG's discussion was that adherence to the antimicrobial component of anthrax PEP wanes over time and could be as low as 50% four weeks after initiating PEP. This is particularly concerning as the immune response to AVA at 4 weeks is significantly lower for the IM route of administration compared to the SC route. However, by 8 weeks when the antimicrobial component of PEP stops, this difference goes away.

The WG concluded that the data do not favor a change from the current licensed route of administration of AVA for PEP that would allow the IM route of administration to be used as an alternative route during a large anthrax event. This is supported by data that optimal immune response at 4 weeks is obtained by administration of AVA by the SC route, a time when as many as half the individuals might have self-discontinued their antimicrobial component of PEP. However, if AVA is inadvertently given by the IM route, the WG advised that there is no need to re-administer the dose by the SC route. The corrective action is to complete the rest of the series SC.

Discussion Points

Dr. Messonnier acknowledged that this was a complicated equation to balance all of these issues. While she was not sure of the right answer, she wanted to make sure that all of the pieces were laid out fairly. She said she was interested in hearing from those who would have to operationalize this in terms of whether they thought the issues pertaining to the different needle sizes and potentially two different vaccines being administered differently would be realistically easy in the field. For full disclosure, she indicated that she is the senior author on the paper regarding adherence. In 2001, substantial numbers of people were recommended antibiotics months after their exposure. In New York City and New Jersey, it was not just risk perception but it was that they wanted people to take antibiotic 6 weeks later. She thought a better metric of adherence was in the people in subgroups who actually saw themselves to be at risk, which is not fully displayed in the paper in the subcategories in each of those states who felt the risk of exposure were much different and much higher. She was not certain that 25% was the right number to use, because it was more like 60% in high-risk groups. The issue of how to deal with the immunogenicity data is very complicated, but the interpretation of cross-species animal models is a point of much contention among the researchers who work in this field. FDA also struggled with how to interpret those data. In the 10 to 15 years since these studies started, people have turned over and some of the perceptions have changed. Dr. Messonnier said she was struggling with viewing this as simplistic as antibody levels are different and, therefore, there is a straight-line conclusion that predicts protection would be different. She emphasized that she thought there were some issues with which the WG needs to struggle.

Dr. Hunter asked whether the WG reviewed any of the data related to vaccine administration errors in clinical practice regarding needle length and various other errors. If not, he thought they might have come to different conclusions if they had done that given the frequency that this occurs. While he said he did not know the data well, he did know that it is quite concerning.

Dr. Cohn pointed out that the consideration was vaccine use by public health in certain settings versus in the private practice setting.

Dr. Hunter indicated that as someone who reviews vaccine administration errors of 50 or more public health nurses, it is necessary to have reports of vaccine administration errors to ensure that they are doing their job correctly. If there are no errors, they are not reporting it correctly. Especially in emergency response situations and based on the chaos he experienced in the demonstration, he would have even more concerns personally.

Dr. Bower added that in the context of a mass vaccination campaign involving hundreds of thousands to millions of people, people will be recruited who may not be as familiar with administration and/or just-in-time training will be done. This was another reason the WG favored the simplest way to administer the vaccine.

Dr. Maldonado (AAP) inquired as to whether studies in children are planned. She noted that the guidelines are limited with regard to the pediatric populations, given that adult guidelines are being used as is done for many other vaccines and antimicrobials. However, the reviews of disease in children show that the ability to identify disease in children compared to adults will be different. There is evidence that the morality rates differ between children and adults as well. The AAP encouraged more studies regarding vaccine use and PEP among children.

Dr. Bower replied that there is a plan to assess this vaccine in children in a de-escalating plan that will begin with 17 to 18-year olds. If this looks good, they will move to 16 to 17-year olds and so forth. It will take a long time to assess various age groups, but that is the current plan.

Dr. Messonnier clarified that this would be in the event of an event, and that she thought Dr. Maldonado was asking about plans to conduct any pre-event clinical trials in pediatric populations. There is a study protocol for this, but funding has not been allocated.

Dr. Kimberlin (AAP) pointed out that 22% to 23% of the US population is comprised of children. If they could vote, that might stimulate some direction of funds.

Regarding Dr. Maldonado's point, Dr. Grabenstein (Merck) indicated that the reason there are no safety data in children is that there is no immunogenicity data in children because there are no dosing data among children. Not only is there not funding, but also it is not clear that there is will. There may be a presumptive dose for a child such as is done with tetanus toxoid, but until someone studies it, that would be the only basis for dosing.

Dr. Bresnitz (Merck) said that as a personal comment, he was a New Jersey State Epidemiologist during the anthrax attack and was exposed in a postal facility. Thus, he had the unenviable opportunity to take ciprofloxacin for 60 days. This was not very pleasant though his was a minor AE. At the time, the anthrax program had a post-event focus and was late. It was under an IND and was 3 doses versus 6 doses. Frankly, he did not support the program in New Jersey. Very few people took it as it was 75 days after exposure. The point he wanted to make was that policy was being developed on the fly at that time, but the key is communication. Much work has been done over the last 15 years, but communication at the time of exposure is key to getting whomever is exposed to take antibiotics, get vaccinated, or both. This and tailoring risk to what the real risk is are key to achieving better adherence rates. The risk was high in New Jersey and Brentwood; whereas, the risk was not very high in Florida.

Following up on Dr. Messonnier's point about IM versus SC, Dr. Quinn noted that based on the point estimates of the responses in humans, clearly the SC route achieves the higher response in the earlier weeks. However, the IM route catches up by week 8. Also, antibiotics are begun during emergency responses. The animal data indicate that both routes of administration give fairly high level predictive probabilities of survival. Moving forward, he would like them to keep the door open to use either/or depending upon the situation when faced with an emergency response.

Evidence-Based Recommendations Work Group Update

Wendy Carr, PhD
ACIP Evidence-Based Recommendations Work Group Lead
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Carr reminded everyone that the purpose of the Evidence-Based Recommendations WG (EBRWG) is to provide a forum for discussion of best practices for the evidence-based recommendation process for ACIP, including development and use of GRADE evidence tables and an evidence to recommendation framework to ensure consistency and enhance

transparency in the development of ACIP recommendations, with the goal of developing a uniform approach to evaluation and use of the evidence base for ACIP recommendations.

In support of this purpose, the aims of the WG defined in the Terms of Reference propose additional guidance for the ACIP evidence-based recommendation process, including GRADE and subsequent use of an evidence to recommendation framework, specifically for three areas:

1. Improving and harmonizing the development and use of GRADE evidence tables by the ACIP WGs
2. Developing criteria to guide the determination of when GRADE evidence tables should be prepared in support of a given recommendation
3. Further defining the process of going from the certainty of the evidence base as presented by the GRADE tables to recommendations, in particular ensuring that the additional factors that contribute to decision-making are considered and communicated.

Regarding the first aim to harmonize development and use of GRADE tables, several CDC WG leads presented their experience using GRADE methodology for past recommendations to the WG. Several areas were identified for which additional guidance would be useful. These included: 1) applying GRADE methodology to the evaluation of immunogenicity data, including further clarifying when evidence should be rated down for indirectness when used as a surrogate outcome for efficacy; 2) the acceptability of rating up a body of evidence after previously rating it down; 3) the assessment of observational data using GRADE, in particular ensuring that the confidence generated by strong observational data is reflected in the ultimate evidence rating; and 4) evaluating burden of disease. The next steps for moving forward with this goal of harmonizing the development of GRADE Tables are to develop draft Frequently Asked Questions (FAQ) documents that provide more explicit guidance on how to consistently approach topics that often generate questions during the use of GRADE by ACIP WGs.

The second aim of the WG centers around providing reference materials to clarify when GRADE evidence profiles should be prepared when evaluating the evidence for a recommendation. A draft algorithm has been developed that provides questions that should be considered when deciding whether it would be advantageous to prepare evidence tables. This algorithm will be piloted and any revisions will be incorporated in the reference materials.

The third aim of the WG is to provide additional structure and clarity for the process during which factors in addition to the evidence base are considered when formulating recommendations. The GRADE WG, a collaboration of methodologists, clinicians, and others working to develop, refine, and provide guidance regarding the GRADE evidence-based recommendation approach, have outlined a process to support movement from evidence to decisions. This has been termed Evidence to Decision (EtD) or Evidence to Recommendation (EtR) framework. The framework is presented as a table that includes key background information, criteria that should be considered, and conclusions.

One advisory group that has adopted the EtR framework is the WHO Strategic Advisory Group of Experts on Immunization (SAGE). Members of the SAGE Secretariat presented the EtR methodology currently used by SAGE to the EBRWG in addition to the discussion of the successes and challenges that have been so far encountered. A recent example of a

completed SAGE EtR table can be found at the WHO website at this link:
http://www.who.int/immunization/policy/position_papers/denque/en/

When queried about potential development of a similar EtR framework for ACIP, feedback from members of the EBRWG and CDC WG leads was positive. A draft ACIP-specific Evidence to Recommendation framework has been developed based upon the SAGE EtR table and the GRADE EtD framework with feedback from both the EBRWG and CDC work group leads. Each element of the framework has been customized to the needs of ACIP to provide additional structure and clarity in the communication of the spectrum of elements considered during recommendation development. The draft framework is currently being piloted.

As mentioned previously, the EtR framework is presented as a table that includes key background information, criteria that should be considered, and conclusions. The criteria that should be considered fall into several broad topic areas. Each of these areas contains individual questions that solicit judgements concerning each element and presentation of the available evidence. The topic areas that are included in the draft ACIP EtR framework are shown here:

- Statement of Problem
 - Public health priority
 - Burden of disease
- Benefits and Harms
 - Balance of desirable and undesirable effects
 - Certainty in evidence (evidence profiles)
- Values and Preferences of target population
- Acceptability to stakeholders
- Resource Use
 - Health Economic Analyses
- Feasibility
 - Implementation considerations

More specifically, the *Statement of the Problem* is an issue that the recommendation is intended to address. This area covers presentation of information regarding why the issue is considered a public health priority. It often will include information regarding burden of disease and other considerations that contributed to the need for a recommendation to be developed. The *Benefits and Harms* area includes both presentation of the available evidence for benefits and harms, as well as the certainty in this evidence. The preparation of GRADE evidence profiles will typically be part of this section. In circumstances where evidence tables were not prepared, a description of the rationale for the decision not to prepare tables will be provided. The “When to prepare GRADE evidence profiles” algorithm mentioned under Aim #2 would be used as a tool to assist with this determination. Finally, the evaluation and determination of the balance of the benefits and harms is also a key component of this criterion. The *Values and Preferences* of the target population is another element of the draft framework, where consideration is given to the perception of the benefits and harms and how these are valued by potential recipients as well as providers. Consideration is also given to the *Acceptability to Stakeholders* of the recommendation. The *Resource Use* component of the framework encompasses the

information provided by Health Economic Analyses, while the *Feasibility Category* includes implementation considerations. A tool is also under development to assist WGs in completion of this section.

The rationale, evidence, and judgements made in the framework culminate in the communication of the type of recommendation. In the draft ACIP EtR framework, the following 4 types of recommendations are possible:

- “We recommend against the intervention”
- “We recommend that the intervention not be routinely recommended for all persons, but be available for individual clinical decision-making”
- “We recommend the intervention”
- “We do not recommend the intervention at this time”

If the framework is formally adopted, implementation and use of the framework will result in the use of these 4 types of recommendations and will replace the labeling of recommendations as “Category A” or “Category B.” The EtR framework is currently being piloted and feedback from the pilots are being incorporated. In addition, the framework elements are being further defined and guidance is being developed on completion of the framework. The EBRWG intends to present the draft framework to ACIP during the February 2018 meeting.

The following is a summation of the proposed timeline for development of additional guidance materials:

- During November / December 2017 and January and February 2018, the EBRWG meetings will focus on specific elements of the EtR framework
- The draft EtR framework will be presented during the February 2018 ACIP meeting
- During March, April, and May 2018, the EBRWG meetings will focus on refining guidance on the development and use of GRADE evidence tables
- The proposals to address key questions will be presented during the June 2018 ACIP meeting
- During the June 2018 ACIP meeting, the final proposals will be presented for an ACIP vote on the proposed modifications

Discussion Points

Dr. Kempe asked whether the last category “We do not recommend the intervention at this time” was supposed to indicate an open-ended might be considering it.

Dr. Carr replied that the WG members felt that it was important to include this category instead of just having an option to recommend against an intervention, given that there may be times when there is not sufficient evidence or there are other factors that would not enable ACIP to make a recommendation at that time.

Dr. Moore asked how the evidence recommendation process works when there is a general population for whom the intervention may be less important, a Category B type of equivalent, but it is routinely recommended for certain subsets of the population. That is, do there have to be separate frameworks for each group?

Dr. Carr responded that the WG is working on developing guidance for this. There are different ways this could be approached, which may depend upon whether similar populations can be grouped together to have a draft framework for several different populations, or that could be included in the same framework. It is really about being able to present the information in a clear and transparent way.

In terms of preferences and values, Dr. Szilagyi suggested that it might be helpful to provide some guidance about the types of data, level of intensity, what is meant by *preferences and values*, and who the target population is (e.g., providers, patients, et cetera).

Dr. Carr indicated that the WG is currently developing a guidance document and that she will make sure this type of information is included.

Referring to Slide 8, Dr. Grabenstein (Merck) inquired as to how to interpret Dr. Carr's comment about resource use and cost-effectiveness analyses. He wondered if for the assumptions that go into the health economic analyses there is intent to assess the strength of evidence that underlies the various assumptions. That would have helped ACIP considerably the previous day.

Dr. Carr responded that the *Resource Use* section is part of the generic GRADE EtR. The way the WG is determining this is by health economic analyses.

In terms of presenting the certainty of evidence around the underlying assumptions, Dr. Cohn indicated that there is a summary of the evidence that goes into it and a comment section. One of the questions that could be answered under the comments section regards how much data supported some of the assumptions of the analysis.

Dr. Dana Meaney-Delman (CDC) asked whether the evidence framework includes information about when to conduct a systematic review, and specifically when conducting a systemic review when a meta-analysis would be necessary.

Dr. Carr replied that this is not part of the framework at this point, some background information would go into that. There is always going to be an evaluation of the evidence that is available, but whether the Cochrane methods for a systematic review would be used might be another story.

Dr. Schaffner (NFID) observed that indirect effects are not explicitly addressed, even though this is an important public health aspect of vaccine and vaccine decision-making. It has always bemused him that a specific part of the GRADE process does not address indirect effects.

Dr. Carr indicated that this issue has been raised repeatedly. It fits under the *Benefits and Harms* section, which will have questions specific to this. There is a plan to include indirect benefits in the draft guidance.

Respiratory Syncytial Virus

Gayle Langley, MD, MPH
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Dr. Langley reminded everyone that the ACIP Respiratory Syncytial Virus (RSV) WG was formed in 2016 to evaluate the potential use of RSV vaccines in older adults. At the time the group formed, there was a vaccine product targeting the adult population in Phase III trials. The vaccine candidate is now back in Phase II development. There currently are vaccine and immunoprophylaxis products targeting infants in later stages of development. There is a maternal vaccine designed to passively immunize infants with antibodies in Phase III, and a monoclonal antibody product that would directly be given to infants in Phase IIb trials. The ACIP charter states that the guidance will address use of vaccines and may include recommendations for administration of immune globulin preparations shown to be effective in controlling disease for which a vaccine is available.

Since the maternal vaccine and antibody products currently under development could result in overlapping recommendations, ACIP will develop recommendations for vaccines and antibody products that are licensed in the future. There will be two ACIP WGs: 1) The RSV Pediatric WG to consider products targeting children directly or through maternal vaccination; and 2) The RSV Adult WG to consider products targeting adults. There may be overlapping membership between the groups, and each will convene according to when products come closer to licensure. The RSV Pediatric WG is anticipated to begin meeting in Winter or Spring 2018.

The terms of references for the RSV Pediatric WG are to:

- Review the epidemiology and burden of RSV disease in children and pregnant women
- Review the efficacy, immunogenicity, safety, and cost-effectiveness of RSV vaccines and immune globulin products in pregnant women and children
- Provide evidence-based recommendations regarding use of RSV vaccines and newly developed immune globulin products in pregnant women and children
- Identify areas in need of further research for informing potential future vaccine and immune globulin recommendations

The timing for reconvening the RSV Adult WG will be as needed. A copy of the new terms of reference are available upon request.

Vaccine Supply

Dr. Jeanne M. Santoli
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Dr. Santoli presented an update on the adult and pediatric HepB vaccine supply. She reported that Merck is not currently distributing its adult HepB vaccine and will not be distributing vaccine through the end of 2018. The dialysis formulation of HepB vaccine is not affected. GSK has sufficient supplies 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 time.

Merck is not currently distributing its pediatric HepB vaccine through the end of 2017. GSK has sufficient supplies of pediatric HepB vaccine to address the anticipated gap in Merck's pediatric HepB vaccine supply during this period; however, preferences for a specific presentation (i.e., vial versus syringe) may not be met uniformly during this time.

CDC's Vaccine Supply/Shortage Webpage is kept updated for members of the public and can be found at: <http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm>

Day 2: Public Comment

Walter A. Orenstein, MD, DSc (Hon)
Associate Director, Emory Vaccine Center
Director, Emory Vaccine Policy and Development
Professor of Medicine, Pediatrics, Epidemiology, and Global Health, Emory University

Dr. Orenstein indicated that October 26th marked the anniversary of the world's last reported case of naturally acquired smallpox, which occurred in Somalia in 1977.




Certification

Upon reviewing the foregoing version of the October 25-26, 2017 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.

Appendix A: Letters Submitted to ACIP for the October 2017 Meeting

Influenza



Alachua County

Board of County Commissioners

Ken Cormell, *Chair*
 Lee Pinkoson, *Vice Chair*
 Mike Byerly
 Charles S. Chestnut, IV
 Robert Hutchinson

Administration
 Dr. Lee A. Niblock, CM
 County Manager

April 10, 2017

Ms. Carolyn Bridges MD Associate Director for Adult Immunization, Immunization Services Division,
 National Center for Immunization and Respiratory Diseases,
 Centers for Disease Control and Prevention
 1600 Clifton Road, NE
 Atlanta, GA 30329-4027

Advisory Committee on Immunization Practices (ACIP)
 ACIP Secretariat Amanda Cohn, MD
 ACIP Chair Nancy Bennett, MD, MS
 CDC
 1600 Clifton Road, NE
 Mailstop A27
 Atlanta, GA 30329-4027

RE: Alachua County Florida School Located Influenza Vaccination Program

Dear Colleagues:

At the March 28, 2017 Alachua County Board of County Commissioners meeting, the Commission received a report from the Alachua County Health Department's Administrator, Paul Myers. His annual update on the Control Flu Program revealed a concerning inference that associated the mandated use of flu shots during this year's campaign, instead of the usual intranasal spray, with a 40% reduction in program participation.

This significant reduction in doses administered has resulted in thousands of children, mostly from socioeconomically challenged neighborhoods, lacking the protection that they have been provided in the previous 8 years of the program. The flu shot is not only more traumatic for children, but does not, according to many studies, impart substantially greater protection from influenza disease than the intranasal spray.

It is the Commission's understanding that the CDC's current language regarding the intranasal spray states that it "should not be used". We urge the CDC to reconsider this language and provide a softening of its position. At a minimum, permissive language for school based programs is strongly recommended. Vaccinating significantly less children with a shot that *might* be more effective versus immunizing many more children with the intranasal spray that *may* be less effective is a questionable strategy at best, and ignores a large body of scientific evidence that supports the vaccine effectiveness of the intranasal spray. What is certain is that requiring shots lowers vaccine uptake and therefore renders large numbers of children, and those they come into contact with, unprotected from influenza.

12 SE 1st Street ■ Gainesville, Florida 32601 ■ Tel. (352) 264-6900 ■ Fax (352) 338-7363
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 Commissioners' E-Mail: bocc@alachuacounty.us ■ Home Page: www.alachuacounty.us
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Page 2

Alachua County has long supported the School Located Influenza Vaccination Program that has, until this year, utilized FluMist. We strongly encourage the CDC to re-evaluate its position on FluMist by mid-June 2017 at the latest, so that our program can utilize FluMist for the upcoming 2017/2018 campaign. The intranasal spray has proven to decrease influenza associated morbidity, school and work absenteeism, in addition to saving millions of dollars in direct and indirect healthcare costs.

Thank you for your immediate attention to this matter. Please contact me should you have any questions or require additional information.

Sincerely,



Ken Cornell, Chair
Alachua County Commission
Chr17.076

KC/GP/lg

cc: Board of County Commissioners
Lee A. Niblock, County Manager
Michele Lieberman, County Attorney
Gina Peebles, Assistant County Manager
Paul Myers, Alachua County Health Department



Alachua County Board of County Commissioners

Ken Cornell, *Chair*
Lee Pinkoson, *Vice Chair*
Mike Byerly
Charles S. Chestnut, IV
Robert Hutchinson

Administration
Dr. Lee A. Niblock, CM
County Manager

June 15, 2017

Advisory Committee on Immunization Practices (ACIP)
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ACIP Chair Nancy Bennett, MD, MS
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email acip@cdc.gov

Ms. Carolyn Bridges MD Associate Director for Adult Immunization, Immunization Services Division,
National Center for Immunization and Respiratory Diseases,
Centers for Disease Control CDC
1600 Clifton Road, NE
Atlanta, GA 30329-4027
email - ctb1@cdc.gov

RE: Alachua County Florida School Located Influenza Vaccination Program

Dear Dr. Cohn,

Thank you for the opportunity to speak with you on May 15, 2017, regarding Alachua County's School Located Influenza Vaccination Program. This call was a follow-up to my letter dated March 29, 2017 referencing the 40% reduction in overall program participation (K-12) that we directly attribute to the requirement to use shots versus the intranasal spray.

As you requested, we have further analyzed this year's program data to answer the 4 questions listed below. We utilized school rosters, further denoted by program vaccinated/non-vaccinated students, compared to the State of Florida's immunization registry, FLSHOTS. It should be noted that all pediatric providers in Alachua County utilize FLSHOTS.

1. What was the change in program participation for the primary target group (K-5) as compared to last year (2015 vs. 2016)?
 - a. Of the 6081 K-5 students immunized by the program in 2015, 2293 were immunized by the program in 2016; a reduction of 62.3%.
2. Of those K-5 students who participated in the 2015 school program, but not in 2016, how many received the immunization from a different provider?

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- a. 529 K-5 students who participated in the school program in 2015, but not in 2016, received the vaccination from a non-school program provider.
3. What demographic was impacted and by how much?
 - a. In 2015, 6081 K-5 students participated in the program. In 2016, 3259 of them were not vaccinated at all; a reduction of 53.6%. Of those, 1699 were VFC eligible for a reduction in VFC students of 52.2%
 4. What was the impact of lower vaccination coverage on morbidity?
 - a. K-12 students presenting to school health clinics with Influenza like illness increased from 2015 to 2016 in Alachua County Schools.

Clearly, Alachua County, relying on hard data, experienced a significant reduction in immunization coverage for the target group of K-5 grades. This group we affectionately label "the super-spreaders". Disproportionately affected were the social-economically challenged demographic; one that can least afford to become ill and one that suffers worse health outcomes from doing so. Our data does not mirror that of the referenced NIS that indicated a reduction in immunization coverage of 1%-2% from 2015 to 2016.

Thank you for the opportunity to provide additional input. I hope you find these data compelling and serve as a basis to consider a softening of the ACIP's language regarding the utilization of the intranasal influenza vaccine that currently states that the spray "should not be used". I would reiterate my previous request that the Alachua County Program be supported by the ACIP in utilizing the intranasal spray to maximize immunization rates, reduce influenza associated morbidity and provide in-US data for further policy considerations. I look forward to the results of the ACIP meeting on June 21, 2017 and am available at your convenience for continued dialogue.

Sincerely,



Ken Cornell, Chair
Alachua County Commission
Chr17.114

KC/PM/lg

cc: Board of County Commissioners
Dr. Lee A. Niblock, County Manager
Michele Lieberman, County Attorney
Gina Peebles, Assistant County Manager
Paul Myers, Alachua County Health Department
David Kim MD, Adult Immunization, Immunization, Services Division



Alachua County Board of County Commissioners

Lee Pinkoson, *Chair*
Charles S. Chestnut IV, *Vice Chair*
Mike Byerly
Ken Cornell
Robert Hutchinson

Administration
Michele L. Lieberman
Interim County Manager

February 20, 2018

Advisory Committee on Immunization Practices (ACIP)
ACIP Secretariat Amanda Cohn, MD
ACIP Chair Nancy Bennett, MD, MS
CDC
1600 Clifton Road, NE
Mailstop A27
Atlanta, GA 30329-4027
email acip@cdc.gov

RE: Alachua County Florida School Located Influenza Vaccination Program

Dear Colleagues:

As a follow-up to last year's correspondence (please see attached) regarding availability of the influenza intranasal spray vaccine, it is our understanding that the ACIP plans to vote on a recommendation this week. We hope that the data supporting the efficacy of the revised intranasal vaccine presented to the ACIP is compelling enough to yield a positive vote for its' use in the 2018-2019 season. If the ACIP reinstates a recommendation for use of the intranasal vaccine, we urge CDC to facilitate its' use by ensuring that it is on the VFC list of approved vaccinations and equally important, that it is available for use by early Fall 2018.

It is our understanding that pre-book orders for the VFC Program closed on February 9, 2018, despite the impending vote of the ACIP on the intranasal vaccine. Please consider establishing a special pre-book as soon as possible so that at a minimum, the approximately 63 State VFC providers can ensure that the intranasal spray, that has been demonstrated to increase uptake of life saving vaccines in our local children, is available for our School Located Influenza Vaccination Program in early Fall 2018.

The 2017-2018 flu season continues to be harsh and particularly deadly to children. Getting vaccinated has been positively correlated to lower mortality and lessening of disease severity. As noted in previous correspondence, our Control Flu Program has been negatively impacted by the unavailability of the intranasal spray for the last two years as vaccination rates have been reduced by approximately 40%, mostly in the lower socioeconomic demographics. Not surprisingly, adverse impacts due to influenza like illness has increased.

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Page 2

We are confident that CDC will protect the health of our children and by extension, our community, by heeding the recommendations of a community that has demonstrated that by vaccinating significant percentages of our students, community immunity can be achieved.

Thank you for your immediate attention to this matter. Please contact me should you have any questions or require additional information.

Sincerely,



Lee Pinkoson, Chair
Alachua County Commission
Chr18.042

LP/PM/pm

cc: Board of County Commissioners
Michele L. Lieberman, Interim County Manager
Sylvia Torres, Interim County Attorney
Paul Myers, Alachua County Health Department

From: Kit Kubitz [mailto:mesondk@yahoo.com]
Sent: Friday, September 22, 2017 1:16 AM
To: Advisory Committee on Immunization Practices (CDC) <acip@cdc.gov>
Subject: Public comment on review of antivirals for influenza for October 25 ACIP Meeting

Ms. Stephanie Thomas and ACIP staff and members

Enclosed is a public comment, which I request be made available to the Advisory Committee on Immunization Practices (ACIP) for its Oct. 25 meeting in connection with any discussion of influenza vaccines, effectiveness, availability, and therapy.

The comments address the need for the ACIP to review and make updated recommendation on the use of antivirals during both normal flu seasons and as contingency planning for emergency or pandemic flu occurrences, including reviewing the availability of conventional and new antivirals, the composition of stockpiles, and the need for development or possible Emergency use authorization of new antivirals, which may be available before effective vaccines can be developed in some cases.

I have provided my name, contact information, role (individual) and topic on this one page comment. Please make this comment available to the ACIP and include it in the record of the ACIP meeting. Let me know if more information is required.

Kermit R. Kubitz
415-412-4393
mesondk@yahoo.com

Comments to Advisory Committee on Immunization Practices
For Meeting of October 25-26, 27

Name: Kermit R. Kubitz 468 Lansdale Ave, San Francisco, CA 94127
Organization: Individual health care patient and consumer
Email: mesondk@yahoo.com
Topic: Use of antivirals for flu season and pandemic flu through stockpiling,
development of new antivirals, and pandemic control

COMMENTS

The Advisory Commission on Immunization Practices (ACIP) should consider three topics related to antiviral use for influenza. These topics are:

1. Availability of antivirals for influenza during normal influenza seasons.
2. Development and use of new and novel antivirals, including IV and Broad Spectrum Antivirals (BSAV)
3. Stockpiling and composition and availability of antivirals

The ACIP makes recommendations about vaccination, but also issues guidance about use of antivirals for influenza. The ACIP should recognize that in view of the level of, or partial effectiveness of, vaccination, that antivirals, including new antivirals, may be important in treating and mitigation of the impact of normal and emerging new influenza types. As influenza is constantly changing and evolving, so must therapies for influenza be updated to reflect the most effective new therapies in the form of antivirals, especially in vaccines provide only limited protection.

There are three FDA-approved influenza antiviral drugs recommended by CDC for use against recently circulating influenza viruses: [Relenza \(zanamivir\)](#), [Tamiflu \(oseltamivir phosphate\)](#), and [Rapivab \(peramivir\)](#). Each of these antivirals has different characteristics. Some are oral, but a recently approved drug, Rapivab, is an IV antiviral. Rapivab was also recently approved by the FDA for pediatric use. The ACIP should consider updating recommendations to include consideration of when each type and method of application antiviral should be used in upcoming flu seasons. For example, it may not be appropriate to use antivirals which interfere with virus replication with live attenuated vaccines.

There are also promising new approaches to development and use of new, either Influenza type specific, or Broad Spectrum antivirals. The ACIP should ask for a briefing from the CDC and FDA on these new antivirals, for consideration in when an how to recommend their use, and whether it is appropriate to expedite development and regulatory review. The ACIP should also seek briefing on the Strategic National Stockpile (SNS) of antivirals and the composition, whether prior or new antivirals. There have recently been reports of antisense oligonucleotide antivirals which interfere with viral replication by masking the RNA necessary for viral replication.

A phase 1 clinical trial published in the *British Journal of Clinical Pharmacology* found that radavirsen -- an antisense oligomer that inhibits the production of certain influenza proteins -- is safe and well-tolerated in healthy individuals. Additional studies on radavirsen's potential as a treatment for influenza are warranted. In the 56-participant trial, pharmacokinetic analyses indicated that at 8mg/kg, radavirsen is expected to be effective in the treatment of influenza. "This is the first demonstration of the safety and tolerability and pharmacokinetics of an antisense oligonucleotide for the treatment of influenza A," wrote the authors of the study. The ACIP should be informed and closely monitor the status of such new antivirals, and recommend expedited development and regulatory approval, including EUA readiness, if warranted by emerging flu types and conditions.

Hepatitis



6185 Buford Hwy Bldg G
Norcross, GA 30071

February 7, 2018

RE: Comments on the ACIP's Review and Consideration of HEPLISAV-B (2/21/18 Meeting)

To the Members of the Advisory Committee on Immunization Practices:

I write to provide comment on behalf of CPACS Cosmo Health Center and the Atlanta Hep B United Coalition with regards to the consideration of HEPLISAV-B. Hep B United Atlanta is a partner coalition of Hep B United and has the mission to promote coalition building, education, testing, and follow up for communities with the highest rates of disease, particularly immigrant, refugee, and Asian American Pacific Islander communities. In partnership with CPACS Cosmo Health Center, HBU Atlanta links patients to critical follow up care which includes bridging the gaps to vaccination.

Through our screening efforts in the greater Atlanta we found that only 21% of our target population were immune due to vaccination and 41%, were vaccine eligible. Of those who were vaccine eligible, nearly half these susceptible patients were between the ages of 18 and 40, the "child-bearing range", and posed the risk for perinatal transmission should they develop acute infection. Nearly all of these susceptible patients were also uninsured, and many were below the poverty line.

For these vulnerable communities in particular, the full cost of three doses of vaccine, which they are often paying out of pocket for, the number of days taken off of work, and the logistics of getting to a health center for vaccination are all barriers to completing the 3 dose series. In addition, the prolonged period of 6 months to complete the series interval leaves many patients, particularly migrant and transient workers, with loss to follow-up. As a Community Health Center dedicated to working with those who are uninsured and below the poverty line, we do believe that having the new 2 dose vaccine series will improve vaccination rates by potentially reducing overall cost to the patient, decreasing number of visits, and expediting series completion.

Thank you for the opportunity to offer our experiences and comments.

Sincerely,
Amitha Sampath, MD, MPH, FAAP
Associate Medical Director, CPACS Cosmo Health Center
amitha.sampath@cpacs.org

Advisory Committee on Immunization Practices (ACIP) Secretariat
[1600 Clifton Road](#), N.E., Mailstop A27
Atlanta, GA 30329

RE: Comments on the ACIP's Review and Consideration of HEPLISAV-B (February 21, 2018 Meeting)

To the Members of the Advisory Committee on Immunization Practices:

Thank you for the opportunity to be here to add my voice along with those of scientists, health experts, and advocates in support of the new science-based, two-dose hepatitis B vaccine regimen, HEPLISAV-B.

I have been receiving treatment for hepatitis B close to 4 years now, but thinking back it amazes me how lightly I took this disease. Even after knowing I had Hepatitis B, several years passed before I received treatment.

As a member of the diverse Lesbian, Gay, Bisexual and Transgender community, I was there because I wanted to protect myself against HIV/AIDS. I am well aware of those risks. I was there to start on PrEP (pre-exposure prophylaxis) and it was there that I was told my viral load was in the hundreds of millions.

I share this anecdote to show how little I knew, and the public knows, about this disease. I am fortunate to stumble upon treatment, but many others may not be. The rate of hepatitis B infections in adults increased 20.7% in 2015 alone. At least 5,000 lives are unnecessarily lost each year from liver failure or liver cancer.

The availability of two-dose vaccines over 1 month instead of the 3 doses over 6 months is a critical tool to protect many more Americans. Considering the low percentage of those who currently complete all three doses, this is one less barrier for vulnerable and at-risk communities to receive the necessary protection.

There is no cure for hepatitis B. Disease prevention through more effective vaccines is critical to reducing the spread of the disease and to break the cycle of infection among families and partners. I count myself among the fortunate, but I also believe that in this resource rich country, the health of Americans should not be left to chance. Through evidence-based policies, I believe we can better protect all Americans.

Thank you again for this opportunity.

Binh T. Ly
223 N. George Mason Dr., Unit 3, Arlington, VA 22203
binhtly@vt.edu

From: Amy Shen Tang
To: [Advisory Committee on Immunization Practices \(CDC\)](#)
Cc: [Janice Lyu](#)
Subject: FW: ACIP recommendation for new 2 dose hep B vaccine
Date: Monday, February 12, 2018 1:37:51 PM

To the Advisory Committee on Immunization Practices (ACIP),

This letter is in support of ACIP's recommendation for the FDA-approved HEPLISAV-B Hepatitis B vaccine for adults 18 years and older.

Our federally qualified health center in New York City serves a largely Asian immigrant population at risk for hepatitis B virus (HBV). Over the years, we have screened more than 55,000 adult patients for hepatitis B, approximately 15% who are susceptible to HBV infection and whom we offer HBV vaccination with the currently available 3-shot vaccination series. Approximately one-third of adults offered HBV immunization at our health center do not complete all 3 vaccines that must be given over a minimum of 6 months.

These are largely adults who are at increased risk for HBV infection due to their birth from a region with high to intermediate prevalence of HBV or household contact with someone with HBV. Ensuring completion of the hepatitis B vaccination series is of particular importance in our patient population to prevent further transmission of HBV.

As a community health center, we follow ACIP guidance for immunization and know that without an ACIP recommendation, HEPLISAV will not be distributed to our at-risk population. Please recommend HEPLISAV-B as an available option for immunization of adults who need hepatitis B vaccination.

I have no conflicts of interest to declare.

Sincerely,

Amy Shen Tang, MD
Hepatitis B Program Director
Charles B. Wang Community Health Center
268 Canal St.
New York, NY 10013
Email: astang@cbwchc.org
Phone: 212-379-6999



3805 Old Easton Road
Doylestown, PA 18902
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February 7, 2018

Advisory Committee on Immunization Practices (ACIP) Secretariat
1600 Clifton Road, N.E., Mailstop A27
Atlanta, GA 30329

RE: Comments on the ACIP's Review and Consideration of HEPLISAV-B (February 21, 2018 Meeting)

To the Members of the Advisory Committee on Immunization Practices:

On behalf of the Hepatitis B Foundation and the Hep B United coalition, thank you for the opportunity to provide comments on ACIP's consideration of HEPLISAV-B. We represent a community of research scientists, public health and patient advocates, and hepatitis B service providers who are all pleased HEPLISAV-B, the new two-dose hepatitis B vaccine regimen, received FDA approval.

In the U.S., an estimated 2.2 million Americans are chronically infected with hepatitis B (HBV). At least 5,000 of these individuals die prematurely each year from cirrhosis, liver failure or liver cancer. Even with availability of current HBV vaccines, there are up to 70,000 new infections each year. This number is exacerbated by the ongoing opioid crisis, affecting primarily young adults who should be protected by vaccination. In 2015 alone, the rate of acute HBV infection in the U.S. increased by 20.7%, rising for the first time since 2006, with the sharpest increases in new cases occurring largely in states that have been impacted by the opioid epidemic.

National survey data indicate that the overall HBV vaccine coverage rate among US adults is 25% - and only 32.6% of adults between the ages of 19 and 49 years are fully covered by the three-dose series. Recent studies also suggest that hepatitis B vaccine coverage is low among people with diabetes and HIV-infected individuals, two additional high-risk groups. It is critical to increase HBV vaccination coverage among high-risk populations and young adults born prior to 1991, when HBV vaccination for infants became routine. The 2017 CDC National Progress Report on Hepatitis Elimination reveals the U.S. is behind our national target and a 63.8% reduction from the 2015 reported acute HBV infection rate is needed to meet the 2020 goal of 0.50 cases per 100,000 U.S. population.

Hep B United is a national coalition with partners in 18 states. Our partners have found that one of their biggest challenges is vaccine completion among highly impacted communities. In 2011-2013, our coalition partner in Philadelphia pilot tested a mobile HBV vaccine clinic, removing the barriers of cost, language, and transportation for susceptible individuals. Even with removing these barriers, only 13% of those who received a first dose of vaccine returned for their third dose, while completion of the second dose remained high, at 81 percent.

We believe having the new two-dose vaccine will play a significant role in the prevention and elimination of hepatitis B in the U.S. Thank you again for this opportunity to comment.

Kate Moraras, MPH (Speaker) | kate.moraras@hepb.org
Senior Program Director, Hepatitis B Foundation and Director, Hep B United



Advisory Committee on Immunization Practices (ACIP)
February 21, 2018
Testimony of Bekeela Davila
Program Coordinator, National Viral Hepatitis Roundtable (NVHR)
1612 K St NW
Suite 1202
Washington, DC 20006
bdavila@nvhr.org
SUBJECT: HEPLISAV-B Hepatitis B Vaccine

On behalf of the National Viral Hepatitis Roundtable, a coalition of 500+ organizations working to end the hepatitis B and C epidemics in the United States, I want to thank the Advisory Committee on Immunization Practices for the opportunity to testify today. I am here to express NVHR's strong support for the Committee's recommendation of the HEPLISAV-B hepatitis B vaccine.

Now, more than ever, we need this vaccine. An estimated 2.2 million Americans are living with hepatitis B, with up to 70,000 new infections each year. This number continues to grow as a result of the opioid crisis. Reported cases of hepatitis B, which can be transmitted via injection drug use, increased 20 percent in the year 2015 alone. Recent data indicate that only a quarter of adults age 19 and older are fully immunized, as adults aged approximately 25 years and older were not routinely vaccinated against hepatitis B at birth in the United States. Meanwhile, an estimated 5,000 to 6,000 Americans die each year of hepatitis B-related liver complications.

Approval and recommendation of the HEPLISAV-B vaccine has the potential to turn the tide in the battle against the hepatitis B epidemic. Prior to the approval of this vaccine, patients had to comply with a three-dose regimen, administered over six months. The availability of a two-dose vaccine, administered over a one-month period, will significantly boost vaccination rates and save countless lives. This safe and effective vaccine, taken over a shorter period of time, could be offered not just in traditional clinical settings but also at syringe access programs and substance use treatment programs. Simply put, the widespread availability of this vaccine can slow and stop the spread of new infections and prevent thousands of deaths in this country.

In sum, NVHR strongly supports recommendation of the HEPLISAV-B as a new and powerful tool in the fight to eliminate hepatitis B in the United States.

Herpes Zoster

Ruxandra Draghia, MD, PhD
Vice President
Public Health and Scientific Affairs

Merck & Co., Inc.
PO Box 1000, UG2AB-32
351 N. Sumneytown Pike
North Wales, PA 19454
Tel 267-305-0054



August 11, 2017

CAPT Nancy Messonnier, MD, USPHS
Director, National Center for Immunization and Respiratory Diseases

CDR Amanda Cohn, MD, MPH, USPHS
Executive Secretary, Advisory Committee on Immunization Practices (ACIP)

Centers for Disease Control and Prevention (CDC)
1600 Clifton Road, NE
Atlanta, GA 30329

Subject: Herpes Zoster Vaccines Discussion, ACIP Meeting, June 21, 2017

Dear Drs. Messonnier and Cohn,

We at Merck greatly appreciate the vital role the CDC and ACIP play in our nation, protecting the public's health and guiding the use of vaccines. We share the goal of improving individual and public health through vaccine discovery, development, and delivery.

We are writing to you concerning the ACIP Herpes Zoster (HZ) Work Group's interim policy opinion of the investigational adjuvanted HZ subunit (HZ/su) vaccine (Shingrix[®], GSK) presented at the ACIP meeting on June 21, 2017. The Herpes Zoster Work Group's interim majority opinion favors a preferential or differential recommendation for patients 50 years of age and older of Shingrix over ZOSTAVAX[®] (Zoster Vaccine Live) (ZVL), a live attenuated vaccine licensed in the United States of America since 2006. Merck strongly objects to a policy that would adopt this interim opinion. This letter delineates the scientific basis of our objections, rooted in ACIP's own charter, known implementation issues for adult vaccines, and certain unknowns regarding HZ/su.

As you know, the U.S. Food and Drug Administration (FDA) is currently considering an application for licensure of Shingrix for use in the prevention of HZ and related complications among certain eligible populations. The FDA will convene a meeting of the Vaccines and Related Biologic Products Advisory Committee to discuss this vaccine's application on September 13, 2017. Should the FDA approve this vaccine, it will have been demonstrated that the vaccine is efficacious in the eligible population when used according to the dosing instructions in the vaccine's product circular, with a safety profile as described in that circular. Contraindications, warnings, and/or precautions are likely to be defined as well. A well-controlled Phase 1 to 3 studies program will have served as the basis of licensure of the vaccine.

However, Merck considers that there are insufficient data to warrant an ACIP preferential or differential recommendation for this vaccine over ZOSTAVAX. Historically, ACIP has infrequently made a preferential recommendation and not at first licensure of a vaccine. A preferential or differential recommendation for one vaccine over another generally has been based on a demonstration that the “preferred” or “differentially-recommended” candidate vaccine has substantial clinical and/or economic benefits over the other vaccine in real-world use. This includes both use of a vaccine as intended (regimen administered as studied in clinical trials in appropriate populations); sub-optimal use of the vaccine due to the imperfections of real-world health care delivery; and, a broadening of use of the vaccine to under- or un-studied populations. Furthermore, the benefits of a candidate vaccine that may warrant a differential or preferential recommendation should be gained with an acceptable real-world cost effectiveness compared to that of the comparator vaccine. None of these critical data are available for HZ/su.

Merck’s position is that any newly licensed vaccine for HZ should have the same recommendation as ZOSTAVAX at initial licensure, and should accumulate data and evidence of real-world effectiveness through actual implementation to inform any future adjustments to that recommendation. According to comments by Dr. Kathleen Dooling (CDC co-lead, Herpes Zoster Work Group) at the June ACIP meeting, the additional time post-licensure to accumulate this information is estimated at 1-8 years, depending on the outcome.

Basis for Merck’s Position

According to the CDC’s description of the ACIP charter, “Committee deliberations on use of vaccines to control disease in the U.S. *shall* include consideration of disease epidemiology and burden of disease, vaccine efficacy *and effectiveness*, vaccine safety, economic analyses and *implementation issues*” (italics added for emphasis) (CDC, 2016; <https://www.cdc.gov/vaccines/acip/committee/charter.html>). It is Merck’s position that several of these required (“*shall include*”), fundamental considerations – specifically, *effectiveness* and *implementation issues* – have not been assessed for the HZ/su vaccine, chiefly because real-world data and experience are lacking for this vaccine candidate. Because of the critical distinction between efficacy and effectiveness, the ACIP charter states, “The committee may revise or withdraw their recommendation(s) regarding a particular vaccine as new information on disease epidemiology, vaccine effectiveness or safety, economic considerations or other data become available.” Consistent with that, as real-world evidence of effectiveness in practice is accumulated for the HZ/su vaccine after it is licensed, the ACIP should consider those data and the need for any revised recommendation.

Merck’s concerns are consistent with questions and concerns raised by ACIP members and liaison representatives (as well as Merck staff) during the June ACIP meeting, specifically:

- A preferential recommendation at first availability is inconsistent with CDC’s and ACIP’s past practices and is not warranted in this instance, with only efficacy data generated from clinical trials available at this point.
- The interim majority opinion favoring a preferential recommendation is not supported by currently available evidence. It is predicated on assumptions that can be confirmed (or refuted) only through real-world experience that is not yet available, such as:
 - Observed two-dose adherence to the HZ/su series in an adult population;
 - Verified effectiveness and durability after a single dose of HZ/su;

- Experience with adjudicating the administrative complexity of a 2-dose vaccine with variable insurance coverage depending on the insurance benefit design (e.g., medical vs. pharmacy benefit).
- A differential recommendation for use of the HZ/su vaccine in the population ages 50-59 years is not supported by available post-licensure durability data. Historically, the ACIP declined to recommend the use of ZOSTAVAX in the 50-59 age cohort because of what it considered to be limited durability data in the clinical trial (Schmader, 2012) and lack of effectiveness data (CDC, 2014).
- A preferential or differential recommendation will have an impact on available ZOSTAVAX supply beyond what would be expected with the entry of a competitor into the marketplace. Because a preferential or differential recommendation would cause a significant reduction in utilization of ZOSTAVAX, Merck would by necessity reduce manufacturing of the vaccine based on anticipated demand. As the production of ZOSTAVAX is a lengthy process, Merck would therefore be unable to respond efficiently to any unexpected changes in demand for ZOSTAVAX that could arise from unanticipated issues with HZ/su, including non-adherence to the two-dose regimen or supply disruptions that could arise for any vaccine.

Additionally, a preferential or differential recommendation is likely to lead many healthcare systems to stock only the HZ/su vaccine, effectively restricting the market to a single, untried-in-practice vaccine. A preferential or differential recommendation could thus create a barrier to choice for providers and patients, thereby inhibiting their ability to make personalized medical choices based on individual patient / product attributes. For example, a provider who knows his or her patient rarely adheres to therapy regimens may prefer to recommend Zostavax based on the concern that the patient would not get the two doses needed for the HZ/su vaccine. The following sections provide historical background and address in detail the unknowns and pros/cons regarding a preferential or differential recommendation as presented during the June ACIP meeting by Dr. Dooling.

Section 1: Historical Background:

Background on ZOSTAVAX

Currently, the CDC and ACIP recommend the use of ZOSTAVAX for eligible individuals 60 years of age and older, despite a labeled indication by the FDA for use among eligible individuals 50 years of age and older. Based on the Shingles Prevention Study (SPS) (Oxman, 2006), ZOSTAVAX was licensed and recommended for individuals 60 years of age and older in 2006, with the CDC and ACIP publishing recommendations for use of the vaccine in 2008 (CDC, 2008). In 2011, based on the ZOSTAVAX Efficacy and Safety Trial (ZEST) (Schmader, 2012), the FDA extended approval of ZOSTAVAX to the 50-59 year cohort. However, CDC and ACIP declined to expand the recommendation of ZOSTAVAX to the 50-59 population. Initially, the stated reluctance related to supply (CDC, 2011), but these supply issues were resolved in early 2012. Subsequently, the CDC and ACIP were unwilling to extend the recommendation because of lack of information on the durability in that age cohort beyond the approximately 2 years of follow-up of subjects in ZEST, and because of econometric models that showed that the vaccine was less cost-effective if administered in a 50-59 cohort (CDC, 2014).

Background on ACIP Precedents and Consistency across Work Groups

The CDC and ACIP have historically declined to make a preferential recommendation of one vaccine over another when multiple vaccines are available. Instead, they have adopted a position of choice, which has the merits of ensuring that real-world implementation evidence is gathered and assessed and concomitantly promoting free-market competition and minimizing the risk of vaccine shortages in the event of unforeseen production or safety issues.

For example, with HPV vaccines, CDC declined to make any formal declaration of preference for administration among females (ACIP, 2010), even after quadrivalent Gardasil® was recommended for boys and men in 2011, based on protective effects against anogenital warts. Even following the 2015 licensure of Gardasil 9®, which provides significantly broader coverage than either the bivalent vaccine or the quadrivalent vaccine, the ACIP refrained from either a preferential or differential recommendation for girls and women (ACIP, 2015).

During the summer of 2014, ACIP and CDC recommended that during the 2014-2015 influenza season, live attenuated influenza vaccine (LAIV) should be used for healthy children 2 through 8 years of age when immediately available and when there were no contraindications or precautions against getting that vaccine. That recommendation had to be withdrawn due to observed lack of real-world effectiveness in prior seasons (CDC, 2015; <https://www.cdc.gov/media/releases/2015/s0226-acip.html>).

Section 2: Unknowns discussed at June 21st ACIP Meeting

During the June 2017 ACIP meeting, Dr. Dooling presented a summary of the unknowns and pros/cons of a preferential recommendation, which elicited questions and concerns from ACIP members and liaison representatives. Below is a summary of Merck's assessment of these unknowns. Detail is attached as an addendum to this letter.

Unknown #1: Two-dose adherence with HZ/su

- Work Group Estimate: *Within a 1- to 2-year period, adherence will likely change as the program matures and providers become familiar with HZ/su reactogenicity profile (K. Dooling presentation, slide 21)*

Comment: The extent of series completion with the HZ/su vaccine in the real world is unknown. The fulfillment of the 2-dose regimen from the actively monitored ZOE 50/70 pivotal efficacy trials cannot be used for a base case, let alone used as a lower bound of the sensitivity analysis for series completion in modeling. Series completion is a pivotal parameter in case-burden reduction and cost-effectiveness modeling. It is crucial to acknowledge the tentativeness and lack of real-world evidence for any assumptions of this parameter.

Significant real-world implementation challenges exist related to actual series completion of multi-dose adult vaccine series or regimens (Nelson, 2009, Patterson, 2017). These challenges include:

- a) possible Grade 3 reactions with each dose;
- b) possible patient out-of-pocket cost sharing for each dose, depending on the benefit design of their insurance plan(s); and,
- c) inconsistencies in site of vaccination administration, as more than half of herpes zoster vaccinations in the United States take place in a pharmacy, where the most common pharmacy administered adult vaccinations are single dose (Influenza, ZOSTAVAX, PCV13). The disproportionate percentage of herpes zoster administration in the pharmacy is based on coverage under Medicare Part D, the pharmacy benefit for Medicare-eligible patients. For adults not yet eligible for Medicare, ages 50-64, and covered by commercial insurance, the location of herpes zoster vaccine administration could be

either in a clinician's practice setting or in a pharmacy, adding additional uncertainty regarding uptake and series completion due to inconsistencies in claim adjudication, patient tracking, and follow-up methodologies.

Because there are no real-world data on series completion for the HZ/su vaccine, Merck used data from a published paper (Nelson, 2009) on series completion of hepatitis A and hepatitis B vaccines among adults to estimate as inputs for a base case and sensitivity analyses. The Merck model presented at the ACIP meeting included a base-case value of 73% – a value set at the request of the CDC. Our original analysis submitted to the CDC included our base case of series completion of 43.6%, which we contend is a more appropriate estimate, given additional studies released since our original analysis (see below).

Specifically, two additional studies utilizing more recent data on adult hepatitis A and hepatitis B vaccine series completion from Truven Health Analytics have been completed, one sponsored by GSK, the other by Merck.

- 1) Patterson et al. (2017) (GSK-sponsored study) found that among commercial and Medicare patients aged ≥ 19 years, 32% to 36% completed the hepatitis A vaccination series and 39.6% to 48.9% completed the hepatitis B vaccination series from 2007-2015.
- 2) Trantham et al. (2017) (Merck-sponsored study) found that among adult commercial and Medicare patients aged ≥ 19 years, 32% completed the hepatitis A vaccination series and 31% completed the hepatitis B series from 2008-2015. Among older adults, completion rates for hepatitis A were 38%, 39%, 32%, and 26% in adults 50-59, 60-64, 65-69, and 70+ years of age, respectively. Completion rates for the hepatitis B series were 39%, 40%, 29%, and 25% in adults 50-59, 60-64, 65-69, and 70+ years of age, respectively.

At the June 2017 meeting, ACIP member Dr. Allison Kempe requested analyses using 25% and 50% as the input for series completion in the CDC model. Merck will use these values to rework the model and has offered to present the data to the Herpes Zoster work group (Merck letter to K. Dooling, July 15, 2017). In addition, we recommend that the CDC present analyses across a range of values for series completion when CDC model results are presented in October 2017, consistent with the uncertainty of this parameter in real-world practice.

In summary, recent studies of real-world series completion of Hepatitis A and B vaccines suggest that series completion with HZ/su will be less than the base case in both manufacturers' models. Overestimation of the value of this parameter leads to more favorable cost-effectiveness analyses of the HZ/su vaccine.

Unknown #2: Vaccine Efficacy [VE] and durability of 1 dose HZ/su

- *Work Group Estimate: 2- to 3-year period needed for an observational study in a large HMO (e.g. 1M unvaccinated adults) to accumulate sufficient 1-dose HZ/su recipients. 4+ years required for age-specific estimates and duration of protection (K. Dooling presentation, slide 21)*

Comment: There are no publicly presented clinical data to either demonstrate vaccine efficacy or effectiveness and durability of one 50-mcg dose of the HZ/su, or even inform an estimate of those parameters. Indeed, the selection of a 2-dose regimen for the HZ/su pivotal trials was based on phase II immunogenicity studies that judged a single 100-mcg dose regimen likely to be inadequate for protection. These data indicated that a 2-dose vaccine (50 mcg gE per dose), administered 2 months apart, provided higher peak gE-specific cell-mediated immunity (CMI), compared to a single 100-mcg

dose of gE 1 month after the final dose. gE-specific CMI returned close to baseline values at 12 and 36 months post single dose (Chlibek, 2014). It is crucial to acknowledge the tentativeness and lack of real-world evidence for any assumptions of this parameter. In the models presented at the June ACIP meeting, and assumptions for a preferential recommendation, efficacy/effectiveness after one 50-mcg dose is a pivotal parameter in case-burden reduction and cost-effectiveness modeling.

To our knowledge, there have never been any immunologic or efficacy assessments of a single 50-mcg dose. Based on oral comments by GSK's Len Friedland, MD, at the June ACIP meeting, the one-dose vaccine efficacy/effectiveness value used in GSK's HECON model was based on phase II immunogenicity data with the 100-mcg dose (not the dose expected at licensing), but he did not state or share actual data showing why GSK's model had a higher VE for one 50-mcg dose of HZ/su compared to ZOSTAVAX at all ages. If there are data to support this assumption, that data should be presented publicly. According to Dr. Friedland, a one-dose durability assumption was based on the waning rate of one dose of ZOSTAVAX with a linear decline. As pointed out by one of the ACIP members, and supported by post-licensure studies, effectiveness of ZOSTAVAX does not wane in a linear fashion (Baxter, 2016). ZOSTAVAX effectiveness drops from the first to second year after vaccination, and wanes thereafter slowly from the second year forward. In our model, we do fit a linear function only after the first year. There is no scientific basis to extrapolate the waning rate of ZOSTAVAX to a single dose of HZ/su, and applying a waning rate such as that observed after the second year following ZOSTAVAX is incomplete and inappropriate.

Moreover, HZ/su and ZOSTAVAX are different vaccines with different mechanisms of action. It may not be appropriate to use data from one vaccine to inform assumptions for the other, especially when the assumption is not based on the anticipated indication of the investigational vaccine. At a scientific meeting in Venice, Italy, in May 2017, Dr. Rino Rapuolli, Chief Scientist and Head of External Research & Development at GSK Vaccines, stated to the assembly (with Merck representation in the audience) that there are no data publicly available on single-dose VE, nor is a single dose indication expected.

In summary, the effectiveness, durability, and waning rate of one dose of HZ/su are unknown. Overestimation of the value of this parameter leads to more favorable cost-effectiveness analyses of the HZ/su vaccine.

Unknown #3: Possibility for rare safety events with HZ/su, which relies on a new adjuvant

- *Work Group Estimate: A 1- to 2-year period may be sufficient for surveillance for rare adverse events (K. Dooling presentation, slide 21)*

Comment: Merck's position is that at the time of licensure, there are sufficient data to inform the efficacy and safety of medicinal products including vaccines. Merck is committed to study our medicines and vaccines, and to monitor real-world effectiveness and safety, with a goal of furthering the body of data regarding its products. This being said, we do take note of the comments of Dr. Dooling at the June ACIP meeting. We also note that post-licensure safety studies on ZOSTAVAX have been conducted and published. As well, approximately 40 million doses of ZOSTAVAX have been distributed globally (29 million in the US) since licensure. Given the limited number of subjects who will have received HZ/su at the time of expected licensure, a preferential or differential recommendation absent real-world evidence would be premature.

Unknown #4: Vaccine effectiveness (VE) and durability of HZ/su beyond 4 years

- *Work Group Estimate: 4- to 8-year period beyond licensure would be necessary to study and report on long-term effectiveness (K. Dooling presentation, slide 21)*

Comment: At the June, 2017 ACIP meeting, Dr. Andrew Leidner presented an overview of Merck's and GSK's cost-effectiveness analyses (CEA) of HZ vaccination. There were several significant uncertainties regarding pivotal model inputs, including vaccine effectiveness and durability beyond 4 years. As outlined in Dr. Craig Roberts' letter to Dr. Dooling on July 14, 2017, requesting consideration of this issue in CDC's CEA to be presented in October, vaccine efficacy after two doses of HZ/su is substantial, but the pivotal trials show some decline in vaccine efficacy over the 4 years in the trial. The GSK model assumes HZ/su VE of more than 30 years, based on limited 9-year immunogenicity data. These latter data were presented at the Feb 2017 ACIP meeting. The 9-year immunogenicity data arose from a small phase II study in Europe of a homogeneous population of 70 subjects, 60 years of age and older, and unrepresentative demographically of the subjects in ZOE 50/70. Close inspection of the data presented in Feb 2017 shows that the gE-specific CMI drops ~ 4-fold from the peak value 1-month post dose 2. Although no confidence intervals were presented in the study, the lower quartile of the values at 9 years overlaps with the third quartile at baseline on a log scale.

As mentioned previously, the CDC and ACIP were previously unwilling to extend the recommendation for ZOSTAVAX to the 50-59 population because of lack of information on the durability in that age cohort.

Unknown #5: Care-seeking among vaccinees with reactions

Comment: GSK has presented several studies to ACIP, including ZOE 50/70, where the significant reactivity of their vaccine has been described. As summarized in the CDC's GRADE analysis, 17% of HZ/su vaccinees overall are expected to have a Grade 3 reaction, which involves interference with activities of daily living as part of the definition. A significant proportion of individuals had Grade 3 reactions with each dose of HZ/su and the average duration was 1-2 days depending on the extent of the reaction. There are no real-world data to describe patterns of health care-seeking behaviors among HZ/su vaccinees with reactions or how this may impact series completion of a multi-dose vaccine. It is uncertain at this juncture how major pharmacy chains would perceive the acceptability of, or their preparedness for, administering an adult vaccine associated with a 17% rate of Grade 3 events.

Unknown #6: Insurance coverage

(See detailed response in addendum under non-preferential policy cons)

Comment: Reimbursement for herpes zoster vaccination comes from three major sources: commercial insurance, Medicare Part D, and Medicaid. Comments supporting a preferential recommendation made by Dr. Dooling at the June ACIP meeting incorrectly represented the ability of insurance plans to select one ACIP-recommended vaccine over another based on cost.

- **Commercial Insurance:** Under the Affordable Care Act (ACA), all commercial insurers are required to provide first-dollar coverage for all ACIP Category A and B recommended vaccines, except for 'grandfathered plans'. The latter plans currently represent a small fraction of total coverage, which the Centers for Medicare and Medicaid Services (CMS) has said may remain in force through the end of 2018 – barring health system changes that may be enacted by Congress and signed into law by the President. It is important to note, however, that for adults under age 65 covered by commercial plans, vaccines administered in pharmacies may not be covered, because pharmacies may be deemed out of network. This could lead to significant unplanned out-of-pocket expenditures for each dose (or declination of vaccination) for commercially insured beneficiaries.

- **Medicare Part D:** All Medicare Part D plans are required by law to include all FDA-licensed vaccines as a benefit. Plans may tier beneficiary co-pays for vaccines according to their willingness to cover the costs of specific vaccines.
- **Medicaid:** Most state Medicaid programs include ZOSTAVAX as a Medicaid benefit. At the end of calendar year 2016, 44 states, plus the District of Columbia included some degree of coverage. However, coverage varies by age (50-64 or 60-64), by health status (when deemed medically necessary), and by site of care (e.g., only in long-term care facilities). These differences should be factored into implementation considerations and equitable access should be assessed.

Summary

In summary, the CDC and HZ Work Group have enumerated many unknowns as well as pros and cons regarding a preferential or differential recommendation for the HZ/su vaccine at first licensure. We have provided comments addressing the unknowns. The addendum provides additional detail outlining our concerns with the pros and cons of a preferential recommendation outlined by Dr. Dooling in June. In addition, we plan to send a separate letter commenting on the issue of revaccination in those previously vaccinated with ZOSTAVAX.

We reiterate our position that existing data are insufficient at first licensure to warrant a preferential or differential recommendation for Shingrix over ZOSTAVAX.

Merck asks that the CDC help ensure consistency regarding the role of data and evidence in substantiating recommendations across ACIP work groups and the types of recommendations made across ACIP work groups. We expect that the ACIP Herpes Zoster Work Group will provide an objective, evidence-based assessment of the existing clinical and implementation-science data, coupled with a robust evaluation of the unknowns and information surrounding the pros/cons throughout the completion of the ACIP/CDC decision-making process.

Merck respectfully requests you share this letter with the Herpes Zoster Work Group, relevant members of the CDC staff, each ACIP member and each liaison member. We would appreciate that all those listed receive the letter by the end of August so that they have time to consider the detailed issues well in advance of the October ACIP meeting. Merck requests that the letter be made part of the public record on the deliberations by the CDC and ACIP on the use of herpes zoster vaccines.

Thank you for your careful and objective consideration of the points outlined in this letter. If you would find it helpful, my team and I would be happy to discuss these issues with you on the phone or in person at the CDC at your convenience.

Sincerely,



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Vice President, Public Health and Scientific Affairs
Merck Vaccines

cc: Dr. Nancy Bennett, Dr. Kathleen Dooling, Dr. Eddy Bresnitz

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Addendum

PROS and CONS of preferential/differential and non-preferential recommendations: (as outlined by K Dooling, June 2017)

Preferential Policy

PROS	CONS
<ul style="list-style-type: none"> • <i>Substantially more prevention of HZ, PHN and complications</i> <p><u>Comment:</u> This assessment is tenuously based on unsupported assumptions of a) 100% series completion; b) greater one-dose effectiveness and durability of HZ/su at all ages compared to ZOSTAVAX; and c) presumed durability of VE for the completed series of HZ/su. At the October 2017 ACIP meeting, the CDC should provide estimates of number of cases prevented based on more realistic inputs for series completion, 1-dose effectiveness, 1- and 2-dose durability and a vaccination recommendation at 50 years and older for each vaccine.</p>	<ul style="list-style-type: none"> • <i>Reversal of preference may be needed if unexpected safety signal or poor VE (in RW) is observed with HZ/su</i> <p><u>Comment:</u> CDC has experience with the need for abrupt reversal of policy decisions in the form of FluMist® (2015) and RotaShield® (1999).</p>
<ul style="list-style-type: none"> • <i>HZ/su more cost-effective under most assumptions</i> <p><u>Comment:</u> Note first that the models presented were based on a vaccination policy of 60 and over, whereas the PICO scenario in the GRADE analysis was for 50 and over and the preferential recommendation being considered is for 50 and over.</p> <p>As is well known, cost-effectiveness analysis (CEA) modeling relies on inputs to parameters based on available evidence. The CEA calculated by the two manufacturers differed widely and favored HZ/su because of markedly different input assumptions, several not based on any published or presented data. Even with that, the</p>	<ul style="list-style-type: none"> • <i>Will lead to more Grade 3 reactions following vaccination</i> <p><u>Comment:</u> The expected frequency of Grade 3 reactions with HZ/su could influence provider and public behavior in terms of acceptability and adherence. See comments in the text of the letter regarding <i>Care seeking among vaccinees with reactions</i> under unknowns.</p>

<p>Scenario 2 sensitivity analysis in the GSK model yielded results that were very similar to the Merck base case.</p>	
<ul style="list-style-type: none"> • <i>HZ/su is refrigerator stable (decrease provider barriers)</i> <p><u>Comment:</u> Based on Merck-supported 2015 qualitative market-research interviews with physicians and integrated delivery systems conducted by an independent third party, vaccine storage currently has minimal influence on choice or a decision whether to stock ZOSTAVAX. In another 2015 qualitative market-research, interviews of pharmacists, refrigerated storage was noted as an important feature for less than ~10% of respondents.</p>	<ul style="list-style-type: none"> • <i>Requires 2 doses (increases program barriers)</i> <p><u>Comment:</u> Reliance on administration of 2 doses for efficacy necessarily leads to reliance on provider and public behavior to complete the series. See comments in the text of the letter regarding <i>2-dose adherence with HZ/su and Care seeking among vaccinees with reactions under unknowns.</i></p>

Non-preferential Policy

PRO	CON
<ul style="list-style-type: none"> • <i>Supports competition</i> <p><u>Comment:</u> Competition is important because:</p> <ul style="list-style-type: none"> • it offers choices to providers and consumers in different circumstances to provide individualized, evidence-based care; • encourages manufacturers to optimize customer service; • provides redundancy in case of supply disruptions; • encourages greater education of both HCPs and the public about disease burden and the benefits of vaccination. 	<ul style="list-style-type: none"> • <i>Large differences in VE will result in thousands of preventable herpes zoster cases and hundreds of PHN cases (over the lifespan) (Based on a cohort of 10,000 60 year olds)</i> <p><u>Comment:</u> Statement relies on untested assumptions. See comments in the text of the letter regarding <i>Substantially more prevention of herpes zoster, post-herpetic neuralgia and complications</i> under Preferential Recommendation, PRO above.</p>
<ul style="list-style-type: none"> • <i>2 manufacturers safeguard stable vaccine</i> 	<ul style="list-style-type: none"> • <i>Some insurers/healthcare delivery systems</i>

supply

Comment: With the licensure of a second vaccine to prevent herpes zoster and its complications, competition will likely decrease the current demand for ZOSTAVAX. Market share depends on many factors, including vaccine attributes and price, assuming a similar recommendation for both vaccines. However, a *preferential or differential recommendation at the time of licensure* would abruptly favor uptake of HZ/su and thus accelerate decrease in demand and, subsequently, production of ZOSTAVAX. If there would be any supply disruptions after HZ/su licensure impacting its availability to HCPs and the public, Merck would be unable to promptly respond to abrupt changes in demand. Merck potentially could begin to step up production of ZOSTAVAX, but a return to the market with adequate supply could easily take substantially more than a year.

*may choose to cover only the less**expensive vaccine if no preference is stated*

Comment: This statement is not factually correct. Reimbursement for ZOSTAVAX, and HZ/su vaccine, once licensed, comes from three major sources: commercial insurance, Medicaid, and Medicare Part D.

- **Commercial Insurance:** Under the Affordable Care Act (ACA), all commercial insurers are required to provide first-dollar coverage for all ACIP Category A and B recommended vaccines (except for 'grandfathered plans'). Currently, about 50-60% of commercial insurers provide coverage for ZOSTAVAX to subscribers 50-59 years of age, despite the lack of an ACIP recommendation in that age cohort. More than 98% of commercial insurers provide coverage for the 60-64 population.
- **Medicaid:** Most state Medicaid programs include ZOSTAVAX as a Medicaid benefit. At the end of calendar year 2016, 44 states, plus the District of Columbia, included coverage. However, coverage varies by age (50-64 or 60-64), by health status (when deemed medically necessary), and by site of care (e.g., only in long-term care facilities). Inconsistencies in Medicaid coverage across states result in disparities in uptake by age, race/ethnicity, income, health status, and residence. These differences should be factored into implementation considerations and equitable access should be assessed.
- **Medicare:** All Medicare Part D plans are required by law to include all ACIP recommended vaccines as a benefit. Plans then tier the dollar value of the co-pays for vaccines according to their internal processes. Merck's market research shows

that higher out-of-pocket expenses lead to a lower likelihood that beneficiaries will be vaccinated (these data have been presented to the HZ work group). We have seen no data to support the statement that Medicare Part D plans are more likely to cover HZ/su than ZOSTAVAX with a preferential or differential recommendation, with or without a higher price of the HZ/su vaccine. Acquisition price per regimen could affect tiering of copays.

- **Health care systems:** Hospitals and health care systems may choose to provide only one zoster vaccine within their formulary, given a choice. Formulary committees make decisions based on benefit/risk assessments, implementation issues and price. We have seen no data to support the statement that health care systems are more likely to cover only ZOSTAVAX unless there is a preferential recommendation, with or without a price differential. In fact, Merck solicited input from a spectrum of healthcare providers, including pharmacy chains, on their plans for stocking herpes zoster vaccines if there is a preferential recommendation versus a neutral recommendation. Most have stated they would only stock the HZ/su vaccine with an ACIP/CDC preferential recommendation, whereas they would stock both vaccines with a neutral recommendation.

Comment: An ACIP member at the June 2017 meeting stated that health systems may choose to include only the single-dose vaccine in their formulary because it will be easier to meet quality measures. However, to date there are no NCQA, PQA or NQF developed/endorsed quality measures assessing the provision of herpes zoster vaccine.

	<p>Health systems have widely adopted the two-vaccine pneumococcal regimen adopted by ACIP in August 2014, and not chosen to offer only one vaccine based on cost.</p>
	<ul style="list-style-type: none"> • <i>Onus on providers to compare safety and efficacy</i> <p><u>Comment:</u> The onus is always on providers to compare the risk/benefits of alternative vaccines, just as they do other drug choices. Clinicians will be in the best position to assess patient tendencies to fulfill various 1- or 2-dose regimens and to determine the acceptability of post-vaccination adverse events.</p> <p>In terms of precedent, the ACIP encouraged HCPs to evaluate the relative merits of three HPV vaccines, Gardasil, Gardasil9, and Cervarix and did not make a preferential recommendation. This is also true for Hib formulations and multiple influenza formulations.</p>

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Atlanta, GA 30329
Subject: Herpes Zoster Vaccines Discussion, ACIP Meeting, June 21, 2017, Revaccination Policy

Dear Drs. Messonnier and Cohn,

Thank you for indicating that a response will be sent to my letter of August 11 concerning the ACIP Herpes Zoster (HZ) Work Group's interim policy opinion of the investigational, adjuvanted HZ subunit (HZ/su) vaccine (Shingrix, GSK). In that letter, I stated that we planned to send a separate letter commenting on the issue of revaccination with HZ/su in those previously vaccinated with ZOSTAVAX® (ZVL). This letter summarizes our concerns with the ACIP potentially recommending revaccination of prior ZVL recipients with HZ/su.

As with the issue of available science informing a preferential HZ/su vaccination recommendation, a recommendation to revaccinate individuals who had previously been vaccinated with ZVL entails knowns, unknowns, and pros and cons. We have organized our comments around statements from slides 23 and 25 in Dr. Katherine Dooling's June ACIP presentation (presented in the gray boxes, below).

1. HZ/su efficacy

- HZ/su is more efficacious than ZVL in all age categories
- A substantial amount of HZ and PHN could be prevented by vaccinating this population with HZ/su
- HZ/su is significantly more efficacious over 6 years, with vaccine efficacy (VE) > 97% in the first year which is maintained above 85% in the first 4 years for all ages
- For prior ZVL recipients, HZ/su is a new vaccine

Well-controlled pivotal trials have demonstrated that a regimen of two doses of HZ/su is more efficacious than one dose of ZVL in all age categories. However, the HZ/su clinical data publically presented are limited to 4 years of follow-up of VE. If, per statement in Dr. Dooling's June ACIP presentation, 6 years of follow-up data are available, they should be publically disclosed. Also, the availability of a "new" vaccine only serves as the prompt for consideration for making a

revaccination recommendation. The relevant factors informing a recommendation are vaccine efficacy, reactogenicity, durability, safety, cost-effectiveness, and implementation issues for both the “new” and “old” vaccines. For example, Gardasil9[®] was a new vaccine with expanded coverage over Gardasil[®], yet the ACIP did not recommend revaccination of individuals who had previously received a complete series of GARDASIL[™] (Meites, 2016).

While the policy question proposed by the WG was “Should individuals previously vaccinated with ZVL receive HZ/su?”, we would also suggest a discussion of revaccination with ZVL as part of the policy discussion, as this strategy would help prevent additional cases of Herpes Zoster (HZ) and post-herpetic neuralgia (PHN). It should be noted that ZVL does not have an indication for revaccination in its label, and HZ/su vaccine is not expected to have an FDA-endorsed indication for revaccination within its product circular.

2. ZVL Durability

- Experimental and observational studies indicate significant waning of protection from ZVL
 - VE drops the first year after receipt (15-25%)
 - By 6 yrs post vaccination, VE <35%
 - Negligible protection by 10 years
- 31% of the US population 60 yrs and older followed ACIP recommendations and received ZVL. A significant fraction of ZVL recipients now have very low vaccine protection for HZ and PHN.

The Long-Term Persistence Substudy (LTPS) is an estimation study without a concurrent control group (Morrison, 2013). The WG has previously been critical of the LTPS methodology because the comparison group consists of historical controls and the study only included a third of the vaccinated individuals from the Shingles Prevention Study (Oxman, 2005). Protocol 024 (P024; Baxter, 2017), the Kaiser Permanente Northern California (KPNC) post-licensure study, is a robust study of the effectiveness of ZVL (published online at <https://doi.org/10.1093/aje/kwx245>). We consider that P024 is the most methodologically sound observational study of ZVL effectiveness and point out that slide 16 in Dr. Klein’s presentation at the June meeting is a more accurate representation of ZVL waning than data from the LTPS (Klein N, 2017).

Although vaccine effectiveness (V_{Eff}) for HZ does drop in the first year as shown in the first interim analysis of P024, the decrease does not follow a linear decline. V_{Eff} stabilizes after the first year, with significant person-years of follow-up to year 5 in the first interim analysis. After that, there are fewer person-years of follow-up and the point estimates of V_{Eff} become less stable. We did fit a linear function to years two and beyond in the modelling data using P024 data, and found that V_{Eff} does not fully wane until approximately 20 years post-vaccination, depending on the age group at vaccination (Leidner, 2017).

The statement in slide 25 that ZVL provides “negligible protection by 10 years” appears to be based on the LTPS study, which was designed to estimate V_{Eff} against HZ relative to historical controls, and is not informative with respect to V_{Eff} against PHN. Other studies, including P024, outlined by Ms. Guo in the GRADE analysis presented at the June ACIP meeting, describe long term effectiveness against PHN (Klein N, 2017). These are extremely useful data to consider when assessing the benefit of revaccination for an older age cohort.

The statement that a significant fraction of ZVL recipients now have very low vaccine protection for HZ and PHN is not supported by several of the post-licensure studies published to date. (See slides 12 and 13 from Ms. Gou’s GRADE analysis presented at the June ACIP meeting.) Given the

limitations of LTPS, and without any robust post-licensure studies following individuals for up to 10 years, this statement has limited validity.

The National Health Interview Survey (NHIS) data from 2012 indicated that 20.1% of the population had been vaccinated with ZVL (increased from 14.4 % and 15.8% in 2010 and 2011, respectively). This approximates the fraction of individuals who are more than 5 years post vaccination with ZVL, many of whom still having significant benefit from ZVL in preventing both HZ and PHN based on P024 (Baxter, 2017, Klein 2017). The NHIS data prior to 2012 indicate there are few individuals who might be eligible for revaccination if a revaccination policy is applied to people who were vaccinated 5 years previously. Moreover, choosing 5 years as the time interval for a revaccination recommendation is not supported by the post-licensure data. Given the limited incremental benefit of revaccination at 5 years when ZVL effectiveness against PHN remains high, a longer interval before revaccination seems warranted and the decision on revaccination should be postponed until there are more robust data available on the durability of ZVL beyond 5 years.

3. Safety/Immunogenicity of HZ/su

- In a small study (Zoster-048, GSK), vaccination with HZ/su 5 yrs following ZVL did not alter the safety or immunogenicity of HZ/su
- Prior ZVL receipt should not be a contraindication to receiving HZ/su
- HZ/su should be considered for people who have already received ZVL

The GSK Zoster-048 study has not been completed (Colindres, 2017). GSK indicated that they plan to assess immunogenicity in this study at 1 and 12 months post-revaccination. Only the data at one month post vaccination have been presented, and for ACIP to make a recommendation on revaccination before the study is completed would be premature. It should be pointed out that in this study, the mean age of the vaccinees was ~71 years, and the years from previous ZVL vaccination was 6.7 years (SD 1.1 years, age range not provided). Based on P024 data, revaccination at 5 years in this relatively young vaccinee age group would be premature. The CDC/ACIP should carefully evaluate the appropriate time and time interval that would warrant a revaccination recommendation.

4. Price/Health Economics modelling

- WG is awaiting a final price for HZ/su and accompanying cost effectiveness analyses

Final price and durability of protection after revaccination are important model inputs needed to complete cost-effectiveness analyses and inform a recommendation on revaccination.

I trust that these comments will be considered by the CDC, the HZ WG, the full ACIP, ACIP liaison members and the public in formulating scientifically-based policies.

Thank you for your consideration of these issues.

Sincerely,



Ruxandra Draghia, MD, PhD
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cc: Dr. Nancy Bennett, Dr. Kathleen Dooling, Dr. Eddy Bresnitz

Reference List:

Baxter R, Bartlett J, Fireman B, et al. Effectiveness of live zoster vaccine in preventing postherpetic neuralgia (PHN). Oral presentation, ID Week, New Orleans, 2016.

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Colindres R. Immunogenicity and safety of Shingrix in adults previously vaccinated with a live-attenuated herpes zoster vaccine (Zoster-048 Study). ACIP Meeting, Atlanta, June 21, 2017.

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Leidner AJ. Overview of two economic models that assess the cost effectiveness of herpes zoster vaccinations. ACIP Meeting, June 2017.

Meites E, Kempe A, Markowitz LE. Use of a 2-Dose Schedule for Human Papillomavirus Vaccination — Updated Recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep* 2016;65:1405–1408. DOI: <http://dx.doi.org/10.15585/mmwr.mm6549a5>.ACIP.

Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005; 352:2271-84.

Schmader KE, Levin MJ, Gnann JW Jr, et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. *Clin Infect Dis*. 2012 Apr; 54(7):922-8.

Japanese Encephalitis

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April 6, 2017

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Centers for Disease Control and Prevention
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Dear Dr. Cohn,

I am writing on behalf of an Expert Advisory Group on Japanese Encephalitis Prevention which first met in November 2014 in conjunction with the 63rd Annual Meeting of the American Society of Tropical Medicine and Hygiene (ASTMH). The Advisory Group reconvened in 2015 and 2016. Our focus has been to address the need for changes in the current Japanese Encephalitis vaccine recommendations in light of new data on epidemiology and the availability of a new vaccine (Ixiaro) since the initial Advisory Committee on Immunization Practices (ACIP) guidelines were first drafted and subsequently revised.

After the 2014 ASTMH meeting, a letter (attached) was sent to Dr. Larry Pickering from our group encouraging strong consideration for revision of the current Japanese Encephalitis (JE) vaccine recommendations and language. The recommendations for children had been addressed at the June 2013 ACIP meeting but the rationale to limit consideration to the childhood indication and to not consider expansion of recommendations to cover new categories for additional travelers at risk was unclear to us. In our letter the justification for making changes was discussed and new recommendations reflecting the current "at risk" areas and needs of high and low risk travelers were suggested.

When we convened in November 2015 at ASTMH, the expert group reviewed the standing ACIP recommendations on JE vaccine and reaffirmed the need for consideration of the changes and updated recommendations contained in our 2014 letter to the ACIP. A number of peer reviewed publications in support of the updated recommendations were presented (bibliography available upon request). We have been disappointed that no action had been taken by the ACIP and this we reaffirmed at our meeting at ASTMH in November 2016.

The Expert Advisory Group would like to reiterate that the JE vaccine recommendations have essentially been unchanged since 1993 despite a new safe effective vaccine (licensed in 2009) and clear changes in the epidemiology and the risks for JE.

Adherence to the current recommendations has been poor in part because of conflicting and confusing language. For example, the ACIP JE recommendation only covers travelers going to areas of risk for a duration of one month or longer and then lists "considerations for the use of JE vaccine". The short-term traveler's considerations are outdated and lengthy. On the other hand the current CDC JE VIS includes short-term travelers in its recommendations if they "will visit rural areas and spend a lot of time outdoors", "travel to an area with an outbreak" or "are not sure of travel plans" but does not include "considerations".

We strongly believe this issue needs to be on the agenda of the next ACIP meeting and serious consideration be given to updating the recommendations to reflect the points made as a result of our careful consideration of the evidence. I or any other member of our group would be available for discussion if this would help frame the issue more effectively.

With best regards.

Sincerely,



Bradley A. Connor, M.D.

Chair, Expert Advisory Group on Japanese Encephalitis Prevention
Clinical Professor of Medicine
Weill Cornell Medical College
Past President
International Society of Travel Medicine (ISTM)

On behalf of the other Advisory Group members:

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Northwestern University School of Medicine
Vice President, Health, Safety, Security & Productivity
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Jay S. Keystone, M.D.
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Director, Toronto Medisys Travel Health Clinic
Tropical Disease Unit Toronto General Hospital

Meningococcal



The header of the letter features a blue background with the NMA logo on the left, which consists of a stylized white circle with a smaller circle inside, followed by the text "NMA" in large white letters and "NATIONAL MENINGITIS ASSOCIATION" in smaller white letters below it. To the right of the logo, the website addresses "www.nmaus.org" and "www.preteenvaccines.org" are listed in white text.

February 22, 2018

Dear Members of the Advisory Committee on Immunization Practices:

We are writing to you to share our story about our youngest daughter, Sara, who passed away in October 2014 from Serogroup B meningococcal disease.

Sara Beth Stelzer was only 18 years old and a freshman at San Diego State University when she passed away. We thought she had the flu, but meningitis took her from us only 36 hours after her first symptoms.

Sara was quirky, funny and confident. She sang often and danced constantly. As a straight-A student and class clown, she strived for the best academically while inspiring the most contagious laughter. Sara and her two best friends were the school mascots, the Three Musketeers, entertaining everyone at the football games with their antics. Sara had a silly side, but also had a passion for government affairs and creating a better future for her peers; a passion she shared with so many in an organization called Youth and Government.

Sara was a true California girl – spending sunny days dancing on the beach, and winter days dancing in the snow. When our family moved to Switzerland during her middle school years, she remained a California girl at heart, but developed a wanderlust for travel and experiencing cultures from around the world. She dedicated her summers to Global Leadership Adventures, where she met like-minded kids who shared a desire to impact the world around them. Traveling to Costa Rica and Peru, Sara immersed herself in these cultures, giving back to the local communities.

Sara lived a full life in the short time she was with us. She lived for the moment and always put a smile on people's faces with her cheerful disposition. When you lose someone, memories are all you have left. Sara left us beautiful moments that we reflect on to help us smile until we reunite again.

We urge the ACIP to make MenB a routinely recommended vaccine. We know this is not a common disease, but it can have devastating consequences. There have been many outbreaks on college campuses in recent years. They have all been serogroup B. Parents and older adolescents think they are going to school protected because they have gotten the MenACWY vaccine. The permissive or category B recommendation is confusing, even for healthcare professionals.

P.O. Box 60143
Fl. Myers, FL 33906
www.nmaus.org



www.nmaus.org
www.preteenvaccines.org

We have and will continue to visit college campuses with our story and reach out to as many students, parents and on-campus healthcare professionals as possible to educate them about the importance of the vaccination and to raise awareness of meningococcal disease symptoms.

We thank you for your consideration.

With sincere gratitude,

Laurie and Greg Stelzer
NMA Advocates

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Provider Neutral Language



Pediatric Nurse Practitioners
NATIONAL ASSOCIATION OF

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Amanda Cohn
Centers for Disease Control and Prevention
Advisory Committee on Immunization Practices
1600 Clifton Road
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Re: Provider Neutral Language

Dear Amanda Cohn:

On behalf of our more than 8,500 members and their pediatric patients throughout the United States and military installations abroad, the National Association of Pediatric Nurse Practitioners (NAPNAP) commends the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices for developing and distributing clinician and patient education materials and guidelines.

NAPNAP members are part of a larger population of advanced practice registered nurses (APRNs) which includes certified nurse practitioners, certified registered nurse anesthetists, certified nurse-midwives and clinical nurse specialists. Totalling more than 340,000 healthcare professionals, our primary interests are patient wellness and improving patient access to safe and cost-effective healthcare services. In every setting and region, for every population particularly among the rural and medically underserved, America's growing numbers of highly educated APRNs advance healthcare access and quality in the United States and promote cost-effective healthcare delivery.

Given the growing influence of APRNs in today's health care, we urge the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices to use provider neutral language in all digital and print communications and materials. When government agencies and other healthcare organizations use "doctor" or "physician", it undermines the critical role of APRNs, their years of education and clinical experience, national board certification and state licensure. Recommendations such as "call your doctor" imply that an APRN is not capable of addressing a patient question, adverse event and ability to prescribe medicine. The standard of care for patients treated by APRNs is the same as that provided by a physician or other healthcare provider in the same type of setting; therefore, all clinicians should be referenced in a fair, equal and consistent way.

By using provider neutral language such as "healthcare provider," "healthcare practitioner," or "clinician," in your materials and guidelines, we believe you will increase APRN acceptance and usage of the essential tools and resources you produce. More importantly, the standardization will increase patient confidence and recognition in the changing healthcare workforce.

If you have questions, please contact me at president@napnap.org or NAPNAP Executive Director Cate Brennan at 917-746-8270.

Sincerely,



Tresa Zielinski, DNP, RN, APN-NP, CPNP-PC
President

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