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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
February 21-22, 2018
Atlanta, Georgia

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Final - February 12, 2018

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Centers for Disease Control and Prevention
1600 Clifton Road, NE, Tom Harkin Global Communications Center, Kent "Oz" Nelson Auditorium
Atlanta, Georgia 30329
February 21-22, 2018

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
Wednesday, February 21			
8:00	**Welcome & Introductions**		Dr. Nancy Bennett (ACIP Chair) Dr. Amanda Cohn (ACIP Executive Secretary; CDC)
8:30	**Hepatitis Vaccines**		
	Introduction		Dr. Jose Romero (ACIP, WG Chair)
	Review of GRADE (HEPLISAV-B)	Information	Dr. Aaron Harris (CDC/NCHHSTP)
	Considerations and proposed recommendations	& Discussion	Dr. Sarah Schillie (CDC/NCHHSTP)
	Public comment		
	Vote	**Vote**	Dr. Sarah Schillie (CDC/NCHHSTP)
	Hepatitis A post-exposure prophylaxis GRADE	Information	Dr. Noele Nelson (CDC/NCHHSTP)
	Considerations and proposed recommendations	& Discussion	Dr. Noele Nelson (CDC/NCHHSTP)
	Public comment		
	Vote	**Vote**	Dr. Noele Nelson (CDC/NCHHSTP)
10:15	***Break***		
10:30	**Influenza Vaccines**		
	Introduction		Dr. Chip Walter (ACIP, WG Chair)
	Fluarix Quadrivalent: efficacy in children 6-35 months of age		Dr. Leonard Friedland (GSK)
	Surveillance update		Ms. Lynnette Brammer (CDC/NCIRD)
	VE update	Information	Dr. Brendan Flannery (CDC/NCIRD)
	Results of a randomized trial of a new H1N1 LAIV strain in US children	& Discussion	Dr. Raburn Mallory (MedImmune/AstraZeneca)
	Review of LAIV for 2 through 17 year olds		Dr. Lisa Grohskopf (CDC/NCIRD), Dr. Jill Ferdinands (CDC/NCIRD)
	Considerations and proposed recommendations		Dr. Lisa Grohskopf (CDC/NCIRD)
	Public comment		
	Vote	**Vote**	Dr. Lisa Grohskopf (CDC/NCIRD)
	VFC Vote	**VFC Vote**	Dr. Jeanne Santoli
12:45	***Lunch***		
1:45	**Evidence Based Recommendations**		
	Introduction	Information	Dr. Grace Lee (ACIP, WG Chair)
	Evidence to Recommendations Framework	& Discussion	Dr. Wendy Carr (CDC/NCIRD)
	Public comment		
	Vote	**Vote**	Dr. Wendy Carr (CDC/NCIRD)
2:30	**Anthrax**		
	Introduction		Dr. David Stephens (ACIP, WG Chair)
	Update on IM route of administration of vaccine	Information	Dr. William Bower (CDC/NCEZID)
	Dose-sparing strategies when demand for vaccine excess	& Discussion	Dr. William Bower (CDC/NCEZID)
	Duration of antimicrobial component of PEP when used in combination with anthrax vaccine		Dr. William Bower (CDC/NCEZID)
3:45	***Break***		
4:00	**Human Papillomavirus (HPV) Vaccines**		
	Introduction		Dr. Peter Szilagyi (ACIP, WG Chair)
	9-valent HPV vaccine safety data - VAERS update		Dr. Jorge Arana (CDC/NCEZID)
	9-valent HPV vaccine rapid cycle analysis, Vaccine Safety	Information	Dr. Jim Donahue (Marshfield Clinic)
	Harmonization of upper age for male and female vaccination recommendations	& Discussion	Dr. Lauri Markowitz (CDC/NCIRD)
	Trends in HPV-associated cancers in the United States		Dr. Elizabeth Van Dyne, (CDC/NCCDPHP)
	Epidemiology of HPV infection in males		Dr. Anil Chaturvedi (NIH/NCI)
5:30	**Public Comment**		
5:45	**Adjourn**		

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Final - February 12, 2018

Thursday, February 22

8:00	**Agency Updates & Unfinished Business** CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NIH, NVPO	Information	Dr. Nancy Messonnier (CDC/NCIRD); *Ex Officio* Members
9:00	**Pneumococcal** Introduction PCV13 Effectiveness: Case Control Study PCV13 Direct and Indirect Effects among Adults ≥65 Year Old PCV13 effectiveness against pneumococcal pneumonia among U.S. Adults Estimating Burden of Pneumococcal Pneumonia among Adults in the U.S. Progress of the research agenda to inform potential policy change	Information & Discussion	Dr. Grace Lee (ACIP, WG Chair) Dr. Tamara Pilishvili (CDC/NCIRD) Dr. Tamara Pilishvili (CDC/NCIRD) Dr. John M. McLaughlin (Pfizer Vaccines) Dr. Almea Matanock (CDC/NCIRD)
10:30	**Vaccines and other biologics for prevention and treatment of healthcare-associated infections** Update	Information	Dr. Anthony Fiore (CDC/NCEZID)
11:00	***Break***		
11:30	**Meningococcal Disease** Introduction Epidemiology of meningococcal disease among college students – United States, 2014-2016	Information & Discussion	Dr. David Stephens (ACIP, WG Chair) Dr. Sarah Meyer (CDC/NCIRD)
12:00	**Japanese Encephalitis (JE) Vaccine** Introduction Review of JE and work group plans	Information & Discussion	Dr. Chip Walter (ACIP, WG Chair) Dr. Susan Hills (CDC/NCEZID)
12:15	**Vaccine Supply**	Information	Dr. Jeanne Santoli (CDC/NCIRD)
12:20	**Public Comment**		
12:30	**Adjourn**		

Acronyms

CDC	Centers for Disease Control & Prevention
CMS	Centers for Medicare and Medicaid Services
DoD	Department of Defense
DVA	Department of Veterans Affairs
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRSA	Health Resources and Services Administration
IHS	Indian Health Service
JE-VC	Vero cell culture-derived Japanese encephalitis
NCHHSTP	National Center for HIV, Hepatitis, STD and TB Prevention [of CDC/OID]
NCIRD	National Center for Immunization & Respiratory Diseases [of CDC/OID]
NCEZID	National Center for Emerging and Zoonotic Diseases [of CDC/OID]
NCI	National Cancer Institute
NIH	National Institutes of Health
NVPO	National Vaccine Program Office
PCV13	13-valent pneumococcal conjugate vaccine
VFC	Vaccines for Children
WG	Work Group

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Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
AAPC	Average Annual Percent Change
ABCs	Active Bacterial Core Surveillance
AbxPEP	Antimicrobial Component
ACA	Affordable Care Act
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
AE	Adverse Events
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
AIM	Association of Immunization Managers
AIRA	American Immunization Registry Association
ANA	American Nurses Association
ANCA	Anti-Neutrophil Cytoplasmic Antibody
Anti-HBsAg	Hepatitis B Surface Antigen
AOA	American Osteopathic Association
AOM	Acute Otitis Media
APhA	American Pharmacists Association
ARI	Acute Respiratory Illness
ASTHO	Association of State and Territorial Health Officers
AVA	Anthrax Vaccine Adsorbed
AVRP	Anthrax Vaccine Research Program
B anthracis	*Bacillus anthracis*
BARDA	Biomedical Advanced Research and Development Authority
BBB	Blood Brain Barrier
BIO	Biotechnology Innovation Organization
BLA	Biologics License Application
C. diff	*Clostridium Difficile*
CAIV	Cold Adapted Influenza Vaccine
CAP	Community-Acquired Pneumonia
CAPiTA	Community-Acquired Pneumonia Immunization Trial in Adults
CARB	Combating Antibiotic-Resistant Bacteria
ccIIV4	Cell-Culture Quadrivalent Vaccine
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CID	*Clinical Infectious Disease*
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CKD	Chronic Kidney Disease
CLABSI	Central Line-associated Bloodstream Infection
CLD	Chronic Liver Disease
CMaxSPRT	Conditional MaxSPRT
CMS	Center for Medicare and Medicaid
COI	Conflict of Interest

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COID	Committee on Infectious Diseases (AAP)
COP	Correlates of Protection
COPD	Chronic Obstructive Pulmonary Disease
CPACS	Center for Pan-Asian Community Services
CpG	Immunostimulatory Cytidine-Phosphate-Guanosine
CRPS	Complex Regional Pain Syndrome
CSS	Churg-Strauss Syndrome
CSTE	Council of State and Territorial Epidemiologists
CV	Cardiovascular
CVD	Cardiovascular Disease
DBD	Division of Bacterial Diseases
DC	District of Columbia
DHA	Defense Health Agency
DHQP	Division of Healthcare Quality Promotion
DICP	Division of Injury Compensation Programs
DMSS	Defense Medical Surveillance System
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
D-QIV	Fluarix® Quadrivalent
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
ELC	Epidemiology and Laboratory Capacity
ELISA	Enzyme-Linked Immunosorbent Assays
EMA	European Medicines Agency
EMR	Electronic Medical Record
EPIC	Etiology of Pneumonia in the Community
Epi-X	Epidemic Information Exchange
EPV	Events Per Variable
ERIB	Epidemiologic Research and Innovations Branch
ESA	Exact Sequential Analyses
ESRD	End-Stage Renal Disease
EtD	Evidence to Decision
EtR	Evidence to Recommendation
EU	European Union
EUA	Emergency Use Authorization
EUI	Emergency Use Instructions
FDA	Food and Drug Administration
FFA	Free Fatty Acid
FluSurv-NET	Influenza Hospitalization Surveillance Network
FQHC	Federally Qualified Health Center

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FY	Fiscal Year
GAVI Alliance	Global Alliance for Vaccines and Immunisation
GBS	Guillain-Barré Syndrome
GCC	(Tom Harkin) Global Communications Center
GMT	Geometric Mean Titers
GP	General Practitioner
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HAI	Healthcare-Associated Infection
HAI	Hemagglutination Inhibition
HAP	Hospital-Acquired Pneumonia
HAV	Hepatitis A Virus
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HBV	Hepatitis B Virus
HCP	Healthcare Personnel / Providers
HCUP	Healthcare Cost and Utilization Project
HCW	Healthcare Workers
HepA	Hepatitis A
HepB	Hepatitis B
HCAP	Healthcare-Associated Pneumonia
HHS	(Department of) Health and Human Services
HI	Hemagglutinin Inhibition
HICPAC	Healthcare Infection Control Practices Advisory Committee
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
ICICLE	Influenza Clinical Investigation for Children
ICU	Intensive Care Unit
ID	Influenza Division
IDSA	Infectious Disease Society of America
IDSC	Infectious Disease Surveillance Center
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
IM	Intramuscularly
IPD	Invasive Pneumococcal Disease

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IPEDS	Integrated Postsecondary Education Data System
IPs	Infection Preventionists
IRB	Institutional Review Board
ISD	Immunization Services Division
ISO	Immunization Safety Office
ITP	Immune Thrombocytopenia
IV	Intravenous
JEV	Japanese Encephalitis Vaccine
JID	*Journal of Infectious Diseases*
JIT	Just-In-Time
LAIV	Live Attenuated Influenza Vaccine
LRI	Lower Respiratory Illness
MAE	Medically Attended Adverse Event
MaxSPRT	Maximized Sequential Probability Ratio Test
MCM	Medical Countermeasures
MDCK	Madin-Darby Canine Kidney
MedDRA	Medical Dictionary for Regulatory Activities
MenACWY	Meningococcal Conjugate
MenB	Serogroup B Meningococcal Disease
MeSH	Medical Subject Heading
MGI	Mean Geometric Antibody Titers
MI	Myocardial Infarction
MMR	Measles, Mumps and Rubella
MMWR	*Morbidity and Mortality Weekly Report*
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSM	Men Who Have Sex With Men
NACCHO	National Association of County and City Health Officials
NAP	National Action Plan
NAPNAP	National Association of Pediatric Nurse Practitioners
NAS	National Academy of Sciences
NBPP	Non-Bacteremic Pneumococcal Pneumonia
NCAI	National Coalition of Adult Immunization
NCES	National Center for Education Statistics
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCHS	National Center of Health Statistics
NCI	National Cancer Institute
NCIRD	National Center for Immunization and Respiratory Diseases
NFID	National Foundation for Infectious Diseases
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NHP	Non-Human Primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIID	National Institute of Infectious Diseases
NIS	National Immunization Survey
NIS-Flu	National Immunization Survey-Flu
NMA	National Meningitis Association
NNDSS	National Notifiable Diseases Surveillance System

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NNV	Number Needed to Vaccinate
NP	Nasopharyngeal
NPCR	National Program of Cancer Registries
NVAC	National Vaccine Advisory Committee
NVHR	National Viral Hepatitis Roundtable
NVPO	National Vaccine Program Office
NVT	Non-Vaccine Types
NYC	New York City
OP	Oropharyngeal
PACCARB	Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PEP	Post-Exposure Prophylaxis
PHE	Public Health England
PHL	Public Health Laboratories
PHN	Post Herpetic Neuralgia
PhRMA	Pharmaceutical Research and Manufacturers of America
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
pIMDs	Potential Immune Mediated Diseases
PIR	Post-Injection Reaction
POI	Primary Ovarian Insufficiency
POTS	Postural Orthostatic Tachycardia Syndrome
PR	Puerto Rico
PrEP	Pre-Exposure Prophylaxis
PRNT	Plaque Reduction Neutralization Test
PT	Preferred Terms (MedDRA)
QALY	Quality-Adjusted Life-Year
QIV	Quadrivalent Influenza Vaccine
Q-QIV	FluLaval® Quadrivalent
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RIV	Recombinant Influenza Vaccine
RNA	Ribonucleic Acid
ROBINS-I	Risk of Bias in Non-randomized Studies of Interventions
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
S. aureus	*Staphylococcus aureus*
S. pneumoniae	*Streptococcus pneumoniae*
SAB	Spontaneous Abortion
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunization (WHO)
SAHM	Society for Adolescent Health and Medicine
sBLA	Supplemental Biologics License Application
SC	Subcutaneous
SCC	Squamous Cell Carcinoma
SCCS	Self-Controlled Case Series
SCRI	Self-Controlled Risk Interval
SEER	Surveillance, Epidemiology, and End Results

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SES	Socioeconomic Status
SME	Subject Matter Experts
SNiPP	Surveillance for Non-invasive Pneumococcal Pneumonia
SNS	Strategic National Stockpile
SPR	Seroprotection Rate
SSI	Surgical Site Infection
SQ	Subcutaneous
TATFAR	Trans-Atlantic Task Force on Antimicrobial Resistance
$TCID_{50}$	Tissue Culture Infectious $Dose_{50}$
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis
TIV	Trivalent Influenza Vaccine
TLR	Toll-Like Receptor
TND	Test-Negative Design
UAD	Urinary Antigen Detection
UAT	Urinary Antigen Test
UK	United Kingdom
URI	Upper Respiratory Infection
US	United States
US-IPD	US Combined Individual Patient-Level Analysis
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
VIS	Vaccine Investment Strategy
VLP	Virus-Like Particles
VRBPAC	Vaccine and Related Blood Products Advisory Committee
VSD	Vaccine Safety Datalink
VT	Vaccine Type
VT-CAP	Vaccine-Type Community-Acquired Pneumonia
VTE	Venous Thromboembolism
VxPEP	Vaccine Component
VZV	Varicella Zoster Virus
WG	Work Group
WGS	Whole Genome Sequencing
WHO	World Health Organization
WSW	Women Who Have Sex With Women
YF	Yellow Fever
YF-Vax®	Yellow Fever Vaccine®
ZVL	Zoster Vaccine Live

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

Nancy Bennett, MD, MS
ACIP Chair

Amanda Cohn, MD
Executive Secretary, ACIP / CDC

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

Dr. Cohn welcomed everyone to the February 2018 ACIP meeting. She indicated that the proceedings of this meeting would be accessible to people not in attendance via the World Wide Web, and welcomed those who could not attend the meeting in person. She then recognized others in the room who were to be present throughout the duration of the meeting to assist with various meeting functions: Ms. Stephanie Thomas and Ms. Natalie Greene.

She noted that handouts of the presentations were distributed to the voting ACIP members and were made available for others on the tables outside of the auditorium. Slides presented during this meeting will be posted on the ACIP website approximately two weeks after the meeting concludes after being made visually accessible to all viewers, including the visually disabled. The live webcast will be posted within four weeks following the meeting, and the meeting minutes will be available on the website within approximately 90 to 120 days following the meeting.

The next ACIP meeting will be convened at the Centers for Disease Control and Prevention (CDC) on Wednesday and Thursday, June 20-21, 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 May 16, 2018 and for US citizens registration closes June 11, 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.

Dr. Bennett announced the following guests, member substitutions, and new Liaison and *Ex-Officio* representatives:

Guests

- ❑ Dr. Alejandro Cravioto, Chair, World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE)
- ❑ Dr. Jon Abramson, Chair, Global Alliance for Vaccines and Immunisation (GAVI Alliance) Vaccine Investment Strategy (VIS) Steering Group
- ❑ Dr. Kazunori Oishi, Director of Infectious Disease Surveillance Center (IDSC), National Institute of Infectious Diseases (NIID), Japan
- ❑ Students from the University of Alabama School of Public Health

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Liaison Representatives

- American Immunization Registry Association (AIRA) was welcomed as a new liaison organization with Rebecca Coyle, Executive Director, serving as the liaison
- Dr. Mike Brady, representing American Academy of Pediatrics (AAP) Committee on Infectious Diseases (COID)
- Dr. Corey Robertson, Pharmaceutical Research and Manufacturers of America (PhRMA)
- Amy Walker, Biotechnology Innovation Organization (BIO)

Ex-Officio Members

- Dr. Melinda Wharton, Acting Director of the National Vaccine Program Office (NVPO), representing NVPO
- Dr. Barbara Mulach, representing the National Institutes of Health (NIH)
- Jillian Doss-Walker, representing the Indian Health Services (IHS)

Update on ACIP Membership

- Drs. Hank Bernstein and Dr. Sharon Frey were welcomed as new ACIP Voting Members whose terms will run from July 2017 through June 2021.
- Ms. Cynthia Pellegrini will serve an additional 1-year term from July 2017 through June 2018.

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. People who planned to make public comments were instructed to visit the registration table at the rear of the auditorium where Ms. Stephanie Thomas would record their name and provide information on the process. People making public comments were instructed to provide three pieces of information: name, organization if applicable, and any conflicts of interest (COI). Registration for public comment also was solicited in advance of this meeting through the *Federal Register*. Given time constraints, individuals were asked to limit their public comments to 3 minutes total. Participants unable to present comments during this meeting were invited to submit their comments in writing for inclusion in the meeting minutes.

To summarize COI provisions applicable to the ACIP, as noted in the ACIP Policies and Procedures manual, members of the ACIP agree to forgo participation in certain activities related to vaccines during their tenure on the committee. For certain other interests that potentially enhance a member's expertise while serving on the committee, CDC has issued limited COI waivers. Members who conduct vaccine clinical trials or serve on data safety monitoring boards (DSMBs) may present to the committee on matters related to these vaccines, but are prohibited from participating in committee votes on issues related to those vaccines. Regarding other vaccines of the concerned company, a member may participate in discussions, with the provision that he/she abstains on all votes related to the vaccines of that company. It is important to note that at the beginning of each meeting, ACIP members state any COIs.

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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.

Dr. Bennett called the roll to determine whether any ACIP members had COIs. The following COIs were declared:

- Dr. Frye has a contract with NIH Division of Microbiology and Infectious Diseases (DMID) and served on a board for Bavarian Nordic within the last year

Dr. Bennett then requested that the Liaison and *Ex Officio* members introduce themselves. A list of Members, *Ex Officio* Members, and Liaisons is included as Appendix A.

Hepatitis Vaccines

Introduction

José Romero, MD, FAAP, FIDSA, FPIDS
Chair, Hepatitis Vaccines Work Group

Dr. Romero reminded everyone of the Hepatitis Work Group (WG) terms of reference for hepatitis A (HepA) vaccines and hepatitis B (HepB) vaccines, which are as follows:

HepA
- Update HepA recommendations:
  - ACIP Routine Recommendation for Hepatitis A Vaccine, *MMWR* 2006 May 19;55(RR-7):1-23

- Use of HepA vaccine for post-exposure prophylaxis (PEP) among adults >40 years
  - Update to: Prevention of hepatitis A after exposure to hepatitis A virus (HAV) and in international travelers. Updated recommendations of the ACIP, *MMWR* 2007 Oct 19;56(41):1080-4

HepB
- New ACIP recommendations for HEPLISAV-B™, licensed by the Food and Drug Administration (FDA) on November 9, 2017

- Updated Recommendations and Report: Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices, *MMWR* 2018 Jan 12;67(RR-1):1-31

WG considerations between November 2017 and February 2018 have included the following:

HepA
- Risk factors for HAV infection: HIV and immunocompromised
- Review of homelessness as a risk group discussion
- Review of HAV virus PEP and international travel draft policy statement

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HepB

- ❑ HEPLISAV-B™ Grading of Recommendations Assessment, Development and Evaluation (GRADE)
- ❑ HEPLISAV-B™ considerations and proposed recommendations
- ❑ Draft Policy Note: Recommendations of the Advisory Committee on Immunization Practices for Use of a Hepatitis B Vaccine with a Novel Adjuvant

Presentations for this session focus on the following:

- ❑ HEPLISAV-B™ GRADE
- ❑ HEPLISAV-B™ considerations, proposed recommendations, vote
- ❑ Hepatitis A PEP GRADE
- ❑ Hepatitis A PEP and international travel considerations, proposed recommendations, vote

In terms of next steps, the WG ultimately plans to present the full updated HAV statement for a vote and will continue deliberations on adult HepB vaccination.

Review of GRADE HEPLISAV-B™

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Division of Viral Hepatitis
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Dr. Harris presented the results of GRADE for HEPLISAV-B™ vaccine. This analysis included development of the policy question, consideration of critical outcomes, review and summarization of evidence of benefits and harms, and evaluation of the quality of evidence. In addition, the WG reviewed the limited health economic data and developed a non-preferential recommendation and summarization of the GRADE category.

The policy question was, “Should HEPLISAV-B™ vaccine be recommended for adults on a 2-dose schedule over 1 month?” To GRADE the evidence, the population, intervention, comparison, outcomes (PICO) format was utilized. The population was adults 18 years and older. The intervention was HEPLISAV-B™ administered in 2 doses over 1 month. The comparison included existing licensed HepB vaccines for adults in the US. While all licensed vaccines were included in the search, the search yielded only Engerix-B® comparative studies. The outcomes evaluated were HepB infection, mild adverse events (AEs), serious adverse events (SAEs), and cardiovascular safety. The outcome of preventing HepB infection was determined to be of critical importance. For harms, mild AEs were determined to be important, and SAEs and cardiovascular events were deemed to be critical.

A systematic review was performed of Medline (OVID), CAB Abstracts, Embase, Global Health (OVID), Scopus, and Cochrane. Search terms included: “HEPLISAV” or “HBV-ISS” or “HBsAg-1018” or “1018 immunostimulatory sequence” or “hepatitis B surface antigen-1018 ISS.” Articles were included if they presented immunogenicity or disease endpoints or safety data on HEPLISAV™. Articles were excluded that focused on non-human primates, basic science, secondary data analyses, immunogenicity outcomes for non-licensed formulation or use of HEPLISAV™, general reviews or opinion perspectives, or if data were unable to be extracted.

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The search yielded 141 abstracts, of which 70 duplicates were excluded and 71 unique abstracts were reviewed. Of those, 35 were excluded due to relevance and 36 full articles were reviewed. Of the 36 remaining articles, 31 were excluded because they did not include primary data or the population of interest, or data could not be abstracted. There was 1 additional article published after the search was conducted that was included. In summary, the search strategy yielded 6 articles that were included for GRADE.

This table summarizes the standardized initial evidence types by study design for GRADE:

Initial Evidence Type	Study Design
1	Randomized controlled trials (RCTs), or overwhelming evidence from observational studies
2	RCTs with important limitations, or exceptionally strong evidence from observational studies
3	Observational studies, or RCTs with notable limitations
4	Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

This table summarizes the characteristics of included studies for Outcome #1: Hepatitis B infection in GRADE:

Outcome #1: Hepatitis B infection
Characteristics of included studies

Study	Type	Population	Intervention	Comparison	Main Outcomes*	Funding	Site
Halperin, 2006 *Vaccine*	RCT, phase II	99 healthy adults, 18-28 years	HEPLISAV at 0 and 8 weeks	Engerix-B at 0, 8, and 24 weeks	Seroprotection rate (anti-HBs ≥ 10mIU/mL)**	Dynavax	2 centers in Canada
Halperin, 2012 *Vaccine*	RCT, Phase III	2415 healthy adults, 18-55 years	HEPLISAV at 0 and 4 weeks	Engerix-B at 0, 4, and 24 weeks	Seroprotection rate (anti-HBs ≥ 10mIU/mL)**	Dynavax	Canada and Germany
Heyward, 2013 *Vaccine*	RCT Phase III	2452 healthy adults, 40-70 years	HEPLISAV at 0 and 4 weeks	Engerix-B at 0, 4, and 24 weeks	Seroprotection rate (anti-HBs ≥ 10mIU/mL)**	Dynavax	29 sites in US, 3 in Canada
Jackson, 2017 *Vaccine*	RCT Phase III	8374 adults, 18-70 years, excluding HIV and history of autoimmune disease	HEPLISAV at 0 and 4 weeks	Engerix-B at 0, 4, and 24 weeks	Seroprotection rate (anti-HBs ≥ 10mIU/mL)**	Dynavax	USA

* No studies included disease endpoints
** Seroprotection rate after receiving complete vaccine series

There were no studies that looked at HepB infection as an outcome, so immunogenicity was used as a surrogate outcome, more specifically the seroprotection rate (SPR), which was defined as antibody to HepB surface antigen (anti-HBsAg) ≥ 10mIU/mL after vaccine series completion, which was usually 24 to 28 weeks after receipt of the first dose. Of note, HEPLISAV™ was administered at 0 and week 8 for Halperin 2006 and at 0 and week 4 for other studies. For HEPLISAV™, the SPR ranged from 90% to 100% versus 70% to 90% in the comparison group, with a number needed to vaccinate (NNV) between 5 and 10.

The initial evidence level for HepB as an outcome was 1 because all 4 studies were randomized controlled trials (RCTs). There were no serious concerns for risk of bias, inconsistency, or imprecision. However, there were serious concerns for indirectness. There were no studies that looked at HepB infection as an outcome and used immunogenicity data only. For Halperin 2006, the intervention was HEPLISAV™ series at 0 and 8 weeks, which is not the licensed

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series. Other considerations were that all studies were funded by Dynavax Technologies Corporation. As a result, the evidence type was downgraded from type from 1 to 2.

These tables summarize the characteristics of included studies for Outcomes #2, #3, and #4: Adverse Events:

Outcomes #2, 3, 4: Adverse events
Characteristics of included studies

Study	Type	Population	Intervention	Comparison	Main Outcomes*	Funding	Site
Halperin, 2006, *Vaccine*	RCT Phase II	99 healthy adults, 18–28 years	HEPLISAV at 0 and 8 weeks	Engerix-B at 0, 8, and 24 weeks	Any mild adverse events (local, systemic), SAE	Dynavax	2 sites in Canada
Halperin, 2012, *Vaccine*	RCT Phase III	2415 healthy adults, 18–55 years	HEPLISAV at 0 and 4 weeks	Engerix-B at 0, 4, and 24 weeks	Any mild adverse events (local, systemic), SAE (related not reported)	Dynavax	Canada, Germany
Sablan, 2012, *Vaccine*	RCT Phase III	412 healthy adults, 40–70 years	HEPLISAV at 0, 8, and 24 weeks (placebo at week 4)	Engerix-B at 0, 4, and 24 weeks (placebo at week 8)	Any mild adverse events (local, systemic), SAE	Dynavax	5 sites in Korea, 2 sites in Philippines, and 1 site in Singapore
Heyward, 2013, *Vaccine*	RCT Phase III	2452 healthy adults, 40–70 years	HEPLISAV at 0 and 4 weeks	Engerix-B at 0, 4, and 24 weeks	Any mild adverse events (local, systemic), SAE, cardiovascular events	Dynavax	29 sites in US, 3 sites in Canada

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Outcomes #2, 3, 4: Adverse events
Characteristics of included studies, continued

Study	Type	Population	Intervention	Comparison	Main Outcomes*	Funding	Site
Janssen, 2013, *Vaccine*	RCT Phase III	521 adults with chronic kidney disease, 18–75 years	HEPLISAV at 0, 4, and 24 weeks	Engerix-B at 0, 4, 8, and 24 weeks	Any adverse events, SAE, cardiovascular events	Dynavax	46 sites in US, 3 sites in Canada, 9 sites in Germany
HBV 23	RCT Phase III	8368 adults, 18–70 years, excluding HIV and history of autoimmune disease	HEPLISAV at 0 and 4 weeks	Engerix-B at 0, 4, and 24 weeks	Any mild adverse events, SAE (related not reported), cardiovascular events	Dynavax	US

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In terms of the characteristics of the 6 included studies that reported AE, the 4 studies listed in the left table above were all RCTs. Sablan 2012 was not included in the benefits GRADE because it used a non-licensed 3-dose series of HEPLISAV™. They all reported mild and SAEs, but cardiovascular events were reported only in Heyward 2013. Of note regarding the 2 additional RCT studies that reported mild AEs, SAEs, and cardiovascular events, HBV 23 is not yet published and Janssen 2013 was not included in benefits GRADE because it used a 3-dose series for HEPLISAV™.

To summarize in aggregate any mild AEs, injection site reactions, and systemic reactions for all studies included, a similar proportion of mild AEs were reported in HEPLISAV™ compared to Engerix-B® at 45.6% versus 45.7%. A higher proportion reported injection-site reactions in HEPLISAV™ compared to Engerix-B® at 35.5% versus 30.8%. The majority of these were arm redness and soreness. There were fewer systemic reactions reported in HEPLISAV™ compared to Engerix-B® at 28.1% versus 30.1%.

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In terms of the SAEs for the 6 studies included, 4 studies reported SAEs that were considered to be related to vaccine. The reported SAEs were similar between HEPLISAV™ and the comparison groups. The 1 related SAE in the HEPLISAV™ group was an individual with progression of chronic kidney disease (CKD) stage IV to end stage renal disease 28 days after receiving dose 1, while the 1 related SAE in the Engerix-B® group was in an individual who developed reactive airway disease due to Churg-Strauss Syndrome (CSS) and anti-neutrophil cytoplasmic antibodies positive (ANCA+) vasculitis 42 days after receiving dose 3. Regarding the reported cardiovascular events in 3 studies in aggregate, the authors note that subjects with cardiovascular AEs had more than 1 cardiovascular disease risk factor. There were more cardiovascular events reported in HEPLISAV™ recipients compared to Engerix-B®, but this was not statistically significant.

For the type of evidence for AE outcomes, there were no serious concerns for risk of bias, inconsistency, indirectness, or imprecision. However, other considerations are that all studies were funded by Dynavax Technologies Corporation, and AEs from HBV 23 are unpublished. Nonetheless, the evidence type was the highest level, 1, for all studies.

This table summarizes the characteristics of 3 studies that were excluded from GRADE:

Outcomes #1,2, 3, 4: Adverse events
Characteristics of excluded studies

Study	Type	Population	Intervention	Comparison	Main Outcomes*	Funding	Site
[a]Halperin, 2012, *Vaccine*	Obs	41 healthy adults, 18–39 years	HEPLISAV at 0 and 4 or 8 weeks	None	SPR, any adverse events, SAE	Dynavax	1 site in Canada
[b]Halperin, 2013, *Human Vaccines & Immunotherapeutics*	RCT	Healthy adults, 18–65 years who did not respond to 3 doses (N=35) or 4-6 doses (N=24) of licensed HBV vaccine	HEPLISAV 1 dose followed by 2 additional Engerix-B doses	Engerix-B followed by up to 2 additional Engerix-B doses	SPR, any adverse events, SAE	Dynavax	2 sites in Canada
[c]Janssen, 2015, *Vaccine*	Subgroup analysis	328 adults with chronic kidney disease	HEPLISAV at 0, 4, and 24 weeks	Engerix-B at 0, 4, 8, and 24 weeks, double doses	SPR, any adverse events, SAE	Dynavax	US, Canada, Germany

a. Unable to abstract data since safety data presented in Figure only and non control/placebo
b. Unable to abstract safety data from the way data presented in Table 4; recipients only received 1 dose of HEPLISAV
c. Subgroup analysis of data from Janssen.2013.Vaccine, already included data in estimates of effect

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Halperin 2012 was excluded because it was not possible to abstract safety data as it was only presented in a figure and there was no comparison group. Halperin 2013 was excluded because it was not possible to abstract safety data and recipients received both Engerix-B® and HEPLISAV™, but only one dose of HEPLISAV™. Janssen 2015 was excluded because it was a subgroup analysis of data from Janssen 2013, and data from the main study were already included in GRADE.

The analysis had certain limitations. All data are from the same funding source, Dynavax Technologies Corporation. The generalizability may be limited because 21% of patients in 3 of 6 studies were not in the US. Of the patients in 2 studies, 18% were from Canada and Germany which may be similar to US population, and 3% of patients from 1 study were from Korea, Philippines, and Singapore, which may differ. All data are from clinical trials and no real-world data exist. Studies have not looked at disease endpoints like HepB infection, and

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cardiovascular events were not reported in all studies. No long-term data published on immunogenicity and AEs exist.

To summarize GRADE of HEPLISAV-B™ compared to the licensed HepB vaccine, Engerix-B®, the beneficial outcomes included were HepB infection, which was downgraded from 1 to 2 due to indirectness with use of the seroprotection rate as a surrogate for protection. Regarding harmful outcomes, mild and SAEs reported showed no differences detected between HEPLISAV™ and comparison populations with an evidence type of 1. While more cardiovascular events were reported in HEPLISAV™ recipients compared to Engerix-B®, this was not statistically significant and the evidence type was 1.

Information gaps remain. There was indirectness since there was no study looking at HepB infection as an outcome, there are no real-world cohort data, and long-term protective immunity is unknown. There was one industry funded cost-effectiveness analysis that showed HEPLISAV™ use had an incremental cost-effectiveness ratio (ICER) < $25,000 per quality adjusted life (QALY) year compared to Engerix-B® for diabetic patients, patients with CKD, patients with end-stage renal disease (ESRD), healthcare workers (HCW), and travelers [Kuan, 2013, *Vaccine*]. However, more populations are needed in future cost studies. Post-licensure studies will be included in future workgroup considerations.

Discussion Points

Dr. Belongia requested clarity regarding the risk window for cardiovascular events.

Randall Hyer (Dynavax Technologies) replied that the window varied from the length of follow-up in the HBV 16 and 23 Phase 3 studies at 13 months following a dose of HEPLISAV™.

HEPLISAV-B™: Considerations and Proposed Recommendations

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Centers for Disease Control and Prevention

Dr. Schillie reminded everyone that HepB is an infection of the liver caused by the HepB virus (HBV). It is transmitted through percutaneous or mucosal exposure to blood or body fluids. HBV is highly infectious and remains viable on environmental surfaces for at least 7 days. It can be transmitted in the absence of visible blood. Symptoms include anorexia, malaise, abdominal pain, nausea, vomiting, and jaundice. Extra-hepatic manifestations (e.g., skin rashes, arthralgias) may also occur [Bond et al., Lancet 1981;317:550-551; Trepo et al., Lancet 2014;384:2053-2063].

Acute HepB infection is symptomatic in 30% to 50% of adults. The fatality rate is <1.5%, but is higher in adults ≥55 years. Fulminant infection occurs in less than 1% of cases, but often results in death or liver failure necessitating transplantation [Surveillance for Viral Hepatitis – United States, 2015; https://www.cdc.gov/hepatitis/statistics/ 2015surveillance; McMahon et al., JID 1985;151:599-603; Trepo et al., Lancet 2014;384:2053-2063].

Chronic HepB infection develops in 90% of persons infected during infancy and less than 1% to 12% of persons infected as adults. Chronic infection more often develops in the immunosuppressed and persons with diabetes. Persons with chronic HepB have a 15% to 25% risk for premature death from cirrhosis or liver cancer. An estimated 850,000 to 2.2 million

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persons are living with HBV infection in the US [Hyams, CID 1995;20:992-1000; Surveillance for Viral Hepatitis – United States, 2015 (https://www.cdc.gov/hepatitis/statistics/2015surveillance); Roberts et al., Hepatol 2016;63:388-397; Wasley et al., JID 2010;202:192-201; Kowdley et al., Hepatol 2012;56:422-23].

Although the reported number of acute HepB cases declined from approximately 8000 in the year 2000, the number of cases increased from 2014 to 2015 concomitant with the increase in injection-drug use. There were 3370 cases reported in 2015, which corresponds to an estimated 21,900 cases when considering under-ascertainment and under-reporting. The incidence of acute HepB cases is highest among 30 through 49-year old age groups and lowest among the 0 through 19-year old age group as a result of routine infant vaccination that has been recommended since 1991 [National Notifiable Diseases Reporting System (NNDRS); Surveillance for Viral Hepatitis – United States, 2015 (https://www.cdc.gov/hepatitis/statistics/2015surveillance).

HepB vaccines first became available in the US in 1981 as a plasma-derived vaccine. Recombinant vaccines became available in 1986 and have replaced plasma HepB vaccines. Currently recommended HepB vaccines are safe, immunogenic, and effective. Anaphylaxis occurs at a rate of 1.1 per million doses administered among yeast-sensitive individuals. HepB vaccine is generally administered as a 3-dose series and protection lasts at least 30 years. Booster doses are not routinely recommended [Stratton et al., National Academies Press 2012;435-503; Bohlke et al., Pediatr 2003;112:815-820; Bruce et al., JID 2016;214:16-22; Schillie et al., *MMWR* 2018;67:1-31].

Currently recommended monovalent formulations available for all ages include Engerix® and Recombivax®. Combination formulations include Pediarix® for individuals 6 weeks through 6 years (comprised of HepB, diphtheria, tetanus, pertussis, polio) and Twinrix® for those ≥18 years of age (comprised of HepA, HepB). Persons recommended for HepB vaccination include all infants and children aged <19 years; persons at risk for infection by sexual exposure (e.g., sex partners of HBV-infected persons, persons with multiple sex partners, men who have sex with men); persons at risk for infection by percutaneous or mucosal exposure to blood (e.g., injection-drug users, household contacts of HBV-infected persons, healthcare and public safety workers, persons with end-stage renal disease and dialysis patients, adults with diabetes); others (e.g., international travelers to regions with high or intermediate HBV endemicity, persons with HCV and CLD disease, persons with HIV infection, incarcerated persons); and all persons seeking protection from HBV infection [Schillie et al., *MMWR* 2018;67:1-31].

With regard to serologic evidence of protection, antibody to hepatitis B surface antigen (anti-HBs) ≥10mIU/mL measured 1 to 2 months after vaccine series completion corresponds to vaccine-induced protection. Among healthy individuals age less than 40 years, 30% to 55% have protective antibody levels after 1 dose, 75% after 2 doses, and ≥90% after 3 doses. Lower 3-dose seroprotection is associated with advanced age, diabetes, renal disease/dialysis, obesity, chronic illness, and smoking. Among persons with diabetes, seroprotection proportions range from 30% to 94%. Among persons receiving dialysis, seroprotection proportions range from 10% to 84% [Sit et al., World J Hepatol 2015;7:761-768; Asan et al., Int Urol Nephrol 2017;49:1845-1850; Leuridan et al., CID 2011;53:68-75; Jack et al., JID 1999;179:489-492; Schillie et al., Diab Care 2012;35:2690-2697].

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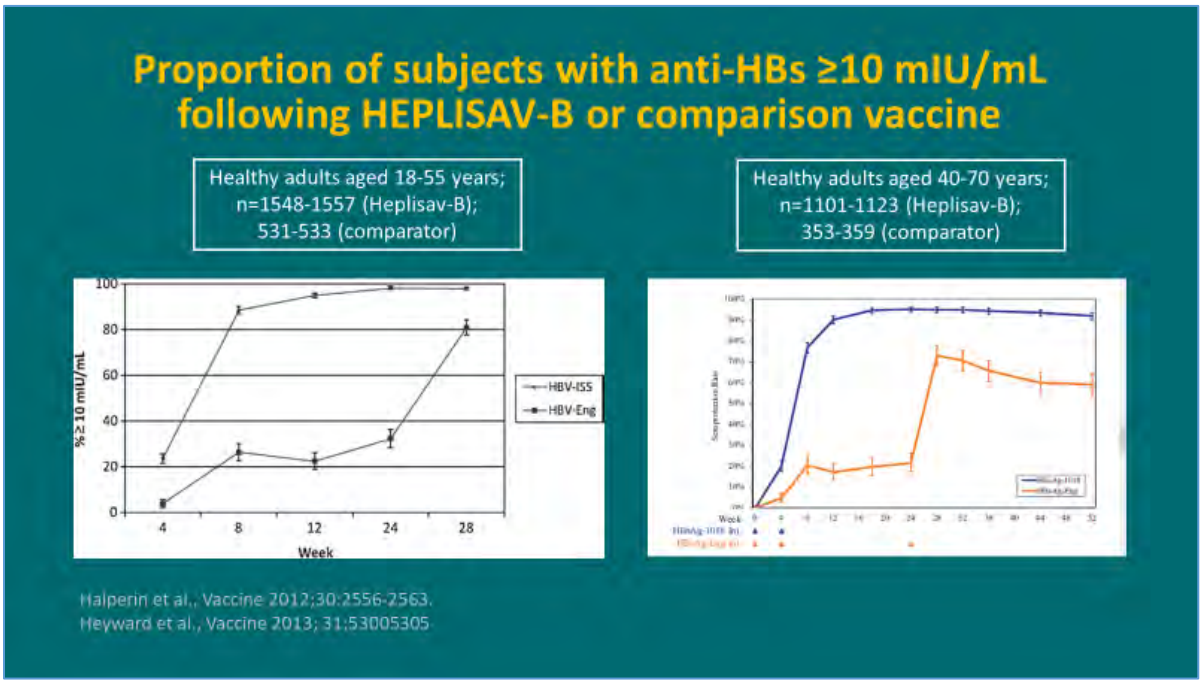
Three-dose HepB vaccine coverage for subgroups of adults for whom vaccination is recommended ranges 12% to 26% for persons with diabetes to 61.4% for healthcare personnel (HCP) [National Health Interview Survey (NHIS)].

Among adult Vaccine Safety Datalink (VSD) enrollees, roughly 40% to 60% completed the HepB series within 1 year of initiation, while fewer than 5% completed the series between 1 to 2 years and greater than 2 years after initiation. About 15% to 26% received only 1 dose, while 13% to 21% received 2 doses [Nelson et al., Am J Public Hlth 2009;99:S389-397].

HEPLISAV-B™ was licensed by the FDA on November 9, 2017. It is indicated for active immunization against infection caused by all known subtypes of HBV in persons aged ≥18 years. It is administered in a series of 2 doses, separated by 1 month. HEPLISAV-B™ uses the novel 1018 adjuvant consisting of immunostimulatory cytidine-phosphate-guanosine (CpG) motifs, which binds Toll-like receptor 9 (TLR9) to stimulate directed immune response to HepB surface antigen (HBsAg).

Studies demonstrate high rates of seroprotection with HEPLISAV-B™. Approximately 90.0% to 100.0% of subjects receiving HEPLISAV-B™ obtained seroprotective antibody levels versus 70.5% to 90.2% of subjects receiving the comparison vaccine. Among subjects with Type 2 diabetes mellitus, 90% of HEPLISAV-B™ recipients versus 65% of comparison vaccine recipients attained seroprotective antibody levels. Among subjects with CKD, 90% of subjects receiving 3 doses of HEPLISAV-B™ versus 81% of subjects receiving 4 double doses of comparison vaccine attained seroprotective antibody levels [Halperin et al., *Vaccine* 2006;24:20-26; Halperin et al., *Vaccine* 2012;30:2556-2563; Heyward et al., *Vaccine* 2013; 31:53005305; Jackson et al., *Vaccine* 2018;36:668-674; Janssen et al. *Vaccine* 2013;31:5306-5313; HEPLISAV-B package insert 11/2017].

These graphs depict the proportion of healthy subjects with anti-HBs ≥10 mIU/mL following HEPLISAV-B™ shown by the upper line or comparison vaccine shown by the lower line:



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HEPLISAV-B™ recipients attained earlier and greater seroprotection than comparison recipients. By Week 12 in both studies, at least 90% of HEPLISAV-B™ recipients had antibody levels of at least 10 mIU/mL.

HEPLISAV-B™ has also been studied in vaccine non-responders, although the sample sizes are small. Among non-responders to 3 prior doses, 53% of HEPLISAV-B™ (n=19) versus 38% of comparison recipients (n=16) attained seroprotective antibody levels. Note that this was not statistically significant. Among non-responders to 4 to 6 prior doses, 64% of HEPLISAV-B™ recipients (n=11) versus 58% of comparison recipients (n=12) attained seroprotective antibody levels. This also was not statistically significant. Among non-responders to 4 to 6 prior doses, 55% of HEPLISAV-B™ recipients (n=11) versus 8% of comparison recipients (n=12) attained antibody levels ≥100 mIU/mL, which was statistically significant [Halperin et al., Hum Vacc Immunotherap 2013;9:1438-1444].

The safety and reactogenicity of HEPLISAV-B™ has been assessed in clinical trials. Mild AEs occurred with similar frequency among HEPLISAV-B™ and comparison recipients. SAEs occurred more commonly among comparison recipients in aggregate, although herpes zoster (HZ) occurred more commonly among HEPLISAV-B™ recipients in one unpublished study. Cardiovascular events occurred more commonly among HEPLISAV-B™ recipients at 0.27% versus 0.14% in comparator recipients. Potentially immune-mediated AEs varied among studies. Safety will be further assessed through post-marketing studies [Halperin et al., *Vaccine* 2006;24:20-26; Halperin et al., *Vaccine* 2012;30:2556-2563; Heyward et al., *Vaccine* 2013; 31:53005305; Jackson et al., *Vaccine* 2018;36:668-674; Janssen et al. *Vaccine* 2013;31:5306-5313; HEPLISAV-B package insert 11/2017; U.S. FDA, HEPLISAV-B; (https://www.fda.gov/BiologicsBloodVaccines/ Vaccines/ApprovedProducts/ucm584752.htm)]. In summary, GRADE was deemed to be evidence Type 2 for benefits and evidence Type 1 for harms.

With respect to the WG's considerations, the WG discussed series interchangeability in terms of a vaccine series initiated with HepB dose(s) from another manufacturer and completed with HEPLISAV-B™ and the minimum dosing intervals related to interchangeability. The WG also addressed post-vaccination serologic testing following HEPLISAV-B™ and revaccination for non-responders using HEPLISAV-B™. ACIP recommends that when feasible, doses from the same manufacturer should be used to complete the series. However, vaccination should not be deferred because a previously used manufacturer's dose is not available. Minimum intervals are Dose 1-2: 4 weeks, Dose 2-3: 8 weeks, and Dose 1-3: 16 weeks. Doses administered at less than the minimum interval should be repeated, and there are no maximum intervals [Kroger et al., General Best Practice Guidelines for Immunization. Accessed 2/16/18; Schillie et al., *MMWR* 2018;67:1-31].

Regarding interchangeability, the WG proposes that the 2-dose series only applies when all doses in the series consist of HEPLISAV-B™. When a vaccine series is initiated with 1 dose of a vaccine from a different manufacturer and must be completed with HEPLISAV-B™, 3 total HepB vaccine doses should be administered. Minimum intervals should be heeded. However, a series containing 2 doses of HEPLISAV-B™ administered at least 4 weeks apart is valid, even if the patient received a single earlier dose from another manufacturer.

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ACIP recommends post-vaccination serologic testing consisting of anti-HBs for certain persons following HepB vaccination including: hemodialysis patients, HIV-positive and other immunocompromised persons, HCP, sex partners of HBV-infected persons, and infants born to HBV-infected mothers. Persons with anti-HBs <10 mIU/mL should be revaccinated. Revaccination can initially consist of 1 vaccine dose followed by antibody testing. If anti-HBs is <10 mIU/mL, 2 more doses should be administered and followed again by antibody testing. Alternatively, revaccination may consist of 3 doses followed by antibody testing. Administration of more than 2 complete HepB vaccine series (i.e., 6 doses) is generally not recommended, except for hemodialysis patients and other immunocompromised persons [Schillie et al., *MMWR* 2018;67:1-31].

HEPLISAV-B™ may be used for revaccination following an initial HepB vaccine series that consisted of doses of HEPLISAV-B™ or doses from a different manufacturer, including among HCP. Post-vaccination serologic testing and revaccination guidance remains unchanged. Administration of more than 2 complete HepB vaccine series (note that 2 doses of HEPLISAV-B™ comprise a series) is generally not recommended, except for hemodialysis patients and other immunocompromised persons.

In summary of the WG's deliberations, HEPLISAV-B™ is likely to improve HepB vaccine series completion and result in earlier protection due to the administration schedule of 2 doses over 1 month. This schedule may be especially beneficial for persons with anticipated low adherence, such as injection drug users. HEPLISAV-B™ will also likely result in improved immunogenicity in populations with typically poor vaccine response, such as the elderly, persons with diabetes, and dialysis recipients. Post-marketing surveillance studies and additional data, including safety, pertaining to the use of HEPLISAV-B™ will be reviewed as they become available, and recommendations will be updated as needed prior to a preferential consideration. Future economic analyses may inform cost-effectiveness considerations of HEPLISAV-B™, including its use among persons at an increased risk for vaccine non-response.

Discussion Points

Dr. Walter requested further details about what has been agreed to in terms of the post-marketing safety surveillance studies Dr. Schillie mentioned.

Dr. Schillie replied that the FDA has worked with Dynavax Technologies Corporation on post-marketing surveillance studies. She invited FDA or Dynavax representatives to further elaborate on the intent of the post-marketing studies.

Dr. Sun (FDA) replied that there are a number of post-marketing surveillance studies. One study was required because in the large safety trial, Study 23, a signal was observed for myocardial infarction (MI). Therefore, FDA made it a requirement for the signal to be investigated further within the context of a Kaiser Permanente non-randomized study. The other one is a commitment. The difference between a requirement and a commitment is related to the level of concern for the safety signal. The commitment was to assess the occurrence of HZ, given that an increase in incidence was observed in Study 23.

Dr. Belongia said he assumed there would be a VSD study as well. In addition, he wondered whether the 1018 adjuvant is used in other licensed products in the US or elsewhere.

Dr. Schillie clarified that HEPLISAV-B™ is the first vaccine for humans in which this adjuvant is being used.

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Dr. Bernstein said he was surprised that the HepB vaccine coverage in HCP was only 60%, and asked whether there was an explanation for that.

Dr. Schillie replied that there was not an explanation and they also wondered why that was so low given the recommendations, that the institution pays for the vaccine costs, and that the employees are a captive audience. The 60% is for 3-dose coverage and was the average for all HCP, and it does vary somewhat. HCP with direct patient responsibilities have higher coverage than that; whereas, those without direct patient care responsibilities have lower coverage.

With the number of adjuvanted vaccines now available, including influenza vaccine and SHINGRIX, Dr. Walter asked whether there were any comments regarding the use of this vaccine with other adjuvanted vaccines.

Dr. Schillie responded that there are no data to make a recommendation one way or the other.

To put this in the context of other vaccines, Dr. Cohn pointed out that while preclinical studies were not conducted using these vaccines simultaneously, the general approach to immunizations is that they can be given at the same time in different limbs.

Dr. Hunter asked whether multiple adjuvanted vaccines are used in Europe or other markets.

Dr. Ward (SME) said they were not to his knowledge.

Dr. Lee requested clarification for certain populations why the benefit/risk balance seemed very different from the average population, and whether this was a series of steps and the next step would be focused on high-risk populations where the benefit/risk balance might suggest that a preferential recommendation might be helpful.

Dr. Schillie replied that the intent for this session was to explore a non-preferential recommendation. Once further studies are conducted, including safety and cost-effectiveness studies, it might be appropriate at that point to consider a preferential recommendation for those with historically poor adherence or groups with historically poor response to HepB vaccine.

Dr. Riley inquired as to whether there were any data on different race/ethnicity populations with this vaccine.

Dr. Schillie responded that one of the initial comments by FDA was that some of the early Phase 3 trials did not include a racially diverse group of subjects. As a result, the Sablan study that Dr. Harris talked about previously was predominantly among Asian persons. It is Dr. Schillie's understanding that the manufacturer addressed the FDA's concerns about the lack of a diverse racial subject population.

Dr. Lee asked whether the guidance would include this additional information to provide guidance to clinicians in the absence of a preferential recommendation for people who seem to be at high-risk for failure.

Dr. Schillie responded that it is the intention to note that different population groups who may achieve higher seroprotection with this vaccine versus other vaccines or populations who might have low adherence with other vaccines may be especially appropriate for HEPLISAV-B™.

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Dr. Whitley-Williams (NMA) asked whether the post-marketing studies reflect more of the diverse population in the US.

Dr. Schillie invited a representative from the manufacturer to respond with their intentions regarding post-marketing surveillance.

Randall Hyer (Dynavax Technologies) replied that they are conducting post-marketing surveillance within Kaiser Permanente-Southern California, which is quite a diverse population group.

To follow up on Dr. Belongia's observation, Dr. Messonnier asked whether someone from CDC would comment on the routine post-marketing surveillance that will be conducted through the VSD.

Dr. Shimabukuro (ISO) replied that CDC will be conducting VSD and Vaccine Adverse Event Reporting System (VAERS) monitoring as CDC does for all newly licensed and recommended vaccines, and also will explore the feasibility of conducting an epidemiologic study in the VSD to examine acute MI.

Dr. Hayes (ACNM) reminded everyone that outpatient healthcare is not regulated in this country, so the vast majority of people who work in private offices are not vaccinated. Thus, the 60% probably represents only those who work in hospitals and institutions.

Dr. Romero made a motion to accept the vote presented on Dr. Schillie's Slide 29, which Dr. Belongia seconded. No further discussion was posed.

Public Comments

Amitha Sampath, MD
Center for Pan-Asian Community Services/Cosmo Health Center

I want to thank you for this opportunity to provide public comment. My name is Amitha Sampath. I am a Physician and Associate Medical Director at a Federally Qualified Health Center (FQHC) called Center for Pan-Asian Community Services (CPACS)/Cosmo Health Center. I want to provide comment on behalf of ourselves and the Atlanta Hep B United Coalition. We work to promote coalition building, education, testing, and follow-up for particularly vulnerable communities such as immigrants and refugees. I want to provide some feedback from our work that we've done. In our screening efforts we've found that only about 21% of our target population is immune to the vaccination and 41% were vaccine-eligible. More than half of these were in the childbearing range 18 to 40 years old, which poses a risk for perinatal transmission. Nearly all of the population was also uninsured and below the poverty line. So, for these vulnerable communities in particular, bearing the full cost of 3 doses of the vaccine, which they are often paying out-of-pocket for, the number of days taken off of work, and the logistics of getting to the healthcare center can pose a barrier to completing the series. So, we do agree with the Work Group and support the vaccine and expedition to completion. Thank you for allowing comments.

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Bekeela Davila, MPH
Program Coordinator
National Viral Hepatitis Roundtable

On behalf of the National Viral Hepatitis Roundtable (NVHR), a coalition of 500 plus 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 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% in the year 2015 alone. Recent data indicate that only a quarter of adults aged 19 and older are fully immunized and adults aged approximately 25 years and older were not routinely vaccinated against hepatitis B at birth in the United States. Meanwhile, an estimated 5000 to 6000 Americans die each year of hepatitis B-related complications. Approval and recommendation of the HEPLISAV-B™ hepatitis 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 3-dose regimen administered over 6 months. The availability of a 2-dose vaccine administered over a 1-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 in syringe access programs and substance 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 HEPLISAV-B™ as a new and powerful tool in the fight to eliminate hepatitis B in the United States. Thank you.

Binh T. Ly
Urban Affairs and Planning
Virginia Tech | National Capital Region

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 2-dose hepatitis B vaccine regimen, HEPLISAV-B™. As an individual living with hepatitis B, I have been receiving treatment for hepatitis B for close to 4 years now. But, thinking back, it amazes me how lightly I took the disease. Even after knowing I had hepatitis B, several years passed before I received treatment. As a member of the diverse lesbian, gay, bisexual, transgender (LGBT) community, I sought treatment because I wanted to protect myself against STDs (sexually transmitted diseases) and HIV/AIDS. I was well aware of those risks. But when I went into seek treatment, I was told that my viral load was in the hundreds of millions. I share this anecdote just to show how little I knew, and the public knows, about hepatitis B. I am fortunate to have stumbled upon treatment, but many others may not be. The rate of hepatitis B infections in adults increased 20% in 2015 alone. In the US, at least 5000 lives are unnecessarily lost each year from liver failure or liver cancer. The availability of 2-dose vaccines over 1 month instead of 3 doses over 6 months is a critical tool to protect many more Americans considering the low percentage of those who currently complete all 3 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 shouldn't be left to

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chance and through evidence-based policies, I believe we can better protect all Americans. Thank you again for this opportunity.

Kate Moraras, MPH
Senior Program Director
Hepatitis B Foundation
Hep B United National Coalition

Thank you very much for this opportunity to comment. I won't repeat the statistics already mentioned, but some additional ones [are that] national survey data indicate that overall HBV vaccine coverage among US adults is very low, 25%, and only 32.6% of adults between the ages of 19 and 49 years are fully covered by the 3-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 vaccination of infants became routine. Additionally, as we have seen the rise in the opioid crisis and the rise in adults of acute hepatitis B infection, the *CDC National Progress Report on Hepatitis Elimination* reveals that we are behind our national target to reduce acute hepatitis B infection. A 63.8% reduction is needed to meet our 2020 goal, so a 2-dose vaccine series is critical to address this. I represent a coalition with partners in 18 states, and many of our partners have found that one of their biggest challenges is vaccine completion among highly impacted communities. One example is in 2011 to 2013, Philadelphia pilot tested a mobile hepatitis B vaccine clinic, removing the barriers of cost, language, and transportation for susceptible individuals. Even with removal of 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%. So, we believe that having a new 2-dose vaccine will play a significant role in the prevention and elimination of hepatitis B in the US. Thank you very much.

Larry O'Connor, PharmD
Dallas County Medical Reserve Corps

I'm a retail pharmacist in Ft. Worth who is starting a travel vaccination clinic. Patient medication adherence and compliance rates are low, probably in the 20% range. If healthcare workers can't get their HepB vaccination rates up—I'm diabetic and I've had my second but not my third shot, so I'm not self-righteous. I also have a question for the drug reps. Are there any programs with the drug reps working with behavioral therapists to try to figure out a way, or nudges, for changing human behavior? Because anybody with a 3-vaccine series, if the healthcare professionals can't do it, how can the regular civilians be expected to? Instead of going to a 2-vaccine series, it would be just as effective to work with behavioral therapists and have programs that encourage people to finish the series rather than spending more money. I mean, both are effective, but behavioral therapy is probably a lot less expensive and a little bit faster to get people to comply with.

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Amy Shen Tang, MD
Hepatitis B Program Director
Charles B. Wang Community Health Center

Dr. Shen Tank submitted a letter, which is included in Appendix B of this document.

Motion/Vote HEPLISAV-B™ Recommendation

Dr. Romero moved to approve the non-preferential recommendation for HEPLISAV-B™ with the language as presented stating that, "HEPLISAV-B™ is a Hepatitis B vaccine that may be used to vaccinate persons aged 18 years and older against infection caused by all known subtypes of HBV." Dr. Belongia seconded the motion. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Dr. Cohn invited ACIP members to share comments about their votes if they wished.

Dr. Stephens said he had a slight reservation, though he thought this was a huge advance and a step forward. He is concerned about the MI signal and the use of the new adjuvant, and certainly urged ACIP to continue to review the post-marketing data carefully.

Dr. Hunter inquired as to how soon ACIP would receive an update on the post-marketing data.

Dr. Messonnier clarified that there are two kinds of data. The VSD data will require people to be using the vaccine to develop a substantive database. She called upon Dr. Sun to comment on the post-marketing data that FDA is requiring.

Dr. Sun (FDA) replied that the FDA approval letter makes references to specific dates. The likely date of completion for the MI study is May 31, 2020. He also made a slight clarification from his previous statement. In addition to what he mentioned for the post-marketing studies, there also will be studies assessing autoimmune diseases and HZ and there will be a pregnancy registry as well. Those are all included in the post-marketing surveillance.

Hepatitis A Post-Exposure Prophylaxis GRADE

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

Dr. Nelson presented on GRADE for HepA vaccine for PEP in adults >40 years of age. In terms of the GRADE process, the components followed by the WG for this evaluation included development of the policy question, consideration of critical outcomes, review and summarization of evidence of benefits and harms, evaluation of quality of evidence, assessment of population benefit, considerations for formulating recommendations, and ACIP

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recommendation and GRADE category. The policy question for consideration was, "Should hepatitis A vaccine be recommended instead of immune globulin (IG) as PEP for prevention of hepatitis A disease in adults >40 years of age?" The population of interest was "healthy adults >40 years of age. The intervention of interest was "Hepatitis A vaccine administered within 14 days of exposure." The WG looked for studies that compared IG administered within 14 days of exposure to HAV. The outcomes the WG considered were: HAV infections, deaths, hospitalizations, AEs, and immunogenicity. Outcome measures in the evidence profile included one benefit outcome (immunogenicity) and four harm outcomes (HAV infection, deaths, hospitalizations, AEs). All outcomes were determined to be of critical importance.

The WG conducted a systematic review of data on HepA vaccine in adults aged >40 years, including a search of PubMed and EMBASE from January 1, 1992 through January 7, 2017. The search terms included "hepatitis A vaccine*" and "HAV vaccine* and articles in adult humans were included. There were no language restrictions on the initial searches and articles were included from any country. Articles were excluded that focused solely on children or did not provide information on ages of included individuals; did not include data on HAVRIX® or VAQTA®, the two single antigen HepA vaccines currently licensed in the US; included only safety data or discussed vaccine introduction without providing new data; reported only data on individuals with underlying conditions; and provided data only ≥28 days after the first dose of HepA vaccine, as these data would not be applicable in an outbreak setting.

The search yielded 782 unique abstracts from PubMed and 257 unique abstracts from EMBASE. Of these, 936 articles were excluded because of relevance. The primary reasons for exclusion were that the studies included no adults >40 or results of adults >40 could not be separated out (n=118), included no results for <28 days post-vaccination (n=137), included vaccines other than HAVRIX® or VAQTA® (n=43), included animals other than humans (n=2), focused on assay development (n=7), could not be obtained in English (n=30), only included safety data (n=30), included only individuals with underlying conditions (n=29), or focused on vaccine introduction (n=540). A total of 103 full articles were reviewed and 95 were excluded. Reasons for exclusion were that the studies included no adults >40 or results of adults >40 could not be separated out (n=32), the full article could not be obtained or could not be obtained in English (n=30), included no results for <28 days post-vaccination (n=17), focused on vaccine introduction (n=13), or other reasons (n=2). One additional article was originally missed because of mis-specified Medical Subject Heading (MeSH) terms and was added, as was an article e-published in December 2016, but not added to PubMed until after the search was complete.

As a reminder, this table summarizes the standardized initial evidence types by study design for GRADE:

Initial Evidence Type	Study Design
1	Randomized controlled trials (RCTs), or overwhelming evidence from observational studies
2	RCTs with important limitations, or exceptionally strong evidence from observational studies
3	Observational studies, or RCTs with notable limitations
4	Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

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This table summarizes the characteristics of the studies included for Benefit Outcome #1: Immunogenicity:

Outcome #1: Immunogenicity*

Author, year	Study Design	No. of subjects	Population	Immunogenicity results
Briem et al., 1994	3	60	40 to 62 years, Iceland	Seroconversion (≥20 mIU/mL anti-HAV) at 15 days: **77%** GMT at 15 days: 262 mIU/mL (range: 65-995 mIU/mL)
Reuman et al., 1997[a]	3	23	≥ 40 years, U.S.	Seroconversion (≥10 mIU/mL anti-HAV) at 2 weeks: **31%** GMT at 2 weeks: 6.1 mIU/mL
Van Der Meeren et al., 2015	3	80	≥ 40 years, Belgium, Finland, Iceland	Seroconversion (≥20 mIU/mL anti-HAV) at 15 days: **79.7%** (68.8-88.2%) GMT at 15 days: 126.5 mIU/mL (88.6-180.7 mIU/mL)
Goilav et al., 1995	3	306	Mean age 24 years (range 18-63), UK, Belgium, Germany, France	Seroconversion (≥20 mIU/mL anti-HAV) at 2 weeks: **76.1%** (95% CI: 71.2-81.1%) GMT at 2 weeks: 30.8 mIU/mL (95% CI: 28.1-33.7)
Bertino et al., 1998[b]	3	153	≥ 30 years (median age 42 years), U.S.	Seroconversion (≥10 mIU/mL anti-HAV) at 2 weeks: **46%** GMT at 2 weeks: 10.0 mIU/mL
Williams et al., 2000[c]	1	149	Mean age 42, Alaska Natives	See results for Nelson et al., 2014[a]
Nelson et al., 2014[c]	3	172	40-49 years; 50-59 years; ≥ 60 years, Alaska Natives	Seroconversion (≥20 mIU/mL anti-HAV) at 15 days: 40-49 years: **74%** (n=125); 50-59 years: **54%** (n=37); ≥ 60 years: **30%** (n=10) GMTs at 15 days: 40-49 years: 26.09 mIU/mL (n=125); 50-59 years: 12.80 mIU/mL (n=37); ≥ 60 years: 1.62 mIU/mL (n=10)

*No immune globulin comparator studies were identified in the systematic review
[a]VAQTA 25U
[b]VAQTA 50U results shown
[c]Nelson et al. 2014 is a reanalysis of Williams et al., 2000 with defined age groups.

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The population age ranges varied for Outcome #1. The correlate of protection (limit for seroconversion) also varied. In some studies, it was ≥10 mIU/ml and in others it was ≥20 mIU/ml. Only 3 articles included in the final review had direct comparisons between adults ≤40 years of age and adults >40 years of age: 1) Briem, a retrospective cohort conducted in Iceland; 2) Reuman, a retrospective cohort conducted in the US); and 3) Van der Meeren, a post-hoc retrospective pooled analysis from 3 randomized clinical trials conducted in Belgium, Finland and Iceland. In the Briem study, seroconversion at 15 days occurred in 77% of persons age 40 through 62 years. The Reuman study used half the current recommended adult dose of VAQTA® (25 U), and 31% of adults >=40 years seroconverted at 2 weeks. In the Van Der Meeren study, seroconversion occurred in approximately 80% of adults >= 40 years of age.

Two studies included adults >40 years of age in the population, but did not present results differentiated by age: 1) In Goilav, a multicenter, controlled, randomized, open, comparative study performed in the United Kingdom (UK), Belgium, Germany, and France, seroconversion occurred in about 76% of adults age 18-63 years; and 2) In Bertino et al, an observational study conducted in the US, 46% of adults >=30 years seroconverted. The only study to stratify by age groups >40 years was Nelson et al., a reanalysis of Williams et al., which included adults with a mean age of 41 years. Seroconversion occurred in 74% of adults age 40 through 49 years, 54% of adults age 50 through 59 years, and 30% of adults age >=60 years within 15 days.

Hepatitis A infection was described in 3 studies: 1) Parron et al, which included adults >40 years in Catalonia; 2) Freeman et al, which included adults >=40 years in Australia, and Whelan et al, which included adults >=41 years in the Netherlands. Deaths, hospitalization, and AE outcomes were evaluated in these studies and AEs were evaluated in all studies.

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The following table depicts outcomes #1-4:

Outcome #1-4

Outcome	No. of subjects (# studies)	Incidence in comparison group	Incidence in vaccinated	Vaccine efficacy	Absolute risk	Number needed to vaccinate
Hepatitis A infection	130 (3 observational)	N/A	4 cases (3.1%)	N/A	N/A	N/A
Deaths	130 (3 observational)	N/A	None reported	N/A	N/A	N/A
Hospitalizations	130 (3 observational)	N/A	None reported	N/A	N/A	N/A
Serious adverse events	974 (9 observational)	N/A	None reported	N/A	N/A	N/A

Four cases among adults >40 years were identified in the 3 studies with information on HAV infection. Of note, one of these cases occurred in a 43-year-old man, but no other information was provided. Incidence in the comparison group could not be assessed because no studies were identified that compared IG and vaccine in adults >40 years. Vaccine efficacy (VE), absolute risk, and NNV also could not be evaluated in these studies.

The evidence types are explained here for reference:

- ⊕⊕⊕⊕/A/High/**Evidence Type 1**: We are very confident that the true effect lies close to that of the estimate of the effect.
- ⊕⊕⊕○ /B/Moderate/**Evidence Type 2:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- ⊕⊕○○ /C/Low/**Evidence Type 3**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- ⊕○○○/D/Very low/**Evidence Type 4**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

These studies had several limitations. There were no RCTs identified comparing HepA vaccine and IG in healthy adults >40 years of age. Only one study, a sub-analysis, contained immunogenicity data on discrete age ranges over age 40 years. No articles provided explicit estimates of efficacy of HepA vaccine in adults >40 year of age against disease endpoints. Most studies included persons from outside of the US (Europe, UK, Australia), though these populations may be similar to the population in the US.

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In terms of the GRADE summary, the benefit outcome of immunogenicity was downgraded for inconsistency. Immunogenicity results in older adults showed high variability by study, with orders of magnitude differences in geometric mean titer (GMT) results. The evidence was also downgraded for indirectness, given that 4 of 6 studies did not provide results broken down by age group, included younger individuals, or did not provide details on age ranges. Immunogenicity was downgraded for imprecision, given that the studies included very few adults in the oldest age groups. Only one study provided results for adults >60 years and this included only 10 subjects. HAV incidence, death, and hospitalizations were downgraded for risk of bias since 2 of 3 studies were surveillance studies, with little information provided about the potential for missed follow-up. The overall evidence type for benefits and harms was 4.

Considerations and Proposed Recommendations

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

Dr. Nelson next discussed considerations for use of HepA vaccine for PEP and international travel. She indicated that the proposed updates to current 2007 HepA vaccine recommendations for PEP and international travel include recommendations for PEP with IG or HepA vaccine for the following groups: Children aged <12 months and persons for whom vaccine is contraindicated; Healthy persons; Immunocompromised persons and persons with CLD, and Pregnant women. *Provider Guidance on Risk Assessment and Clinical Decision Making for Post-Exposure Prophylaxis* is proposed to be included. Specifically, this guidance would focus on exposure due to close personal contact, exposure in child care centers, exposure due to common-source food exposure, exposure in settings providing services to children and adults, and exposure in natural disaster settings with flooding. The proposed recommendations for pre-exposure protection against HAV for travelers would include specific updates for the following groups: Infants aged <6 months; Infants aged 6-11 months; Healthy persons aged >12 months; and Immunocompromised persons and persons with CLD.

The HepA policy questions are as follows:

- *Post-Exposure Prophylaxis*
  - Q1a. Should hepatitis A vaccines be recommended for post-exposure prophylaxis for all persons age ≥12 months?
  - Q1b. Should IG be recommended at age >50 years in addition to vaccine?

- *International Travel*
  - Q2. Should hepatitis A vaccines be administered to infants age ≥6-11 months of age pre-travel (unless the infant is traveling to an area with no endemic measles transmission)?

- *Post-Exposure Prophylaxis and International Travel*
  - Q3. Should vaccine (or vaccine with addition of IG) for PEP and vaccine for International travel be administered to pregnant women due to the risk of adverse fetal outcomes if the woman is infected with hepatitis A virus during pregnancy?

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Regarding Hep A background epidemiology and vaccine coverage, the number of reported HAV cases declined substantially overall from 13,397 in 2000 to 1390 cases in 2015. Within this time period, the number of reported cases increased from 2012 through 2013 and again from 2014 through 2015, primarily due to outbreaks. The overall decline is due to the success of HepA vaccination, which was introduced incrementally in 1996 with universal childhood recommendation for children age 12-23 months recommended in 2006. From 2000 through 2015, rates of reported HAV infections declined, except for a slight increase in 2012 and 2013 among all age groups except those aged 0-9 and 10-19 years. When comparing the 2015 HAV infection rates of all age groups, persons aged 20-29 years had the highest rate at 0.6 cases/100,000 population and persons aged 0-9 years had the lowest rate at 0.1 cases/100,000 population. The reported rate of acute hepatitis A for all children age 0-19 is under the healthy people 2020 target of 0.3 cases/100,000 population [NNDSS].

The HepA vaccine coverage in 2016 is shown in the following table

Children[1]	Adolescents[2]	Adults[3]
❑ 60.6% for children age 19-35 months, ≥2 doses ❑ 86.1% for children age 19-35 months, ≥1 dose	❑ 64.4% for adolescents age 13-17 years, ≥2 doses ❑ 73.9% for adolescents age 13-17 years, 1 dose	❑ 9.5% for adults ≥19 years, ≥2 doses ❑ 13.4% for adults 19-49 years, ≥2 doses ❑ 5.4% for adults ≥50 years, ≥2 doses
1. Hill HA, et al. Vaccination Coverage Among Children Aged 19-35 Months - United States, 2016.*MMWR* 2017;66:1171–1177. 2. Nelson NP, et al. Hepatitis A Vaccination Coverage Among Adolescents (13-17 years) in the United States, 2008-2016. Vaccine 2018. (volume/issue pending) 3. Vaccination Coverage Among Adults in the United States, National Health Interview Survey, 2016 https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/NHIS-2016.html#hepA		

There have been multiple HAV outbreaks over the past 5 years, including outbreaks related to contaminated food and person-to-person transmission. A multi-state outbreak associated with frozen pomegranate arils imported from Turkey occurred in 2013. There were 165 confirmed cases, of which 42% of cases were hospitalized, 2 cases developed fulminant hepatitis, and 1 case required a liver transplant. An outbreak associated with raw scallops occurred on Oahu and Kauai, Hawaii in 2016. There were 292 confirmed cases and 74 hospitalizations. A multistate outbreak of HAV linked to frozen strawberries occurred in 2016. There were 129 confirmed cases and 59 hospitalizations.

Considerations and Proposed Recommendations

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HepA vaccine coverage in 2016 is shown in the following table:

Children[1]	Adolescents[2]	Adults[3]
❑ 60.6% for children age 19-35 months, ≥2 doses (which is likely underestimated since the first dose can be given up to age 23 months, with the second dose administered at least 6 months after the first) ❑ 86.1% for children age 19-35 months, ≥1 dose	❑ 64.4% for adolescents age 13-17 years, ≥2 doses ❑ 73.9% for adolescents age 13-17 years, 1 dose	❑ 9.5% for adults ≥19 years, ≥2 doses ❑ 13.4% for adults 19-49 years, ≥2 doses ❑ 5.4% for adults ≥50 years, ≥2 doses

1. Hill HA, et al. Vaccination Coverage Among Children Aged 19-35 Months - United States, 2016.*MMWR* 2017;66:1171–1177.
2. Nelson NP, et al. Hepatitis A Vaccination Coverage Among Adolescents (13-17 years) in the United States, 2008-2016. Vaccine 2018. (volume/issue pending)
3. Vaccination Coverage Among Adults in the United States, National Health Interview Survey, 2016 https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/NHIS-2016.html#hepA

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There have been multiple HAV outbreaks over the past 5 years, including outbreaks related to contaminated food and person-to-person transmission. A multi-state outbreak associated with frozen pomegranate arils imported from Turkey occurred in 2013. There were 165 confirmed cases in this outbreak, of which 42% of cases were hospitalized, 2 cases developed fulminant hepatitis, and 1 case required a liver transplant. An outbreak associated with raw scallops occurred on Oahu and Kauai, Hawaii in 2016. In that outbreak, there were 292 confirmed cases and 74 hospitalizations. A multistate outbreak of HAV linked to frozen strawberries occurred in 2016. There were 129 confirmed cases and 59 hospitalizations [Collier MG, et. al. Outbreak of hepatitis A in the USA associated with frozen pomegranate arils imported from Turkey: an epidemiological case study. Lancet Infect Dis. 2014 Oct;14(10):976-81; http://www.vdh.virginia.gov/blog/2016/09/10/hepatitis-a-investigation/; http://www.cdc.gov/hepatitis/outbreaks/2016/hav-strawberries.htm].

An outbreak of HAV in multiple states among people who are homeless and people who use drugs has been ongoing since 2017. California had a case count of 694 as of February 9, 2018, with 454 hospitalizations and 21 deaths. Michigan had a separate outbreak with a case count of 751 as of February 14, 2018, with 609 hospitalizations and 25 deaths. Utah had an outbreak related to the California outbreak with a case count of 181 as of February 20, 2018, and 90 hospitalizations. In addition, there are active investigations in Kentucky and Missouri [https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/Immunization/Hepatitis-A-Outbreak.aspx; http://www.michigan.gov/mdhhs/0,5885,7-339-1550_2955_2976_82305_82310-447907--,00.html; http://health.utah.gov/epi/diseases/hepatitisA/HAVoutbreak_2017].

The current ACIP recommendations for PEP and international travel were approved in 2007 and are as follows [*MMWR*. 2007 Oct 19;56(41):1080-4]:

- Persons who recently have been exposed to HAV and who previously have not received hepatitis A vaccine should be administered a single dose of single-antigen hepatitis A vaccine or immune globulin (IG) (0.02 mL/kg) as soon as possible.
  - For healthy persons aged 12 months–40 years, single antigen hepatitis A vaccine at the age-appropriate dose is preferred.
  - For persons aged >40 years, IG is preferred; vaccine can be used if IG cannot be obtained.
  - For children aged <12 months, immunocompromised persons, persons who have had chronic liver disease diagnosed, and persons for whom vaccine is contraindicated, IG should be used.
- All susceptible persons traveling to or working in countries that have high or intermediate hepatitis A endemicity should be vaccinated or receive IG before departure. Hepatitis A vaccine at the age-appropriate dose is preferred to IG. The first dose of hepatitis A vaccine should be administered as soon as travel is considered.
  - One dose of single-antigen hepatitis A vaccine administered at any time before departure can provide adequate protection for most healthy persons.
  - Older adults, immunocompromised persons, and persons with chronic liver disease or other chronic medical conditions planning to depart to an area in <2 weeks should receive the initial dose of vaccine and also simultaneously can be administered IG (0.02 mL/kg) at a separate anatomic injection site.

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- Travelers who elect not to receive vaccine, are aged <12 months, or are allergic to a vaccine component should receive a single dose of IG (0.02 mL/kg), which provides effective protection for up to 3 months.

The evidence for the 2007 recommendations is based on a HepA vaccine post-exposure trial conducted in Kazakhstan and published in 2007. In this study, 1090 household or daycare contacts of 920 index cases were enrolled. The ages of enrolled persons ranged from 2 to 40 years of age. Enrolled persons were included if exposure to an index case occurred within 2 weeks after index case symptom onset. Enrolled persons were excluded from the study if there was a history of HAV infection, HepA vaccine, or IG in the previous 6 months. The study design was a randomized non-inferiority study comparing HepA vaccine (VAQTA®) or IG. The primary outcome was laboratory-confirmed symptomatic HAV during the 15 to 56 days post-exposure. The study found that HepA vaccine efficacy was similar to that of IG. The study's pre-specified criterion for non-inferiority was met. In the per-protocol analyses, 25 primary end points were reached among vaccine recipients (4.4%) and 17 were reached among immune globulin recipients (3.3%), yielding a relative risk among vaccine recipients as compared with IG recipients of 1.35 with a confidence interval of 0.70 to 2.67 [Victor JC, et al. Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. *NEJM*. 2007 Oct 25;357(17):1685-94].

Since the Victor study in 2007, few studies have evaluated HepA vaccine response among adults ≥40 years of age. No RCTs are available, and limited studies are available with data broken down in discrete age groups >40 years. No direct comparisons between HepA vaccine and IG are available for older adults. It is unlikely that additional post-exposure efficacy data would become available, because of the difficulties of conducting post-exposure efficacy studies of IG and vaccine [Link-Gelles R, Hofmeister MG, Nelson NP. Use of hepatitis A vaccine for PEP in individuals over 40 years of age: a systematic review of published studies and recommendations for vaccine use. In peer review].

The recommended dose of IG was increased in September 2017 from 0.02 mL/kg to 0.1 mL/kg. This change was made due to concerns about decreased HAV IG antibody potency, likely resulting from decreasing prevalence of previous HAV infection among plasma donors, leading to declining anti-HAV antibody levels in donor plasma [Nelson NP. Updated Dosing Instructions for Immune Globulin (Human) GamaSTAN S/D for Hepatitis A Virus Prophylaxis. *MMWR*. 2017 Sep 15;66(36):959-960].

Challenges exist with the current PEP recommendations from 2007. In recent years, there has been an increase in HAV outbreaks requiring PEP as described earlier. State and local health departments report that timely receipt of intramuscular IG has been difficult since most providers and health departments do not routinely stock it. There is often a need for multiple injections of IG per dose, particularly for adult patients, due to the increased dosing to 0.1mL/kg and subsequent increase in volume of the IG dose. This has resulted in challenges related to IG cost and administration. In recent outbreaks, state and local health departments have opted to administer HepA vaccine, which confers long-term protection, to persons age >40 years for PEP.

Returning to the policy considerations for PEP, as a reminder the questions were:

- ❑ *Q1a. Should hepatitis A vaccines be recommended for PEP for all persons age ≥12 months?*
- ❑ *Q1b. Should IG be recommended at age >50 years in addition to vaccine?*

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The WG considerations were as follows:

- Advantages of HepA vaccine compared to IG:
  - Induction of active immunity and longer protection
  - Greater ease of administration compared to IG
    - Increased need for multiple injections of IG due to the increase in dose (volume) of the IG dose
  - Hepatitis A is routinely available
    - IG is available in the US from only one manufacturer (Grifols Therapeutics, Inc.)
    - IG is not routinely stocked by many providers and health departments making timely administration of intramuscular IG challenging [Ridpath A, et al. Hepatitis A Cases Among Food Handlers: A Local Health Department Response-New York City, 2013. J Public Health Manag Pract 2017]
  - Hepatitis A vaccine might cost less per dose, particularly when multiple injections of IG are needed

- Using vaccine for PEP in persons age >40 years brings US practice in line with other countries that provide PEP

- In the US some states suggest using vaccine for PEP in adults age >40 years, for example:
  - California Department of Public Health suggests consideration of HepA vaccine for PEP in persons 41-59 years of age because it confers long-term immunity.
  - Michigan Department of Health and Human Services suggests consideration of HepA vaccine for PEP in persons 41 through 74 years of age if IG is in short supply. When indicated for use, IG should be given within 2 weeks of exposure. (interim guidance)

In addition to a literature review, the WG reviewed current HepA PEP recommendations in other countries for which the results are shown here:

Recommendations for HAV PEP in Other Countries

Contact	Canada, Ontario (2013)	Canada, NACI (2016)	UK (2009)	Australia (2009)	Argentina (2014)	Israel (2015)	US (2007)
Healthy, < 2 months	IG	IG	Vaccinate caregivers	IG	IG	IG	IG
Healthy < 2-5 months	IG	IG	Vaccine caregivers OR unlicensed use of vaccine OR exclude from childcare	IG	IG	IG	IG
Healthy, 6-12 months	IG	Vaccine	Vaccine caregivers OR unlicensed use of vaccine OR exclude from childcare	IG	IG	IG	IG
Healthy, 1-39 years	Vaccine	Vaccine	Vaccine	Vaccine	Vaccine + IG	Vaccine	Vaccine
Healthy, 40 years	Vaccine	Vaccine	Vaccine	Vaccine	Vaccine + IG	Vaccine	Vaccine
Healthy, 41-49 years	Vaccine	Vaccine	Vaccine	Vaccine	Vaccine + IG	IG	IG
Healthy, 50 years	Vaccine + IG	Vaccine	Vaccine	Vaccine	Vaccine + IG	IG	IG
Healthy 51-59 years	Vaccine + IG	Vaccine	Vaccine + IG	Vaccine	Vaccine + IG	IG	IG
Healthy, ≥ 60 years	Vaccine + IG	May get vaccine + IG	Vaccine + IG	Vaccine	Vaccine + IG	IG	IG
Immunocompromised	Vaccine + IG	Should get vaccine + IG	Vaccine + IG	IG		IG	IG
Chronic liver disease	Vaccine + IG	Should get vaccine + IG	Vaccine + IG	IG		IG	IG

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Countries generally agree on the use of vaccine for PEP in healthy adults 1 to 40 years of age. Likewise, there is general agreement that IG, with or without vaccine, is ideal for immunocompromised individuals and those with CLD.

Limited data suggest protection at 15 days post-vaccination for adults 40 to 49 years of age. Among adults ages 50 to 59 years, data suggest substantial protection by 30 days post-vaccination. These data are shown here and were partially described in the GRADE presentation:

Age	Number	Seroconversion*, 15 days	Seroconversion*, 30 days
40-49 years	125	74%	90%
50-59 years	37	54%	81%
≥60 years	10	30%	50%

[Nelson NP, et al. Hepatitis A vaccination for PEP in persons aged 40 years and older. Vaccine. 2014 May 23;32(25):2939; *Seroconversion to anti-HAV positive, defined as ≥20 mIU anti-HAV]

Though the age ranges are not discrete, two studies that evaluated immunogenicity in adults age >=40 years had a comparison group and are shown here:

Author, Year	No. of Subjects	Population	Immunogenicity Results
Briem et al., 1994	60 113	40 to 62 years, Iceland 20-29 years, Iceland	Seroconversion (≥20 mIU/mL anti-HAV) at 15 days: **77%** GMT at 15 days: 262 mIU/mL (range: 65-995 mIU/mL) Seroconversion (≥20 mIU/mL anti-HAV) at 15 days: **90%** GMT at 15 days: 282 mIU/mL (range: 41-2589 mIU/mL)
Van Der Meeren et al., 2015	80 80	≥ 40 years, Belgium, Finland, Iceland 20-30 years,	Seroconversion (≥20 mIU/mL anti-HAV) at 15 days: **79.7%** (68.8-88.2%) GMT at 15 days: 126.5 mIU/mL (88.6-180.7 mIU/mL) Seroconversion (≥20 mIU/mL anti-HAV) at 15 days: **92.3%** (84.0-97.1%) GMT at 15 days: 219.4 mIU/mL (168-286.5 mIU/mL)

For the Briem study, seroconversion was 77% for persons age 40 to 62 years compared to 90% for persons age 20 to 29 years at 15 days. In the Van der Meeren study, seroconversion was 79.7% for persons age >=40 years and 92.3% for persons age 20 to 30 years at 15 days. Another study with a comparison group, Reuman et al, included a lower dose of vaccine than is currently recommended and was not included.

The WG's perspective is that it is unlikely that additional post-exposure efficacy data will become available, because of the difficulties of conducting post-exposure efficacy studies of IG and vaccine. Administering vaccine provides long-term protection and is beneficial for a substantial number of adult recipients even in older ages, such as >60 years. There are limited data and evidence of lower efficacy in older adults age >50 years at 15 days and age >60 years at 30 days. HAV infection is more severe in these older age groups. IG, in addition to HepA vaccine, might be beneficial for persons in these age groups. Data are limited on vaccine or IG failures; however, reports of failures are rare. If IG or vaccine is not available, the available product should be administered as soon as possible. The person may return for the second product if available within 14 days of exposure. The summary of proposed recommendations

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for PEP is that vaccine should be administered to healthy persons ≥12 months and vaccine with addition of IG should be administered to healthy persons >50 years of age based on provider guidance risk assessment and availability of vaccine or IG.

As a reminder, the policy question for international travel was:

- ❑ *Q2. Should hepatitis A vaccines be administered to infants age ≥6-11 months of age pre-travel (unless the infant is traveling to an area with no endemic measles transmission)?*

The WG considerations were that IG cannot be administered simultaneously with MMR vaccine, which is recommended for infants age 6 through 11 months traveling internationally from the US. Administering HepA vaccine in infants is off-label and doses administered prior to age 12 months are considered invalid. Infants receiving HepA vaccine would need to complete the full 2-dose HepA vaccine series beginning at 12 months of age or 6 months after the invalid dose to gain long-term immunity. Infants 6 through 11 months traveling in countries classified as having no endemic measles transmission (e.g., Western Hemisphere), but where HAV may remain at intermediate or high endemicity, IG may be used. Routine administration of MMR vaccine may be delayed because it may be administered no earlier than 3 months after IG administration [Nelson NP. Updated Dosing Instructions for Immune Globulin (Human) GamaSTAN S/D for Hepatitis A Virus Prophylaxis. *MMWR*. 2017; Sep 15;66(36):959-960; McLean HQ, et al. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2013;62:1-34].

The WG's perspective is that due to the severity of measles in infancy compared to HAV infection in infancy, MMR vaccine should be administered preferentially to IG. Administration of HepA vaccine, which would be an off-label use, and MMR vaccine to infants age 6 through 11 months would provide protection against HAV and measles and allow for simultaneous administration. The summary of the proposed recommendations for international travel is that children 6 through 11 months of age should receive vaccine, or IG if measles is not endemic in the region of travel.

As a reminder, the policy question for PEP and international travel for pregnant women was:

- ❑ *Q3. Should vaccine (or vaccine + IG) be administered for pregnant women due to the risk of adverse fetal outcomes if the woman is infected with HAV during pregnancy?*

Under the current guidelines from 2007, there are no specific pregnancy related recommendations for HepA PEP. The WG discussed a number of issues relating to HepA and pregnancy. First, a study by Moro et al in 2014 on HepA vaccine safety during pregnancy found no pattern of AEs in pregnant women or their infants following vaccination during pregnancy[1]. Second, the WG discussed a review published in November 2015 that found that generally, infants born to mothers with HAV infection are healthy, with rare exceptions. However, another review found that while HAV infection during pregnancy is generally not associated with serious outcomes, there is some association between infection and preterm labor, placental abruption, and premature rupture of membranes[3]. There does not appear to be an increased risk of mortality for either the mother or baby associated with HAV infection during pregnancy. Third, vaccination of pregnant women who have a specific risk or who lack a risk but want protection is included in the CDC Adult Immunization Schedule under "Medical and Other Indications" [[1] Moro PL, Museru OI, Niu M, Lewis P, Broder K. Reports to the Vaccine Adverse Event Reporting System after hepatitis A and hepatitis AB vaccines in pregnant women. Am J Obstet Gynecol

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2014;210:561 e561-566; [2] Chaudhry SA, Koren G. Hepatitis A infection during pregnancy. Can Fam Physician 2015;61:963-964; [3]Elinav E, Ben-Dov IZ, Shapira Y, Daudi N, Adler R, Shouval D, Ackerman Z. Acute hepatitis A infection in pregnancy is associated with high rates of gestational complications and preterm labor. Gastroenterology. 2006 Apr;130(4):1129-34. PubMed PMID: 16618407].

The WG perspective is that administration of HepA vaccine during pregnancy is safe. Risk of gestational complications exists if a pregnant woman is infected with HAV. Vaccine provides long-term protection. IG administration in addition to vaccine can be considered based on infection risk. The summary of the proposed recommendation for both PEP and international travel is that for PEP, pregnant women should be administered vaccine with the addition of IG based on provider guidance of risk assessment and availability of vaccine or IG. For international travel, pregnant women should be administered vaccine.

The proposed recommendations for discussion included the following:

Q1a. Hepatitis A vaccines should [be] administered for PEP for all persons age ≥12 months.

Q1b. IG should be administered at age >50 years in addition to vaccine.

Q2. Hepatitis A vaccines should be administered to infants age ≥6-11 months of age pre-travel (unless the infant is traveling to an area with no endemic measles transmission).

Q3. Hepatitis A Vaccine (or vaccine + IG) should be administered to pregnant women due to the risk of adverse fetal outcomes if the woman is infected with HAV during pregnancy.

Discussion Points

Regarding the challenges Dr. Nelson outlined for IG, Dr. Belongia inquired as to whether there is any better technology on the horizon such as monoclonal antibodies and if there are likely to be some better options than IG in the future.

Dr. Nelson replied that there are none that she is aware of.

Regarding the 6 to 11-month-old age group, Dr. Lee asked whether the WG was recommending revaccination after they return from travel once they age into the appropriate category. Regarding the pregnancy question, she asked whether there was an estimate of the NNV to prevent an adverse outcome of pregnancy due to HAV infection and an estimate of the number of women who might be prophylaxed.

Dr. Nelson indicated that regarding the 6- to 11-month group, the recommendation was for revaccination once they age into the appropriate category. They would still receive 2 doses of vaccine after 12 months of age. They would not be able to receive the first dose until at least 6 months afterward. Regarding the pregnancy question, she did not have the NNV or an estimate of the number of women who might be prophylaxed.

Dr. Neuzil (IDSA) expressed some concern with the caveat for the measles issue, noting that she travels and works all over the world. It is known that measles occurs in low- and high-resource locations, it is highly transmissible, and outbreaks have occurred because of transit through airports and at Disney World for example. She emphasized that they should be sure

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they wanted to include the exception in the recommendation and stressed that it will be very difficult to interpret from a practical standpoint.

Dr. Nelson indicated that while the WG has discussed this issue, they could reconsider whether that exception is needed.

Dr. Kimberlin (AAP) wondered whether the contraindication of giving the MMR and HepA vaccines was based on data suggesting either an increase in AE or an impact on immunogenicity, or if it was because there were no data focused on whether these can be given simultaneously.

Dr. Cohn said she thought there was some confusion about the measles language as sometimes what was shown on the slide did not correspond exactly with what was presented, so she requested that Dr. Nelson recap what could and could not be given together.

Dr. Nelson clarified that while HAV IG cannot be given concurrently with MMR vaccine, HepA vaccine and MMR vaccine can be administered simultaneously.

Dr. Messonnier requested that Dr. Nelson restate the current recommendation.

Dr. Nelson stated that the current recommendation is that HepA vaccine can be given to infants ≥12 months of age.

Dr. Walter agreed with Dr. Neuzil that for practical purposes for the 6- to 12-month age range, it will be difficult for the practitioner who has both of these vaccinations in his or her office to try to figure out where a measles-endemic area is and where there is an outbreak. Therefore, he wondered why they were making this distinction.

Dr. Nelson replied that consideration could certainly be given to the vote without that distinction.

Dr. Romero agreed, but the WG considered it to be important for the ACIP to discuss. Though the WG concluded that it was prudent to leave in, it could be removed if it was causing a lot of confusion.

It appeared to Dr. Atmar from the data presented that the immunogenicity for the 40- to 50-year age group was inferior to that of younger age groups, and not as inferior to those over 50 years of age. With an incubation period of 2 to 6 weeks for HAV and less than 20% of people in the 40- to 50-year age group with protective antibody levels concerned Dr. Atmar. He wondered whether the WG considered removing the preferential recommendation for IG in that age group. There are no data to indicate whether it will be equally efficacious, nor are there likely to be such data. Dr. Stephens shared this concern regarding reduced immunogenicity.

Dr. Moore said she certainly thought it would be much simpler to recommend giving both MMR and HepA vaccines routinely to the 6- to 11-month age group. However, it is still acceptable to give IG in some cases if the clinician and family prefer to administer to IG, but only in situations if they are going to places where measles has been eliminated. The WG did not want to go as far as to say that a medically appropriate product that can protect against HAV should no longer be used under any circumstances. She certainly thought it could be more simply stated that both vaccines should be used for MMR and HAV in that age group if there is a clinical decision about IG. It will protect against HAV in that age group, but there are stronger considerations around measles protection that should be borne in mind.

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Dr. Messonnier inquired as to whether it is known how many infants are in the 6- to 11-month category who would need vaccination, and where they are being seen? Clinical decision making differs between an average pediatrician trying to interpret this language versus a physician whose specialty is travel medicine, who is probably much more aware of what is meant by "measles-endemic countries."

Dr. Nelson responded that while she did not have the number of infants in this category who would need vaccination, her understanding is that the majority of these infants in that age range would be seen by a general pediatrician.

Ms. Pellegrini asked whether the WG discussed the nature of exposure for persons over 40 and stratified based on that. It sounded like IG would provide short-term protection for a few months, and that would perhaps be most appropriate for a foodborne exposure that hopefully would be a one-time episode. However, homeless individuals or IV drug users would likely have ongoing exposure for which the vaccine might be more appropriate.

Dr. Nelson replied that the guidance that would accompany the recommendation discusses the risk. If a person falls into one of the high-risk groups, such as MSM or IV drug use, they could receive vaccine with the addition of IG, particularly if they are immunocompromised or have CLD. At 30 days after vaccination, there is 90% or more seroprotection. The concern is in the 15-day window while the immune response is increasing.

From a programmatic standpoint, Dr. Moore said she thought one of the major considerations around IG is that most health departments and clinicians do not have it readily available and time is of the essence in these situations. When people who have been exposed are found, it is often at the end of the 14-day window. The intent of the recommendation is to ensure that the clinician gives what is readily available immediately, which is the vaccine. If they need to scramble to get the IG because they need to provide more assurance, they can do that but have not wasted time telling a patient to return when the IG comes in. This should help programmatically in terms of providing protection more efficiently to more people who need PEP who otherwise might miss the window of opportunity for protection at all.

As part of the WG, Dr. Zahn (NACCHO) noted that another of the considerations when describing the nature of the exposure is that the biggest issue public health faces is that a lot of these exposure events are foodborne situations. In that scenario, it is not clear how many exposures there are in the beginning. The number of people exposed may be in the hundreds or thousands. In general terms, the risk of that sort of exposure is a lot lower than someone who is a household contact. If 1000 people are exposed and several hundred of them are of an older age group, local public health departments are not going to be able to get IG very often. Therefore, one of the thoughts was that having vaccine as an option is much more practical and deserves consideration.

Regarding healthy persons >50 years of age, Dr. Kimberlin (AAP) noted that the data on seroconversion at 15 days was 50 through 59 years and ≥to 60 years. He wondered whether this should be ≥50 years of age of if they literally meant 51 years of age and older.

Dr. Nelson clarified that currently, the recommendation is through age 40. The next increment would be 41 through 50 and the next increment after that would be 51 through 60, so >50 years.

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Dr. Messonnier requested that Dr. Ward make a comment about the intent of these recommendations.

As some of the comments pointed out, Dr. Ward (SME) indicated that these changes reflect that vaccine does afford protection at any age for a sizeable proportion of the population. However, in some situations for the older group at the highest risk for severe HAV infection, IG is appropriate but depends on the situation and that is where provider guidance comes into play to help providers understand when IG is really the most indicated versus for some of the lower risk exposures in which vaccine is more practical.

Given the confusion and suggestions made, Dr. Romero proposed that it might be more appropriate for the WG to revisit and revise the proposed language to make it clearer and present it to ACIP during the June 2018 meeting.

Dr. Bennett pointed out that there was no urgency to take the vote during this meeting. With no objections posed to Dr. Romero's proposal, it was agreed that the WG would revisit the language and present the revised version at a later time.

Dr. Cohn noted that two individuals were signed up to give public comment prior to the anticipated HepA vote, but since they were not taking a vote on this issue at this point, she opted to move these public comments to the end of the day with the rest of the general public comments.

Revised Policy Considerations (Presented Day 2; Unfinished Business)

José Romero, MD, FAAP, FIDSA, FPIDS
Chair, Hepatitis Vaccines Work Group

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

Dr. Romero indicated that the WG met the previous evening to address some concerns that the voting ACIP members expressed regarding questions of HepA prophylaxis and use of HepA vaccine in individuals greater than 40 years of age. The WG reworded the questions to address those concerns. He reminded the members that the data presented are the only data that exist currently and that it is unlikely any new data will become available in the foreseeable future.

Dr. Nelson presented the revised questions, along with provider guidance and WG consideration, as follows:

Q1a. Hepatitis A vaccines should be administered for PEP for all persons age ≥12 months.

Q1b. In addition to hepatitis A vaccine, IG may be administered to persons age >40 years depending on the provider's risk assessment.

Provider guidance will help providers evaluate the need for IG based on age, immune status and underlying conditions (such as CLD and immune suppression), exposure type or risk of transmission (such as restaurant-related cases versus household exposures), and availability of IG. As presented the previous day, numerous hepatitis outbreaks have occurred over the last 5

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years. Guidance for health departments on proper administration of vaccine and IG in these situations is critical.

Q2. Hepatitis A vaccine should be administered to infants age 6-11 months of age traveling outside the United States when protection against hepatitis A is recommended.

In terms of WG considerations, as stated in the current ACIP recommendations for MMR, "All persons aged ≥6 months who plan to travel or live abroad should ensure that they have acceptable evidence of immunity to measles, rubella, and mumps before travel. Travelers aged ≥6 months who do not have acceptable evidence of measles, rubella, and mumps immunity should be vaccinated with MMR vaccine. Before departure from the United States, children aged 6 through 11 months should receive 1 dose of MMR vaccine…" Immune globulin and MMR vaccine should not be administered simultaneously. Therefore, infants aged 6-11 months who will be traveling internationally who also need protection against HAV should receive a single dose of HepA vaccine. Infants should then complete the full, 2-doses of MMR and HepA vaccines at ≥12 months of age as recommended.

Discussion Points

Dr. Bennett clarified that the previous day, they discussed 3 issues simultaneously. During this session, the plan was to address and vote on one question at a time.

Dr. Romero made a motion to accept the first question as proposed, which Dr. Szilagyi seconded.

Dr. Kimberlin (AAP) said he thought the previous day the question had >50 years of age but was now >40.

Dr. Nelson indicated that the WG changed it during their discussions the previous evening due to concerns regarding immunogenicity in adults over 40 years of age. The underlying thought regarding use of vaccine remained the same; that is, anyone ≥12 months of age would receive vaccine. The decision to administer IG over age 40 would be based on provider risk assessment, giving providers an option to administer IG as well in the 40 through 49-year age range.

Dr. Atmar said this addressed the concern he had regarding the lower immunogenicity seen in the small study for those 40 through 49 years of age of approximately 74% to 75% at 15 days.

Dr. Moore reminded everyone that the current recommendation says to consider IG above 40 years of age, so this merely goes back to the current age cutoff rather than raising it to 50 as considered the previous day.

Dr. Cohn clarified that the proposed language was adding HepA vaccine as an initial and first step toward prevention.

Dr. Messonnier expressed some confusion as she thought the language the previous day pertained specifically to outbreak response; however, none of that sentiment seemed to be reflected in the revised recommendation. She said she felt like a general internist making a decision about IG on a one-to-one basis puts a lot of responsibility on a clinician who probably does not have the context. If done in an outbreak setting, she would assume that public health would be giving additional guidance that would help clinicians make that decision. The

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language that the clinician should make the decision based on X, Y, and Z seemed to need some verbiage about the context and the outbreak. While it was not the actual recommendation, the provider's risk assessment concerned her in that too much emphasis was being placed on individual clinicians.

Dr. Nelson clarified that the intent was for any situation in which PEP is needed, which is usually in an outbreak or suspected outbreak situation.

Dr. Hunter asked whether they were saying that this would take away local public health's ability to only administer IG for a household contact of one person and decide not to give the vaccine to that person.

Dr. Bennett agreed that individual clinicians know remarkably little about HAV management in the post-exposure setting. She thought the considerations could be placed in the guidance regarding choosing to use IG or not.

Dr. Moore agreed that public health is involved in even individual cases of HAV where only family members are involved but it is still a reportable condition, and the state or local health department would be engaged with the provider to help them make that decision. She thought the intent was that public health would be engaged and providers would not be left on their own. That surely could be put in the guidance for providers to make it clear that it is reportable and help is available in terms of making decisions.

Dr. Hahn (CSTE) indicated that public health is very involved even in individual cases. She agreed that including language in the guidance about consulting public health would be beneficial, because they would be very engaged.

Dr. Smith (ASTHO) indicated that Arkansas does not have local public health. They are all one health department there. He felt like the wording proposed would give public health the guidance they need and would give him the guidance he needed as an internist as well.

Dr. Bennett clarified that the reason she was pushing back on this a little bit was that people do show up in a physician's office having a post-exposure situation and often public health does not hear about it for a couple of days. She thought having the guidance would be important for all clinicians.

Dr. Bernstein asked how someone's immune status to HAV play into whether they need vaccine.

Dr. Nelson replied that someone who is immunocompromised might need the addition of IG, depending upon their immunodeficiency. That also will be discussed in the provider guidance.

Dr. Cohn pointed out that another question that may be asked pertains to whether someone is previously vaccinated with a complete series.

Dr. Nelson responded that additional PEP is not recommended for someone who is completely vaccinated.

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Dr. Zahn (NACCHO) emphasized that if someone presents to a clinician's office who has HAV infection or has had an exposure to HAV, it is a nationally reportable disease. As soon as a case of hepatitis A presents, public health would not want that person to leave the clinic without public health being aware of it and having a plan for exactly how to proceed. He thought that the guidance should make clear that hepatitis A is always reportable and any decisions should be made in conjunction with public health.

Dr. Cohn indicated that no one was signed up for public comment.

Motion/Vote #1: Question 1

Dr. Romero made a motion to accept the first question as proposed, which Dr. Szilagyi seconded:

Q1a. Hepatitis A vaccines should be administered for post-exposure prophylaxis for all persons age ≥12 months.
Q1b. In addition to hepatitis A vaccine, IG may be administered to persons age >40 years depending on the providers risk assessment.

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

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

Dr. Romero made a motion to accept the second question as proposed, which was seconded by Ms. Pellegrini.

Regarding the guidance language, Ms. Pellegrini asked whether the statement that "Infants should then complete the full, 2-doses of MMR and HepA vaccines at ≥12 months of age as recommended" meant they would receive 1 more dose or would start the series over and receive 2 more doses. The word "complete" seemed to be confusing because it made it seem that they began with the ≥12 months of age dose.

Dr. Romero indicated that the WG could revise the language for clarity.

Dr. Hunter said it looked like the guidance could go in the MMR recommendations rather than the HepA recommendations, especially the way it was written. While he thought it was very well-written and should go somewhere, when he read it the first time it struck him as measles guidance.

Dr. Nelson clarified that it was from the measles recommendation.

Dr. Cohn added that these are the WG considerations and the language of the measles recommendations with which they were trying to align, which they were suggesting be in the document.

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Dr. Walter thanked the WG for simplifying the language, which he thought would be much easier to implement in practice.

Dr. Moore said the WG was trying to make clear that every child 6 through 11 months who sets foot outside of the US should get an MMR vaccine, and since IG should not be given with MMR, by default they should be given the HepA vaccine if they need HAV protection.

Dr. Kimberlin (AAP) liked the simplicity but pointed out that the language did not actually state "do not give IG and HepA." He would add "should receive a single dose of HepA vaccine and should not receive IG." He said he would be comfortable with this being included in the guidance pertaining to the recommendation.

Dr. Messonnier asked if there would be discussion regarding whether simultaneous administration would be acceptable. She recalled that the previous day, it was very specific to HepA and MMR.

Dr. Romero indicated that the WG would ensure incorporation of the suggestions for the guidance.

Motion/Vote #2: Question 2

Dr. Romero made a motion to accept the second question as proposed, which Ms. Pellegrini seconded:

Q2. Hepatitis A vaccine should be administered to infants age 6-11 months traveling outside the United States when protection against hepatitis A is recommended.

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

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

VFC Resolution

Dr. Jeanne M. Santoli & Cindy Weinbaum, MD
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Weinbaum indicated that the purpose of this resolution was to add recommendations for infants 6 through 11 months of age traveling to countries outside the US for which protection against HAV is recommended and to revise the language regarding PEP to match the most current ACIP recommendations.

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Eligible Groups

- Infants 6 through 11 months of age traveling to countries outside of the US for which protection against HepA is recommended (new)
- All children 1 through 18 years of age (remains unchanged)

Dr. Santoli indicated that the first part of the recommended vaccine schedule wording would be revised to include the following language:

> *All children should receive hepatitis A vaccine at 1 year of age (i.e., 12-23 months). Vaccination should be completed according to the licensed schedules below. Children who are not vaccinated by 2 years of age can be vaccinated at subsequent visits. Catch-up vaccination of unvaccinated children should be administered to children aged 2 through 18 years.*

The table for the vaccine schedule remains unchanged, with the exception of the revision of the third footnote pertaining to Twinrix to shorten it:

Vaccine[1]	Age	# of Doses	Schedule[2]
Havrix (pediatric formulation)	1 year	2 doses	0, 6-12 months
Vaqta (pediatric formulation)	1 year	2 doses	0, 6-18 months
Twinrix (adult formulation)[3]	18 years	3 doses	0, 1, 6 months

[1]Use of brand names is not meant to preclude the use of other hepatitis A vaccines where appropriate.
[2] 0 months represents timing of the initial dose; subsequent numbers represent months after the initial dose.
[3] Only persons 18 years of age are eligible to receive Twinrix through the VFC program.

Recommended intervals remain unchanged:

Vaccine[1]	Min Age (Dose 1)	Minimum interval between doses		
		Dose 1 to 2	Dose 2 to 3	Dose 1 to 3
Havrix (pediatric formulation)	12 months	6 months	n/a	n/a
Vaqta (pediatric formulation)	12 months	6 months	n/a	n/a
Twinrix (adult formulation)	18 years	1 month	5 months	6 months

[1] Use of brand names is not meant to preclude the use of other hepatitis A vaccines where appropriate.

The wording for the recommendation for the use of HepA vaccine for PEP was modified slightly in order to match more closely with the recommendations voted on during this meeting:

> *Healthy persons aged 12 months through 18 years, who have been exposed to HAV within the prior 14 days and have not received hepatitis A vaccine previously should receive a single dose of hepatitis A vaccine as soon as possible. The hepatitis A vaccine series can be completed with the second dose at least 6 months after the first dose.*

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A new Selected Special Categories was added:

- ❑ A single dose of hepatitis A vaccine should be administered to infants age 6-11 months of age traveling to counties outside the United States for which protection against hepatitis A is recommended on CDC's Traveler's health website (https://wwwnc.cdc.gov/travel/). Infants should then receive the full 2-dose hepatitis A vaccine series at ≥12 months of age as recommended. (new)

- ❑ Persons administered IG for whom hepatitis A vaccine is also recommended should receive a dose of vaccine simultaneously with IG. For persons who receive vaccine, the second dose should be administered according to the licensed schedule to complete the series. The efficacy of IG or vaccine when administered >2 weeks after exposure has not been established. (remains unchanged)

The recommended dosage and contraindications and precautions remain unchanged and are as follows:

Recommended Dosage
Refer to product package inserts.

Contraindications and Precautions

The following conditions are contraindications to the administration of hepatitis A vaccine:

1. Allergy to vaccine components
   -Anaphylactic reaction to the vaccine or a constituent of the vaccine
2. Acute, moderate, or severe illness with or without a fever

The following condition is a precaution to the administration of hepatitis A vaccine:

1. Pregnancy
   -The safety of hepatitis A vaccination during pregnancy has not been determined; however, because hepatitis A vaccine is produced from inactivated HAV, the theoretical risk to the developing fetus is expected to be low. The risk associated with vaccination should be weighed against the risk for hepatitis A in women who may be at high risk for exposure to HAV.

The standard statement regarding updates based on published documents was added:

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

Discussion Points

Dr. Romero made a motion to accept the VFC Resolution as proposed, which Dr. Belongia seconded.

Dr. Walker asked whether MMR for travel for children under 12 months of age was currently covered under the VFC Program.

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Dr. Bennett said it was unclear to her whether travel vaccines are covered at all under the VFC program.

Dr. Cohn said that travel vaccines are covered under the VFC Program for meningococcal vaccines for travelers who are considered to be at risk.

Dr. Walter emphasized that they should be consistent for all recommendations.

Dr. Santoli indicated that they are able to cover VFC-eligible children who travel. They will check whether this is included for MMR and will bring it back to the group.

Motion/Vote: VFC Resolution

Dr. Romero made a motion to accept the VFC Resolution as proposed, which Dr. Belongia seconded. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Influenza

Introduction

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

Dr. Walter reminded everyone that during the October 2017 ACIP meeting there were updates on influenza surveillance prior to the influenza season, vaccine coverage, and live attenuated influenza vaccine (LAIV) focused on the ferret model for protection for the Slovenia strain; as well as a discussion of a VSD study of spontaneous abortion following inactivated influenza vaccine (IIV). Since the October 2018 ACIP meeting, the WG has engaged in calls twice a month during which members heard updates on: 1) a combined US individual patient-level data analysis of LAIV effectiveness; 2) a systematic review of LAIV effectiveness; and 3) a US pediatric shedding and immunogenicity study from MedImmune.

The agenda for this session included the following topics:

- ❑ Efficacy of Fluarix® Quadrivalent in children 6 through 35 months of age, which received an extended age indication approval down to 6 months of age in January 2018
- ❑ Surveillance update
- ❑ Vaccine effectiveness update
- ❑ Results of a randomized trial of a new H1N1 LAIV strain in US children
- ❑ Review of LAIV effectiveness for 2- through 17-year-olds
- ❑ Considerations and proposed recommendations

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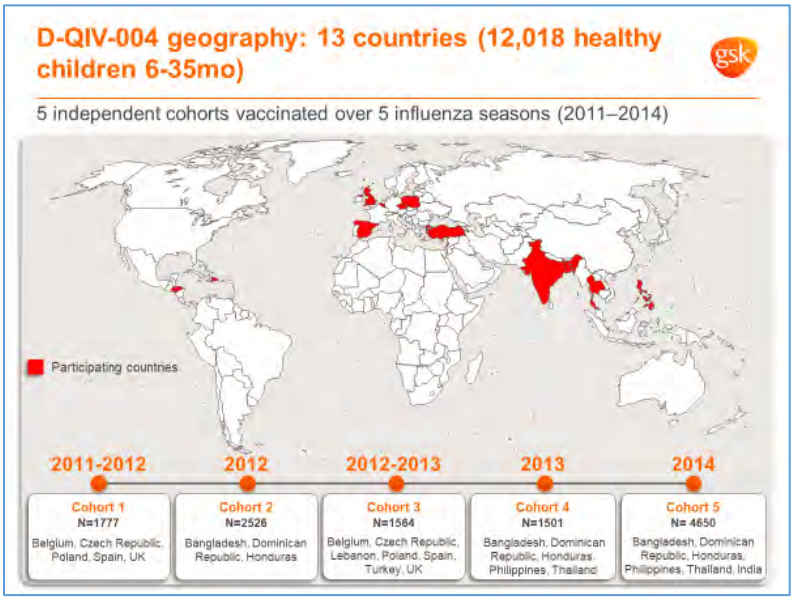
Fluarix® Quadrivalent: Efficacy in Children 6 Through 35 Months of Age

Leonard Friedland, MD
Vice President, Scientific Affairs and Public Health
GlaxoSmithKline (GSK) Vaccines

Dr. Friedland presented the results of Study D-QIV-004, which is a large RCT of 12,000 children providing high-quality data on influenza vaccination prevention in young children 6 through 35 months of age. He pointed out that this trial makes contributions to the evidence base for influenza vaccination of young children, and acknowledged the families who elected to enroll their children in this very large study and their contributions to a generation of clinically relevant information on the use of Fluarix® Quadrivalent in young children.

GSK is proud to have 2 licensed seasonal influenza vaccines in the US Fluarix® Quadrivalent (D-QIV), which is manufactured in Dresden, Germany; and FluLaval® Quadrivalent (Q-QIV), which is manufactured in Canada. The dose of both vaccines for people of all ages is 0.5mL per dose. Both vaccines are now indicated for people 6 months of age and older, with Fluarix® Quadrivalent receiving FDA indication for licensure as young as 6 months of age in January 2018 as noted by Dr. Walter. Both vaccines are also administered intramuscularly (IM) as are all of the currently recommended influenza vaccines for children, though pediatric vaccination rates have remained at about 60% over the last 3 seasons. GSK purposely chose to develop both vaccines with a 0.5mL dose for all people 6 months of age and older because the 0.5mL dose potentially simplifies influenza vaccination by allowing the same vaccine dose to be used for all eligible individuals.

Dr. Friedland focused this presentation on the pivotal registration study, Study D-QIV-004, that supported the recent FDA approval of Fluarix® Quadrivalent for children 6 through 35 months of age. This trial was conducted in 13 temperate and subtropical countries between October 2011 and December 2014. In total, 12,018 healthy children were recruited in 5 independent cohorts each in a different influenza season as depicted in this map:



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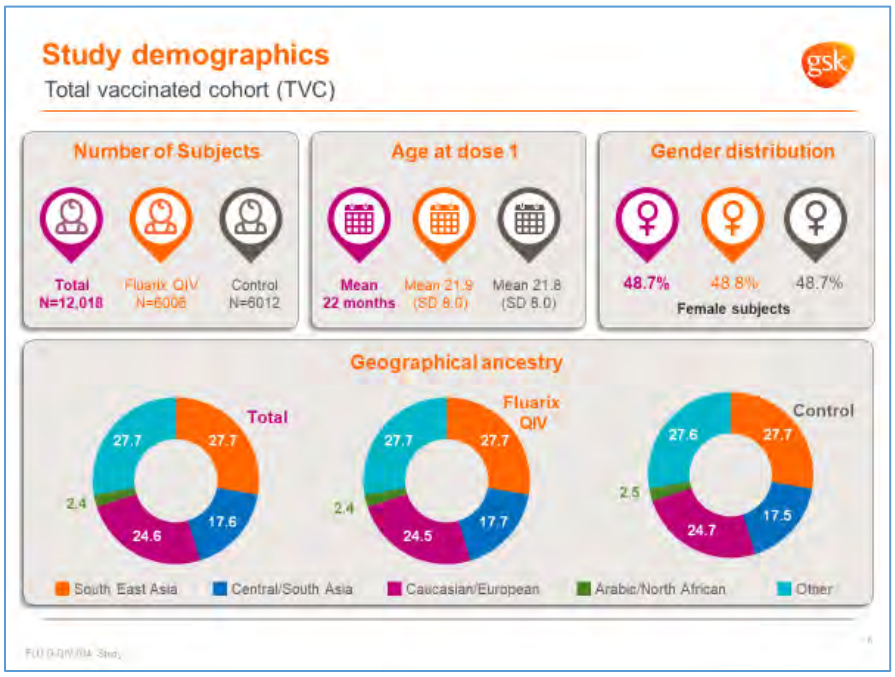
Study D-QIV-004 is a Phase III, observer-blind, randomized, controlled, non-influenza vaccine comparator study. Children were randomized 1:1 to receive Fluarix® Quadrivalent or the non-influenza comparator vaccines. Stratification for enrollment was such that 10% of all enrolled children were between the ages of 6 and 11 months, 35% of all enrolled were between 12 and 23 months of age, and 55% of those enrolled were between 24 and 35 months of age.

Children were to receive 1 or 2 doses of vaccine, with 2 doses to be given to children who were considered to be influenza unprimed, meaning they had not previously received 2 doses of vaccine. In reality, 98% of the 12,000 children enrolled in the study were influenza unprimed. There was also an immunogenicity subset taken from each of the 5 independent cohorts.

Of course, there was influenza surveillance in this RCT. The surveillance period encompassed the peak of influenza season in each country, which was based on available epidemiological data from the different participating countries or regions. These data were obtained from influenza surveillance activities that were conducted by public health bodies. There was also safety follow-up through the entire course of the study, which lasted for each individual patient typically 6 to 8 months.

These are the study demographics of the 12,018 children enrolled:



The mean age of those enrolled was 22 months, approximately 49% were female, and the geographic ancestry is illustrated on the bottom of the above graphic representing the countries that were enrolled. Overall 24% of those enrolled were white, 45% were Asian, and 28% were other, which represented mostly mixed race and Hispanic.

As mentioned, this was a controlled trial in which control subjects received a non-influenza control vaccine. For subjects <12 months of age, the control vaccine was two IM doses of PCV13 at Day 0 and at Day 28. For subjects ≥ 12 months of age, which represented virtually everybody in the study, the first dose of control vaccine was HepA vaccine at Day 0 and the second dose was varicella vaccine at Day 28.

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The study used the following definitions for severity of influenza disease:

Severity of Influenza Disease	Definition
Any severity	Temperature ≥38°C and any of these symptoms: cough, runny nose, nasal congestion, and/or breathing difficulty
Moderate-to-severe influenza	Laboratory-confirmed influenza with temperature >39°C, physician-diagnosed acute otitis media, and/or lower respiratory tract illness (e.g., cases of physician-diagnosed pneumonia, lower respiratory tract infection, bronchiolitis, bronchitis and croup infection (laryngotracheitis))
Severe	Serious extrapulmonary complication (e.g., myositis, encephalitis or other neurologic condition including seizure, myocarditis pericarditis or other serious medical condition), hospitalization in the intensive care unit (ICU), supplemental O2 for >8 hours

The intention in evaluating moderate-to-severe influenza was to dichotomize cases into categories of mild illness versus illnesses that are associated with the most clinical aspects of influenza.

The study had two primary objectives, which were prevention of: 1) reverse transcriptase polymerase chain reaction (RT-PCR) confirmed moderate to severe influenza due to any influenza strain; and 2) RT-PCR confirmed influenza of any severity due to any influenza strain. The study also had 7 secondary objectives, which included prevention of: 1) lower respiratory illness (LRI) associated with RT-PCR confirmed influenza; 2) culture-confirmed moderate to severe influenza due to vaccine-matching influenza strains; 3) culture-confirmed influenza of any severity due to vaccine-matching influenza strains; 4) culture-confirmed moderate to severe influenza due to any influenza strain; 5) culture-confirmed influenza of any severity due to any influenza strain; 6) acute otitis media (AOM) associated with RT-PCR confirmed influenza; and 7) RT-PCR confirmed severe influenza.

In terms of the study procedures to detect and confirm influenza cases, active and passive surveillance started 14 days after the last vaccination and lasted until the end of the influenza activity period to detect episodes of Influenza-like illness (ILI), AOM, or LRI. Nasal swabs were then collected from subjects with ILI, AOM, or LRI for RT-PCR confirmation of influenza A or B. RT-PCR confirmed samples were then further evaluated by RT-PCR sub-typing or deoxyribonucleic acid (DNA) sequencing to identify influenza A subtype (H1N1 or H3N2) or B lineage (Victoria or Yamagata). Then there was viral culture confirmation for influenza A or B. Culture-confirmed samples were then further characterized for antigenic match to the vaccine strains.

Regarding the efficacy results, the study met its two confirmatory primary objectives by demonstrating VE against moderate-to-severe RT-PCR-confirmed influenza at 63.2% and VE against any severity of RT-PCR-confirmed influenza of 49.8%. With regard to the 7 secondary objectives, VE against RT-PCR-confirmed influenza-associated LRI was 54%; culture-confirmed influenza A and/or B disease due to matching influenza strains was 77.6% for moderate-to-severe and 60.1% against any severity; culture-confirmed influenza A and/or B disease due to any seasonal influenza strain was 63.8% for moderate-to-severe and 51.1% against any severity; and RT-PCR confirmed influenza-associated AOM was 56.6%. The study enrolled healthy individuals. As a result, there were very few cases of severe disease that met the study

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criteria. Only 5 children had severe complications of influenza, which limited the ability to conclude on VE against severe influenza.

The attack rates and VE by strain are depicted in the following table:

Strain	Fluarix QIV N = 6006	Control N = 6012	Vaccine Efficacy	
	Attack rate (%)	Attack rate (%)	%	95% CI
A/H1N1	0.22	0.77	72.1	49.9; 85.5
A/H3N2	0.88	1.86	52.7	34.8; 66.1
B/Victoria	0.05	0.25	80.1	39.7; 95.4
B/Yamagata	0.37	1.21	70.1	52.7; 81.9

Attack rates were highest for H3N2 and B/Yamagata over the course of the study. Yet in terms of the proportion of antigenic matching strains, most A/H3N2 and B/Victoria isolates were vaccine-mismatched. Looking at VE per strain against RT-PCR confirmed protection against moderate-to-severe influenza, protection against H1N1 was 72.1%, protection against H3N2 was 52.7%, protection against B/Victoria was 80.1%, and protection against B/Yamagata was 70.1%. A substantial proportion of healthcare utilization is associated with childhood influenza. Compared with control vaccine, Fluarix® Quadrivalent reduced healthcare utilization such as general practitioner (GP) visits, emergency department (ED) visits, and antibiotic use associated with influenza by 47%, 79%, and 50% respectively.

As mentioned earlier, there was an immunogenicity sub-cohort from each of the 5 independent cohorts throughout the study. It is important to recall that 98% of the 12,000 children enrolled in the study were considered influenza-unprimed. The immunogenicity secondary objective was to evaluate the immunogenicity of Fluarix® Quadrivalent with respect to hemagglutination inhibition (HI) antibody response 28 days after completion of vaccination. In terms of the pooled results of the 5 individual cohorts, Fluarix® Quadrivalent was highly immunogenic against all vaccine strains, showing high GMTs and seroprotection rates compared to controls. Regarding the increase in mean geometric antibody titers (MGIs) pre- and post-vaccination and seroconversion rates for each of the 4 vaccine strains, Fluarix® Quadrivalent vaccination resulted in anywhere from 9- to 17-fold increases in MGIs after vaccination and also high seroconversion rates to each strain.

The safety objectives were to: 1) evaluate the reactogenicity of Fluarix® Quadrivalent and non-influenza vaccine controls in terms of local solicited symptoms during 7 days after each vaccination, general solicited symptoms during 7 days after each vaccination, and unsolicited symptoms during 28 days after each vaccination; and 2) further evaluate the safety of Fluarix® Quadrivalent and non-influenza vaccine controls in terms of medically attended AEs (MAEs) during the entire study period, SAEs during the entire study period, and potential immune-mediated-diseases (pIMDs) during the entire study period. Here is a schematic of the way safety information was collected in the study:

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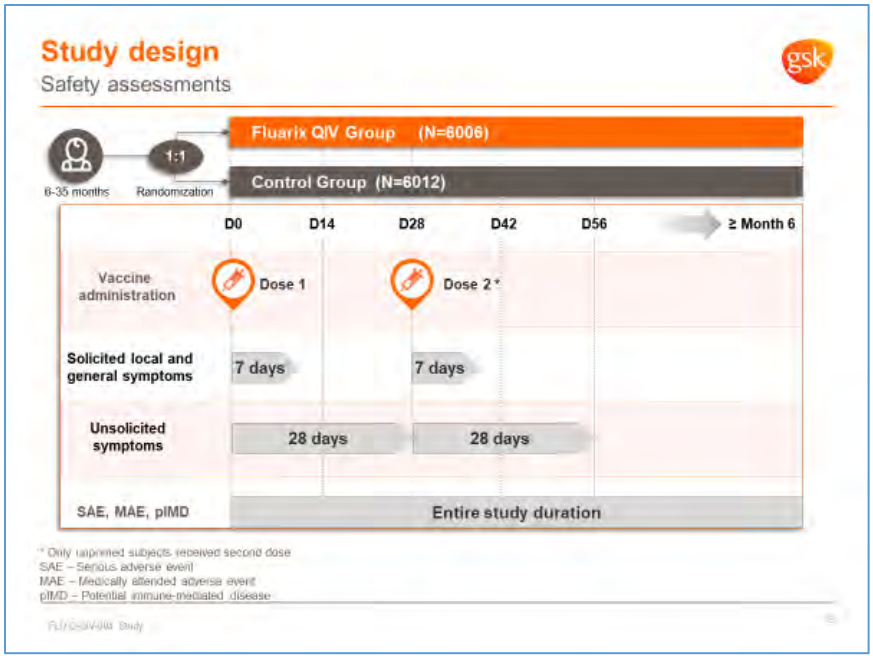

In terms of the incidence of solicited local symptoms of injection site pain, redness, and swelling reported by subjects in the study 7 days post-vaccination for Dose 1 and Dose 2, rates of solicited symptoms after each dose were similar between those who received influenza vaccine and those who received the non-influenza control vaccines. In general, reported rates were lower after Dose 2 compared to Dose 1. Similarly, for the incidence of solicited systematic symptoms reported 7 days post-vaccination for Dose 1 and Dose 2, reported rates were similar in those who received influenza vaccine compared to those who received the non-influenza control vaccines. In general, report rates were lower after Dose 2 than after Dose 1.

The rates for incidence of unsolicited symptoms, MAEs, SAEs and pIMDs in subjects who received Fluarix® Quadrivalent and those in the control arm were similar as reflected in the following table:

Subjects With at Least One Reported	Fluarix QIV (N=6006) n (%)	Control (N=6012) n (%)
Unsolicited AE (28 days post-vaccination)	2640 (44.0)	2679 (44.6)
- Grade 3 unsolicited AE	160 (2.7)	149 (2.5)
Unsolicited symptom with medically attended events (entire study duration)	3885 (64.7)	3988 (66.3)
- Grade 3 unsolicited MAE	200 (3.3)	211 (3.5)
Serious Adverse Event (entire study duration)	217 (3.6)	201 (3.3)
Potential immune-mediated diseases (entire study duration)	5 (0.1)	0 (0)

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There was an imbalance in pIMDs throughout the course of the entire study, which spanned 6 to 8 months. There were 5 reports in those who received Fluarix® Quadrivalent compared to no reports in those who received control vaccines. A detailed review was conducted of each of these individual cases. There were some confounding factors and, in all cases, there was insufficient evidence of a causal association.

With respect to the relevance of this study, this was a large RCT of over 12,000 young children that provided high quality data on vaccine prevention of influenza illness in young children. The study collected data from different regions over multiple seasons, thus providing a typical VE value. There was a large dataset with exploratory analyses by subtype/lineage and also by age group. The application of a classification method was employed to categorize the clinical severity of influenza cases, and the impact of influenza vaccination on outcomes related to healthcare utilization were assessed.

In conclusion, Fluarix® Quadrivalent at the 0.5-mL dose in young children 6 through 35 months of age demonstrated efficacy of 63.2% against moderate-to-severe influenza and 49.8% against RT-PCR confirmed influenza any severity. This was in the setting of mismatch to circulating strains. Fluarix® Quadrivalent reduced healthcare utilization, including antibiotic use, GP visits, and ED visits related to confirmed influenza illness. Healthcare utilization was lower among those who received Fluarix® Quadrivalent compared to the non-influenza control vaccine. Fluarix® Quadrivalent was immunogenic against all 4 vaccine strains. The safety and reactogenicity profile was similar to vaccines used in same age group, and no safety signals were observed. The 0.5-mL dose indicated for all eligible individuals 6 months of age and older potentially simplifies influenza vaccination. Importantly, these study results support universal vaccination of all children from 6 months of age and older to prevent influenza.

Discussion Points

Ms. Pellegrini congratulated GSK for including a very diverse cohort of children from across the world, presumably many levels of socioeconomic status (SES), and so forth. She inquired as to whether they broke down the results based on geography, race/ethnicity, or other factors.

Dr. Friedland emphasized that GSK was very proud to have conducted such a large study generating high-quality data. The large dataset allowed them to look at many factors, including efficacy by age, gender, country, et cetera. In general, the results all pointed in the same direction that the vaccine is highly effective against moderate-to-severe influenza and influenza of any severity, including by strain.

Dr. Szilagyi requested additional information regarding the 5 cases of pIMDs investigated in terms of whether they had pre-existing conditions, time since vaccination, et cetera.

Dr. Friedland replied that in a large study, many reports will occur. All of the cases reported occurred at background rates that would be expected in the general population. The first case was a patient who presented 21 days after the second dose of vaccination with a high fever of 39.4°C, a petechial rash, an evaluation that ruled out serious bacterial invasive disease, and was noted to have thrombocytopenia. The diagnosis was immune thrombocytopenia (ITP), which resolved on its own 7 days later. Another case occurred 33 days after the first dose of a patient who then presented with a URI, fever, ear pain, and facial asymmetry. The diagnosis was facial paralysis, which resolved on its own within 2 months. There was a case of a child 13 days after Dose 2 who developed nephrotic syndrome who had a normal renal biopsy. There was another case 8 days after Dose 1 of a patient who developed facial paralysis. Of note, this

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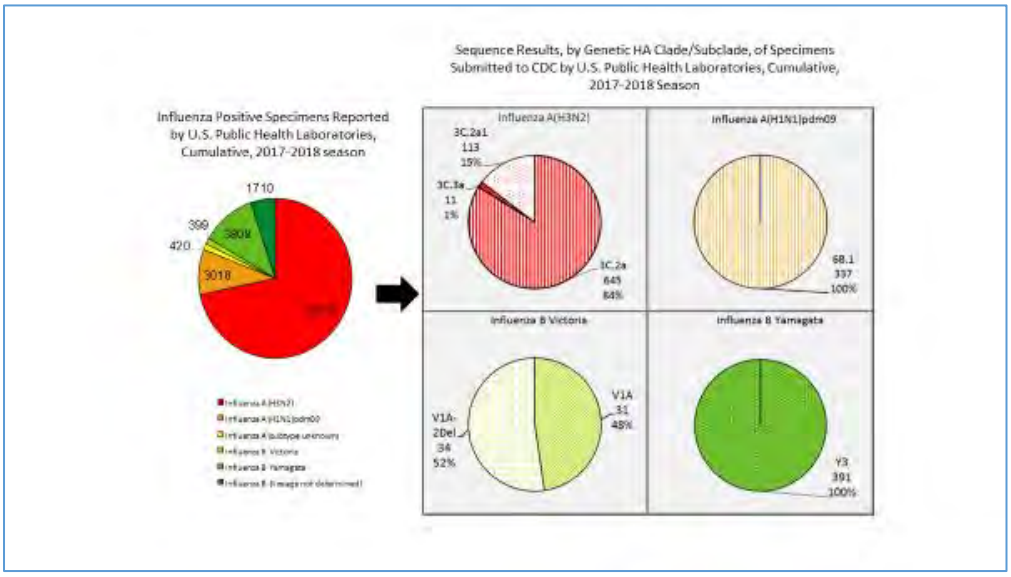
patient had received varicella vaccine 23 days earlier. The fifth case was a child who 206 days after the second dose of vaccination was diagnosed with celiac disease.

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 influenza surveillance activity for the 2017-2018 influenza season through the week ending February 10, 2018. In terms of influenza virologic surveillance, data reported to CDC by clinical laboratories across the country are used primarily to assess the percentage of specimens that are testing positive for influenza to track the course of the season. Since the week ending January 13, 2018, the percent of specimens testing positive for influenza has remained fairly consistent for quite a while at a range of between 26.1% to 26.7% positive. The percent positive to date for influenza A may have peaked during the week ending January 13th and has decreased from 21.8% positive down to 16.9% positive for the week ending February 10th. At the same time, the percent positivity for influenza A has been decreasing, the percent positive for influenza B has been increasing. Influenza B has increased to 9.6% positive for the most recent week. In terms of data from the US Public Health Laboratories that offers a more detailed view of the circulating viruses, for season overall about 82% of all viruses have been influenza A, although that has declined to 66% for the most recent week. Among the influenza A viruses that are subtyped for the season overall, 89% have been H2N2 viruses. Among the influenza B viruses, 91% that have been lineage tested have belonged to the B/Yamagata lineage.

This graphic shows the genetic groups that each of the viruses belong to:



The left side shows the overall number of viruses reported through surveillance to put the data on the right into context. The majority, 84%, of A(H3N2) fall into the 3C.2a genetic group, which is the genetic group to which the vaccine strain belongs, 15% belong to the subgroup 3C.2a1 and a small proportion, 1%, belong to 3C.3a which is the older group that the A/Switzerland vaccine strain came from. All of the A(H1N1) viruses belong to the 6B.1 genetic group, which is

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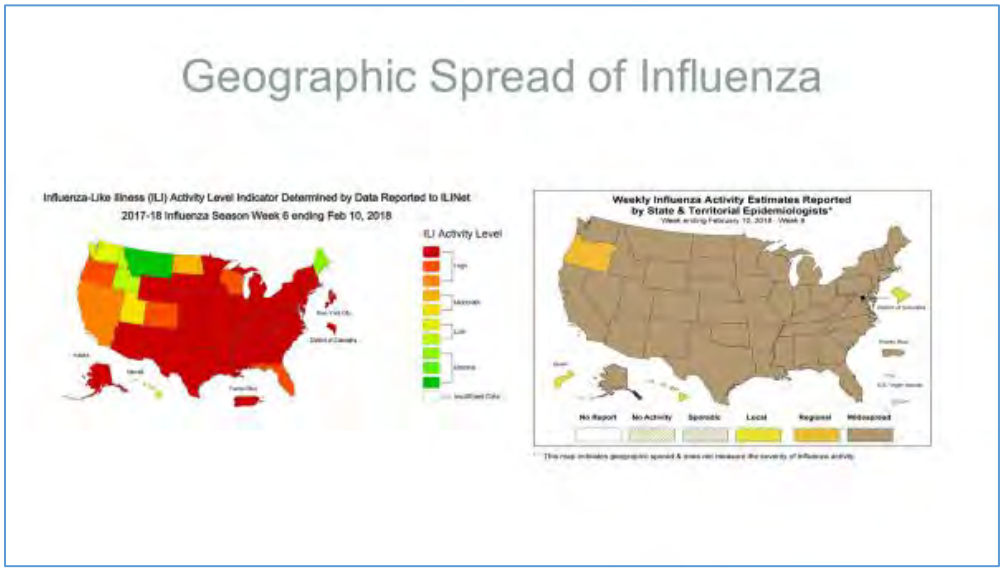
the same genetic group that the vaccine belongs to. For the B/Victoria viruses, all of the viruses belong to the V1A genetic group, but about 52% belong to a subgroup that has a 2 amino acid deletion in the HA and are referred to as V1A-2Del or double deletion variance. All of the B/Yamagata viruses belong to the Y3 genetic group.

In terms of the antigenic characterization of US influenza A viruses collected from October 1, 2017 to present, all 205 A(H1N1)pdm09 viruses antigenically characterized using ferret post-infection antisera were A/Michigan/45/2015-like, the H1N1 component of the 2017-2018 vaccine. Of the 297 A(H3N2) viruses, 291(98.0%) were well-inhibited by ferret antisera raised against A/Michigan/15/2014, a cell propagated A/Hong Kong/4801/2014-like reference virus representing the H3N2 component of the 2017-2018 vaccine. Basically, what this means is that noticeable antigenic drift is not being observed in these viruses. Of the viruses tested, 64.4% were well-inhibited by ferret antiserum raised against the egg-propagated A/Hong Kong/4801/2014 reference virus. Of the 51 B/Victoria linage viruses tested, 28 (45.1%) reacted poorly with ferret antisera raised against cell propagated B/Brisbane/60/2008 reference virus, representing a B component in both quadrivalent and trivalent influenza vaccines for the 2017-2018 season and these viruses had the V1A-2Del HA. All 202 of the B/Yamagata lineage viruses were antigenically similar to the cell propagated B/Phuket/3073/2013 reference virus, representing a B component in the quadrivalent influenza vaccines for the 2017-2018 season.

In terms of illnesses caused by these viruses, 7.5% of outpatient visits were for ILI in the most recent week. This is higher than has been observed since the 2009 pandemic, when the peak was 6.1% for seasonal influenza and more similar to what was seen during the 2009 pandemic when it peaked at 7.7%. In terms of state-level influenza activity levels, 43 states, New York City (NYC), the District of Columbia (DC), and Puerto Rico (PR) reporting high ILI activity. during the most recent week or 46 of the possible 53 jurisdictions. More than half of all jurisdictions have been at a high ILI activity level since the week ending December 30, 2017. Previously, the largest number of jurisdictions reporting high in a single week was 31. ILI activity has been considerably higher than in the past, and has remained high for quite a while.

These maps compare ILI activity and geographic spread of influenza:



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The maps illustrate that even the states not showing high levels of ILI activity are having geographically widespread influenza. For the first 3 weeks of 2018, 49 states reported widespread influenza activity each week. For the most recent 3 weeks, 48 states reported widespread activity. This is a very long period of time with very sustained widespread activity.

The cumulative rate of influenza-associated hospitalizations thus far has been 67.9/100,000 persons. That rate has been highest for people 65 years of age and older at 294.9/100,000 followed by those 50 through 64 years of age at 72.8/100,000. Comparing the overall rate observed this year with all seasons for which there are data since the pandemic, not only is the overall rate higher than any other season for the same week, but also it is higher than the end of season rate for any season previously. The rate is higher than the same week in time and is approaching but not quite yet the end of season rate for the 2014-2015 season. In terms of the percentage of death certificates filed with the National Center for Health Statistics (NCHS) that have pneumonia or influenza listed, it looks like this percentage may have peaked during the week ending January 20th at 10.4%, which is considerably above the epidemic threshold for that week of 7.3%. However, it is still lower than the peak percentage observed in 2014-2015 of 10.8% and 2012-2013 of 11.1%. There have been 84 influenza-associated pediatric deaths reported to CDC. Interesting about these deaths is that the distribution of viruses differs from what is being seen in the surveillance data overall. Thus far, 19 of those deaths were due to H1N1 viruses, 19 due to H3N2 viruses, 23 due to influenza A viruses that were not subtyped, and 23 due to influenza B virus infection.

Regarding vaccine virus selection for the 2018-2019 season, the WHO Consultation on the Composition of Influenza Virus Vaccines for Use in the 2018-2019 Northern Hemisphere Influenza Season was convened for February 19-22, 2018. The announcement of their decision was anticipated to be made on February 22nd. The FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting will be held on March 1, 2018 to determine the US-specific strains.

To summarize, influenza A(H3N2) viruses have predominated during the 2017-2018 season. However, influenza B activity is increasing and influenza activity may not have peaked yet. ILI activity is the highest observed since the 2009 pandemic. Final severity cannot be determined until the end of the season, but particularly for adults, hospitalization rates and mortality could be similar to or even exceed those seen during the severe 2014-2015 season. The majority of circulating stains are similar to those contained in the 2017-2018 vaccine. B/Victoria lineage viruses are the only viruses clearly showing antigenic drift, but these represent <1% of currently circulating viruses. Vaccine virus recommendations for the 2018-2019 influenza season are in the process of being made and will be available shortly.

Vaccine Effectiveness Update

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

Dr. Flannery provided an update on the 2017-2018 interim VE estimates from the Flu VE Network. The US Flu VE Network sites include: Baylor Scott and White Health, Kaiser Permanente Washington, Marshfield Clinic Research Institute, University of Michigan, and University of Pittsburgh.

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As a reminder of the Flu VE Network methods, enrollees include outpatients 6 months of age and older with acute respiratory illness (ARI) defined essentially as cough ≤7 days duration. The dates of enrollment for these data are November 2, 2017 through February 3, 2018. The analysis uses a test-negative design that compares vaccination odds among influenza RT-PCR positive cases and RT-PCR negative controls. Vaccination status for the interim estimate is defined as receipt of at least one dose of any 2017-2018 seasonal influenza vaccine according to medical records, immunization registries, and/or self-report. VE is calculated as 1 – adjusted odds ratio x 100%. Several variables are included in adjusted estimates: study site, age, self-rated general health status, race/Hispanic ethnicity, interval from onset to enrollment, and calendar time.

There were 4562 outpatients enrolled from November 2, 2017 through February 3, 2018 at the 5 sites. About 38% (1712) tested positive for influenza via RT-PCR, and 2850 (62%) tested negative via RT-PCR. The distribution of the positive cases was 67% A/H3N2, 12% A/H1N1pdm09, 3% A un-subtyped, 15% B/Yamagata, 0.2% B/Victoria, and 3% B no lineage. A/H3N2 was the predominant type at all 5 sites, while B/Yamagata was the predominant B virus. Through the week of February 3, 2018 the number of enrolled participants who were influenza positive or negative closely followed the ILI activity at the sites, with a lower percent positivity at the end of December 2017 and increasing rapidly through the beginning of February 2018 to about 50% in the last few weeks of enrollment before these data were drawn.

The number vaccinated among the influenza positive patients was 43% overall, while the percent vaccinated among the influenza negative patients was about 53%. There was an overall adjusted VE of 36% with a confidence interval of 27% to 44%. The estimates were statistically significant in the 6 month to 8 year olds at 59% and among the 18 through 49 year olds at 33%. None of the other age groups had statistically significant VE estimates. For A(H3N2)-specific estimates, there was an overall adjusted estimate of 25% that was statistically significant with a confidence interval of 13% to 36%. The only age group that had statistically significant estimates was the 6 months to 8-year-old age groups. The estimates were low and not statistically significant for all of the other age groups.

Of note, the vaccine reference virus was updated for A(H1N1)pmd09 for this season making this the first season with the A/Michigan virus included in the vaccines. The overall adjusted VE was 67%, which was higher than during the 2015-2016 season with the previous vaccine strain, and was statistically significant in children 6 months to 17 years of age and 18 through 64 years of age. The estimate was slightly lower and non-significant in those 65 years of age and older for A(H1N1)pmd09. For influenza B, most of the influenza vaccine in the US Flu VE Network for all ages is quadrivalent, so the question of inclusion of B/Victoria in trivalent vaccine is perhaps not as relevant except for those 65 years of age and older. VE is not broken out by vaccine type until the end of season estimates when medical and immunization records are available. The overall estimate for all types of influenza B was 42% and was statistically significant in the 6 months to 17 years of age and 18 through 64 years of age groups, and slightly lower in those 65 years of age and older and not statistically significant.

In summary, the interim results for the 2017-2018 season through February 3, 2018 indicate an overall VE of about 36%. This was slightly lower at 25% for A(H3N2) for all ages, but was statistically significant. Of note, VE was about 51% in children aged 6 months through 8 years and was statistically significant. No other age groups had statistically significant VE estimates against A(H3N2) at this time point. VE was higher at this interim estimate for A(H1N1) at 67%, and was slightly higher at 42% for all influenza B viruses, which were primarily B/Yamagata. The final VE results will be shared at the end of season. Final VE is used to calculate averted

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burden (cases, doctor visits, hospitalizations, deaths). After the surveillance update with comparisons of previous severe influenza seasons such as 2014-2015, even with low VE, vaccination averts thousands of hospitalizations each year. During 2014-2015, the estimate was about 47,000 influenza hospitalizations prevented with a range from 11,000 to 144,000. It is expected that the final season VE will be helpful in assessing averted burden this season.

This interim estimate highlights the challenges with understanding the A(H3N2) component of influenza vaccines. A couple of studies are examining A(H3N2) effectiveness for this season. One of the studies of note is from the Department of Defense (DoD) VE which is assessing VE for IIV4 egg-based vaccines versus cell-cultured quadrivalent vaccines (ccIIV4) in their active military influenza surveillance population and military dependents through the Armed Forces Health Surveillance Branch (AFHSB) and US Air Force School of Aerospace Medicine (USAFSAM). Data from this study is anticipated to be presented to the WG and eventually to ACIP in the next several months. The other study is a comparative VE study by the FDA and Centers for Medicare and Medicaid Services (CMS), which will examine hospitalization and medically-attended influenza rates by vaccine type (ccIIV and IIV, SD, HD and adjuvanted vaccines).

CDC is studying immune responses to vaccine for this season as well as the effects of prior infection and/or vaccination. Repeated vaccination is relevant this season because the A(H3N2) component is the same as in the 2016-2017 vaccine. This study also will examine the birth cohort in an effort to better understand why VE appeared to be higher in those 6 months to 8 years of age compared to other age groups. In addition, vaccine response by vaccine type and prior vaccination will be examined closer to the end of season. This season, CDC has increased sequencing of positive specimens from the Flu VE Network using next-generation sequencing to assess ongoing changes in the A(H2N2) viruses.

Discussion Points

Dr. Bernstein was impressed by the fact that half of the influenza A cases were H1N1. He inquired as to whether among the pediatric deaths there was a breakdown of age and the overall percentage of those who were vaccinated.

Dr. Brammer replied that among the children with H1N1, more than half were less than 8 years of age. The vaccination rate among the children with H1N1 were not any different than normal, which is about 20% to 25%.

Dr. Romero asked whether there are any data on serious complications such as myocarditis or encephalitis in children.

Dr. Brammer responded that while CDC does collect that information, she would have to look it up.

Dr. Riley asked whether there are any data on children less than 1 year of age, and whether mothers were vaccinated.

Dr. Brammer replied that unfortunately, the mother's vaccination status is not collected with this surveillance.

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Dr. Sun (FDA) recalled mention of immunogenicity with the cell- versus the egg-based vaccines, noting that even though this year is a match for H3N2 there seems to be a confounder. While he realized that the cell-based vaccines have been available only since 2012, he wondered whether previous seasons have been assessed to determine whether the discrepancy between cell- and egg-based vaccines has had a similar effect on overall effectiveness.

Dr. Brammer indicated that Dr. Katz had joined the meeting by phone from Geneva and invited her to make comments on that.

Dr. Katz responded that this is a common phenomenon observed with H3N2 viruses. Because of the changes seen with egg adaptation and having impact on the antigenic profile of viruses, antigenic drift is always compared to the cell-propagated reference viruses. No evidence of antigenic drift has been observed as Dr. Brammer indicated with her data. However, it is routinely observed that the proportion of circulating viruses when tested for similarity to the reference egg-grown virus are typically never as good as compared with the cell-grown references viruses. That is a common theme with the H3N2 viruses over many past seasons.

Dr. Whitley-Williams (NMA) asked about the total number of deaths overall that were influenza-related, and whether such data is available broken down by race/ethnicity.

Dr. Brammer responded that there is not currently a total number for all age groups. While there will be an estimate at the end of the year, she did not think they would have the ability to break that data down by race/ethnicity.

Dr. Bennett added that some of those data are available through the Emerging Infections Program (EIP) at the end of the season, and those will be available by race and age.

Dr. Messonnier pointed out that pediatric deaths are nationally notifiable; therefore, CDC has those data. However, overall deaths are not nationally notifiable. The influenza program uses the data they have to make estimates, but it is not exactly equivalent to the pediatric data.

Ms. Pellegrini noted that the presentations did not include anything specifically about pregnant women, and inquired as to whether any signals of concern had been observed among pregnant women this season.

Dr. Brammer responded that the data she would have to reflect that would be the hospitalization rates, which did not differ among pregnant women from what has been observed in previous years.

Dr. Hunter requested clarification regarding whether the influenza and pneumonia data include race and ethnicity from the death certificates.

Dr. Brammer replied that race and ethnicity are on the death certificates, but CDC receives a subset of those data that do not include that information. However, they can request that information from NCHS.

Dr. Zahn (NACCHO) noted that children 6 months through 8 years of age seemed to do better. He asked whether other countries that have experienced issues with VE and have concerns with egg adaptation have noticed this difference as well.

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Dr. Flannery indicated that there are some data from the European Network and Canada, but the numbers are too small to separate out better effectiveness in younger children from the preliminary estimates for this season. The trend and overall rates are similar to those observed in the US, but the numbers are smaller in other networks.

In terms of pediatric deaths, Dr. Quach (NACI) inquired as to whether there are any data of the proportion of children who were considered previously healthy.

Dr. Brammer indicated that she did assess this the previous day and thought it was about half.

Dr. Szilagyi said he was puzzled by the 9 through 17-year-old data. While he understood that they did not yet have prior vaccination history since this was the interim analysis, he asked whether there was something different about that age group including the cases compared to prior years.

Dr. Flannery said CDC is wondering about this as well. The first point to make is that there is really no difference between the 9 through 17-year-old and any of the other age groups over 8 years of age just because the confidence intervals include all of those estimates. If VE is very low, some of the point estimates are expected to be negative, so they are not as alarmed by the negative point estimate. However, it is concerning that they are all low. Regarding differences in sites, there was a very intense activity early season in Texas. The Texas site has the lowest vaccine coverage in this age group. Though the study design should take care of that, it is interesting that there was a larger proportion of vaccinated 9 through 17-year olds among the cases this year, and a lower proportion of vaccinated controls or the influenza negatives. The 35% vaccinated rate among influenza negatives is somewhat lower than typically seen in previous seasons.

Results of a Randomized Trial of a New H1N1 LAIV Strain In US Children

Raburn Mallory, MD
Senior Director Clinical Development
MedImmune/AstraZeneca

Dr. Mallory presented the results of a clinical study MedImmune/AstraZeneca conducted to evaluate the shedding and immunogenicity of a new H1N1 strain that was included in LAIV, or FluMist®, for the first time this season. The study was conducted to determine whether the new strain that was picked based on some improvements made to the strain selection process for LAIV was more immunogenic than was shed in a higher proportion of subjects than with the previous strain that had reduced effectiveness.

LAIV is not currently recommended in the US due to reduced effectiveness for H1N1 strains seen in the 2013-2014 and 2015-2016 influenza seasons. The pooled estimate of effectiveness in those seasons was around 25%. MedImmune/AstraZeneca conducted an investigation to determine the reasons for this reduced effectiveness for H1N1 strains. Using newly developed assays, they discovered that the post-pandemic H1N1 vaccine strains used in those seasons replicate less well compared to older highly efficacious LAIV strains. Based on these findings, they selected a new H1N1 strain, A/Slovenia, that was included in the vaccine for the first time this season. A clinical study was conducted to see if the new strain produced higher levels of antibody responses than an older strain, the A/Bolivia H1N1 strain, that had been used in the 2015-2016 season that had reduced effectiveness. During this session, Dr. Mallory presented results from this study showing that the new A/Slovenia strain induced statistically higher

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seroconversion rates compared to the older strain after both the first and second doses of the vaccine. In fact, the immune responses seen for the new strain were similar to those seen for a previous highly efficacious H1N1 strain that had been included in the vaccine previously. The findings from the clinical study validate the improvements that MedImmune/AstraZeneca made in its strain selection process, and the new strain selection process will be applied to all future LAIV strains. The results will be submitted to the FDA, the European Medicines Agency (EMA), and other regulatory bodies on an annual basis for review.

Regarding the study design, 200 children 2 to less than 4 years of age were enrolled. Young children were enrolled as LAIV shedding and immune responses are highest in these young children, and this would offer the best opportunity to differentiate between the H1N1 strains in the study. Subjects were randomized to one of three arms. One arm received a trivalent version of the vaccine used in 2015-2016 with the A/Bolivia H1N1 strain, another arm received a quadrivalent version of the vaccine used in 2015-2016 with the same A/Bolivia strain, and the third arm received the quadrivalent vaccine used 2017-2018 with the new A/Slovenia H1N1 strain. A trivalent arm was included in the study to see if interference might be occurring for the A/Bolivia strain in the quadrivalent formulation, given the fact that this strain had been shown to have reduced replicative fitness in the laboratory. All subjects in the study received two doses of vaccine 28 days apart and immune responses were assessed at baseline, before the second dose, and again 28 days later. Shedding evaluations were conducted on days 2, 3, 4, 5, and 7 and again after the second dose on days 30, 32, and 34. Shedding was evaluated less frequently after the second dose, as it was known from older LAIV studies that shedding would be lower after this dose for all subjects.

In terms of the vaccine strains used in each of the study arms, the 2015-2016 trivalent arm had the A/Bolivia H1N1 strain, the A/Switzerland H3N2 strain, and a single B strain—the B/Phuket strain from the Yamagata lineage. The 2015-2016 quadrivalent arm had these same 3 strains and an additional B/Brisbane strain from the B/Victoria lineage. The 2017-2018 arm had the new A/Slovenia H1N1 strain, a new H3N2 strain recommended by the WHO for that season, the A/New Caledonia strain 2014, and the same two B strains as the other quadrivalent vaccines. The two quadrivalent arms, Arms 2 and 3, represent the commercial vaccine that was manufactured and distributed for those seasons.

The primary endpoint of the study was hemagglutination inhibition (HAI) antibody seroconversion rates after both the first and second doses of the vaccine. For immunogenicity, in addition to HAI responses, the investigators also looked at neutralizing antibodies, nasal IgA responses, and the proportion of children who had an immune response using any one of the three assays. For shedding, the proportion of subjects shedding by day, the number of days of shedding, and viral titers were examined. Safety assessments included solicited symptoms, AEs, and SAEs.

The median age of subjects enrolled was 35 months, and there was a fairly even balance between male and female subjects. About 45% of the subjects enrolled in the study had not been previously vaccinated for influenza. The aim was to enroll about 50% of subjects without a history of influenza vaccination, as the subjects who had not been vaccinated were more likely to be seronegative at baseline, and because data were available from older LAIV studies about how seroconversion rates in these children might correlate with LAIV efficacy. In terms of subject disposition, 195 of the 200 subjects completed the study and no subjects withdrew due to an AE.

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In terms of the shedding results, the data for days 4 and 5 indicate that the A/Slovenia strain is being shed by a higher proportion of subjects than the A/Bolivia strains. This is consistent with improved replicative fitness for this strain seen in the laboratory investigation. As expected, shedding after the second dose of the vaccine was lower for all strains. Regarding shedding in seronegative subjects, this replicative advantage for the A/Slovenia strain may be occurring as early as day 3. With regard to HAI antibody seroconversion rates after both the first and second dose of vaccine, the study met its primary endpoint. The new A/Slovenia strain demonstrated statistically higher seroconversion rates after both the first and second dose of vaccine. Seroconversion rates in seronegative children were generally higher, with the A/Slovenia strain again showing higher seroconversion rates than the A/Bolivia strains in either the trivalent or quadrivalent formulations.

Post-hoc analyses were performed of statistical significance for these endpoints and were adjusted for multiple comparisons. Neutralizing antibody responses after Dose 1 were similar to the HAI responses with the A/Slovenia strain, showing somewhat higher responses than the A/Bolivia strain. IgA responses for the A/Slovenia strain were somewhat lower than for the A/Bolivia strain, while the percentage of subjects who had an antibody response in any of the 3 assays was similar across the study arms. However, antibody responses after 2 doses of the vaccine were more consistent. The A/Slovenia strain showed higher HAI responses, neutralizing responses, and IgA responses and a higher percentage of subjects showed an antibody response using any one of these three assays.

Taken as a whole, these data indicate that the A/Slovenia strain, selected for its improved replicative fitness, induced higher levels of immune response than the previous A/Bolivia strain in either a trivalent or quadrivalent formulation of the vaccine. The data suggest that there may be a potential for interference occurring with the A/Bolivia strain in terms of the HAI neutralizing antibody responses. However, the shedding data showed earlier and the IgA responses are less consistent with this conclusion. Any potential interference for the A/Bolivia strain is likely related to the fact that it has decreased replicative fitness, as shown by the laboratory investigation. It is important to note that the new A/Slovenia strain induced higher antibody responses than the A/Bolivia strain whether it was included in a trivalent or quadrivalent vaccine formulation.

In terms of how the HAI seroconversion rates seen in this study compare to those seen in older LAIV studies for which there are seroconversion and efficacy data, the seroconversion rates for the A/Slovenia and A/Bolivia strains in the current study can be compared to seroconversion rates for 2 and 3-year-old children from two older FluMist® studies in which the H1N1 component of the vaccine had high levels of efficacy. Seroconversion rates for the A/Bolivia strain were lower than those previously seen, which is consistent with the reduced effectiveness for this strain seen in the 2015-2016 season. Conversely, the new A/Slovenia strain induced notably higher seroconversion rates. The fact that seroconversion rates were similar to those seen in the older studies in which the H1N1 vaccine strain was highly efficacious strongly suggests that the new A/Slovenia strain is likely to have improved effectiveness against circulating H1N1 strains.

To summarize the H1N1 data from the study, the A/Slovenia strain was shed by a higher proportion of subjects from Day 4 through Day 7 after Dose 1 of the vaccine. The study met its primary endpoint, as HAI seroconversion rates were significantly higher for the A/Slovenia strain than for the A/Bolivia strain. Similar results were seen for neutralizing antibodies and for nasal IgA responses. Finally, the A/Slovenia HAI seroconversion rates were similar to those seen in

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children vaccinated with a highly efficacious pre-pandemic AH1N1 strain, suggesting that the strain is likely to have improved effectiveness.

While the study was specifically designed to compare the A/Slovenia and A/Bolivia strains to address concerns about H1N1 effectiveness, there are shedding and immunogenicity data for the other strains in the study. Given that H3N2 strains have predominated in recent seasons, including the current one, Dr. Mallory showed how the immune responses for the two H3N2 strains in the study compared to immune responses for older LAIV H3N2 strains with high levels of efficacy. Seroconversion rates for the both the A/Switzerland strain and the A/New Caledonia/2014 strain were high and comparable to those seen for 3 highly effective H3N2 strains. These data indicate that recent H3N2 strains in the quadrivalent formulation of the vaccine have remained highly immunogenic with antibody responses similar to strains that were in the trivalent formulation. As heard earlier in the day, the effectiveness of both LAIV and IIV for H3N2 strain in recent seasons has not been the 75% to 90% shown earlier. From studies conducted in 2016-2017, both LAIV and IIV had consolidated estimates of effectiveness of about 45% in children. This reduced effectiveness for the H3N2 strains is likely due to the issues Dr. Katz mentioned regarding egg adaptation that has resulted in a degree of antigenic mismatch between the vaccine strains and circulating strains, which has resulted in more moderate effectiveness.

Before concluding, Dr. Mallory summarized key improvements MedImmune/AstraZeneca has made to the way strains are selected for LAIV. The first change made was to assess the growth of new LAIV strains in nasal epithelial cell culture. Previously, the growth of LAIV strains was assessed for fitness in Madin-Darby Canine Kidney (MDCK) cells and in eggs for post-pandemic H1N1 strains. However, for post-pandemic H1N1 strains, these results were not predictive of replication in human cells. The second change made was to add the tissue culture infectious dose$_{50}$ ($TCID_{50}$) assay to the methods to quantify or measure the potency of new strains. They had previously used the fluorescent focus assay (FFA) to quantify strains, which measures the ability of viruses to infect cells and express proteins on their surface. The $TCID_{50}$ assay on the other hand measures the spread of vaccine virus from infected to uninfected cells, which requires the viruses to sustain multiple rounds of replication. For pre-pandemic H1N1 strains included in the vaccine, these assays gave very similar results. However, for post-pandemic H1N1 strains, the $TCID_{50}$ assay gave values of up to 3 logs or 1000-fold lower than the FFA results. This means that the post-pandemic H1N1 strains with reduced effectiveness may not have sustained intranasal replication to the levels needed for optimal effectiveness. To fix this issue, all future strains included in the vaccine will be evaluated during the strain selection process using the new assays described, and the $TCID_{50}$/FFA results will be reported to the FDA and other regulatory authorities as part of the data MedImmune/AstraZeneca submits every year to support ongoing licensure of the vaccine.

To summarize, MedImmune/AstraZeneca conducted an investigation to determine the reasons for the reduced effectiveness of recent H1N1 vaccine strains in 2013-2014 and 2015-2016. They discovered that these strains replicated less well compared to older strains. A new H1N1 strain was selected, the A/Slovenia strain, with improved replicative fitness in the laboratory for inclusion in the vaccine for this current 2017-2018 season. The new strain was compared to a previous strain with reduced effectiveness in the clinical study just described, and the new A/Slovenia strain was more immunogenic, demonstrating immunogenicity similar to a highly effective pre-pandemic H1N1 strain. MedImmune/AstraZeneca believes that the data generated from the pediatric study validate the changes made to improve the selection of LAIV strains. The new strain selection process will be applied to all future LAIV strains, with the data reviewed by the FDA and EMA on an annual basis. Finally, MedImmune/AstraZeneca believes

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that LAIV is an important vaccine option for providers, patients, and parents in the US and in other countries where it continues to be recommended for use.

Discussion Points

Dr. Atmar inquired as to whether testing for future strains to be included the vaccine include H3 and B strains, and whether these criteria have been applied to past non-H1 strains to show that no issues were identified with replicative fitness.

Dr. Mallory replied that there are future plans to include H3 and B strains, and the criteria have been applied to these strains. The results show that for the highly efficacious strains seen in the past, the FFA and $TCID_{50}$ assays are very close together. Moving forward in the current seasons, the criteria will be refined.

Dr. Hunter said that as a clinician, he was very impressed that MedImmune/AstraZeneca is doing everything they can to determine theoretically what is occurring with the vaccine. However, he also wondered what future data they would have that relates to his patients in terms of whether this really prevents infection.

Dr. Mallory responded that FluMist® or Fluenz™ is the vaccine of choice in the UK for their national immunization program. Public Health England (PHE) generates effectiveness data on an annual basis. Those results are not available yet for the current season, but these are expected soon. The effectiveness data will continue to be generated. When H1N1 circulates again next, there will be effectiveness estimates for the vaccine from PHE and possibly from other countries such as Finland and Canada where the vaccine is being used and VE estimates are being generated.

Dr. Bernstein applauded the efforts to address the issues identified since the previous vaccine versions under-performed in comparison with IIV. He believes that having an intranasal product is an important part of a vaccine program, since it is a universal recommendation. His struggle is in translating shedding into VE. With a small number of subjects, 200 total subjects in 3 different arms, it was not clear to him how that translated into confidence that this will be effective in the clinical setting.

In terms of the size of the study, Dr. Mallory indicated that they picked 200 subjects because this would offer the ability statistically to see difference of about 20% to 25%. They felt that differences in immunogenicity of about 20% to 25% between the strains would be clinically relevant. If the study was larger, they might be able to say that differences of 5% to 10% immunogenicity was statistically different, but they did not feel that these differences in immunogenicity would be clinically relevant. The size was based on what they thought would be clinically relevant differences. In terms of how shedding and immunogenicity data can be generalized to effectiveness, that is why they went back and compared the seroconversion results. Regarding the GMTs in two of the older studies, the H1N1 component was highly effective. It is very reassuring to see that the results observed with the new A/Slovenia strain were consistent with those previous results. Also seeing that the A/Bolivia strains were somewhat lower coincided with the reduced effectiveness of that strain points to the general applicability of these findings.

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Dr. Romero asked whether there are any data to suggest that there is no interference with the seroconversion rates to type B. In the original version of the vaccine, shedding was a concern in terms of spreading to other individuals who might be at risk for immunocompromising conditions. He wondered whether recommendations regarding shedding would be issued with the new vaccine.

Dr. Mallory replied that the effectiveness for the B strains in the vaccine has been consistent in the trivalent and quadrivalent formulations. There is no evidence that interference is occurring for the B strains. In terms of shedding, in the original version of the vaccine, a large shedding study was done that showed a very low rate of transmission. There was only one case among 200 children. The shedding rates seen in the current study are similar to those seen in previous studies, so he does not expect that there will be any changes to the recommendations regarding who can receive the vaccine.

Dr. Szilagyi pointed out that in the real world in this age group, more than half of children are previously vaccinated. He asked what the findings were for the number who were previously vaccinated.

Referring to Slide 24 in his back-up sides, Dr. Mallory indicated that as expected the seroconversion rates were somewhat lower in vaccinated subjects. However, they were not markedly different than for all subjects.

In terms of the study design, Ms. Pellegrini asked why the decision was made to give all of the participants 2 doses when those who were previously vaccinated would have been recommended for only 1 dose.

Dr. Mallory responded that one goal of the study was to see whether they could differentiate between the H1N1 strains in terms of shedding and immunogenicity. They also had the data from the old LAIV studies for which they had seroconversion rates and efficacy data. Those were 2 dose data, so they made the decision to give subjects 2 doses so they could compare the seroconversion rates of the older strains that were known to be highly efficacious.

Ms. Pellegrini asked whether that meant that they could probably expect real-world usage results to be closer for those populations to Dose 1 results instead of the Dose 2 results. That is, if they recommend the vaccine, those children who are previously vaccinated would receive only 1 dose of LAIV.

Dr. Mallory replied that they might expect to see seroconversion rates at about that level. The efficacy of a single dose across the age group indicated has been extensively reviewed by the FDA, and it is known that the vaccine works in subjects who receive a single dose.

Dr. Messonnier clarified that one of the complicated issues in looking at these data is that, in fact, while people have been previously vaccinated, they would not have been previously exposed to this H1N1 strain because it is a new strain for that population.

Dr. Mallory confirmed this and said that this is why they looked at results in seronegative subjects.

Dr. O'Leary (PIDS) recalled that one of the first hints that there was less effectiveness with LAIV versus IIV was in older children 9 through 17 years of age. Therefore, he was curious about the decision to study this in only the younger children.

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Dr. Mallory clarified that the reason they picked younger subjects for this study was because they knew that shedding and immunogenicity would be higher in these younger subjects, and this would give them the ability to differentiate between the strains. They also had data for the younger subjects about how a highly efficacious strain should perform.

Dr. Brady (AAP) said he was still trying to understand how shedding and immunogenicity would pertain to eventual effectiveness. He noted that slide 13 shows high efficacy rates of 92% and 82% efficacy with the A/New Caledonia strain, yet it appeared that the lower seroconversion rates had the higher efficacy. This was taking a leap of faith that the true correlate of protection has been identified based on the studies MedImmune/AstraZeneca has conducted. While MedImmune/AstraZeneca had conducted a lot of spectacular studies, a major concern regards whether they have truly identified what initially caused the lack of effectiveness and by looking at immunogenicity, whether the correct correlate has been identified.

Dr. Mallory pointed out that the efficacy was 92% and the seroconversion rate in seronegative subjects was 57%, which he thought was because the majority of children in Study 1 actually were already immunized. So, the old subjects and the seronegative subjects do not look that different. Regarding whether shedding and immunogenicity for LAIV correlate with efficacy, the first correlation is in the younger children, which predicts the effectiveness of the vaccine.

Dr. Quach (NACI) wondered whether there are plans to repeat such a study in the second year. Canada has used less LAIV than the US mainly because of cost containment. LAIV has been used in some provinces only in subgroups of children needing more protection. She asked if repeated exposure to LAIV resulted in decreased effectiveness, which might explain why Canada has not observed this.

Dr. Mallory responded that this study is not designed to look at the effects of prior immunity on effectiveness. However, the effects of prior immunity and vaccine efficacy and effectiveness have been studied extensively in both the observational studies that CDC and MedImmune/AstraZeneca have reported, as well as in the prelicensure efficacy studies. There is no evidence from any of these studies that prior immunity decreases either the effectiveness or the efficacy of the vaccine. For the 2016-2017 season, there were a couple of studies in Finland and Japan for which they had data on prior immunity. There was no effect of prior immunity in either of those studies. For the 2015-2016 season, there were a couple of studies showing that prior immunity seemed to increase the point estimates for effectiveness.

Review of LAIV for 2 Through 17 Year Olds

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Dr. Grohskopf indicated that her presentation would include some background information to place the issues into context; summaries of two analyses conducted in the CDC Influenza Division (ID), one of which was a combined individual patient-level analysis of LAIV effectiveness, including US effectiveness data from 5 studies and the other of which was a systematic review and meta-analysis of published literature on LAIV effectiveness, which includes both US and non-US data; a discussion of WG considerations; and a proposed recommendation.

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Regarding background, LAIV3 was licensed in 2003 as FluMist®, initially for persons 5 through 49 years of age. In 2007, it was licensed for persons 2 through 49 years of age. It was recommended for use for healthy non-pregnant persons within the indicated age range without a preference for it over any other vaccine. In 2012, LAIV4 was licensed and subsequently replaced LAIV3 in the US for the 2013-2014 season. LAIV4 was similarly recommended for healthy non-pregnant persons within the indicated age range, without preference over other products. In June 2014, ACIP approved a preferential recommendation for LAIV4 for healthy children 2 through 8 years of age. The basis of this recommendation was pre-pandemic data indicating superiority of LAIV to IIV for prevention of influenza among young children. However, in February 2015, the preferential recommendation was removed following analyses that revealed poor effectiveness of LAIV4 against H1N1pdm09 among persons 2 through 17 years of age observed during the 2013-2014 season. In these analyses, LAIV demonstrated no statistically significant effectiveness, whereas IIV was effective.

In June 2015, analysis of early 2014-2015 data revealed no better performance of LAIV4 than IIV against H3N2 viruses. Poor VE was observed for both LAIV4 and IIV during that season, which was marked by an antigenically-drifted H3N2 viruses predominance. In contrast, LAIV3 had been noted to be superior to IIV against drifted H3N2 in a large pre-pandemic RCT. The LAIV4 H1N1pdm09-like virus was changed to A/Bolivia/559/2013/H1N1pdm09 for the 2015-2016 season. This was intended to address findings of studies which revealed poor fitness of the previous LAIV4 H1N1pdm09-like vaccine virus, A/California/7/2009/H1N1pdm09. In June 2016, data from three US studies were presented to ACIP which noted poor effectiveness of LAIV4 against H1N1pdm09 for 2015-2016. Following discussion of these data, LAIV4 was not recommended in the US for 2016-2017, and subsequently also not recommended for 2017-2018.

To summarize some of the data from the CDC US Flu VE Network presented to ACIP in June 2016, the point estimate of LAIV4 effectiveness against H1N1pdm09 viruses was -21% and the confidence interval that included 0 and, therefore, was not statistically significant. Also presented during that meeting were data from MedImmune's Influenza Clinical Investigation for Children (ICICLE) study, showing an LAIV VE against H1N1pdm09 viruses of 50%. While this was higher than that observed in the Flu VE Network, it was still not statistically significant as the confidence interval crossed 0. A third estimate from the US DoD also was presented, which fell in between these two estimates at 15%. However, it also was not statistically significant.

As mentioned, the primary concern in 2015-2016 was poor effectiveness against H1N1pdm09 in the 2013-2014 and 2015-2016 seasons. One issue discussed at that time was the fact that point estimates of LAIV4 effectiveness against H1N1pdm09 varied among the US studies. Also, higher point estimates were observed in studies conducted outside of the US in Canada, UK, Germany, and Finland, which all have continued to use LAIV to date. In general, most of those estimates were not statistically significant either, with one exception. But the point estimates were notably higher. The sources of this variability are not completely understood. A number of possibilities have been discussed, including differences in the use of trivalent as compared with quadrivalent LAIV in different populations; small sample size and imprecision of estimates that accompanies small sample size, which is particularly an issue when looking at individual studies on their own and attempting to stratify by vaccine types and influenza types/subtypes; and differences in the prevalence of prior vaccination among children in different countries and populations—how exposed to vaccine are these children previously when they come into studies?

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As part of the efforts to better understand LAIV VE and the observed variability, two analyses were undertaken within the CDC ID. The first was a combined individual patient-level analysis of US studies (US-IPD). This included 5 US studies with three seasons with use of LAIV4 for 2013-2014 through 2015-2016 seasons. The hope here was to have greater power for age-group specific analyses, and more precise estimates through pooling of data across multiple studies. In addition, it was hoped that numbers would be sufficient for evaluation of the effect of prior vaccination on VE estimates. The second was a systematic review and meta-analysis (SR/MA). This included US and non-US studies from the 2010-2011 season forward. This included an evaluation of the quality of individual studies in terms of risk of bias and problems related to small sample size. Data were pooled for summary VE results and exploration and at least a description of heterogeneity, if not an explanation for it.

The US-IPD analysis was done by Jessie Chung with Brendan Flannery in CDC's ID. These data were presented to the ACIP WG in November 2017. This analysis included data from 5 different US studies, some characteristics of which are summarized here:

Study	N	Study Inclusion	Testing	Current Season Vaccination Status
Influenza Clinical Investigation in Children (ICICLE), MedImmune	3521	ARI with fever <5 days duration	RT-PCR	EMR, immunization registries
Influenza Incidence Surveillance Project (IISP), CDC	1102	ARI with fever and cough/sore throat ≤7 days duration	RT-PCR	EMR, immunization registries
LSU Health Sciences Center (LSU)	3822	Clinical laboratory testing for influenza	Rapid test; RVP of negatives	Immunization registry
US Air Force School of Aerospace Medicine dependents (USAFSAM), US DoD	1935	ARI with fever and cough/sore throat <72 hours duration	Culture, RT-PCR	Immunization registry, parent report
Flu VE Network, CDC	6793	ARI with cough ≤7 days duration	RT-PCR	EMR, immunization registries

The largest source of data in terms of number of observations is the Flu VE network, with almost 7000 observations. All of the studies contributed a substantial amount of data in terms of numbers. However, CDC has probably the most from the Flu VE Network, which drives the findings along with ICICLE and LSU. The methodologies in the studies differed somewhat, but overall, study inclusion criteria and case definitions were relatively consistent.

In terms of the results for IIV, results for any influenza pooled over all three seasons showed significant effectiveness of IIV in the 45% to 48% range depending upon age. There also was significant effectiveness for H1N1pdm09 in the 60% range across all of the age groups.

There was only one H3N2 dominant season in this 3-season period, 2014-2015, during which there were drifted H3N2 viruses. There were less consistent results, with no statistical significance for persons 5 through 8 or 9 through 17 years of age. Significant effectiveness was noted for persons 2 through 4 years of age, which perhaps drives the significant effectiveness

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for the 2 through 17-year olds to 29%. For influenza B, results pooled across all three seasons showed significant effectiveness in all age groups.

To summarize pooled VE for LAIV4 compared with no vaccine, VE across all three seasons for any influenza was not significant for ages 2 through 4, but was significant for the two older age groups. Consistent with previous findings for the 2013-2014 and 2015-2016 seasons, VE for H1N1pdm09 was significant only for the oldest age group 9 through 17 years of age. VE for H3N2 for 2014-2015 was not significant for any age group. VE for influenza B viruses pooled across all three seasons was significant for all age groups from 66% to 71% across the age range.

Concerning prior vaccination, which was posited as one of the possible explanations for differences in VE estimates between US and non-US studies, results of IIV and LAIV VE against H1N1pdm09 pooled from the 2013-2014 and 2015-2016 seasons were compared. They were stratified on vaccination status during the prior season as follows: unvaccinated, prior season receipt of IIV, and prior season receipt of LAIV. Differences in VE estimates persisted despite prior vaccination status, though there was overlap in the confidence intervals. From this information, it does not appear that prior vaccination explains the differences in VE results between IIV and LAIV. With greater numbers it might be possible to see something, but it is not seen here.

In terms of relative effectiveness comparing LAIV to IIV, for any influenza A or B for all three seasons, there was statistically significant advantage to IIV for the 2 through 4 and 5 through 8-year-old groups, as well as 2 through 17-year-olds, but not for the 9 through 17-year olds. For H1N1pdm09, the point estimates and confidence intervals for all age categories and subcategories favor IIV. For H3N2 for the 2014-2015 season, there was significant favoring for IIV to persons 2 through 4 years of age, but not for those 5 through 8 or 9 through 17 years of age. For influenza B, all of the point estimates favor LAIV but the confidence intervals all overlap 1 and, therefore, would not be considered statistically significant.

This analysis has some limitations. These include the fact that the power to detect differences related to prior vaccination was somewhat limited by the sample in the study in that prior vaccination status was available for only one prior year in some studies included. This makes things difficult as previous vaccination status could possibly have been the first dose relative to full vaccination status which for some children in the 6 months through 8-year age ranges requires 2 doses. Additionally, all LAIV during the study period was quadrivalent because these are data from 2013-2014 forward in the US, but both trivalent and quadrivalent IIVs were represented in the comparative analyses.

The SR/MA of studies reporting LAIV effectiveness for the 2010-2011 through 2016-2017 seasons was the result of considerable time and work by Jill Ferdinands, Lisa Grohskopf, Leslie Sokolow, Jessie Chung, Brendan Flannery, and Ivo Foppa. The investigators conducted a structured literature search with the aid of CDC's librarian of MEDLINE, EMBASE, CINAHL, Scopus, ClinicalTrials.gov, and Cochrane Register of Controlled Trials were searched for items indexed between January 1, 2011 and October 31, 2017. English language documents were sought that compiled data for the 2010-2011 through 2016-2017 influenza seasons. These are post-pandemic vaccines, given that they wanted not to include monovalent vaccines for this selection since valent and interference was one of the issues that had been raised at various times. Key terms included: influenza, influenza vaccine (or vaccination, shot, injection, spray, inoculation, mist), live attenuated influenza vaccine, LAIV, cold adapted influenza vaccine, CAIV, FluMist, case-control study, vaccine efficacy, vaccine effectiveness, relative vaccine

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efficacy, relative vaccine effectiveness. Reference lists of retrieved articles were reviewed to identify additional studies that might have been missed in the initial search, titles/abstracts were screened by 2 or more reviewers, and articles were reviewed by 2 or more reviewers.

Included study designs were RCT and observational studies of test-negative case-control and cohort designs. The study population of interest was children 2 through 17 years of age. Estimates were included with ages slightly outside this range, such as 2 through 19-year olds. However, studies with mixed populations predominantly of adults in which it was not possible to separate out the pediatric estimates were not included. The intervention of interest was ≥1 dose of LAIV administered intranasally. Comparators of interest included: unvaccinated groups, placebo, non-influenza vaccine, or intramuscular inactivated influenza vaccine. Outcomes of interest were laboratory-confirmed influenza outcomes (e.g., medically-attended outpatient influenza infection, influenza-associated hospitalizations), in which laboratory confirmation was accomplished by PCR and/or culture.

The quality of studies was evaluated using several tools. For randomized trials, the Cochrane risk of bias tool was used. For observational studies, the ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) was used, another Cochrane Collaboration tool. This tool guides assessment of risk of bias for observational studies in 7 different domains. Domain 1 is risk of bias due to confounding [Cochrane Collaboration, Sterne JAC et al, *BMJ* 2016;355:i4919]. Risk of Sparse Data Bias was also assessed using methods adapted from Greenland et all, which attempt to get at biases that can be induced when there are a lot of analyses and not many cases in a dataset [Adapted from Greenland S, et al, BMJ. 2016 Apr 27;352:i1981)].

In total, 1136 documents were retrieved. Through review, 18 were found to be suitable for inclusion. There were 15 test negative case-control studies, (9 from the US, 3 from the UK, 2 from Canada, and 1 from Germany). There was 1 prospective cohort study, which was from the US. There were 2 cluster randomized studies, both of which were from Canada. There were no individually randomized trials. There was a 19th paper, a retrospective cohort study from Finland, which did not meet testing modality criteria for inclusion. However, because it is an important paper in a number of ways, it was included in a sensitivity analysis to determine its effect on the pooled H1N1pdm09 VE results.

Because there were only 2 cluster randomized trials and because their results cannot be pooled with the observational studies because of their methodological differences, Dr. Grohskopf focused the remainder of this discussion on the 16 observational studies. In terms of the quality assessment for those studies, ROBINS-I was applied to each of these papers. No studies were felt to have low risk of bias and none were felt to have critical risk of bias. Most, 13, were assessed to be of moderate risk and 3 were assessed at serious risk. Sparse data bias risk was assessed for individual estimates within each paper. Most papers reported more than one estimate, so there are more than 16 estimates for sparse data bias. For the 45 estimates of VE of LAIV versus no vaccine for persons 2 through 17 years of age, 16 were assigned low risk, 2 moderate risk, and 21 serious risk. For 6, there was insufficient data to make a determination.

The papers that were assigned serious risk were assigned serious risk due to lack of adjustment in the model for a potential confounding variable of interest. When one approaches papers with this tool, one thinks of potential confounders that should be adjusted for or for which an explanation is given for why there is no adjustment for it. In this case, that was the reason. However, the estimates assigned serious risk most commonly received this designation because events per variable (EPV) were less than 10. This is basically a way of saying that the

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model adjusted for too many variables relative to the number of influenza cases that occurred in that stratum, which can lead to some instability of estimates.

In terms of the odds of influenza A or B virus infection among children receiving LAIV compared to unvaccinated children 2 through 17 years of age by precision, there were 15 papers. One thing that was noted here is that there seemed to be a trend for higher VE for less precise estimates. The pooled odds ratio for all the studies was 0.55 (95% CI 0.44%-0.68%). This translates into a pooled VE of 45% (95% CI 32%-56%), which would be statistically significant.

Regarding the odds of influenza A(H1N1)pdm09 virus infection among children receiving LAIV compared to unvaccinated children 2 through 17 years of age by precision, the pooled odds ratio is 0.75 (85% CI 0.6%-0.94%). This translates into a VE of 25% (95% CI 6%-40%), which is lower than the 45% for all influenza, but is statistically significant.

With respect to the odds of influenza A(H1N1)pdm09 virus infection among children receiving LAIV compared to unvaccinated children 2 through 17 years of age by location (US versus non-US), the estimates are the same as those for precision, but now there are 3 different pooled odds ratios: one for US, one for non-US, and one for all studies. The US estimate is not statistically significant as the pooled odds ratio crosses 1 and represents a VE of 17% with a confidence interval of -6% to 35%. The non-US estimate is significant, presenting a VE of 48% (95% CI 15%-68%). For 3 out of 4 of the non-US studies, the estimates were fairly imprecise, and the papers were also downgraded for study quality due to not adjusting or adjusting for too much. In this case, it was for not adjusting.

Breaking down the same H1N1 data down by formulation for LAIV3 versus LAIV4, the pooled VE for LAIV4 is 24% (95% CI 2%-41%) and is statistically significant. The pooled VE estimate for LAIV3 is not significant at 38% (95% CI -32%-71 %). But it should be pointed out that there are only three estimates here, and they are all fairly imprecise. This can be explained in part by the fact that studies were chosen from 2010 forward, which excluded many studies of LAIV3.

A sensitivity analysis was done in which the effect of inclusion of the Nohynek et al study from Finland on the pooled estimate of effectiveness of LAIV against H1N1pdm09 was examined. This study did not meet laboratory testing criteria for inclusion. It also differs from the included studies in that a very narrow age band is represented—it included children 2 years of age only. It did report an estimate for VE of LAIV against influenza A during the 2015-2016 season, which is presumed to be predominantly H1N1pdm09 based upon surveillance data regarding what was circulating for that season. It was also one of the estimates of LAIV VE from that season that were statistically significant. So, it was felt important to evaluate its effect on the pooled estimate of LAIV VE against H1N1pdm09. The estimate without Nohynek et al was 25% (95% CI 6%-40%). With the inclusion of Nohynek et al, the pooled estimate changed only slightly to 31% (95% CI 13%-46%).

For relative effectiveness estimates for the odds of influenza A(H1N1)pdm09 for children receiving LAIV versus children receiving IIV, there were 4 studies of which 3 were from the US and 1 was from Canada. Three seasons are represented. For this analysis, the relative odds of influenza A(H1N1)pdm09 with LAIV versus IIV was 2.52 (95% CI 1.58%-4.02%). This favors IIV. For influenza B virus infection, there were 5 studies of which 3 were US and 1 was Canada. This represented 4 seasons. In this case, the pooled odds ratio estimate fell on the side favoring LAIV, but the tail of the diamond crossed 1, so this would not be considered statistically significant. In terms of the odds of H3N2 for LAIV receipt compared with unvaccinated, there were 4 studies, all of which were in the US and represented 4 seasons. In this case, the pooled

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odds ratio not only crossed 1, but also sat right on 1, indicating no significant difference between the two vaccines.

Since every plot could not be presented, this table summarizes VE for LAIV versus unvaccinated children for different types and subtypes:

Influenza Type/Subtype	Number of Studies Included	Pooled OR (95% CI)	Pooled VE (95% CI)
Compared to unvaccinated children			
Influenza A or B	15	0.55 (0.44, 0.68)	45% (32, 56)
Influenza A(H1N1)pdm09	10	0.75 (0.60, 0.94)	25% (6, 40)
Influenza A(H3N2)	7	0.62 (0.44, 0.87)	38% (13, 56)
Influenza B (all lineages)	11	0.31 (0.21, 0.48)	69% (52, 79)

In these analyses, there was significant VE for LAIV compared with no vaccine for any influenza A or B, A(H1N1)pdm09, H3N2, and B. The lower VE was for A(H1N1)pdm09, and it should be noted that this was only significant when all US and non-US studies were considered. The estimate including only US studies was not significant.

This table summarizes the relative VE estimates for LAIV as compared with IIV:

Influenza Type/Subtype	Number of Studies Included	Pooled OR (95% CI)
Compared to children receiving IIV in test-negative case-control or cohort studies		
Influenza A or B	8	1.30 (0.87, 1.94)
Influenza A(H1N1)pdm09	4	2.52 (1.38, 4.02)
Influenza A(H3N2)	4	1.01 (0.73, 1.38)
Influenza B (all lineages)	5	0.55 (0.27, 1.12)
Compared to children receiving IIV in cluster randomized trials		
Influenza A or B	3 seasons/1 study	0.89 (0.44, 1.84)
Influenza B (all lineages)	3 seasons/1 study	0.39 (0.10, 1.58)

In these analyses, IIV was favored over LAIV for A(H1N1)pdm09. The bottom of the table summarizes results for Loeb et al, the cluster randomized trial that examined three seasons for which LAIV3 was used.

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In terms of summary points for the US-IPD and SR/MA analyses, looking at LAIV versus no vaccine for influenza A(H1N1)pdm09, there was significant effectiveness for children 9 through 17 years of age in the US-IPD analysis. In SR/MA, there was significant effectiveness only in the non-US studies. There were more imprecise estimates and higher risk of bias for 3/4 of these. No studies in this analysis are from the 2017-2018 season, so there are no estimates of effectiveness for LAIV containing A/Slovenia. In terms of LAIV versus IIV for influenza A(H1N1)pdm09, IIV was better for all age groups in the US-IPD and SR/MA analyses. For LAIV versus IIV for influenza B, the point estimate favors LAIV for both analyses but is not significantly different. For LAIV versus IIV for A(H3N2), IIV was better for children 2 through 4 years of age in the US-IPD analysis. There was no significant difference in other age groups or in the SR/MA analysis.

Regarding limitations for both of these analyses, the B lineages are not analyzed separately. Relatively few estimates report lineage-specific B VE. LAIV4 is compared against a variety of different products, in these cases all IIVs. In general, the relative proportions of IIV3 and IIV4 are not known. In addition, many different IIV formulations are available and little is known about how well they work relative to one another. In general, no US VE data are available for LAIV4 since 2015-2016. VE for the current LAIV4 formulation containing A/Slovenia against A(H1N1)pdm09 viruses is unknown.

To put this work into context in terms of what is new since 2016 and what remains unknown, the putative cause for the poor efficacy of LAIV against H1N1pdm09 in 2013-2014 and 2015-2016 was postulated to be poor replicative fitness of that virus. LAIV4 has contained the new A/Slovenia H1N1pdm09-like virus since the 2017-2018 season. It has not been used a great deal in the US because while it is approved, with no recommendation this is to be expected. However, it was used in the UK, Finland, and Canada. Unfortunately, the current season has been H3N2-predominant thus far. Therefore, there are no H1N1pdm09 VE estimates. Recent shedding and immunogenicity data for the new H1N1pdm09-like virus are encouraging. However, the effectiveness of this formulation against H1N1pdm09 is not known and is likely to remain unknown until the next H1N1-predominant season assuming adequate uptake of vaccine. It is not possible to predict when this will occur.

While variability in VE estimates is anticipated to occur, VE varies with many factors such as host factors (age, health status), influenza type/subtype, and different seasons. Moreover, it is possible that individual vaccines vary in VE. Many influenza vaccines are licensed in the US, with a current total of 13 products. Estimates of effectiveness of individual products may vary, even within a given vaccine category (e.g., among different IIVs). However, in many instances comparative data for different individual products are not available. There are some exceptions, but in general this is not something that is seen. Recommendations for other individual influenza vaccines have not generally been based upon comparative effectiveness data, with the exception of preferential recommendations.

In conclusion, since 2013-2014, a plausible root cause of the poor effectiveness of LAIV4 against H1N1pdm09 has been identified. There is encouraging shedding and immunogenicity evidence that the problem might be addressed with new H1N1pdm09 virus, A/Slovenia. An important caveat is that whether this problem is solved definitively will not be known until there is an effectiveness estimate against H1N1pdm09, and it is unknown when this will occur. New LAIV vaccine virus selection processes are to be applied going forward. Combined analyses indicate that LAIV4 is effective compared with no vaccination against all influenza and influenza B among persons 2 through 17 years of age. IIV was better in these analyses against H1N1pdm09. There is no clear difference in performance of LAIV versus IIV for H3N2. A

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decision to recommend, or not, individual influenza vaccines generally is not based on effectiveness comparisons to other products.

WG Considerations and Proposed Recommendations

Lisa Grohskopf, MD, MPH
National Center for Immunization and Respiratory Diseases
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Dr. Grohskopf reported that there was a great diversity of sentiment in the WG discussions of the LAIV issue, with the WG having heard a lot of data related to LAIV over the last four months in addition to the data heard over the last couple of years. While there is a lot of diversity of opinion, one thing that folks tend to agree about is that influenza is a problem for the pediatric age population. It is an important cause of morbidity and mortality in children. Pediatric deaths associated with laboratory-confirmed influenza has been a reportable condition since 2004. Pediatric influenza deaths have ranged annually from a low of 37 to 171 during non-pandemic seasons since 2004-2005. During the pandemic period, which was somewhat longer, 358 deaths occurred. It is also an important cause of hospitalizations among children as the data from *FluView Interactive* summarize in the following table:

	Hospitalizations/100,000 persons-years	
Season	**0-4 Years**	**5-17 Years**
2013-2014	47.3	9.4
2014-2015	57.3	16.6
2015-2016	42.5	9.7
2016-2017	40.8	15.5

There has been some discussion of benefits versus harms. It is generally agreed that the benefit of the current formulation of LAIV4 against H1N1pdm09-like viruses is not known. There is no effectiveness estimate yet, and it is not known in practical terms when this will occur. Data suggest good effectiveness of LAIV4 against influenza B viruses, and that LAIV4 is comparable to IIV against H3N2. No new intrinsic safety concerns were raised for LAIV4 at the time that the recommendation for its use was removed in June 2016. However, it is recognized that there is potential for harm if the new formulation of LAIV4 is recommended and used and is not effective.

In terms of how the target population views the balance of the benefits and risks, this is somewhat difficult to address in a quantitative manner. However, the WG wanted to share that there have been some communications in the form of published and unpublished letters that have expressed concern that the lack of a recommendation for LAIV may be detrimental in some settings such as school-based clinics. Another point of discussion was that maintaining consumer confidence in influenza vaccines is important in the setting of low VE estimates overall.

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Regarding the WG's perspective on the risk of recommending LAIV without effectiveness data against H1N1 with the new strain, a plausible root cause of reduced effectiveness against H1N1pdm09 was identified (e.g., replicative fitness of H1N1 contained in the vaccine). However, some members expressed the view that other factors may have contributed even if they were not the root cause, such as interference due to the addition of the fourth virus into the vaccine. There are also varying viewpoints regarding the promise of the shedding and immunogenicity data presented earlier, which some viewed as encouraging and about which others expressed concern in terms of the size of the study and problems with using immunogenicity and shedding to gauge the effectiveness of LAIV. Concern was expressed that if the issue is not resolved, there potentially could be more influenza cases. Also expressed was an understanding that influenza VE varies by season for all vaccines, and that initial licensure of some newer vaccines, particularly some more recent quadrivalent vaccines and vaccines that had licensure expanded to different age groups, has been based solely upon immunogenicity data in some cases. Some make the argument that the risk in that respect could be viewed as similar to introduction of a new influenza vaccine product.

In terms of the WG's perspective on the risk that if LAIV is not recommended in the US during the 2018-2019 or some future season, it may not return to market. No one knows what is going to happen, but in view of the fact that it is not clear when effectiveness data will be obtained and that it is difficult to conduct a trial for a vaccine that does not have a recommendation, this is something that comes to mind. There was not any expression that this should be something that drives the decision. However, several ideas raised around this topic were raised. For example, LAIV remains a licensed product by FDA in the US. Another idea that was brought to light through these discussions was the challenge of holding all manufacturers to the same standards for effectiveness of influenza vaccines. For example, the effectiveness of LAIV has been examined specifically each season for the last several seasons. It is a unique product and is the only one in its class that is licensed in the US. For most other individual influenza vaccines, recommendations have not been based upon annual assessment of product-specific VE.

Whether influenza vaccine coverage has been impacted by not recommending LAIV was expressed as a concern when the initial recommendation was made. In October 2017, Dr. Carla Black of CDC's Immunization Services Division (ISD) presented the 2016-2017 pediatric coverage summary data. These data indicated that compared to 2015-2015, national vaccination coverage remained stable during the 2016-2017 influenza season. It is believed that local variation is likely, and there have been reports of reduced coverage in some areas with strong school-based programs that relied on LAIV. There also have been other anecdotal reports from other areas where there was not a noticeable decrement in coverage. Another point to raise is that while national coverage did not decrease, it also did not increase and remains below goal for coverage in the pediatric age group. Coverage was 2% lower in children 5 through 12 years of age, which was a small but statistically significant difference.

This is the table that Dr. Black presented in October 2017 of 2016-2017 coverage reflecting the small but statistically significant decrease among the 5 through 12-year olds and small but statistically significant increase among 13 through 17-year olds, both on the order of about 2%:

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Influenza Vaccination Coverage by Age Group, Children 6 Months–17 Years, NIS-Flu, United States, 2016–17 Season

Age Group	Unweighted Sample Size	%* ±95% CI†	Difference from the 2015–16 Season ±95% CI
6 months–17 years	143,169	**59.0** ± 0.7	-0.3 ± 1.1
6 months–4 years	44,094	**70.0** ± 1.3	0.0 ± 1.9
6–23 months	16,374	**76.3** ± 2.0	1.0 ± 2.6
2–4 years	27,720	**66.2** ± 1.6	-0.6 ± 2.4
5–17 years	99,075	**55.6** ± 0.8	-0.3 ± 1.2
5–12 years	63,130	**59.9** ± 1.0	**-1.9 ± 1.6‡**
13–17 years	35,945	**48.8** ± 1.3	**2.0 ± 1.9‡**

* Percentage vaccinated.
† Confidence interval half-widths.
‡ Statistically significant difference between the 2016–17 season and the 2015–16 season by t-test (P<0.05).

There was not complete agreement among the WG members. Most felt that the issue should be discussed with ACIP. The opinions were somewhat more diverse regarding whether to vote. The idea was also raised that a recommendation would need to acknowledge the current lack of effectiveness data for the current LAIV4 against H1N1pdm09-like viruses. This table summarizes the WG's considerations and summary just discussed regarding whether LAIV should be recommended for the 2018-2019 season:

Policy Question: Should LAIV be recommended for the 2018-19 season?

Factor	WG Interpretation
Problem	• Influenza is an important source of morbidity and mortality among children.
Benefits and harms	• Benefit of LAIV for H3N2 comparable to IIV. • Data suggest good effectiveness for influenza B compared with no vaccine. • Limited immunogenicity and shedding data suggest new H1N1pdm09 virus in LAIV4 may promote improved effectiveness (however, this is not yet known). • No vaccine safety concerns at the time LAIV vaccine was not recommended by ACIP. • Potential for harm if vaccine ineffective.
Values	• Several papers and unpublished and published letters, indicate support for availability of a non-injectable formulation of influenza vaccine.
Acceptability	• Varying levels of accepting risk of vaccine not being as effective against H1N1 and potential detriment to confidence in influenza vaccines.
Implementation	• While national coverage appears not to have been impacted by lack of LAIV recommendation, LAIV is an important option for school-based clinics and may contribute to efforts to increase vaccination coverage.
Summary	• There was not complete agreement on the WG. • Most felt the issue should be discussed at ACIP. • A recommendation would need to acknowledge lack of effectiveness data for current LAIV4 against H1N1pdm09 like viruses.

The following language was proposed for a vote:

> *For the 2018-2019 season, LAIV4 is recommended as an option for influenza vaccination for persons for whom it is otherwise appropriate.*

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Discussion Points

Dr. Romero noted that although ACIP is mandated to assess immunization in the US, the recommendations issued by ACIP are viewed very seriously and have impact around the world. There was a publication in the March 1, 2018 issue of *Clinical Infectious Disease (CID)* by Sanchez from Maryland who commented about the possibility of the impact of a vote by ACIP on the availability of LAIV outside of the US, where some countries use it as a primary vaccine.

It seemed to Dr. Hunter that if he was a clinician with a patient in front of him during an influenza season that the guidance he would need about whether to give LAIV is that if the influenza season is predominantly H1N1, he may consider IIV over the LAIV. If it is currently H3N2 or B, then it does not matter which one he gives.

Dr. Messonnier said she thought the issue was that optimally, patients would be vaccinated before the influenza season begins. Therefore, there will not be the luxury of making a clinical decision based on what is circulating, nor can it be predicted at any point in a season what is going to circulate next. In addition, clinicians have to make decisions about what vaccines to buy long before a patient is in the office. Most clinicians generally stock one type of vaccine and may not have multiple options to offer.

Dr. Frey asked how pediatricians interpret the statement, “LAIV is recommended; however, providers should be aware that the effectiveness is unknown” and if it would make them less likely to use LAIV.

Dr. Bennett clarified that this statement came from the background information rather than the proposed recommendation.

Dr. Brady (AAP) confirmed that many pediatricians have already submitted their orders, so they have not ordered LAIV. Also relevant is that the VFC has not purchased any LAIV, which means that if LAIV is reinstated, a portion of the population would be denied access to the vaccine. That reflects one of the potential harms that could occur, so they must understand that this could create a disparity.

Dr. Messonnier pointed out that the timing is complicated when ACIP makes its recommendations and when the contracting process occurs for influenza vaccines. It is true that they value entirely that the provider community is going to have to implement these recommendations, and making things as simple as possible for that community. In terms of the iterations of what may happen if ACIP were to make a recommendation during this session, it is true that CDC has already completed its VFC procurement process for this year. That means that the VFC contracts are complete. It is possible, and CDC is considering if there is enough of a justification, to reconsider whether additional contracting might be done for this year. That is not CDC’s typical approach, but there may be extenuating circumstances, so they will consider that. If there is not a VFC contract, providers will have a choice. For the upcoming season, providers might choose to harmonize their VFC and non-VFC populations and therefore not purchase LAIV and have only IIV. Providers also might choose to offer LAIV as an option for some of their patients and not for others. By a year from now, if LAIV is re-recommended, that situation would be resolved. Many providers have already completed their purchasing in the private sector for next year. It is very unclear what uptake of this vaccine would be if it was recommended during this meeting. There is a potential for a gap over the next year between private and public use of this vaccine.

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Dr. Lee said she was struggling with this decision. Partly, she was trying put this into the broader context of ACIP's decision-making as a body and whether they are holding this particular vaccine to a higher standard than any of the others. She bet if they looked closely at any individual vaccine they would see season-to-season variability. If they were to try to chase that down, they potentially could compromise the supply. There are never going to be perfect data. With that in mind, she wondered whether they should be holding this vaccine to a different standard. She acknowledged and is worried about potential harm, particularly if they are concerned about pediatric deaths. That does weigh heavily on her. On the other hand, akin to prior decision-making, the proposed language was just making it an option and did not go as far as stating that there should be a preference. She might have a preference about what to recommend, but she was struggling with the language not being preferential and whether there is a second step that occurs post that option.

From the perspective of someone who runs the VFC program for one of the states, Dr. Moore said that they would consider this in the context of vaccine choice. The recommendation is talking about making LAIV equivalent to a lot of other options of brands. While the VFC program strives to provide participating practitioners with as many options as possible, it is not always possible to provide every option for every product. The fact that LAIV might not be readily available in the VFC program this year would not be considered a severe disparity in access, because every child will have access to influenza vaccines. It is just a matter of which brands are available at what times. Some states just provide their clinicians with vaccines and they do not even know which brand they are going to get. The clinicians in the VFC program get the first available product regardless of brand. There are a lot of ways states handle this, and whether they had access to LAIV would never be considered a disparity because they will have access to other options.

Like Dr. Lee, Dr. Bernstein said he was struggling with this and he had a number of concerns. First, he did not feel that there was a sense of urgency to reinstate LAIV4 since there is an alternative IIV. He also felt that shedding was not nearly as indicative of protection as VE as heard before. If influenza vaccine coverage rates had gone down without the availability of LAIV4, he would feel more strongly that it needs to be reintroduced. But actually, the rates have not been notably impacted by having only injectable products available. He was concerned about whether it would be interpreted that ACIP is compromising its interpretation of the science by accepting shedding data that compares favorably to pre-pandemic studies as opposed to actually having ongoing VE data. In some sense, he felt like they might be holding it to a higher standard as suggested by Dr. Lee. On the flipside, they could not ignore the fact that the VE of LAIV4 against H1N1 for two seasons was not good. He thought they needed to keep that in mind. He also emphasized the fact that if they reinstated LAIV4 for 2018-2019, the messaging that would surround such a decision being made without using the gold standard of VE is likely to be very difficult for the public and providers to understand. In addition, the part that really worried him the most was that if ACIP reinstated LAIV4 without knowing its VE during an H1N1 season and then perhaps there is an H1N1 season and it results in increased morbidity and mortality associated with that, it is likely to undermine administration of influenza vaccine for the public, potentially lowering all coverage rates and negatively impacting the country's overall influenza vaccine program. Therefore, he had mixed emotions about this. He thinks ACIP wants to protect as many people as possible, and as a pediatrician, especially children.

Ms. Pellegrini said that in contrast to Dr. Bernstein, she had very few mixed emotions about this. There are other cases in which vaccines are on the market and one is known to be more effective than another, such as zoster. Based on the evidence, one zoster vaccine is known to be much better than the other, but they did not take the other one off of the market. She

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thought the evidence was pretty clear that this vaccine is better than not being vaccinated, and there are children who would not be vaccinated without this option. She suggested putting it out there as an option, giving parents and clinicians the chance to discuss it and figure out what they want to give their children.

Dr. Belongia supported Ms. Pellegrini's comments indicated that he is also in favor of making LAIV an option. He recognized that this was not an easy decision, and they are always challenged to make difficult decisions with incomplete data. This is a prime example of that. Given what is known, he thought the proposed language was a reasonable approach to take. They always have to make decisions based on the best science available at the time. There was more science available to them now than two years ago. He also pointed out that they would not know any of this if not for the Flu VE Network that has only been in existence for about the past 14 years. Prior to that, it was all based on immunogenicity and pre-licensure efficacy studies for the most part. It is a credit to CDC and a value to the American public that this network is able to find this sort of issue. In response to having found that, the manufacturer made a good faith effort to try to understand the root causes of what likely is occurring. If they consider that strain changes are made all of the time based on immunogenicity, this vaccine is a little different insofar as they cannot rely just on immunogenicity because it is a live vaccine. He thought looking at the overall body of evidence based on the *in vitro* replication studies in epithelial cells, there are challenge studies with wild type viruses in ferrets in addition to the pediatric shedding and immunogenicity study. He completely agreed that the shedding and immunogenicity study did not directly transfer to clinical effectiveness and this will not be known until there is an H1N1 season. But looking at the whole body of evidence, they have made a reasonable case, certainly as much as would have been expected for any other vaccine short of running an actual clinical efficacy trial. It looks like the manufacturer found the source of the problem, and it is reasonable to at least allow that to go forward and collect the data to support whether the A/Slovenia strain will provide comparable protection to inactivated vaccines. He also pointed out that the overall VE in the pooled analysis for LAIV was 45% against all influenza strains. The pooled VE for H1N1 was 25%, which is the same as what is being observed currently for inactivated vaccines against H3N2 this season in all ages. It is very tricky when looking at individual seasons, individual subtypes, individual age groups, and different vaccine products. Given the case that has been made with the evidence presented and the proposed language is telling practitioners the best science available at this time, recognizing that it is not known for sure.

Dr. Bennett requested that Dr. Sun comment on FDA's plans for going forward.

Dr. Sun (FDA) indicated that he had a prepared statement as part of this discussion stating, "The FDA licensed FluMist® in 2003. To date, it is the only intranasal influenza vaccine approved in the US for prevention of influenza due to influenza A and B viruses. The approval was based on randomized controlled clinical trials demonstrating safety and effectiveness. The FDA acknowledges that recent observational studies raised concerns about decreased effectiveness of FluMist® Quadrivalent, primarily during seasons in which the H1N1pmd09 strain predominated in the US. During that time, FluMist® has continued to show expected effectiveness against H3N2 and B strains based on similarly designed observational studies both in the US and abroad. Predicting which strains will predominate in future influenza seasons has been challenging historically. Consequently, the licensure of influenza vaccines has been based on prevention of all influenza caused by circulating A and B strains as demonstrated by pivotal prospective randomized controlled clinical trials. The variability of influenza effectiveness from year-to-year is well-recognized and unpredictable. Previously, FluMist® has demonstrated increased effectiveness in young children in some years. Given that

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FluMist® Quadrivalent is a live attenuated influenza vaccine, FDA requested MedImmune to conduct prospective observational post-marketing studies at the time of approval in 2012, the ICICLE study, to assess the vaccine effectiveness in 2 to 17-year olds in the US over the course of 4 years. The study was designed to assess vaccine effectiveness over 4 influenza seasons. Although the fourth year of the study could not be completed due to insufficient use, the first three years' data have corroborated the other observational studies' results and meta-analyses supporting continued overall vaccine effectiveness against influenza. FDA maintains that based on the totality of the pre- and post-licensure clinical and manufacturer data, the benefits of FluMist® Quadrivalent continue to outweigh potential risks. FDA has worked closely with MedImmune to conduct comprehensive root cause analyses of the lower than expected effectiveness against the H1N1pmd09 strain, including new methods and assays, for example, measuring viral replicative fitness and other unique characteristics of the H1N1 pandemic strain. FDA will review and evaluate these new manufacturing and characterization data for each new strain that is incorporated into future vaccines and these additions and improvements in manufacturing and assays to better characterize the H1N1 component, and will be submitted as supplements to the product license and incorporated in future manufacture of the vaccine. FDA will continue to collaborate with CDC and ACIP to ensure continued safety, effectiveness, and optimal use of this and all licensed influenza vaccines."

Dr. Walter made a motion that for the 2018-2019 season, LAIV is recommended as an option for influenza vaccination for persons for whom it is otherwise appropriate. Dr. Hunter seconded the motion.

Dr. Neuzil (IDSA) pointed out that they had all acknowledged the inherent variability of influenza and she agreed completely with Dr. Belongia that this emphasizes the value and importance of surveillance systems. Those systems are also known to have limitations, and she did not think they were ever designed to direct policy on a year-to-year basis and certain subgroups for some of the reasons they had heard predominantly related to power. She would say that there is another limitation that had not been considered, which is that the main outcome is all-severity influenza and generally it is mild disease. She thought they had to be careful in extrapolating that to morbidity and mortality and assume a vaccine might not actually be effective against more severe disease. It is the information they have, but they need to acknowledge that limitation. They were not talking about transmission or other outcomes. They were simply talking about all-severity influenza. She also thought they should be very careful with the use of the word "harm." Influenza vaccines have been studied extensively. They have a very strong safety record. If an inactivated vaccine is better in one year compared to another product in a certain age group for a certain strain, or another one is in a different year, she does not consider that to be harm. She would like them to be more precise with their language and be sure the public understands that these are extremely safe vaccines.

Dr. Atmar responded to a couple of issues Dr. Bernstein raised that had not yet been addressed. He raised the same questions about voting for this kind of recommendation a few meetings ago without VE data. His thinking has evolved since then, both through the WG discussions and discussions with others. At least in part, the reason was that some of the data presented during this session, including from the manufacturer, the shedding data really is not supposed to be a correlate of protection. The manufacturer was asking whether there was evidence of interference or if the H1N1 was less replicatively fit. Dr. Atmar interpreted the data to mean that lower fitness leads to susceptibility to poor immunogenicity, and as a result of other viruses being present in the vaccine, there is interference that takes place and so it has not worked. They identified that as an issue and developed assays to try to prevent that from happening in the future. In fact, their shedding study shows that back when H1N1 worked as a

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component of the trivalent vaccine, similar findings were seen. That is reassuring. Because of that and some of the meta-analyses and systemic review information presented, Dr. Atmar thought it was reasonable to vote for this type of recommendation.

Dr. Stephens referred to the last sentence on Dr. Grohskopf's slide with the blue summary table stating that "A recommendation would need to acknowledge lack of effectiveness data for current LAIV4 against H1N1pdm09 like viruses" as he was confused about what they were doing with this vote.

Dr. Grohskopf clarified that this was not part of the recommendation, but merely a summarization of what went into the proposed language.

Dr. Cohn requested that Dr. Grohskopf show the language that would appear as part of the guidance. She clarified that the vote pertained to whether ACIP would consider recommending LAIV for the next season. The language reading "Although the effectiveness of the new formulation of LAIV4 against H1N1pdm09 viruses is not yet known, available data suggests that the new LAIV4 containing A/Slovenia may provide protection more comparable to that observed with pre-2009 influenza vaccines" would be incorporated into a statement about the vaccine recommendation if the vote is approved. A rationale is always written for the CDC guidance around the recommendation.

Dr. Frey clarified that she was struggling not with whether to approve moving forward with LAIV, but the language she was reading in the handout as she could not reconcile the language.

Dr. Kimberlin (AAP Red Book) indicated that the AAP would not have a full response on this until the data are considered during its spring meeting, which will occur in March. In response to hearing that there would be an ACIP vote, they did receive a couple of calls including one late the previous night to try to pull together their thoughts on this as they currently stood, with the caveat that they will have further deliberations. At the current time, a number of concerns were raised among the AAP and Committee on Infectious Diseases. The meta-analysis that they heard earlier crosses too many different formulations of LAIV3 and LAIV4. It is too blended in other words for what they are seeing to pull out as a strong consideration that LAIV4 has the kind of effectiveness that they are hoping it may have. They just do not see it right now. In addition, a comment was made about influenza vaccine uptake not being hurt by lack of LAIV. There is another product that has not been shown to have the questions surrounding LAIV. The feeling among the discussions to date regards what the urgency is with that. Dr. Brady raised disparity concerns. The number of children assessed in the study MedImmune presented was 67 for the group receiving the new formulation of LAIV4, which is a very small number and does not include effectiveness. Dr. Kimberlin noted that the product was de-recommended because of problems with effectiveness, which has not been resolved to make another comment about whether it should be used in the future. Additional considerations from the AAP are that shedding does not necessarily correlate with efficacy or effectiveness. There are concerns about messaging as well. Under the benefits and harms section on the summary table stating, "potential for harm if vaccine is ineffective" and recognizing the concern with the word "harms," if there is an H1N1 year and this vaccine has been recommended again for use and does not work, that is a sobering sentence for him.

Dr. Lee commented that she thought they were struggling because for the first time they were starting to think about comparative effectiveness as opposed to effectiveness. It used to be that they were always comparing to placebos. To her, this question was really about effectiveness. Is it better than nothing? The answer is that it is better than nothing. Dr. Bernstein raised good

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questions about whether it could augment overall population protection. At this point, she would consider whether it was effective compared to placebo. She proposed an amendment regarding a preferential vote. She wondered whether the group would consider going further in addition to this vote, amending it by stating that there is a preference for IIV over LAIV in the coming season as a consideration.

Dr. Bennett said she did not think that would be an amendment to the proposed language, and instead thought it should be a separate motion.

Dr. Weber (SHEA) noted that in the past there was a statement about LAIV and he quoted directly from the CDC recommendations, “Persons who care for severely immunosuppressed persons who require a protective environment should not receive LAIV, or should avoid contact with such persons for 7 days after receipt, given the theoretic risk for transmission of LAIV.” He asked whether that would be included in the proposed statement and, if so, based on the data seen that children were still exerting at 7 days, whether there would be a recommendation that children who receive LAIV be prohibited from contact in addition to healthcare personnel for longer than 7 days.

Dr. Grohskopf responded that the shedding data for adults tends to be much shorter. Shedding is most pronounced among children with the first dose, and in some previous studies has gone on for longer than a week. She did not believe that was new information, but it is certainly something they can discuss.

Dr. Brady (AAP Red Book) observed that the language shown stated “LAIV is recommended as an option.” Currently, it is an option because it is FDA licensed. In the past two seasons, ACIP specifically said not to use LAIV. Now they were taking a more positive approach by saying it is recommended as an option. He suggested stating, “LAIV is an option for influenza” and moving statement about not using it. By using the term “recommended” would give it more strength and may help to balance the messaging. Again, they will have to explain to people why they are recommending it as an option when it has always been an option.

Dr. Bennet clarified that it was not an option according to ACIP recommendations. She also noted that Dr. Brady’s suggested language would be an amendment to the proposed language.

Dr. Belongia thought Dr. Brady made a good point. Using the term “recommended” could be a source of confusion. Perhaps instead it could state something like “Immunization providers may choose to use any age-appropriate licensed influenza vaccine, including LAIV” that would accomplish the same thing without making it a recommendation.

Dr. Messonnier requested that the language of the amendment be clarified on the screen.

Dr. Grohskopf inquired as to whether there was a necessity in the language that the word “recommended” be used.

Dr. Cohn clarified that there was not such a requirement. While this is an ACIP recommendation, the word “recommendation” does not have to be included.

Dr. Bernstein asked how they would evaluate the use of this vaccine next season in terms of what measures of success would be used to evaluate that this was the right decision.

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Dr. Belongia replied that if the vaccine is allowed to be used, presumably there will be some use of it next season, though not as much as during a normal season because of the issues discussed pertaining to the timing. However, the US Flu VE Network enrolls thousands of people and many children every winter. In a normal season before this decision was made almost two years ago, there were enough enrollments to get a good estimate of LAIV effectiveness. This could be done again, if not next year, if uptake continues to increase presumably the year after that. Of course, it all depends upon whether there is enough H1N1 circulating. If there is not, then they will not learn anything about H1N1.

Dr. Netoskie (AHIP) expressed confusion about the recommendation without the word "recommended" in terms of payment and coverage under the Affordable Care Act (ACA).

Dr. Cohn clarified that it would be included as an option on the schedule.

Dr. Bennett added that anything included on schedule is covered under the ACA regulations.

Dr. Grohskopf noted that they have included a statement early on in the recommendations over the last several seasons that says, "a licensed age-appropriate vaccine should be used."

Dr. Stephens asked whether Dr. Lee was making a motion about a preferential recommendation.

Dr. Bennett clarified that Dr. Lee's motion would be made separately after they finished discussing and voting upon the originally proposed language and amendment to that language.

Dr. Messonnier said she was not sure which way the language was going, and she felt like there were so many alternatives going around, it was hard to know what they were saying. CDC and its implementation partners have to figure out how to communicate ACIP's guidance. She was struggling to know how to communicate some of the language as opposed to the second recommendation by Dr. Belongia.

Motion/Vote #1: Amendment to the Proposed Language

Dr. Walter made a motion to approve, and Dr. Hunter seconded, the proposed recommendation language as presented: *For the 2018-2019 season, LAIV is recommended as an option for influenza vaccination for persons for whom it is otherwise appropriate.*

Based on the discussion, the motion was amended to read: *For the 2018-2019 season, immunization providers may choose to administer any licensed, age-appropriate, influenza vaccine (including LAIV, IIV, and RIV). LAIV4 is an option for influenza vaccination for persons for whom it is otherwise appropriate.*

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

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

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Dr. Moore said she was trying to recall the way that they used to have the wording before they made the change with LAIV. It stated to choose one that was age-appropriate and licensed.

Ms. Stinchfield (NAPNAP) indicated that at Children's Minnesota where she works, they have 12 ambulatory clinics with about 50,000 primary care patients. Their clinicians will like this as much as they like optional vaccine recommendations that they make. It is going to be difficult. Some of their clinics will have 80% VFC children, some are half and half, and some are the opposite. They are committed to the same standard of care for their children regardless of their ability to pay or not pay. When she heard that LAIV would not be a part of the VFC, that is a game-changer. She requested that they have a group assess the financing and potential VFC finance aspects, and whether they can shift to borrow from private to cover VFC children. Disparities will be a problem in the field. In addition, many people talked about messaging and vaccine efficacy messaging during this session. They have been quoting Australian numbers all year long and just had the US numbers. Everyone is quite confused about this, and she would like to see more committee members working with the CDC communications department on what the messages are about influenza.

Dr. Messonnier clarified that the VFC issue was a short-term one for this year. If ACIP were to make this recommendation, a year from now, CDC would have VFC contracts for LAIV. For the upcoming season, because the procurement process is complete, there would be a short-term potential for there being a choice.

Dr. O'Leary (PIDS) said he did not want the issue of just one season for VFC to be downplayed, given that this is a big deal for pediatricians across the country in terms of having to decide which insurance patients have and which vaccines they can receive. Just to reiterate, within PIDS it was clear that this is a difficult decision for ACIP. But the public perception issue is a big problem because if they are wrong and effectiveness is similar to prior seasons where there was essentially no effectiveness and it is a bad H1N1 year, that is a potential disaster.

Regarding the VFC question, Dr. Moore said that because this is just an option as an influenza vaccine, brand choice is not necessarily up to the clinicians who receive VFC products. This would not be considered as any kind of disparity because they have other brands available. It is always the case in the VFC program that they must choose the inventory that is being provided from the VFC program. Borrowing is not permitted between private and VFC stocks, except under extreme circumstances where that can be assured to be reconciled, to which this would not apply. Other states sometimes send whatever product is available first and clinicians use that. VFC programs in states would adapt to whatever CDC contracts are available, and this would be addressed with providers.

Dr. Brady (AAP) suggested that the second sentence was not needed because it was listed above, and it brings more attention.

Dr. Bennett clarified that they just voted on the wording, so they would not be able to make changes at this point.

Dr. Cohn added that they could clarify some of this afterward so long as it does not change the intent of the recommendation.

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Public Comment

Del Bigtree
Informed Consent Action Network

I was previously a producer on the day-time talk show "The Doctors" for 6 years where I won an Emmy Award. I think what has been missed in this discussion is public perception. It is a very difficult discussion to have, watching it is very informative, and no one would want to be having to make the choice you'll be making. What I want to point out is that removing FluMist® was a big story in this country. Unlike other choices you make, the public is very aware that it was taken away. So, when you put it back, the media is going to be very interested in why. When you have to discuss why as the CDC, your response looks very flimsy to me that, "Well, we exchanged the H1N1, and though there is no proof of its effectiveness, we're going to go ahead and recommend it." We're talking about a time where the question of influenza vaccines' effectiveness *period* is a massive question in this country. Everyone is hoping to see a better vaccine and more effective vaccine—maybe a universal vaccine. When you find out ACIP has just approved an old vaccine that may still be ineffective, or may be even worse than ineffective, or what is currently being used, I really question whether you're going to do serious damage to the perception of ACIP and what you're doing here, and the CDC and what it decides to, you know, approve and not approve. The country is looking for a better vaccine, not one that may even possibly be less effective than the one we're using now. Thank you very much.

Andrea Woodruff
Concerned Parent

I heard a great question earlier with the H1N1 strain of the vaccinated versus unvaccinated. It would be nice if you could routinely publish all strains for vaccinated or unvaccinated, especially of pediatric deaths. I would like to know why they are choosing not to be vaccinated. Is it because they don't think it's effective, or did they have an egg allergy, did they have an adverse reaction? That type of information could help me as a parent make better decisions.

A letter was submitted by Almeda County supporting LAIV for school-based clinics that was included in the October 2017 ACIP meeting minutes.

Motion/Vote #2: Amended Language

Based on the discussion and vote, the motion to reintroduce LAIV was amended to read: *For the 2018-2019 season, immunization providers may choose to administer any licensed, age-appropriate, influenza vaccine (including LAIV, IIV, and RIV). LAIV4 is an option for influenza vaccination for persons for whom it is otherwise appropriate.*

The motion on the amended recommendation language carried with 12 affirmative votes, 2 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

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Dr. Bernstein explained that he voted “no” because he was worried that, using a baseball metaphor, they have had two strikes and the 2018-2019 season would be a third strike. Dr. Stephens indicated that he voted “no” because he was concerned about the message this will send.

Dr. Lee moved to recommend that ACIP preferentially recommend IIV or RIV age-appropriate vaccine over LAIV. Dr. Stephens seconded the motion.

Dr. Neuzil (IDSA) urged ACIP members to be very cautious, recalling the H3N2 data shown earlier in the day. If there is really no reason to make a preferential recommendation, she thinks confuses the public if they change recommendations too frequently.

Dr. Belongia echoed that sentiment. For example, when ACIP made a preferential recommendation for zoster vaccine, there was very strong evidence from clinical trials of superiority of that vaccine. This situation is not the same. They hope that the new A/Slovenia strain has fixed the root cause of this. They do not know this for sure, but the uncertainty in his view does not justify a preferential recommendation, given that variation is seen from season-to season and from product-to-product. ACIP does not normally make product-to-product comparisons. If they did that, it would essentially be interpreted as really no change functionally. Therefore, he would not be in favor of a preferential recommendation.

Dr. Walter agreed for the same reasons, given the season-to-season variability and unpredictability of influenza and influenza vaccines, he would not opt for a preference.

Dr. Szilagyi emphasized that a preference to him requires very clear data of the actual vaccine. There is uncertainty, and he did not think they had enough data for a preference.

Ms. Pellegrini said she thought from a messaging point of view, it would make a lot of sense for them to cautiously wade back in with LAIV. They are not ready necessarily to give it their full-fledged endorsement, but are willing to let it be an option in order to collect data over the next couple of years even though there may not be an H1N1 season.

Dr. Hunter suggested that it might make more sense to state, “LAIV is not routinely recommended, but should be available for individual clinical decision-making.”

Dr. Bennett clarified that the vote on the recommendation had already been completed, and this is a different motion to make a preferential recommendation for IIV over LAIV.

Dr. Frey said if they did not want people to use LAIV, she thought they should have voted against it.

Dr. Riley said part of the reason she voted “yes” in the first place was because she was thinking in terms of LAIV versus nothing. She thought they should give people as many options as possible to be vaccinated, because being vaccinated is better than not being vaccinated. To now take the next step and have a preference over which one those vaccines seemed to be taking a step for which she was not sure the data was that compelling.

Dr. Brady (AAP Red Book) noted that while it did not state the word “preference,” Dr. Hunter’s statement actually was a preference. That may be the way to couch it so that it does not appear to state that CDC has a preference, but they do have a perspective.

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Dr. Moore agreed that there were not enough data to make a preferential recommendation at this time. She is more comfortable making a preference only when there are clear data of a difference rather than uncertainty. There is uncertainty every single year.

Dr. Szilagyi clarified that his point was exactly what Dr. Riley was saying. He thought what he was voting on for LAIV was the effectiveness, not the comparative effectiveness. A preference is truly a comparative effectiveness, and he did not think they had that information.

Dr. Lee agreed that while they could not predict what any season would hold, there is a difference for H1N1. She is cautiously optimistic that the date presented during this session would suggest that there would be reasonable effectiveness in a future season. She worried that if this ended up not panning out, ACIP would be reversing its decision again in the following year. To her, this would be a cautious way to wade into the ability to test out the hypothesis without having to reverse it every season. She was hoping this would get them to a point in another year such that they could remove the preferential recommendation once there are some data to review.

Dr. Bennett said she thought the effect of making a preferential recommendation at this time would suppress data going forward because essentially, LAIV would not be used if ACIP made a preferential recommendation. There is good evidence that LAIV is probably as good for B and H3N2 as IIV. As Dr. Szilagyi noted, there are not clear compelling data that IIV is better than LAIV. While they are in an uncertainty zone, she did not think they could make that kind of preferential recommendation, and it will undo the value of having put LAIV back on the table.

Dr. Romero said his personal view on this was that a preferential vote would be exactly what they had been alluding to, which would be evidence of overwhelming, incontrovertible superiority of IIV over LAIV, which there is not.

In terms of the comment regarding not having data next year if LAIV4 is not reinstated, Dr. Bernstein noted that certainly at any time the manufacturer could conduct a research study and get informed consent for a number of patients to be able to look at their new vaccine. Related to what Dr. Lee said, he wondered whether the question was to have a Category B recommendation for LAIV4 versus a Category A for IIV.

Dr. Bennett responded that ACIP no longer uses the terms Category A and B. This is really a preferential recommendation under consideration.

Dr. Stephens said his concern remained. Assuming that the Southern Hemisphere data comes back showing H1N1 and is a warning sign of what could occur in the next season, he wondered if they would be changing their minds about this particular discussion. He was on VRBPAC a number of years ago when this vaccine was approved and was enthusiastic about it. He thinks it is a great platform that should be developed, but is concerned about what they are recommending for the American people.

Dr. Middleman (SAHM) suggested that some of this could be taken care of in the background language, which would be a great place to discuss some of this in the absence of hard data.

Dr. Cohn stated that as Dr. Grohskopf did last year, there is a large amount of data summarizing all of the different vaccine choices available in the background document that accompanies ACIP's annual influenza recommendations in addition to the guidance shown earlier.

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Motion/Vote #3: Preferential Recommendation of IIV over LAIV

Dr. Lee moved that ACIP make a preferential recommendation stating that "*An age-appropriate IIV or RIV vaccine is preferred over LAIV*." Dr. Stephens seconded the motion.

The motion did not carry, with 3 affirmative votes, 11 negative votes, and 0 abstentions. The disposition of the vote was as follows:

3 Favored: Lee, Pellegrini, Stephens
11 Opposed: Atmar, Belongia, Bennett, Bernstein, Frey, Hunter, Moore, Riley, Romero, Szilagyi, Walter
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 was to add LAIV to the VFC Program. For IIV, eligible groups would include all children aged 6 months through 18 years. The recommended schedule would be 1 or 2 doses for children 6 months through 8 years, as noted in the current ACIP recommendations, and 1 dose for children 9 through 18 years.

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

Brand Name	Presentation	Age Indication
Afluria (Trivalent)	0.5 mL pre-filled syringe	>= 5 years
Afluria (Trivalent)	5.0mL multidose vial	>= 5 years
Afluria (Quadrivalent)	0.5 mL pre-filled syringe	>= 5 years
Afluria (Quadrivalent)	5.0mL multidose vial	>=5 years
Fluarix (Quadrivalent)	0.5 mL pre-filled syringe	>= 36 months
Flucelvax (Quadrivalent)	0.5 mL pre-filled syringe	>= 4 years
Flulaval (Quadrivalent)	0.5 mL pre-filled syringe	>= 6 months
Flulaval (Quadrivalent)	5.0 mL multidose vial	>= 6 months
Fluvirin (Trivalent)	0.5 mL pre-filled syringe	>= 4 years
Fluvirin (Trivalent)	5.0 mL multidose vial	>= 4 years
Fluzone (Quadrivalent)	0.25mL pre-filled syringe	>= 6 through 35 months
Fluzone (Quadrivalent)	0.5mL prefilled syringe/vial	>= 36 months
Fluzone (Quadrivalent)	5.0mL multidose vial	>= 6 months

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

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There are no changes proposed to the recommended intervals, dosage, or contraindications and precautions for IIV, which remain as follows:

Recommended Intervals

- ❑ Minimum Age: 6 months
- ❑ Minimum interval between dose 1 and dose 2 (where applicable): 4 weeks

Recommended Dosage

- ❑ Refer to product package insert.

Contraindications and Precautions

Contraindications:

- ❑ History of severe allergic reaction to any component of the vaccine or after previous dose of any influenza vaccine. However, ACIP makes specific recommendations for the use of influenza vaccine in persons with egg allergy (see Influenza Vaccination of Persons with a History of Egg Allergy, in https://www.cdc.gov/mmwr/volumes/65/rr/rr6505a1.htm).

Precautions:

- ❑ Moderate or severe acute illness with or without fever
- ❑ GBS within 6 weeks following a previous dose of influenza vaccine

The second part of the resolution is new for LAIV. For LAIV, eligible groups would include all healthy, non-pregnant children and adolescents (i.e., those who do not have an underlying medical condition that predisposes them to influenza complications) aged 2 through 18 years. The recommended schedule would be 1 or 2 doses, as noted in the current ACIP recommendations, for children 2 through 8 years and 1 dose for children 9 through 18 years.

Recommended intervals, dosage, and contraindications and precautions for LAIV would read as follows:

Recommended Intervals

- ❑ Minimum Age: 2 years
- ❑ Minimum interval between dose 1 and dose 2 (where applicable): 4 weeks

Recommended Dosage

- ❑ Refer to product package insert.

Contraindications and precautions can be found at:
https://www.cdc.gov/mmwr/volumes/66/rr/rr6602a1.htm

The standard statement regarding updates based on published documents would be included as well:

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

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Dr. Santoli indicated that when there is a change in the age indications for a product that is published, CDC is able to update the table to reflect that as a matter of course because the vaccine is already in the program. While that was not the primary purpose of this discussion, she wanted to make that known to everyone.

Motion/Vote: VFC Resolution

Dr. Hunter moved to approve the VFC Resolution as presented. Dr. Romero seconded the motion. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Evidence-Based Recommendations Work Group Update

Introduction

Grace Lee, MD, MPH
ACIP Evidence-Based Recommendations WG Lead

Dr. Lee reminded everyone that the purpose of the Evidence-Based Recommendations WG (EBRWG) is to develop and implement an approach that ensures transparency and consistency in the development of ACIP recommendations. The aims of the WG are to propose additional guidance for the ACIP evidence-based recommendation process by: 1) identifying areas for improvement and harmonization regarding development and use of GRADE evidence tables in ACIP work groups; 2) proposing criteria for determining when to prepare GRADE evidence profiles for vaccine recommendations; and 3) enhancing transparency on the formulation of recommendations by adopting a framework that incorporates GRADE evidence tables and additional factors that contribute to the decision-making process.

The focus of this session was on Aim 3, which has been to develop an Evidence to Recommendation (EtR) framework for use by ACIP. By way of background the GRADE WG developed the Evidence to Decision (EtD) framework to ensure a structured and transparent approach to decision-making, particularly when judgments are required on a range of factors. Their example and process were used as the template that was adapted to what ACIP needs to do. The framework is presented as a table that includes three sections: 1) formulating a question; 2) making assessments on key criteria; and 3) conclusions and providing judgments around each of the criteria to inform those conclusions.

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Evidence to Recommendations Framework

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 presented an update on the development and proposed use of an ACIP EtR framework. In terms of background, ACIP voted unanimously to adopt the GRADE approach to evidence-based decision-making in October 2010. Guidance regarding the GRADE process at the time included evaluation of the quality of evidence and a loosely defined process regarding factors in addition to the evidence that should be considered when making recommendations. The GRADE methodology considers evidence evaluation and the consideration of other elements as a two-step process to approach decision-making. Therefore, while evaluation of the quality of evidence for benefits and harms is a significant and necessary element, it is not the only factor considered when developing a recommendation. Other factors include the balance of benefits and harms, values, and health economic data. In considering how to ensure that the use of the GRADE approach best serves ACIP in its decision-making, it is also helpful to recognize the elements outlined in the ACIP Charter which states, "shall include consideration of disease epidemiology and burden of disease, vaccine efficacy and effectiveness, vaccine safety, economic analyses, and implementation issues."

Dr. Carr took a moment to address a particular point of confusion that often arises that a strong recommendation cannot be made based on low certainty of the evidence. However, precisely because of the separation of evidence evaluation and incorporation of additional factors in the decision-making process, it is possible to make a recommendation no matter what the level of evidence. Here is an excerpt from a recent publication by members of the GRADE WG that clearly describes this concept, "The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach clearly separates the certainty of evidence from the strength of recommendation. This separation allows decision-making based on lower levels of evidence. For example, despite low certainty evidence (derived from case series) regarding the association between aspirin and Reye's syndrome in febrile children, a strong recommendation for using acetaminophen over aspirin is possible. GRADE literature also describes five paradigmatic situations in which a strong recommendation can be made based on low quality evidence" [From: Murad MH, Sultan S, Haffar S, et al. Methodological quality and synthesis of case series and case reports. BMJ Evidence-Based Medicine Published Online First: 02 February 2018. doi: 10.1136/bmjebm-2017-110853].

This is not to say that it is always appropriate, but that it is possible and warranted in some cases. In those cases, it is important to then ensure that other factors contributing to the recommendation are transparently communicated. This is where a more defined process of moving from evidence to recommendations provides a pathway to consistently communicate the full range of the decision-making process. EtD frameworks were developed by the GRADE WG to guide the process of moving from evidence to recommendations or decisions. As such, frameworks are intended to help panels structure discussion and identify reasons for disagreements; be more systematic and explicit about the judgments that they make, the evidence used to inform each of those judgments, additional considerations, and the basis for their recommendations or decisions; and make the process and basis for decisions structured and transparent. Frameworks can also assist users of recommendations by enabling them to understand the judgments made by the panel and the evidence supporting those judgments.

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EtD frameworks include three sections that reflect the main steps in going from evidence to a decision: 1) formulating the question, 2) making an assessment of the evidence, and 3) drawing conclusions. One key feature of EtD frameworks is that they are layered such that they present key messages in the top layer with links to more detailed information. This can include concise summaries of the most important evidence for each criterion summarized in a table or a paragraph of text, and from the framework it is possible to link to information that is more detailed (e.g., a GRADE evidence profile). The 3 content areas are presented in the framework as:

- Background (formulating the question):
  - Details of the question and a brief summary of information to understand the question and why a recommendation is needed

- Criteria (assessment/communication of evidence):
  - Criteria (factors that should be considered) for making the decision
  - Judgments that must be made in relation to each criterion
  - Evidence to inform each of those judgments
  - Additional considerations that inform or justify each judgment

- Conclusions that the panel must reach based on the judgments made for all of the criteria

As mentioned earlier, one of the important aims of the EBRWG was to define a process that provides additional structure and clarity for considering factors in addition to the evidence base when formulating recommendations. Additional factors besides benefits and harms have always been considered; however, the process was not structured. Therefore, how recommendations were formulated based on the evidence may not have always been clear. So, development of an EtD framework tailored to the needs of ACIP will refine those methods for incorporation of additional factors that contribute to decision-making as well as GRADE evidence profiles. One thing to note is that while the generic version of the framework is an EtD table, when decisions are in the form of recommendations, they can also be termed EtR. Similar to other groups when making recommendations, ACIP has chosen to use the EtR terminology and adapt the framework to best fit public health recommendations for vaccines. In addition to extensive feedback received from the EBRWG and CDC WG leads, it was piloted by the Zoster and Mumps WG in preparation for their votes conducted during the October 2017 ACIP meeting. While significant thought has been put into creation of the framework, it is considered to be a living document that will be refined as continued use suggests potential improvements. In addition to basic completion guidance that is included in the framework itself, a more extensive guidance document has also been developed that provides additional detail and practical advice for those drafting the framework in support of an ACIP policy decision. As different types of questions are encountered, it is also anticipated that the guidance document will continue to evolve and improve in assisting users.

As mentioned previously, EtR frameworks are presented as a table that includes key background information, criteria, and conclusions. The criteria that should be considered fall into several broad topic areas, and each of these contains individual questions that solicit judgments concerning each element and presentation of the available evidence. The topic areas included in the draft ACIP EtR framework are as follows:

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- **Statement of Problem** (or issue the recommendation is intended to address)
  - Public health importance
  - Burden of disease and other considerations that contributed to the need for a recommendation to be developed

- **Benefits and Harms**
  - Balance of desirable and undesirable effects
  - Certainty in evidence: Preparation of GRADE evidence profiles will typically be part of this section, or in circumstances where evidence tables were not prepared, a description for the rational for the decision not to prepare tables. "When to Prepare GRADE Evidence Profiles" algorithm is included in the guidance document as a tool to assist users with this determination

- **Values and Preferences** of target population where consideration is given to perception of the benefits and harms and how these are valued by potential recipients

- **Acceptability to key stakeholders**

- **Resource Use**
  - Encompasses information provided by health economic analyses

- **Feasibility**
  - Implementation considerations (note that for this framework, equity is built into this section)

For each of these criteria, the following columns are provided in the EtR framework:

- **Judgments**
  - For the initial framework, these would be draft judgements prepared by the WG that become final after review and modification by the full committee

- **Evidence to inform each judgment**
  - This may be research evidence or evidence obtained from routine data collection
  - If no peer-reviewed body of evidence is available, this should be simply stated and any additional information used to inform the judgment indicated, because the intent is to be transparent about the information that was used to make the judgment, not to imply the need for the development of evidence if it is not available or is not critical for decision-making
  - This can include links to more detailed summaries of the evidence

- **Additional considerations that inform or justify each judgement**
  - Can include other data, assumptions, and/or logic used to make a judgment
  - Different judgments for one or more subgroups
  - Dissenting views of panel members or minority opinions
  - Interpretations of the evidence

Dr. Carr presented each proposed section of the framework. The first section includes the Question, Background, and Problem. This begins with the question outlined in PICO format and includes a location to provide a brief, concise summary of the background information. Then comes the first criterion, which is the problem of public health importance. The column for

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judgments includes corresponding text boxes, followed by columns for evidence and additional information:

Question: Overarching policy question to be answered by the guideline panel (ACIP) using the Evidence to Recommendations (EtR) framework. **Population:** Target population for vaccine (e.g., age range, sex, immune status, pregnancy) **Intervention:** Vaccination (if applicable, dosage and schedule) **Comparison(s):** No Vaccination/Placebo/Control/Standard care/An existing vaccine/Other prevention options **Outcome:** Outcome(s) associated with vaccination (e.g., prevention outcomes or adverse effects)				
Background: The addressed PICO question should be described in detail, and important background information for understanding the question and why a recommendation or decision is needed should be briefly provided.				
	CRITERIA	JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem of public health importance?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☐ *Yes* ☐ *Varies* ☐		

This is the benefits and harms section of the framework. Note that the judgments for the final criterion pertaining to the certainty of the evidence align with the levels of evidence that were defined during the development of GRADE evidence profiles:

	CRITERIA	JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
BENEFITS & HARMS	How substantial are the desirable anticipated effects?	*Trivial* ☐ *Small* ☐ *Moderate* ☐ *Large* ☐ *Don't know* ☐ *Varies* ☐		
	How substantial are the undesirable anticipated effects?	*Trivial* ☐ *Small* ☐ *Moderate* ☐ *Large* ☐ *Don't know* ☐ *Varies* ☐		
	Do the desirable effects outweigh the undesirable effects?	*Favors intervention* ☐ *Favors comparison* ☐ *Favors both* ☐ *Favors neither* ☐ *Unclear* ☐		
	What is the overall certainty of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ *4 Very low* ☐ *3 Low* ☐ *2 Moderate* ☐ *1 High* ☐ Safety of the intervention *No included studies* ☐ *4 Very low* ☐ *3 Low* ☐ *2 Moderate* ☐ *1 High* ☐		

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This is the values section of the framework. This includes how potential vaccine recipients and their families feel about the balance of benefits and harms, and captures whether there is significant variation in this perception among the population:

	CRITERIA	JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
VALUES	Does the target population feel that the desirable effects are large relative to undesirable effects?	No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ | Varies ☐		
	Is there important uncertainty about or variability in how much people value the main outcomes?	Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☐ No important uncertainty or variability ☐ | No known undesirable outcomes ☐		

This section includes acceptability to stakeholders such as providers, manufacturers, and professional societies, and as such the stakeholders may vary according to the vaccine. This section also addresses resource use and feasibility. As noted earlier, the resource use component encompasses the health economic analyses:

	CRITERIA	JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
ACCEPTABILITY	Is the intervention acceptable to key stakeholders?	No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ | Varies ☐		
RESOURCE USE	Is the intervention a reasonable and efficient allocation of resources?	No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐		
FEASIBILITY	Is the intervention feasible to implement?	No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ | Varies ☐		

As part of the development of the framework, a draft checklist tool to assist with the evaluation of possible implementation barriers has been developed and will be piloted.

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Moving to the EtR framework conclusions, conclusions should be based on the judgments made for all of the criteria and should specify a summary of the judgements made for all criteria and implications for the decision, the type of decision or recommendation (e.g., routine recommendation, individual recommendation, or not recommended), and the recommendation in concise, clear, and actionable text. In addition to the critical information, additional information can be included when relevant such as any subgroup considerations that the panel took into account when making a decision; key implementation considerations (in addition to any that are specified in the recommendation), including strategies to address any concerns about the acceptability and feasibility of the intervention; and draft conclusions suggested by the WG who prepared the framework.

This is the conclusion section of the proposed framework. It includes the summary of judgments on the top panel indicating the balance of consequences, the type of recommendation, a space for the recommendation text, and additional considerations:

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced* or *uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐	There is insufficient evidence to determine the balance of consequences ☐
Is there sufficient information to move forward with a recommendation? Yes ☐ No ☐						
Type of recommendation	We do not recommend the intervention ☐	We recommend the intervention for individuals based on clinical decision-making ☐	We recommend the intervention ☐			
Recommendation (text)	Please provide the draft recommendations proposed to ACIP.					
Additional considerations (optional)	Please outline any significant additional considerations (e.g., aspects related to implementation, monitoring and evaluation, research priorities, etc.).					

One thing to note from the proposed framework is that there are 3 types of recommendations that are possible:

- ❑ "We do not recommend the Intervention"
- ❑ "We recommend the intervention for individuals based on clinical decision-making"
- ❑ "We recommend the intervention"

If the framework is formally adopted, implementation of the framework will result in the use of these 3 types of recommendation and will replace the former labeling of "Category A" and "Category B." This will not have any impact on vaccine coverage under the ACA.

In summary, this is a proposed update to the current ACIP evidence-based recommendation process, which is consistent with expansion of GRADE methodology guidance. The precise language is subject to continued improvement, and guidance will be updated as experience is gained. Additional supporting documents are being developed. Previous recommendations will not be retroactively put into the EtR format, but the framework will be used when recommendations are periodically updated. Similar to GRADE evidence profiles, the completed EtR frameworks will be published online. With this in mind, the EBRWG proposed that an EtR framework be adopted and used by ACIP to support decision making.

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Discussion Points

Dr. Romero made a motion to accept the proposed EtR framework as proposed, which Dr. Frey seconded.

Dr. Frey asked whether there were definitions for the 5 possible choices in the judgment section. She said she was relating this to AEs where there are choices on the continuum of whether it is related are not, and which are well-defined.

Dr. Carr replied that there are not specific definitions, but the guidance document includes information to help people make those distinctions. It is similar to a subjective process. Part of the aim of the framework is to transparently communicate what the discussions and deliberations were. Every group may come to a little bit different place with that. The goal is to be able to communicate the rationale for making that judgement rather than necessarily specifying why the judgement should be made.

Dr. Riley applauded the committee for including equity essentially throughout most of the document. It did strike her that it is under benefits and harms and it would be interesting to see when they are trying to make a judgement about benefits to various subgroups. Very seldomly are there actually data, so hopefully these will force some of that when people bring their study data to ACIP to see that various groups have been incorporated in terms of race, ethnicity, pregnancy, et cetera.

Dr. Carr said they hope that one of the goals is that if there is no evidence, something can be presented to address that as well so that it is transparent.

Dr. Bennett indicated that they discussed offline the previous day requesting going forward that almost every presentation address the issue of equity, not so much in terms of how it will play out but in terms of what populations were included and whether there are enough data to examine those populations separately.

Dr. Messonnier reflected back on something Dr. Neuzil said the previous day, which was that while they understand the language “benefit and harms,” there is the potential that the “harms” language could be misunderstood. In the spirit of transparency, she requested that the EBRWG think about if there is a different way to express this as opposed to using that language.

Dr. Schaffner (NFID) said that in these discussions, he continued to be fuzzy about where the potential indirect effects of vaccine implementation will be reflected in this evidence base. This is so important in terms of the previous discussion.

Dr. Carr replied that the EBRWG recognized this as being important to consider and it is included in the guidance document. This is specifically drawn out in the “benefits and harms” section to consider and include any information that is available regarding indirect effects.

Dr. Cohn indicated that copies of the framework could be found in the back outside of the room so that people could look at the evidence and additional information sections.

Regarding Dr. Messonnier’s comments about the benefits and harms, Ms. Stinchfield (NAPNAP) said she thought the communication plan after the decision is made is really about who the target audience it. An audience such as those in the room would clearly understand benefits and harms and may need more of a technical description of the outcomes and

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interventions; whereas, there may need to be a different communication plan for the general public, media, et cetera.

Dr. Sun (FDA) observed that there is a movement afoot to make available clinical trial data and the quality of the decisions always very much rely on the quality of the evidence, and he wondered whether the WG considered in the future how these data would be incorporated in the GRADE process. That is, how would having individual subject data available for independent analysis be addressed in this process?

Dr. Carr said she thought that would fall in with the quality of evidence in the "benefits and harms" section. That is one of the items she mentioned earlier where it is possible to link to more detailed information. Even though there is a summary and interpretation of the information, it would be possible to link to more detailed information so that others could read more about it if they wanted to.

Public Comment

Eddy A. Bresnitz, MD, MSCE, FACP
Medical Director for Adult Vaccines
Medical Affairs and Policy
Merck Vaccines

I didn't have a chance to review the more extensive document itself and maybe it is covered in there, so I apologize for the questions. At the last meeting, I think Stan Plotkin made some remarks about encouraging the use of more preferential recommendations, and there was clearly a lot of discussion at the last meeting about preferential recommendations. In the documents I've seen, I don't see any mention of the criteria for basically the ACIP or even the WG who are recommending a preferential recommendation, and so I know you are about to vote on that, but I think that this needs to be addressed. I think everyone needs to understand what those criteria are for the ACIP to take that kind of basically groundbreaking step on any product—new product or indication for an existing product.

Jefferey Jackson
Interested Citizen

I want to stress the importance of this evidence-making decision. I was here yesterday, and I was listening to the LAIV4 FluMist® discussion, and I see the words today *Recommended* and *Not Recommended*. For someone sitting on this side of the table and understanding the weight that ACIP caries not only to the United States, but for the greater global population, as you all know and as we are learning, these decisions are highly valued and are looked at by many bodies—many regulatory bodies throughout the world and are piggybacked as well. So yesterday when I saw the wordsmithing of "do we take out *recommendation* but recommend it but not say *recommend it*" that gives me concern as a citizen that these things aren't being fully looked at. I mean, the idea of taking FluMist® and bringing it back, and I know that's a little off topic, but bringing it back and then playing around with the word *recommendation* is very confusing not only to the providers, but also like one of the committee members mentioned, for the public messaging. It's very confusing for people on this side of the table, so I urge you to take this vote seriously and to look at really what you're creating here. This is a very important framework. Thank you.

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Discussion Points

Concerning Dr. Bresnitz comments, Dr. Cohn said they appreciated and have heard that feedback. That is a next step for the EBRWG but is not included in the proposed framework. Although the framework would still be used to talk about decisions under discussion in terms of developing probably not criteria but guidelines for how to think about that.

Dr. Lee noted that in terms of the way the question is structured, the intervention and comparison which is usually thought of as placebo but in this instance would be another vaccine, Dr. Bresnitz raised a good question about what level of evidence is needed for making that kind of judgment or decision. The goal was to hopefully bring this to a vote and start to use this framework. As Dr. Carr mentioned, the WG intends this document to be iterative and a process by which they are learning and improving as they go. They anticipate that the transparency around decision-making will continue to be enhanced over time.

Dr. Bennett thanked Mr. Jackson for his comment and emphasized that the entire purpose of the framework is to increase transparency to everyone.

Motion/Vote: Evidence to Recommendation (EtR) Framework

Dr. Romero moved to adopt the Evidence to Recommendation (EtR) Framework as presented. Dr. Frey seconded the motion. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Anthrax Vaccine

Introduction

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

Dr. Stephens reminded everyone that the Anthrax Vaccine WG's terms of reference are to review new data on anthrax adsorbed vaccine (AVA) including the following:

- New safety studies, for which some data have been presented
- Immunogenicity, reactogenicity and logistical considerations for administering AVA via the subcutaneous versus the intramuscular route for administration as post-exposure prophylaxis (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
- Duration of the antimicrobial component of PEP when given in conjunction with AVA

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- 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 following topics were the focus of this session:

- Intramuscular (IM) versus subcutaneous (SC) route of administration for mass vaccination following wide-area release of *Bacillus anthracis* (*B. anthracis*) spores
- AVA dose-sparing strategies when demand for vaccine exceeds supply
- Duration of the antimicrobial component of PEP when given in conjunction with AVA

Update on IM Route of Administration of Vaccine

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

Dr. Bower reviewed the current AVA pre-exposure prophylaxis (PrEP) and PEP licensed indications for adults 18 through 65 years of age, which are as follows

- 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

Although the focus of this session was PEP use of AVA, Dr. Bower thought it was important to mention the route of PrEP administration for context. As a reminder, the Anthrax WG's discussion and advice on route of administration of AVA for PrEP during a public health emergency was presented during the last ACIP meeting. The committee suggested that the logistical challenges of a mass vaccination campaign with AVA warranted further discussion. Therefore, additional information was being presented that was gathered in an update of the WG's discussion.

Dr. Bower briefly reviewed some of the non-logistical issues the WG considered regarding different routes of administration for anthrax vaccine discussed during the last ACIP meeting. Data from 2001 suggest that adherence to the antimicrobial component of anthrax PEP wanes over time and could be as low as 50% by day 30 of a 60-day antimicrobial PEP recommendation. However, the WG believes this estimate might be lower. First, individuals began PEP weeks after the initial exposure at a time when much of the risk had already passed. Second, the results were not stratified by level of risk of the different groups. Now better prepared for a public health emergency, it is expected that PEP will be initiated sooner and public health messaging focusing on the benefits of PEP adherence is expected to result in higher adherence in exposed populations, particularly those at highest risk. There are also higher rates of AEs for the SC compared to the IM route of administration. Although higher AEs could discourage adherence, dropout rates did not appear to vary in healthy adults who received AVA by either the IM or SC route of administration.

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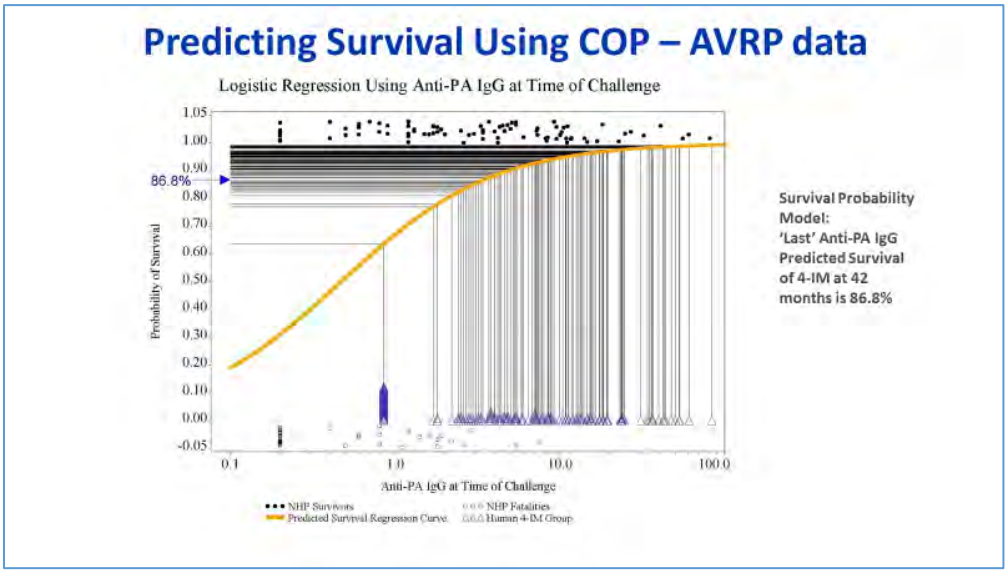
A number of operational concerns related to a mass anthrax vaccination campaign prompted CDC to ask ACIP advice on the route of administration. In terms of supplies for administering vaccine, SC vaccines are usually given with a 5/8" needle, while IM vaccines are given with either a 1" or 1.5" needle. In a large event, CDC's supply of 5/8" needles might be insufficient to administer vaccine by the SC route. Commercial supplies may also be insufficient to fill the need in the short-term. CDC also stockpiles 1" needles for IM vaccination administration. In a large event, it may be necessary to use both 5/8" and 1" needles. Therefore, both SC and IM routes of administration may need to be used.

NuThrax™ is the next-generation human anthrax vaccine, which is currently in Phase 2 trials and is expected to be licensed for IM administration only. CDC's Strategic National Stockpile (SNS) will start transitioning to NuThrax™ in 2018 for use under an Emergency Use Authorization (EUA) while the company seeks licensure. As a reminder, AVA for PEP is currently licensed for administration by the SC route in adults. During the transition from AVA to NuThrax™, which is expected to occur over 4 to 5 years, the SNS will have 2 formulations of anthrax vaccines with 2 different routes of administration for the same indication. Therefore, there may be confusion over which route of administration to use. Additionally, the investigational new drug (IND) provision that allows for AVA to be used in children ages 6 months to 18 years specifies IM administration. This too could make it difficult to ensure that the specific route of administration is used for the specific target population. This situation may lead to administration errors with both vaccines.

In order to administer vaccine to a large number of people in a mass casualty event, the most efficient method available would be needed. Most routine vaccines are given by the IM route and HCP are more accustomed to giving IM injections. Because there is more experience in the healthcare community giving intramuscular injections, this route may be more efficient for quickly vaccinating large numbers of individuals.

Dr. Bower reviewed data presented during the last ACIP meeting as a refresher. This is the Kohberger method for bridging animal and human data to determine correlates of protection (COP) and the model the FDA recommends for predicting survival:



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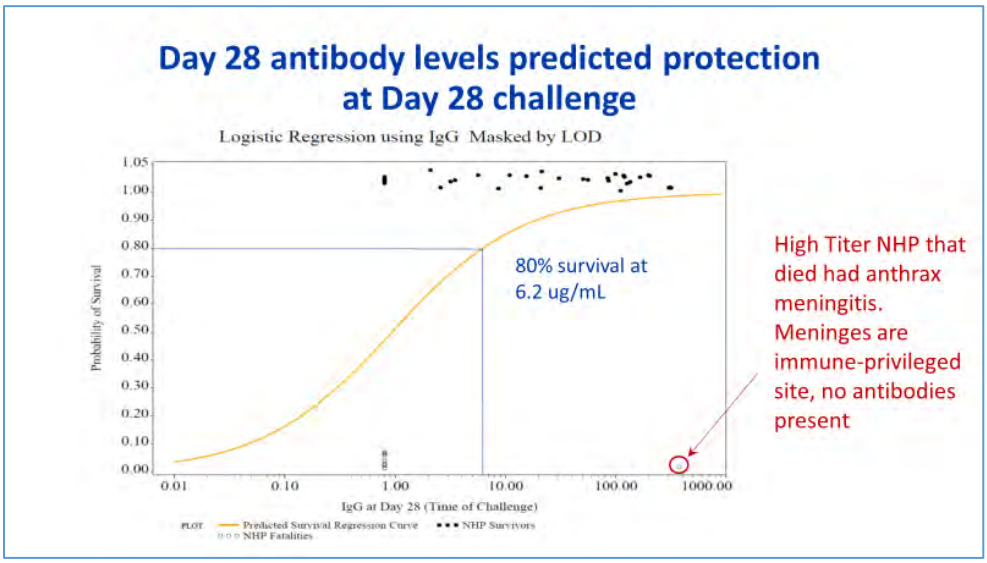
The non-human primates (NHP) were given AVA at 0, 1, and 6 months. On this graph, the x-axis shows concentrations of anti-PA antibody levels at the time just prior to challenge with anthrax at 12, 30, and 52 months. The NHP survivors are represented by black circles at the top of the graph, while non-survivors are represented by the white circles at the bottom. A logistic regression curve of predicted survival is plotted. Probability of survival is on the y-axis based on the NHP anti-PA IgG measurements. The blue triangles are human anti-PA IgG concentrations at 42 months after receiving AVA at 0, 1, and 6 months. Plotting the individual probabilities of survival and taking the average results in the mean survival for the population. In this example, the probability of survival at 42 months after receiving AVA at 0, 1, and 6 months is 86.8%.

To understand the onset of protection for AVA vaccination when used for PEP, a study was designed by the National Institute of Allergy and Infectious Diseases (NIAID) to assess protection after a high-dose challenge at Day 28 in NHP that had received SC AVA at 0 and 14 days. To determine COP in humans, logistic regression was used to plot a survival curve based on immunological response and survival in the NHPs. These data were then used to predict probability of survival in humans receiving AVA by the IM or SC route.

In terms of the study design used to generate the data for the NHP immunological results and survival to challenge, the NHP were given AVA at Days 0 and 14 in doses ranging from 1/3 to 1/243 of the normal human dose. On Day 28, they received a high-dose challenge of aerosolized *B. anthracis* spores[1]. The human immunologic response was generated by giving vaccine to healthy adult volunteers with full doses on Days 0 and 14; 0 and 28; or 0, 14, and 28, which is the currently licensed schedule or with a half dose on Days 0, 14, and 28[2] [[1]Sivko et al; [2]Stark et al].

This graph displays the estimated probability of survival logistical regression curve fitted to the anti-PA IgG concentration data at Day 28 just prior to the anthrax challenge:



The model predicts a greater than 80% survival for anti-PA IgG levels greater than 6.2 ug/mL. As shown by the data, having a detectable antibody level was quite protective. Only one animal had a detectable antibody level who died. This animal developed anthrax meningitis, which is not unexpected because it is known that antibodies cross the blood brain barrier (BBB) more

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slowly. Despite having a high antibody titer, the antibodies might not have prevented development of meningitis and death in this animal. Using these survival curves, the predicted human survival at 28 days following receipt of AVA at Days 0 and 14 is 88.6% if the vaccine is given by the IM route and 92.4% if given by the SC route. This difference is statistically significant. After receipt of the last IM dose at Day 56, the predicted survival is 95.6% if given by the IM route and 96.1% if given by the SC route. This is a non-significant difference.

After reviewing the adherence data for both the antimicrobial and vaccine component of PEP and the logistical considerations in an anthrax mass vaccination campaign, the WG did not favor recommending the IM route of administration as an alternative. The WG reasoned that all needle lengths contained in the CDC SNS could be used to administer AVA by the SC route, and that the different needle lengths would not impede vaccine administration. The WG did not believe that IM administration was necessarily more efficient than SC administration of the vaccine. Although higher rates of AEs for the SC route of administration was a theoretical concern, there was no observable difference in inherent traits for the two routes of administration used in volunteers who participated in a study looking at AEs with AVA given by different routes of administration. Most importantly, the WG continued to favor the SC route as the only route of administration because the immune response AVA at 4 weeks is significantly higher for the SC route of administration compared to the IM route. A faster higher immune response was deemed the most important because of consistent trends for anthrax, other chronic diseases, and clinical experience, which all suggest that adherence to antimicrobials as a component of anthrax PEP wanes over time.

To gather more input on logistical challenges for an anthrax vaccine mass vaccination campaign, CDC approached two groups on the frontlines of preparedness efforts at the local level: National Association of County and City Health Officials (NACCHO) and Association of State and Territorial Health Officers (ASTHO). The NACCHO Medical Countermeasures (MCM) Workgroup addresses issues related to the provision of medical countermeasures for the treatment or prophylaxis in accordance with public health guidance. ASTHO and all 62 MCM Coordinators collectively address the implementation challenges associated with planning, distribution, and dispensing medical countermeasures during a public health emergency by providing CDC with information, feedback, and recommendations. CDC asked these two groups to provide input on how they thought having vaccines with 2 different routes of administration for different target populations could potentially affect the efficacy of the response and the number of people vaccinated in a timely manner.

The reviews were not unanimous, but the consensus for these two groups was that administering vaccines by 2 routes would adversely impact response efficiency. In terms of some of the main challenges foreseen with having to incorporate 2 different vaccines with different routes of administrations, they noted that those who have more serious AEs or hear of people who have more serious reactions are less likely to return for subsequent doses. The individual representing NYC noted that in an anthrax PEP response following exposures to African drum skins, not all potential exposed individuals returned for subsequent vaccination doses precisely due to the AEs following SC administration. A number of representatives voiced concerns that an increased number of vaccination errors would likely occur with multiple routes of administration. Requirements for VAERS reporting of medical errors could slow the response. There also was concern that this might increase legal, ethical, and public relation issues.

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The state and local health emergency preparedness partners believe that there would be resistance to the use of needle lengths not commonly used for routes of administration. They also foresaw logistical challenges associated with matching needles and vaccine supplies at large numbers of points of distribution sites. Training was mentioned by several as an important consideration for a mass vaccination campaign. In a mass vaccination campaign, local providers with little to no training in vaccination techniques may be recruited to provide vaccination. State and local partners felt that IM administration is easier for vaccine providers to learn, and that providing just-in-time (JIT) training on two different modes of administration would slow the response. In addition, some suggested that it might require providers to learn only 1 of the 2 techniques thus doubling the number of staff required.

Given these concerns by the public health emergency preparedness community, the WG modified their earlier advice. The WG still maintains that the SC route of administration should be used in both adults and children whenever possible. However, in a large-scale emergency event these populations should receive AVA by the route that results in the most efficient vaccination campaign. Thus, AVA for PEP may be administered using an IM route of administration if the SC route of administration poses a significant materiel, personnel, or clinical challenge that may delay or preclude vaccination. The WG also thought it would be acceptable for individuals to receive a vaccine by the IM route if they had experienced significant AEs from AVA administered by the SC route.

Dose-Sparing Strategies When Demand for Vaccine Exceeds Supply

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

Dr. Bower reminded everyone of the graph he showed earlier that displayed the estimated probability of survival logistical regression curve fitted to the anti-PA IgG concentration data at Day 28 just prior to the anthrax challenge following AVA receipt at Days 0 and 14. As a reminder of the study design to generate the data for the NHP immunological results and survival to challenge, the NHP were given AVA at Days 0 and 14 in doses ranging from 1/3 to 1/243 of the normal human dose. On Day 28, they received a high-dose challenge of aerosolized *B. anthracis* spores[1]. The human immunologic response was generated by looking at 3 dose-sparing regimens: Arms A (0,14 Day Full Dose); B (0,28 Day Full Dose); and D (0, 14, 28 Day Half Dose) and the current licensed PEP schedule Arm C (0,14,28 Day Full Dose)[2] [[1]Sivko et al; [2]Stark et al].

This graph shows the human anti-PA IgG concentration over time with the various dose-sparing schedules, with the currently licensed schedule show in the purple line:

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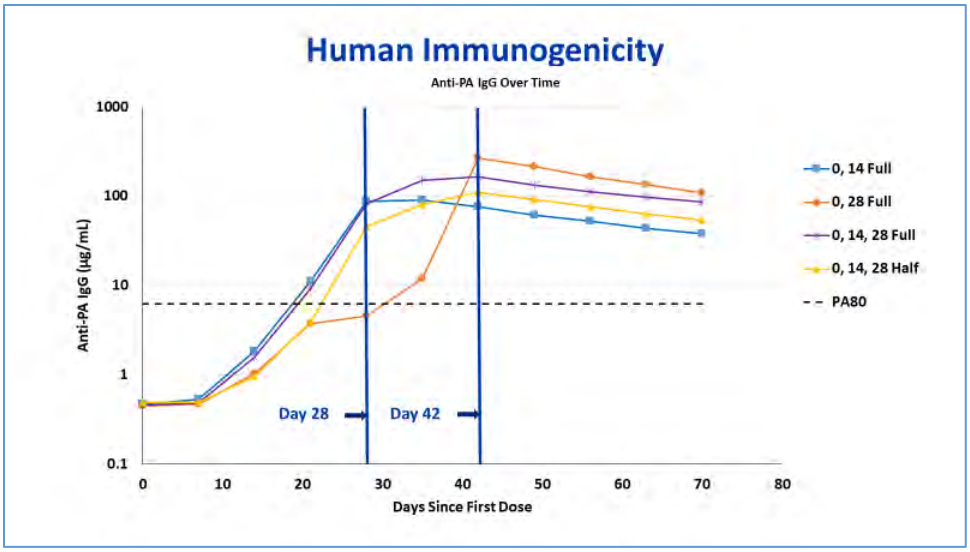
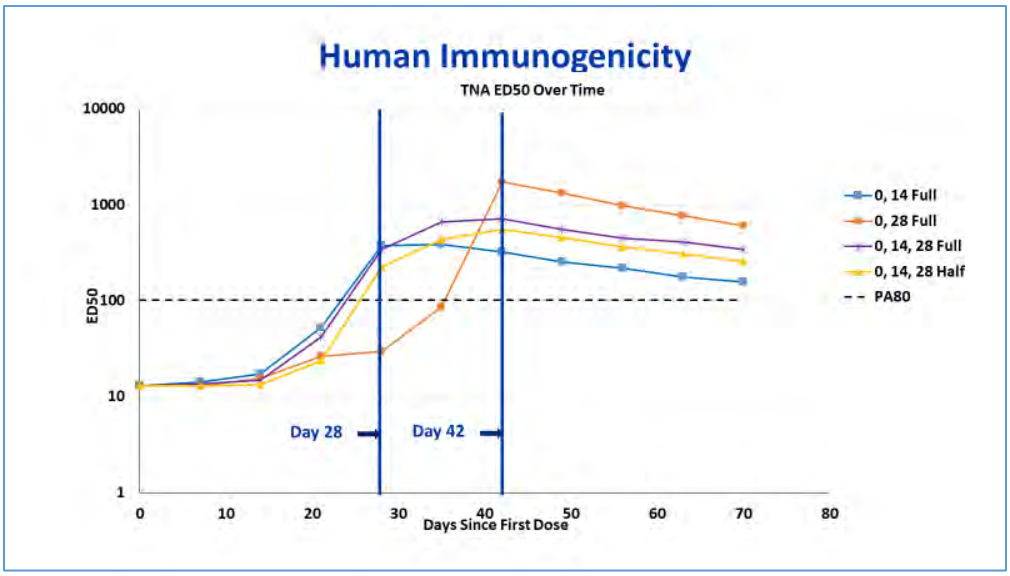


The broken line represents the 80% protection level determined from the correlates of protection model. The first blue line is at Day 28 when individuals received the licensed schedule or the proposed dose-sparing schedules who had received the last dose except for the 0- and 14-day dose-sparing schedule. The second blue line at Day 42 is 2 weeks after the last dose of all of the schedules that end on Day 28 and is at 4 weeks after the end of the Days 0 and 14 dose-sparing schedule.

This graph represents the same data but uses a TNA ED_{50} rather than anti-PA IgG concentration:



This graph shows the same pattern as shown in the previous graph. All dosing schedules are predicted to be highly protective by Day 28 except for the 0- and 48-Day schedules, given that they would have received only one dose up to that timepoint.

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These data show that all of the schedules with a Day 14 dose produce high levels of protection by Day 28. The one schedule lacking a Day 14 dose produced the highest levels from Day 42 onward. As might be expected, the full 3 doses produced higher antibody levels than the half dose schedules. The peak antibody response occurred 2 weeks after the last dose for all regimens, and all were highly protective. This graph summarizes the high levels of predicted survival 2 weeks after the last dose using the various dose-sparing schedules of the currently licensed schedule:

Assay	0, 14 Full	0, 28 Full	0, 14, 28 Full	0, 14, 28 Half
Anti-PA IgG	95.7%	98.1%	97.4%	96.1%
TNA NF_{50}	89.1%	96.7%	94.0%	91.9%

Note that the animal trials used a high-dose challenge at Day 28 with no antimicrobials; whereas, humans in an exposure scenario would only have residual spores 4 to 6 weeks after the initial exposure and concurrent antimicrobial use. Therefore, this is considered to be an extremely conservative worst-case estimate.

The WG agreed that all dose-sparing schedules provided high levels of estimated protection by 2 weeks after the last dose, and that the protection was only slightly less than the estimated protection provided by the licensed schedule. Thus, it seemed reasonable that in an actual or impending vaccine shortage, the benefits of providing protection to a large number of individuals outweighed the risk of slightly lower protective levels. The WG realized that the logistics of a mass vaccination campaign following a wide-area release of *B. anthracis* spores could make receiving the vaccine exactly at 2-week intervals difficult and thus considered a range of 0 and 2 to 4 weeks for the 2 dose-sparing schedules.

The WG agreed that if the demand for vaccine exceeds supply, dose-sparing strategies could provide greater protection to the exposed population as a whole while only slightly lowering the protection provided to some individuals exposed to anthrax. The consensus among the WG was that both of the dose-sparing schedules of either 2 full doses (0.5 mL) at 0 and 2 to 4 weeks or 3 half doses (0.25 mL) at 0, 2, and 4 weeks are acceptable dose-sparing strategies that provide a high level of protection by 2 weeks after the last dose. The selection of the dose-sparing strategy to implement depends on the anticipated shortage. The 2-full-dose strategy will expand the vaccine supply by 50% and the 3-half-dose strategy will expand it by 100%.

The WG also wanted to add a statement to the guidelines stressing the importance of adherence to the antimicrobial component of PEP. This statement would describe the components of PEP that antimicrobials prevent anthrax if taken as prescribed and the rationale behind the 2 components with emphasis that for anthrax PEP to work, the antimicrobial must be adhered to for a minimum of 2 weeks after the last dose of vaccine PEP.

The WG's proposed recommendations for dose-sparing schedules read as follows:

- ❑ Following an exposure to aerosolized *B. anthracis*, PEP has two components taken concurrently: an oral antimicrobial component (AbxPEP) and a vaccine component (VxPEP).

- ❑ When taken as prescribed, AbxPEP prevents anthrax.

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- VxPEP generates a protective immune response that can also prevent anthrax; however this immune response takes time to develop. AbxPEP is critical during this time and must be continued until at least two weeks after the last dose of VxPEP to allow the protective immune response to fully develop.

Discussion Points

Dr. Messonnier asked if in a large event vaccine was going to be given either IM, which is off-label, or because of the size of the event there was a need to use one of the dose-sparing regimen, presumably it would be given under an EUA.

Dr. Bower replied that the dose-sparing schedules would be utilized under an EUA or perhaps Emergency Use Instructions (EUI). Clearly, the dose-sparing schedule would be used only if there was evidence that more people were exposed and going to need PEP than there was vaccine. Though unlikely to happen, in a huge event with a lot of people exposed this potentially could occur. That is the only time that the dose-sparing schedules would be considered.

Harkening back to something brought up earlier in the day about behavioral theory, Dr. Riley asked whether people are more likely to follow the directions in an event for which they see serious risk immediately and if there were any data to know how people would react.

Dr. Bower responded that in his opinion, in an event if people saw others in the hospital due to an anthrax event and were told that the vaccine would protect them, they would get it. He thinks that what really drives people to get the vaccine is their perception of their own level of risk. CDC needs to do a good job of telling people in an exposed area that they need to get the vaccine.

Dr. Hunter indicated that he has played the role of Medical Director in a simulation of an anthrax exposure on a campus and got to decide whether the play actor people got to go to the ED or if they had an allergy, what alternative medications they took. It is a very interesting situation based on having done the simulation. He also did an occupational follow-up of *Brucella* exposure in a laboratory of a group of 6 to 12 people who may have had exposure, and they have to take a similar length of antibiotics with similar side effects. It was amazing how few people wanted to follow up with that, because these antibiotics have a lot of side effects and people are always wondering whether they really had exposure and are really at risk. From his anecdotal experience, he thinks this is a real issue. He asked if they were going to tell people who are having their last dose of vaccine that they have to take antibiotics for another 2 weeks or for the whole 60 days. He asked whether there would be any situations in which there would be reliance on the reduction in the amount of antibiotics that would have to be used because of using vaccine—not a dose reduction of the vaccine, but a dose reduction of the antibiotics.

Dr. Bower noted that the next presentation would address duration of antimicrobials, while this session focused on dose-sparing. If based on the data it does not seem that the length of antimicrobials could be reduced, then even with the dose-sparing regimens the recommendation would continue to be 60 days for antimicrobials. If there is not enough vaccine, then yes, 60 days of antimicrobials would protect people from the initial release. The vaccine also protects from subsequent re-aerosolization as well.

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Dr. Messonnier said she thought Dr. Hunter's question pertained to an insufficient supply of antibiotics. Generally, in most of the scenarios the WG has been working on, the supply constraint is much more narrowly around vaccine. Antibiotics are more widely available, so they are not really considering a scenario in which there is more vaccine than antibiotics because that probably is not realistic.

Dr. Bower concurred, noting that antibiotics are fairly inexpensive and CDC has a lot of antibiotics stockpiled.

Duration of the Antimicrobial Component of PEP When Given in Conjunction with AVA

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

Dr. Bower next discussed the duration of the antimicrobial component of PEP when used in combination with AVA. Given that the same data used to examine dose-sparing strategies formed the basis for discussion regarding duration of antimicrobials in conjunction with vaccine, he did not show the design or graphs again but did point out some of the important findings. For most of the dose-sparing strategies and the licensed schedule, 42 days is 2 weeks after the last dose. For the Day 0 and 14 dose-sparing schedule, Day 28 is 2 weeks after the last dose. The peak response occurs around 2 weeks after the last dose of the currently licensed vaccine and all of the dose-sparing schedules. The peak responses in all of these schedules are highly protective.

This table shows the estimate protection at Days 28, 42, and 63 for the dose-sparing and licensed schedules:

Protection Estimates Over Time

Day 28				
Assay	0, 14 Full	0, 28 Full	0, 14, 28 Full	0, 14, 28 Half
Anti-PA IgG	95.8%	72.6%	95.8%	91.1%
TNA ED_{50}	89.5%	59.9%	89.5%	83.4%
Day 42				
Assay	0, 14 Full	0, 28 Full	0, 14, 28 Full	0, 14, 28 Half
Anti-PA IgG	95.5%	98.1%	97.4%	96.1%
TNA ED_{50}	88.9%	96.4%	93.7%	91.9%
Day 63				
Assay	0, 14 Full	0, 28 Full	0, 14, 28 Full	0, 14, 28 Half
Anti-PA IgG	93.3%	97.0%	96.4%	94.2%
TNA ED_{50}	84.1%	93.9%	91.0%	88.1%

❑ Peak Protection

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Peak protections for all vaccines occurred 2 weeks after the last dose, and high protection is maintained through Day 60 when the antimicrobial component of PEP is currently recommended to end.

The data demonstrate high levels of protection in NHP models and high predictive probability of survival in humans 2 weeks after the second dose of vaccine. Discontinuation of the antimicrobial component of PEP once peak immune response is reached would shorten the antimicrobial requirements and potentially reduce AEs related to continued antimicrobial use. Shortening the duration of the antimicrobial component of PEP might improve adherence.

The WG felt that the antimicrobial component of PEP could be discontinued at 42 days after initiation of vaccine if given on schedule for both the licensed and dose-sparing schedules. However, the second dose of vaccine is critical to produce high antibody titers. To take into consideration that in an emergency response the vaccine may not be given exactly on schedule, the WG advised that immunocompetent individuals should continue antimicrobials for at least 42 days or 2 weeks after their last dose of the vaccine series, whichever comes last. There is no reason to suggest that giving vaccine would lengthen the need for antimicrobial PEP, so the WG saw no need to continue antimicrobials past 60 days, which is the recommended length of antimicrobial PEP when not given in conjunction with vaccine. Persons with an immunocompromising condition that might interfere with the ability to develop an adequate immune response should receive antimicrobials for 60 days concurrent with vaccine. The WG also felt that it was important to note the once vaccine and antimicrobials are completed, any illness within 2 weeks should prompt evaluation for anthrax. If anthrax is suspected, treatment should be with classes of antimicrobials not used for PEP.

The WG's proposed recommendations on antimicrobial duration read as follows:

- For immunocompetent individuals, AbxPEP should be given concurrent with VxPEP and AbxPEP should continue for at least 42 days or two weeks after their last dose of the vaccine series, whichever comes last. Individuals that do not start or complete the vaccine series should receive AbxPEP for 60 days. AbxPEP should not exceed 60 days.

- Persons with an immunocompromising condition that might interfere with their ability to develop an adequate immune response should complete 60 days of AbxPEP concurrent with vaccine. Immunocompromising conditions include [will define].

- Once VxPEP doses and AbxPEP have completed, any illness within 2 weeks should prompt evaluation for anthrax. If anthrax is suspected, treatment should include at least two classes of antimicrobials with activity against *B. anthracis* and anthrax antitoxin. The classes of antimicrobial that are chosen should differ from the class/es of antimicrobial/s used for prophylaxis of that individual.

Discussion Points

Dr. Hahn (CSTE) said that looking at the recommendations her thought is that everybody should get 60 days. In a campaign, people would be going down one line to get their vaccine and another to get their antimicrobials. It will be a challenge to coordinate that, especially if people are getting different doses or if during the campaign a dose-sparing strategy is employed. She thinks there would be mass confusion to do anything other than give everybody 60 days of antibiotics, especially if there are plenty of antibiotics. Also, as noted, some people are not going to come back for the subsequent doses of vaccine. If they have 60 days of antimicrobials,

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they will also be protected. When people do return for their second or third dose would be the time to counsel them on reducing the 60-day antimicrobial component.

Dr. Bower explained that the rationale was to get people off of antimicrobials as soon as there is believed to be an adequate immune response, because there is some risk to taking antimicrobials over a continuous period of time. In terms of causing confusion, he would counter that people with immunocompromising conditions are going to be in the vast minority. Thus, a greater good will be done for the population by keeping them off of antimicrobials if they are not benefitting from those antimicrobials. One of the recommendations was that those who do not finish the vaccine schedule should complete 60 days of antimicrobials.

Dr. Lee asked whether there was any sense of which immunocompromising conditions would be included, and whether both humoral and immune defects would be considered versus either/or.

Dr. Bower said that while he would like to have presented a list, the WG is still working on this, and he wants to speak with additional colleagues who know more about some of the routinely used vaccines to find out what they have come up with for conditions that do not lend themselves to a robust immune response. For example, he would like to know if there are any data to show how asplenic people have responded to the anthrax vaccine. They would like to develop a list of immunocompromising conditions, including advanced age.

Dr. Whitley Williams (NMA) noted that it is often forgotten that children also can be exposed during a bioterrorist attack. She asked whether AVA is now FDA-approved for children.

Dr. Bower replied that it is not licensed in children, so it would have to be under an IND to be used in children. There has been communication with AAP which believes that since there are no data in children, the risk of anthrax in the pediatric population is greater than the unknown risk of AEs related to the vaccine. Basically, the recommendation would be that children would receive the same regimen as adults, but it would have to be given under an IND.

Dr. Whitley Williams (NMD) noted that in a group situation with many children involved, the process of obtaining an IND usually goes through an Institutional Review Board (IRB).

Dr. Bower indicated that CDC has been working with its state and local partners to make sure that they could pull this off. The plan is to get antimicrobials in people very quickly, and the vaccine within a few days after that.

Dr. Weber (SHEA) indicated that the University of North Carolina (UNC) practices for these types of events each year. They set up a 24/7 influenza clinic during which 2000 to 5000 people are immunized. They also have a Co-Chair on their IRB who is on call 24/7, so they can get approval immediately for an emergency IND. That happens at least once a month for some patients with some drugs, so that can be done very fast.

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Human Papillomavirus (HPV) Vaccines

Introduction

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

Dr. Szilagyi indicated that the HPV vaccine session would include two parts, the first an update on HPV vaccine safety, focusing on 9vHPV; and the second background and data for consideration of harmonization of the HPV vaccination age recommendations for males and females.

The HPV vaccine session periodically includes updates on HPV vaccine safety. ACIP has heard few post-licensure safety data on 9-valent HPV vaccine (9vHPV), the only HPV vaccine distributed in the US since late 2016. Since licensure of 9vHPV in December 2014, 29 million doses have been distributed in the US. Dr. Szilagyi indicated that 9vHPV safety data from VAERS and the VSD Rapid Cycle Analysis (RCA) would be presented during this session. These data formed the initial body of evidence on the post-marketing safety profile of this vaccine. As a reminder, the quadrivalent and 9-valent HPV vaccines are quite similar in that they are both virus-like particles (VLP) vaccines and manufacturing is similar. The 9-valent vaccine has more adjuvant content and 5 additional VLPs. There are over 10 years of reassuring and robust safety data for the quadrivalent vaccine.

Dr. Szilagyi indicated that the second part of this session would address a policy issue that the WG has been discussing over the past year, harmonization of HPV vaccination age recommendations for males and females. The current HPV vaccination recommendation is for routine vaccination at age 11 to 12 years although it can be started at age 9 years, with catch-up vaccination through age 26 years for females and age 21 years for males. Males 22 through 26 years of age may be vaccinated. The issue being discussed by the WG is harmonization of the upper age at 26 years for both females and males. Presentations for this section include background and introduction to this issue, data on trends in HPV-associated cancers in the US, and the current understanding of the epidemiology of HPV in males.

9-Valent HPV Vaccine Safety Data: VAERS Update

Jorge Arana, MD, MPH
Immunization Safety Office
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Dr. Arana provided a safety update of 9vHPV vaccine based on data from VAERS. As a reminder, 9vHPV was licensed in the US in 2014[1]. In February 2015, ACIP recommended 9vHPV as one of three HPV vaccines that can be used for routine vaccination in the US[2]. By the end of 2016, manufacturers stopped marketing bivalent (2vHPV) and quadrivalent (4vHPV) vaccine in the US, leaving only 9vHPV available for this country[2]. Approximately 29 million doses of 9vHPV had been distributed in the US between December 2014 – December 2017[3] [[1] https://www.cdc.gov/hpv/downloads/9vhpv-fda.pdf, [2] https://www.cdc.gov/hpv/downloads/9vhpv-guidance.pdf, [3] Kuter B (Merck), personal communication, 25th January 2018].

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In terms of the safety profile described in FDA's regulatory action recommendation based on 7 9vHPV vaccine safety pre-licensure studies[1,2]. Before 9vHPV vaccine was licensed by FDA, the safety of this vaccine was evaluated in more than 15,000 study participants. The results of pre-licensure studies showed that 9vHPV vaccine to be generally well-tolerated. The safety profile was similar to that of 4vHPV; however, there was more injection site-related swelling and erythema after 9vHPV compared to 4vHPV vaccine. Among those inadvertently vaccinated in pregnancy[3] during clinical studies, the proportion of adverse outcomes observed was consistent with those observed in the general population. There was an imbalance in spontaneous abortion (SAB) following 9vHPV vaccine during pregnancy compared to 4vHPV vaccine; however, the SABs observed were within what is expected for early loss of pregnancy. Rates of SAB in the 9vHPV group were not elevated compared to background rates[4] [[1] http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf; [2] https://clinicaltrials.gov/ct2/show/NCT01651949?term=v503&rank=3; [3] 9vHPV is FDA Category B for pregnancy; [4] Wilcox A et al. Incidence of early loss of pregnancy. *NEJM* 1988].

The objective of this presentation was to describe the safety profile of reports submitted to VAERS after 9vHPV vaccine. As a reminder, VAERS[1] is a passive national vaccine safety monitoring system, run by CDC and FDA. Like any passive system, VAERS has strengths and limitations. The strengths are that it is a national database that accepts reports from anyone, it allows for rapid signal detection, can detect rare AEs, and the data are available to the public. The limitations include reporting bias, inconsistent data quality and completeness, and lack of an unvaccinated comparison group. Because of these limitations, it is generally not possible to assess causality using only VAERS data.

VAERS is an important signal detection system that can generate hypotheses and help to identify potential vaccine safety concerns that can be studied in more robust data systems. Surveillance includes US 9vHPV vaccine reports received from December 1, 2014 through December 31, 2017. Pregnancy reports were excluded, given that there is an ongoing separate analysis of pregnancy-related reports following HPV vaccine. Serious[1] reports are defined based on the Code of Federal Regulations 21 CFR 600.80 as death, life-threatening illness, hospitalization, prolongation of hospitalization, or permanent disability. Signs and symptoms of the AEs on each report are coded using the Medical Dictionary for Regulatory Activities (MedDRA)[2] Preferred Terms (PTs). PTs are not mutually exclusive, and a single report may be assigned more than one PT. An automated analysis of 9vHPV reports is performed. Clinical review is done of reports for select conditions of clinical interest. Conditions of historical interest include anaphylaxis, Guillain-Barré Syndrome (GBS), and death. Of more recent interest, reviews have included reports of complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), and primary ovarian insufficiency (POI). Empirical Bayesian[3] data mining is conducted by the FDA and is used to detect disproportionate reporting in the VAERS database for AEs after 9vHPV, and helps to identify AEs reported more frequently than expected after 9vHPV compared with other vaccines in the VAERS database [[1] Based on the Code of Federal Regulations 21 CFR 600.80; [2] Medical Dictionary for Regulatory Activities (https://www.meddra.org/); [3]Bate, A. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiology and Drug Safety, 2009:18: 427-436].

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In terms of reports to VAERS following HPV, meningococcal, and Tdap vaccines from 2006-2017, there was a spike in 4vHPV in 2007 and 2008 following licensure in 2006. There was then a decline, which is a common phenomenon seen in passive systems such as VAERS after licensure of a new product. The same phenomenon is noted for 9vHPV vaccine in 2016 and 2017. To summarize 9vHPV vaccine reports for the first three years post-licensure, there were 7244 total reports. Of those, 31% were female and 22% were males. Note that gender was unknown in almost half of the reports, which is a limitation of the passive system. Overall serious reports were about 3% and deaths comprised 0.1% of all reports. Of the 7244 reports, 64% were made by the manufacturer. The median age was 14 years and median onset interval was Day 0 or the day of vaccination. In 75% of reports, 9vHPV vaccine was given alone. This table shows the most frequently reported signs and symptoms:

Top 10 reported signs and symptoms[1] after 9vHPV in VAERS, Dec 2014-Dec 2017

Non-serious (n=7,058)	N (%)
Dizziness	529 (7)
Syncope	488 (7)
Headache	355 (5)
Injection site pain	316 (4)
Injection site erythema	314 (4)
Nausea	313 (4)
Pyrexia (fever)	283 (4)
Loss of consciousness	273 (4)
Injection site swelling	266 (4)
Pallor	235 (3)

Serious[2] (n=186)	N (%)
Headache	63 (34)
Dizziness	50 (27)
Nausea	48 (26)
Fatigue	42 (23)
Pyrexia (fever)	35 (19)
Asthenia (weakness)	34 (18)
Vomiting	33 (18)
Syncope	29 (16)
Abdominal pain	26 (14)
Loss of consciousness	26 (14)

[1] As coded using the MedDRA preferred terms (PT); more than one code may be assigned to a single event
[2] Based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization or permanent disability

For the above table, it is important to focus on the percent rather than the raw numbers. Local or systemic signs are consistent with what was reported in pre-licensure clinical studies. Dizziness, syncope, and headache were the three most frequent non-serious reports. Headache, dizziness, and nausea were the most common serious reports.

Regarding the clinical review of select conditions beginning with conditions of historical interest, in the data 9 reports of anaphylaxis were reported. After clinical review, 3 reports were confirmed[1] having met the Brighton diagnostic criteria for anaphylaxis. Among these confirmed reports, 2 received 9vHPV alone. The remaining reports did not contain sufficient information. There were 8 reports of GBS, 4 of which were confirmed based on Brighton Criteria for GBS[2]. Of these 4 reports, 3 describe a viral respiratory illness 2 to 4 weeks prior to presentation of GBS symptoms. The remaining reports did not contain sufficient information to make a determination. There were 7 reports of death among which 5 were “hearsay” reports based on indirect information or information that someone saw on the internet and 2 were verified by autopsy and/or certificate of death. The cause of death for these 2 reports were cardiac arrest and cerebellar aneurysm [[1] Ruggeberg et al. Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data Vaccine. 2007 Aug 1;25(31):5675-84; and [2] Sejvar et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011 Jan 10;29(3):599-612].

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Conditions of recent interest also were reviewed. There was 1 report of CRPS for which the information was insufficient, so it was classified as possible CRPS[1]. There were 17 reports of possible POTS, of which 6 partially met the clinical diagnostic criteria for POTS[2]. The remaining reports did not contain sufficient information to confirm a diagnosis of POTS. No pattern of concern was noted. There were 3 reports of possible POI cases; however, these reports did not contain sufficient information to meet diagnostic criteria, or were classified as "hearsay" meaning that they were based on indirect information or read on the internet[3] [[1] Harden et al. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. Pain. 2010; 150(2):268-274; [2] Arana et al. Reports of Postural Orthostatic Tachycardia Syndrome After Human Papillomavirus Vaccination in the Vaccine Adverse Event Reporting System. J Adolescent Health. 2017 Nov;61(5):577-582; and [3] The American College of Obstetricians and Gynecologist. Committee on Adolescent Health. Primary Ovarian Insufficiency in Adolescents and Young Adults. Committee Opinion. July 2014 Number 605].

Empirical Bayesian data mining by FDA colleagues showed disproportional reporting of syncope[1]. Syncope historically was reported disproportionally for 4vHPV. Syncope is a labeled AE. Other PTs signaled but do not represent an AE, such as a drug administered to a patient of an inappropriate age and other administration errors. No other disproportional reporting for 9vHPV has been noted [[1] Data provided by FDA/CBER Division of Epidemiology; and [2] Adverse Effects of Vaccines: Evidence and Causality, Institute of Medicine, Aug 2011 (http://www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx)].

In summary, VAERS received 7244 reports following 9vHPV vaccine during the study period from December 1, 2014 through December 31, 2017. Most (97%) reports were non-serious. The most frequently reported AEs after 9vHPV vaccine were dizziness, syncope, headache, and injection site reactions. Approximately 29 million 9vHPV doses were distributed in the US during this timeframe, with no new safety signals or unexpected patterns observed in VAERS reports. The safety profile of 9vHPV vaccine is consistent with data from pre-licensure trials and post-licensure data on 4vHPV. CDC and FDA will continue to monitor and evaluate the safety of 9vHPV vaccine.

9-Valent HPV Vaccine Safety Data: VSD RCA

Jim Donahue PhD, DVM
Marshfield Clinic Research Institute

Dr. Donahue presented the results of recently completed VSD RCA surveillance that assessed the safety of 9vHPV vaccine. Given that the initial surveillance is sufficiently completed, there will now be a shift to maintenance surveillance that will take advantage of the programmatic infrastructure that has been established in this RCA.

As a reminder, the VSD is a collaboration between CDC and 8 integrated healthcare plans to monitor vaccine safety using active surveillance and observational studies. RCA was developed to permit more rapid assessment of vaccine safety using near-real time data. AE signals are interpreted as potential associations in an RCA. Medical record review or additional investigations are performed as appropriate to determine whether the potential associations are, in fact, true associations. This surveillance is similar to the RCA of 4vHPV vaccine published in 2011 that documented 600,000 doses and found no statistically significant associations [Gee J, et al. *Vaccine* 2011].

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The objectives of the 9vHPV vaccine RCA are to conduct near real-time surveillance from 2015 through 2017 to assess the risks of pre-specified AEs following receipt of 9vHPV vaccine, and to monitor 9vHPV vaccine usage in VSD over time. The RCA design is typically a prospective or hybrid type cohort. The surveillance period for this study was October 4, 2015 through October 3, 2017 and include males and females 9 through 26 years of age who were enrolled in one of the 6 participating VSD sites.

As a reminder, the 9vHPV vaccine recommendation is for routine vaccination at age 11 through 12 years for males and females, females aged 13 through 26 years and males 13 through 21 years who were not adequately vaccinated, and catch-up through age 26 years for certain other groups. A 3-dose series was recommended until October 2016 when ACIP recommended a 2-dose series if receiving first dose before age 15 years [Meites E, et al. *MMWR*, 2016]. There are more antigens and more adjuvant in 9vHPV vaccine compared to 4vHPV vaccine, but they have similar and very good safety profiles based on numerous studies.

In an RCA, pre-specified AEs are identified for monitoring. Ideally, the characteristics of these are that are clinically well-defined, have acute onset fairly rapidly after vaccination, result in a medical encounter, and are biologically plausible. For this RCA, all AEs were included that were monitored in the 4vHPV vaccine analysis. Additional AEs for the 9vHPV vaccine RCA included injection site reactions as these appeared to be more common among the 9vHPV group in clinical trials compared to 4vHPV vaccine, and pancreatitis as this was reported in VAERS following 4vHPV vaccine. This table provides additional details about these AEs and the setting in which they had to occur (outpatient, emergency department, inpatient), the post-vaccination window, and the primary comparison group:

Pre-Specified Adverse Events

Adverse event	Setting	Post-vax window	Primary comparison group
Syncope	OP, ED, IP	Day 0	Concurrent
Injection site rxn, w/ and w/o day 0	OP, ED, IP	0-6, 1-6 days	Concurrent
Allergic Reactions	OP, ED, IP	0-2 ED, IP 1-2 for OP	Concurrent
Seizure	ED, IP	0-42 days	Concurrent
Anaphylaxis	OP, ED, IP	0-2 days	Concurrent
Appendicitis	ED, IP	1-42 days	Historic
Pancreatitis	ED, IP	1-42 days	Historic
Guillain-Barré Syndrome (GBS)	OP, ED, IP	1-42 days	Historic
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	OP, ED, IP	1-180 days	Historic
Stroke	ED, IP	1-42 days	Historic
Venous Thromboembolism (VTE)	OP, ED, IP	1-42 days	Historic

*Historical comparison is based on VSD data from 2007-2014. Concurrent comparison is based on non-HPV vaccination visits during the surveillance period.

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The general RCA approach is near real-time surveillance of AEs using weekly aggregate data. Analyses are performed every week with a fairly straightforward overall approach comparing the observed versus expected counts or to actual counts from unexposed reference groups. Given that these analyses are performed every week, false positives are a concern so sequential analyses are used to detect signals while maintaining a pre-defined Type I error rate. For each AE, subgroups are examined and defined by age, sex, and dose. Medical record review or additional analyses are performed as needed subsequent to a signal.

Two main types of sequential analytic methods were used: Maximized Sequential Probability Ratio Test (MaxSPRT) and the closely related Conditional MaxSPRT(CMaxSPRT)[1] method and the Exact Sequential Analyses (ESA). MaxSPRT methods are optimal for uncommon or rare events such as anaphylaxis, appendicitis, GBS, chronic inflammatory demyelinating polyneuropathy (CIDP), pancreatitis, seizures, stroke, and venous thromboembolism (VTE). The background rates come from two different sources in this RCA study, both of which are historical comparison groups from the 2007 through 2014 VSD. The first comparison group was the general VSD population ages 9 through 26 for which the MaxSPRT approach was used. The second comparison group was the vaccinated population ages 9 through 26 who were vaccinated with non-HPV vaccines routinely given to adolescents (Tdap, TD, meningococcal, HepA, and varicella). The CMaxSPRT approach was used for this group, which is especially designed so that it accounts for the fact that the sample sizes are smaller. If MaxSPRT was used, there would be more issues with inflated type I errors. The ESA is optimal for more common outcomes, but it was done for all AEs in the RCA. In this case, the comparison group was a concurrent comparison group of individuals 9 through 26 years old vaccinated with routine non-HPV adolescent vaccines during the same timeframe of as those vaccinated with 9vHPV [[1]Kulldorff M, et al. A maximized sequential probability ratio test for drug and vaccine safety surveillance. Seq. Anal. 2011;30:58-78; [2]Lewis E, et al. Exact sequential analysis for vaccine safety surveillance. In: NFID 12th Annual Conference on Vaccine Research. 2009].

Once an RCA signal is seen, data quality is assessed for errors, anomalies, or unusual patterns. Typically, a temporal scan analysis is done to identify clustering within the risk window. Medical record reviews are often done to confirm cases, especially if they are serious or uncommon. If concerns remain, additional analytical epidemiology studies are conducted such as self-controlled risk interval (SCRI), case-centered, or case-control studies.

Regarding the results, not surprisingly those 9 through 17 years of age had more vaccinations with the males having had slightly more vaccinations than the females; whereas, the opposite was true for those 18 through 26 years of age. There were a couple of prominent spikes in those 9 through 17 years of age that occurred around August, just before beginning school. That was not observed in the older group 18 through 26 years of age.

For all of the AEs evaluated using MaxSPRT there was only 1 signal, which was pancreatitis in males 18 through 26 years of age. There were 8 exposed cases of pancreatitis in this subgroup. The relative risk was 3.1 and the test statistic was 3.71, which was in excess of the critical value of 2.87. Important to remember about the test statistic and critical value is that once the test statistic exceeds the critical value, it is statistically significant at the 0.05 level. There was no signal for this outcome in the CMaxSPRT analysis. The relative risk was a fairly modest 1.84 and was not statistically significant. Pancreatitis also was evaluated in the ESA in which case the relative risk was a high 4.7, but the p-value was 0.47 so again not significant. Medical record review was done for the pancreatitis cases, which found that for 6 of the 8 cases, the provider or clinician stated in the medical record that there was a cause for the pancreatitis of alcohol, trauma, metastatic cancer, or that they were not pancreatitis. One case

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was determined to be possible, but the provider considered it more likely that the symptoms were related to reflux. That left 1 confirmed incident case without an alternative cause or explanation. Based on the fact that the medical review showed that 7 of the 8 cases were unlikely to be related to the vaccine and that two other analyses showed no signal, no further investigation was warranted. All of the outcomes analyzed using the MaxSPRT were also analyzed using the CMaxSPRT and no signals were generated.

Regarding the ESA results, signals were detected for syncope, injection site reactions, allergic reactions, and appendicitis. This table provides more details about dose-specific signals:

Summary of ESA Signals

Adverse event	Subgroup	RR	Cases (exp.)*
Syncope	Females, 18-26	1.9	98 (67)
	Females, 18-26, dose 1	2.2	65 (35)
	Females, 18-26, dose 2	2.0	60 (25)
Inj. site rxn, includes day 0	Males, 18-26, dose 3	95	3 (2)
	Males, 18-26, dose 1	11.1	14 (9)
	Females, 18-26, dose 1	1.8	71 (34)
Inj. site rxn, excludes day 0	Males, 9-17, dose 3	2.5	29 (18)
Allergic rxn, ED or inpatient	Females, 9-17	2.7	33 (26)
Allergic rxn, outpatient	Females, 18-26, dose 2	1.9	38 (15)
Appendicitis	Males, 9-17, dose 3	2.1	50 (30)

*Counts at first signal

For the most part, the relative risks are fairly modest. The one standout is injection site reactions among males 18 through 26 years of age for Dose 3 with a relative risk of 95. It is important to note that the data in this table comes from the first signal that was generated, which occurred during the first week of surveillance and there were 3 total cases, 2 of which were exposed. Based on the fact that a small number of cases occurred during the first week, it was decided that the best course of action was to follow this outcome fairly closely over the next several weeks. This showed that the total number of cases increased, but the total number of exposed cases did not. The relative risk decreased to about 2 or 3 fairly quickly. A similar phenomenon occurred among males 18 through 26 years of age for Dose 1. Both syncope and injection site reactions were expected based on clinical trials for 9vHPV vaccine and clinical experience with 4vHPV vaccine. Therefore, no follow-up studies were planned for those.

For the allergic reactions that occurred in females 9 through 17 years of age in the ED and inpatient settings, 26 cases were exposed to 9vHPV vaccine. Over two-thirds of the cases turned out to be something else, such as injection site reaction, allergic reaction to food or a drug, or coding errors. Follow-up was also done to determine whether there was a signal in the outpatient setting for this same subgroup of females 9 through 17 years of age. This was done because there was an association between the vaccine and allergic reactions in the ED and

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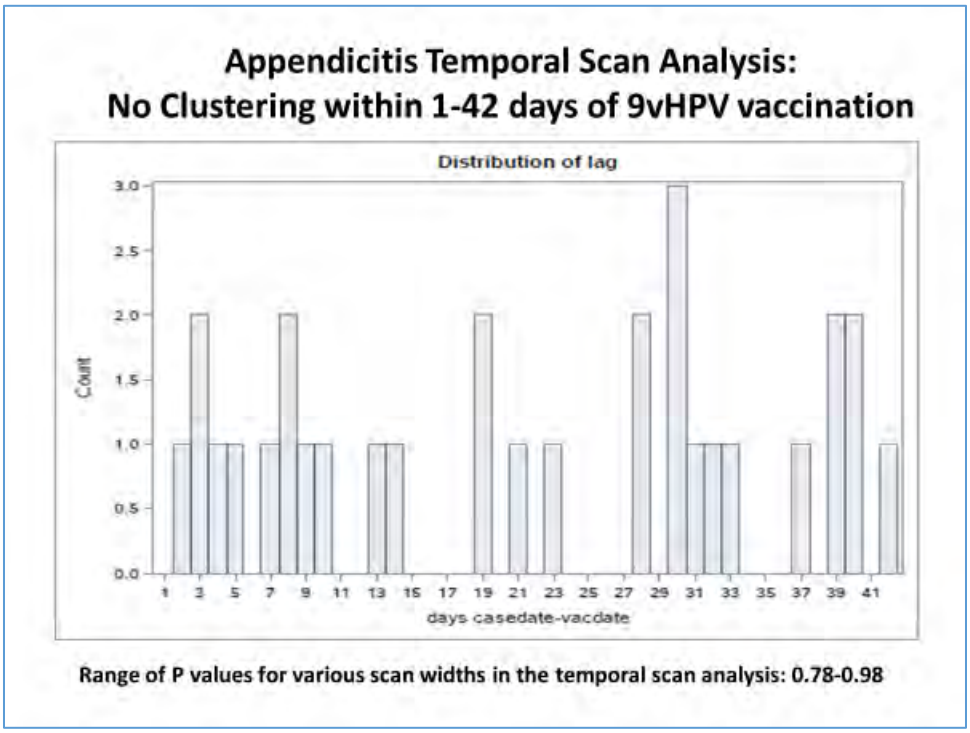
inpatient settings, and it was suspected that some evidence of this also would be found in the outpatient setting. It turned out that there was no signal in the outpatient setting. The relative risk was 0.85 and the p-value was 0.75, so there was no association for that particular setting. Based on the medical record review as well as these analyses, it was determined that no further investigation was warranted. Similarly, for the allergic reaction in the outpatient setting among females 18 through 26 years of age following Dose 2, most of the 15 cases were due to injection site reaction or some other allergy. They were not likely to be related to receipt of 9vHPV vaccine. There also was no signal in the ED and inpatient settings for that particular subgroup. The relative risk was 0.4 and the p-value was 0.75. Again, no signal and no further investigation planned.

For the ESA signal of appendicitis in males 9 through 17 years of age following Dose 3, 30 cases were exposed to 9vHPV vaccine. Of these, 20 were vaccinated with 9vHPV vaccine only and 10 received 9vHPV + concomitant vaccine. The ESA results showed a relative risk of just over 2 with a p-value of 0.03. This particular AE was also assessed with MaxSPRT and CMaxSPRT at the time of the ESA signal and there was no increased risk. In fact, during the entire surveillance period there was no increased risk. The relative risk was 1.3 to 1.6 and did not approach statistical significance.

As mentioned earlier, a temporal scan analysis can be done when there is a signal to look for clustering over time. This bar chart shows the counts of the cases that occurred over the 42-day risk period by when they occurred:



Looking at the bar chart visually, there does not appear to be any clustering. However, the program that produces this also looks at various windows and computes p-values to determine whether they are significant. For all of the windows that were computed, the p-values ranged from 0.78 to 0.98 so clearly no evidence of temporal clustering of appendicitis following vaccination.

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A medical record review was done for appendicitis. The appendicitis diagnosis was confirmed in all 30 exposed cases. All 30 had appendectomies and 28 of 30 were confirmed by pathology. Next, a SCRI analysis was done for appendicitis. The SCRI is a self-controlled analysis like a SCCS. The SCRI includes risk intervals and control intervals that are self-matched within an individual, which inherently controls for time-stable confounders. The risk window used was 1 to 42 days post-vaccination. The main unexposed window was 43 to 84 days during which there were 30 cases, which all were chart reviewed as well. The relative risk was 1.42 with a 95% confidence interval of 0.77 to 2.62, so there was no evidence of a significant association there.

The strengths of the 9vHPV RCA is that there was near real-time access to electronic medical record (EMR) data. The VSD also has the capacity to conduct medical record review as needed. Nearly 900,000 vaccinations were documented, and a variety of analytic methods were used that are largely complementary. One of the limitations when using near real-time data is that they can be unstable. Even though there is a built-in lag period, there can still be some variation and instability. In an observational study like this, there is also the possibility for miscoding or secular trends in coding and secular trends in disease incidence. Seasonality of vaccination and disease can be a limitation, but this was assessed and there was no evidence of this in this RCA study.

To conclude, this particular RCA signaled for several AEs following 9vHPV vaccine receipt. Syncope and injection site reactions were expected, and all other signals were further investigated. The signals for allergic reaction, pancreatitis, and appendicitis were not confirmed after further evaluation. Weekly surveillance has concluded for 9vHPV vaccine, but periodic analysis will be performed to ensure continued safety, especially for some of the more serious and uncommon outcomes such as anaphylaxis, GBS, CIDP, stroke, and VTE. There are not a lot of observations or events in those areas, so with additional surveillance it is hoped that there will be a more refined estimate of risk or lack thereof.

Discussion Points

Referring to Dr. Arana's slide 10, Ms. Pellegrini inquired as to whether the onset interval range was correct at 0 to 751 days.

Dr. Arana confirmed that it was correct. Sometimes reports are received in VAERS years after vaccination.

Dr. Walter asked whether there were any other known risk factors for syncope such as people receiving other vaccines concurrently with 9vHPV vaccine.

Dr. Arana replied that thousands of reports are received in VAERS with syncope. Unfortunately, there is limited information in those reports. In reviewing those, they have observed that some of the patients have received other vaccinations simultaneously.

Dr. Donahue indicated that there were a couple of thousand accounts of syncope. While they have not examined all of those, they do have the ability to determine whether/what vaccines were given in combination with 9vHPV vaccine.

Dr. Bernstein asked how these data are incorporated, if at all, in the Vaccine Information Statements (VISs).

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Dr. Arana responded that they work with their communication team to report this information as quickly as possible on the website, and other teams are also receiving data in terms of VAERS reports.

Dr. Messonnier indicated that the VISs are the responsibility of the Immunization Services Division (ISD) rather than the Immunization Safety Office (ISO).

Dr. Wharton (ISD) replied that the VISs are updated periodically when there is important new information that needs to be included.

Dr. Messonnier added that the ISDs are posted for public comment as well, so it is quite a rigorous process.

Dr. Grogg (AOA) noted that in some of the earlier studies with HPV vaccine, nobody fainted. The importance of post-surveillance is great because the protocol required recipients to lie down for 30 minutes after receipt of the vaccination.

Dr. Donahue indicated that they did not do a systematic sampling of syncope and look at charts, but they did take a small informal look. While it is not reflective of much of anything, a large majority of the 18 cases they assessed were not incident syncope. They were actually "history of" and people presented because they had a syncopal episode and were vaccinated while there.

Harmonization of HPV Vaccination Age Recommendations for Females and Males

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Dr. Markowitz discussed current recommendations for HPV vaccination, a brief history of ACIP policy for HPV vaccination of males, and ACIP WG considerations for harmonization of age recommendation for males and females through 26 years of age.

As a reminder, routine vaccination is recommended at age 11 or 12 for females and males. The series can be started beginning at age 9. For persons who are not previously vaccinated, vaccination is recommended for females through age 26 years and males through age 21 years. Males 22 through 26 years of age may be vaccinated. Vaccination is also recommended for males 22 through 26 years of age who are immunocompromised (including HIV), who are transgender, and/or who have sex with men [*MMWR* 2014;63 (RR05); *MMWR* 2015;64].

The catch-up recommendations do not affect the child and adolescent schedule, but in Figure 1 of the adult immunization schedule there are separate rows for females and males and there is a separate column for those 19 through 21 years of age and 22 through 26 years of age. Harmonization would simplify this particular schedule. In Figure 2 of the adult schedule for adults 19 years of age and older by medical condition and other indications, there is a female row and a male row.

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For a brief overview of the history of the program from 2006 when vaccination was recommended females through 2016, policy changes were made as a result of additional vaccines being licensed, males being added to the program, and data to support the 2-dose schedule. Dr. Markowitz reviewed the changes that specifically affect males from 2009, 2011, and 2015.

In 2009, FDA licensed quadrivalent HPV vaccine for use in males aged 9 through 26 years for prevention of anogenital warts based on data from a clinical trial in males in which the endpoint was anogenital warts. At that time, the trial was ongoing to evaluate efficacy against anal precancers. ACIP reviewed data at that time, including data on epidemiology, sexual behavior, burden of disease, programmatic issues, and cost-effectiveness and decided to wait until there were efficacy data against anal precancers in males before considering a routine recommendation. There also was uncertainty at that time about impact and cost-effectiveness.

In 2009, ACIP made what was called a “permissive recommendation” that quadrivalent vaccine may be given to males 9 through 26 years of age. There are two items of note between 2009 and 2011. First, FDA added prevention of anal cancer in males as well as females as an indication. This occurred after review of results from a trial in males that was submitted as a Supplemental Biologics License Application (sBLA) [Palefsky J, et al. *NEJM* 2011]. Second, vaccination coverage in adolescent girls was increasing but slowly and continued to be low. These data are from the National Immunization Survey-Teen (NIS-Teen) in 2010 showing coverage in females for at least 1 dose of 49% and 3 doses of 32%.

During meetings over several years, ACIP reviewed the cost-effectiveness of including males in the routine program. In all models, male vaccination was less cost-effective than female vaccination. All of the models also showed that the cost per QALY gained of including males depended on a variety of assumptions, including the health outcomes that were included and also female vaccination coverage. With increasing coverage in females, male vaccination became less cost-effective due to herd protection from female vaccination. ACIP also heard data on cost-effectiveness of vaccination of men who have sex with men (MSM). Modeling found that vaccination of MSM is cost-effective through age 26 years [Kim J and Goldie S, *BMJ* 2009; Chesson H, et al. *Vaccine* 2011; Kim J, *Lancet Infect Dis* 2010].

This graphic shows data from one of the models presented to ACIP in 2011 with costs per QALY gained using coverage assumptions based on coverage was in 2010. On the left are females and on the right are males. There are two sets of bars for each, one including all potential HPV-associated outcomes and the other only outcomes for which there is an FDA indication. The different colored bars show the cost per QALY gained for different catch-up age groups and illustrate the increase of cost per QALY with increasing age of vaccination. The yellow bars are the incremental costs per QALY for vaccination of males 22 through 26 years of age. The higher cost per QALY in this age group impacted ACIP considerations for the upper age for males:

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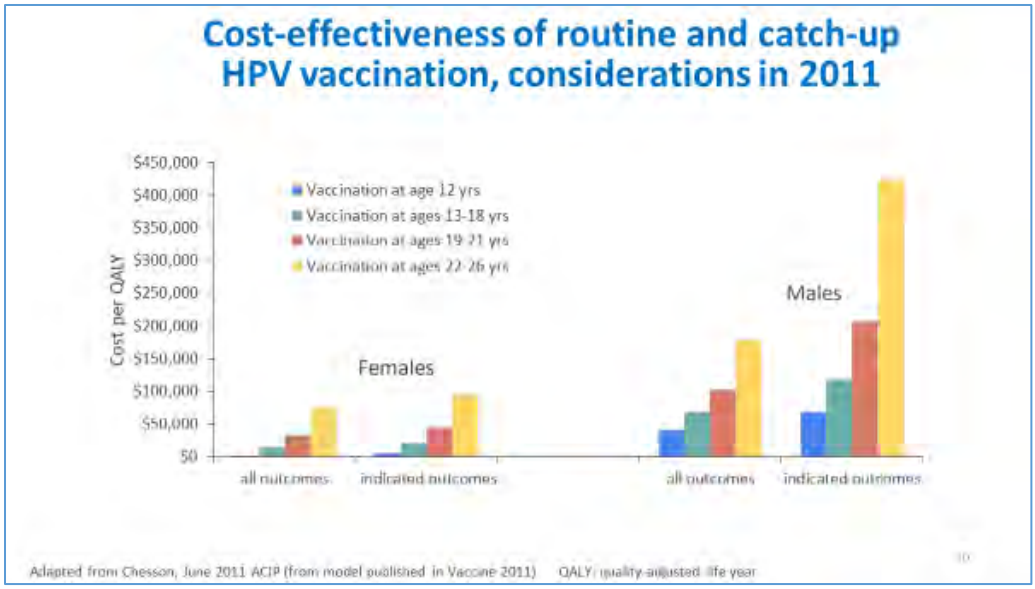

ACIP deliberations and conclusions in 2011 were that quadrivalent HPV vaccine is safe and effective in males. The burden of disease in males justified routine vaccination and there would be likely benefit against all HPV vaccine type-attributable outcomes. Males as well as females should be protected against HPV for equity. Vaccination of adolescent males is cost-effective at current coverage. In addition to protecting heterosexual males and their female sex partners, routine vaccination is the best way to reach MSM and men with this sexual orientation at an age when they could most benefit. As mentioned, ACIP did take into consideration the cost-effectiveness analyses.

Quadrivalent vaccination of males was considered using GRADE. ACIP had just adopted GRADE in 2011. The recommendation was Category A with evidence Type 2. The recommendations for vaccination of males are essentially what they are now. The US was the first country to include routine vaccination of males in the national immunization program. Most countries that have introduced HPV vaccination only have a female program, although more are adopting a gender-neutral vaccination program.

The last policy change was in 2015 when ACIP considered the 9-valent vaccine. FDA licensure for this vaccine was based on an efficacy trial conducted in females and immunobridging studies in females and males. ACIP reviewed 9-valent HPV vaccine using GRADE[1]. ACIP also again reviewed cost-effectiveness at that time, and vaccinating females and males with 9-valent vaccine estimated to be cost-saving compared with 4-valent vaccine[2]. The modeling that was performed considered the current policy for females and males and did not reconsider the age recommendations for males. The recommendation for 9-valent vaccine was Category A with evidence Type 2 for females and Type 3 for males. The lower evidence on males was due to the fact that only immunobridging data were available for the 9-valent vaccine [[1] https://www.cdc.gov/vaccines/acip/recs/grade/hpv-9v.html; and [2]Brisson M et al. *JNCI* 2015].

Over the past year or so, the WG has started consideration for harmonization of the upper age recommendations for females and males. This would simplify the immunization schedule and might facilitate reaching males, including high-risk males.

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For further background for the last part of this presentation, Dr. Markowitz briefly reviewed coverage in the US. ACIP has seen the NIS-Teen data before. Coverage has been increasing in females but slowly, reaching 65% for at least 1-dose coverage and 43% for 3-dose coverage. Coverage has been increasing in males since the routine recommendation in 2001, reaching 56% for at least 1-dose and 32% for 3-dose coverage [Walker T, et al. *MMWR* 2017; 66 NIS-Teen, National Immunization Survey-Teen].

For older individuals 19 through 26 years of age, there are self-reported data from the NHIS. In 2016, at least 1-dose coverage for females 19 through 21 years of age was 51% and 47% for females 22 through 26 years of age. Coverage was lower in males in all of the age groupings. Most of the differences between males and females are due to the 5-year difference between when the routine vaccination was made for females and males and the time it takes for vaccinated individuals to age into the older age groups [Williams W, et al. *MMWR* 2017; Hung MC, et al. https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/NHIS-2016.htm].

Since vaccination is also recommended for MSM through 26 years of age, studies have evaluated coverage in this subgroup. Most of the studies reporting coverage between 2011 and 2015 cannot be directly compared because of differences in methodologies and study populations, but all looked at self-reported receipt of at least 1 HPV vaccine dose among MSM 18 through 26 years of age. While coverage appears to have been increasing, it is still quite low in 2015 at 20.8% [Meites E and Markowitz LE, slide presented at IPV Conference, 2017; NHBS, National HIV Behavior Surveillance; WHBS, Web-based HIV Behavioral Survey among Men Who Have Sex with Men].

To summarize some of the next steps for consideration of harmonization of age recommendations for females and males, although one of the reasons to consider harmonization is to simplify the schedule, the WG also will be updating ACIP on HPV-associated cancers, highlighting changes in the burden in males and females and reviewing the epidemiology of HPV in males. During future ACIP meetings, the WG plans to summarize VE data in males, surveys of values and acceptability regarding the age harmonization policy, and the results of an updated cost-effectiveness analysis. The WG plans to synthesize the evidence using the Evidence to Recommendations (EtR) framework.

As background to the next presentation, Dr. Markowitz noted that population-level impact of the HPV vaccination program is not expected yet on HPV-associated cancers. Monitoring studies in the US have demonstrated an impact of vaccination on HPV prevalence and have shown evidence of decreases in genital warts and cervical pre-cancers in women in their late teens and early 20s. She indicated that the data on trends in HPV-associated cancers were being presented during this session to update ACIP on the burden of disease among males and females and to provide information on the potential impact of the vaccination program.

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Trends in HPV-Associated Cancers in the United States, 1999–2014

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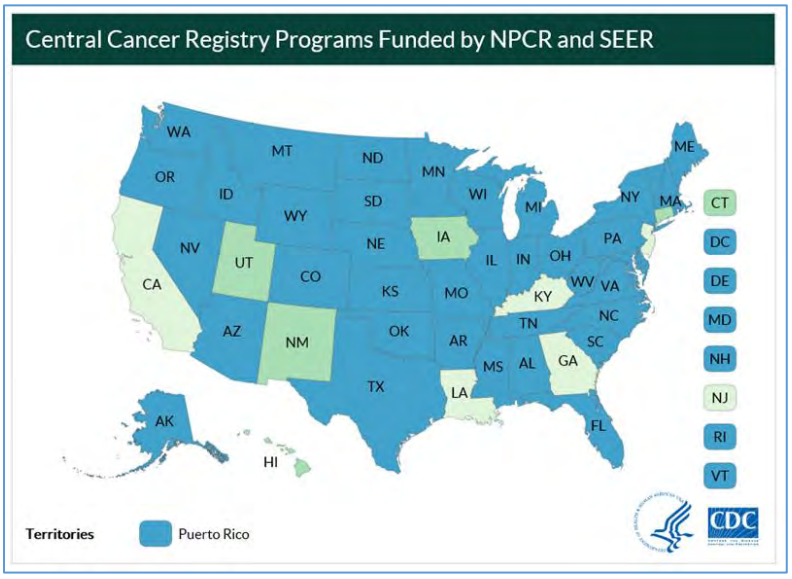
Centers for Disease Control and Prevention

Dr. Van Dyne presented on recent data on trends in HPV-Associated Cancers in the US from 1999 to 2014. HPV is a known cause of cervical cancer, as well as some oropharyngeal, vulvar, vaginal, penile, and anal cancers. Cervical cancer is the only HPV-associated cancer with screening guidelines. There currently are no screening guidelines routinely recommended for other HPV-associated cancers. Because of the long latency period from initial infection to cancer diagnosis, changes are not expected to be observed in HPV-associated cancers due to vaccination at this time. The objective of this presentation was to provide an update on the epidemiology and burden of HPV-associated cancers, which could help to understand where the HPV vaccine could have an impact. Dr. Van Dyne used data to examine trends of HPV-associated cancer types in the US population, looking at these cancer types by age, sex, race, and ethnicity.

Cancer registries do not routinely collect HPV genotyping information. Other studies collect genotyping information, which can then be used to estimate the percentage probably caused by any HPV type. An HPV-associated cancer is defined as cell types in which HPV DNA is frequently found. These include carcinomas of the cervix, which are squamous cell carcinomas (SCCs), adenocarcinomas, and other carcinomas. With other sites, they are only SCCs. These include SCCs of the oropharynx, vulva, vagina, penis, and anus, so they do not include for example sarcomas and melanomas. In addition, the case definition includes being invasive and histologically confirmed.

Cancer data are collected through cancer registries located in all 50 states, DC, and Puerto Rico. Data are reported to two federal registry programs as shown on this map:



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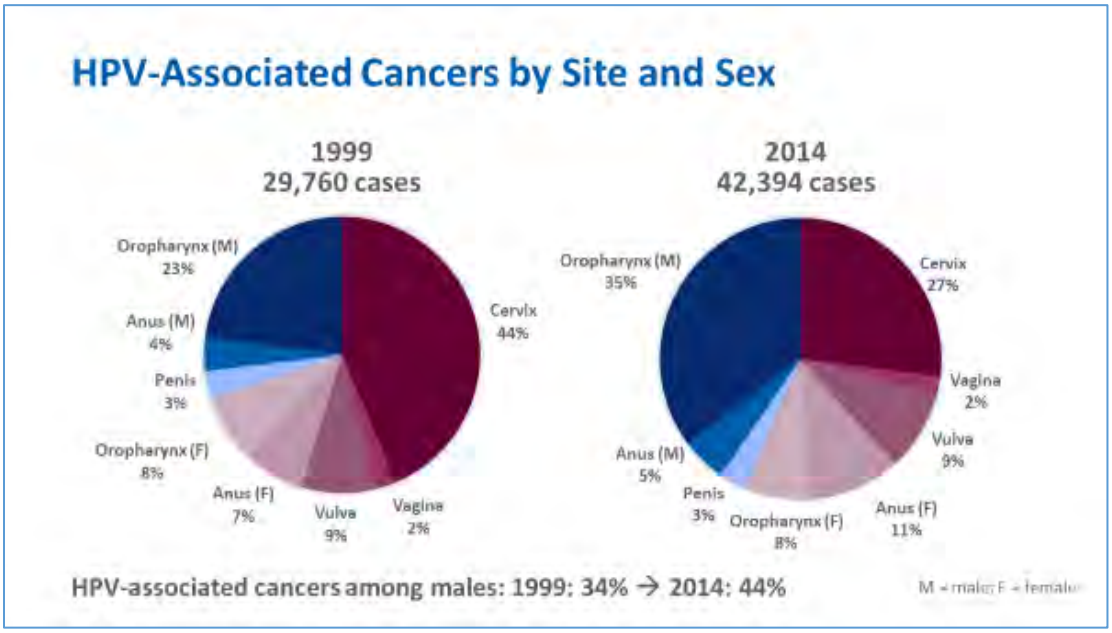
These two programs are CDC's National Program of Cancer Registries (NPCR) in blue and NCI's Surveillance, Epidemiology, and End Results (SEER) Program in green. During 1999 to 2014, the most recent data available, registry data that met specific quality standards covered approximately 97% of the US population.

Average annual percent change (AAPC) is a common method to examine cancer trends using statistical software. AAPC is a summary measure, a weighted average, of percent change per year of cancer incidence rates. For example, an AAPC of 3.0 would be an annual increase of 3% per year. Statistically significant AAPCs were different from zero at the alpha 0.05 level. Rates and trends were calculated by sex, age group, race, and ethnicity. Data were age-adjusted to the 2000 US standard population and data were suppressed for rates, if cases were less than 16 per period.

There were 34,864 cases of HPV-associated cancer diagnosed annually from 1999 to 2014, of which 38% were among males and 62% were among females. The incidence rate was 11.4/100,000 persons per year. These pie charts show data on HPV-associated cancers by site and sex in 1999 to the left and 2014 to the right:



Cervical cancer (in dark red) was 44% of all HPV-associated cancers in 1999 and decreased to 27% of all HPV-associated cancers in 2014. Oropharyngeal cancer among males (in dark blue) was 23% of all HPV-associated cancers in 1999 and increased to 35% of all HPV-associated cancers in 2014. In 1999, 34% of HPV-associated cancers were among males, while in 2014, 44% of all HPV-associated cancers were among males.

In terms of trends for all the HPV-associated cancers from 1999 to 2014, rates of cervical cancer decreased and oropharyngeal cancer among men increased. The trend lines of incidence rates for cervical cancer and oropharyngeal cancer among men crossover in 2009. In 2014, oropharyngeal cancer among men had the highest incidence rate. Rates increased for oropharyngeal cancer among women, anal cancer among men and women, and vulvar cancer. Rates of penile cancer and vaginal cancer were stable.

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To discuss these trends in more depths, for cervical cancer the rate decreased 1.9% per year from 1999 to 2014. This decrease continues a trend observed starting in the 1950s with the introduction of the Pap test when the incidence of invasive cervical cancer declined dramatically. Of note, between 1955 and 1992, cervical cancer incidence declined by more than 60% in the US. In terms of the average annual percent change and 95% confidence interval for cervical cancer by age group, ages 15 through 19 years were suppressed as there were too few cases. Overall, a decrease was seen among all age groups. For women ages 20 through 24 years of age, the rate decreased by 3.8%. Among women greater than 70 years of age, the rate decreased 3.2% per year from 1999 to 2014.

Regarding cervical cancer by race and ethnicity, rates decreased the most among Hispanics and Non-Hispanic blacks. However, rates were also the highest for these two groups. Cervical cancer decreased in all groups except American Indian/Alaska Native (AI/AN). Looking in more detail at cervical cancer trends, from the analysis, the histologies of cervical cancer that declined were SCC and other carcinomas. Adenocarcinomas were stable and arise from cells that may be more difficult to sample during Pap testing. HPV types that cause both SCC and adenocarcinoma are targeted by the HPV vaccine. In the future, declines should be expected to be seen in both SCC and also adenocarcinomas.

In regards to vulvar cancer trends, the rates increased 1.4% per year from 1999 to 2014. In terms of anal cancer trends, rates increased among females and males. For females, rates increased 3.0% per year from 1999 to 2014. For males, rates increased 2.3% per year for the same time period. Several factors could contribute to the increase in anal cancers. Changing sexual behaviors has been investigated, including receptive anal intercourse.

Because oropharyngeal cancers are increasing in men particularly, Dr. Van Dyne presented some addition data for this HPV-associated cancer. To begin with, the locations of oropharyngeal cancer include the soft palate, the side and back walls of the throat, the tonsils, and the back one-third of the tongue, also called the base of the tongue during this presentation. As mentioned earlier, oropharyngeal cancer rates have increased among men and women from 1999 to 2014. Of note, approximately 70% of oropharyngeal cancers are thought to be due to HPV, which is lower than the 90% of cervical and anal cancers that are thought to be due to HPV. The rate of oropharyngeal cancer increased 2.8% per year among men and 0.8 % per year among women from 1999 to 2014. Several factors such as tobacco use, alcohol use, and oral sex behaviors could contribute to oropharyngeal cancer risk. Studies have shown that the increase in oropharyngeal cancer is probably due to increases in oral HPV infection.

Oropharyngeal cancers among men are increasing the most among the older age groups. The rate increase was highest among men ages 60 through 69 years and increased 4% per year from 1999 to 2014. For comparison, rates were stable among women in this same age group. With regard to oropharyngeal cancer by race and ethnicity among men, oropharyngeal cancer rates increased among Non-Hispanic whites and Asian Pacific Islanders and decreased among non-Hispanic blacks. Of note, among black men, special studies have shown a smaller proportion of cancers are attributable to HPV compared with other racial/ethnic groups.

Because cancer registries do not routinely collect HPV genotyping data, sites in the oropharynx that are more commonly HPV DNA positive were assessed. These are in the tonsillar region and base of the tongue. Rates of oropharyngeal cancer among men increased 3.7% per year at the base of the tongue and 3.5% per year at the tonsils. Rates were stable at other sites where HPV is less commonly detected. Specifically, it is the sites where HPV DNA is the most prevalent that are the sites where registry data have shown an increased trend. Among women,

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trends are somewhat similar to men, as oropharyngeal cancer rates have increased among non-Hispanic white and decreased among the non-Hispanic black populations. The rate increase was highest for oropharyngeal cancer among women in the age group 50 through 59 years. Although rates are much lower among women, this is a newer finding to see an increased rate among a sub-group of women.

Regarding the incidence rates of cervical cancer and oropharyngeal cancer among males by age, overall cervical cancer peaks at a younger age than oropharyngeal cancer, but the incidence rates are much higher for oropharyngeal cancer among males above age 49 years. The median age of diagnosis for cervical cancer is 49 years, and the median age of diagnosis for oropharyngeal cancer among males is 59 years. This shows there may be a different amount of time for a vaccine impact between these two groups.

The strengths of this study include that it is a systematic population-based approach to monitor HPV-associated cancers in the US. It uses high quality data from cancer registries. It covers almost the entire US population, so it can be used to look at rare cancers that cannot be looked at with other datasets. This study also assesses trends among age groups and by race and ethnicity. Limitations include that registries do not routinely collect information on HPV DNA status in cancer tissue, so can be used to determine only HPV-associated cancers. Reporting of race and ethnicity uses data from medical records, which might be inaccurate in a small proportion of cases. In addition, registries do not necessarily identify high-risk groups.

In summary, HPV-associated cancer rates were changing from 1999 to 2014. Rates increased for oropharyngeal cancer among men and women, anal cancer among men and women, and vulvar cancer. Rates decreased for cervical cancer and were stable for penile cancer and vaginal cancer. In conclusion, oropharyngeal cancer is now the most common HPV-associated cancer and is increasing, particularly among males. In the future, the HPV vaccine should decrease the burden of HPV-associated cancers, but it may take decades to see population-level impact due to the length of time between the initial HPV infection and the development of cancer.

Epidemiology of HPV Infection in Males

Anil K. Chaturvedi, PhD
National Cancer Institute
National Institutes of Health

Dr. Chaturvedi's presentation focused on the rising incidence rates of oropharynx cancers, the epidemiology of oral HPV infection, and current opportunities for prevention of HPV-positive oropharynx cancers. As noted, the incidence of oropharynx cancer has been increasing significantly in the US since 1999. In fact, this increase in the US has been occurring since the 1980s. Ten years ago, the reasons for this increase were unclear and various investigators hypothesized that this increase could be related to HPV infection given emerging and epidemiologic evidence at that time that showed an etiologic role for HPV in oropharynx cancers.

To test this hypothesis, Dr. Chaturvedi's group conducted a molecular epidemiologic study in three cancers registries in the US. For this study, they retrieved archived tumor tissues for oropharynx cancers that occurred in the 1980s, early 1990s, late 1990s, and 2000s and tested for the prevalence of HPV-infection in these tumor tissues using a variety of molecular assays. In terms of results of HPV prevalence by PCR, during the 1980s, approximately 16% of

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oropharynx cancers were caused by HPV infection. This percentage significantly and substantially increased over time to 72% by the early 2000s. Notably, the vast majority (~90%) of these HPV-positive oropharynx cancers were caused by HPV16. This has key implications for prevention through prophylactic HPV vaccination.

Given that the investigators had the HPV status of the tumors in these cancer registries, they were able to compartmentalize the overall oropharynx cancer incidence rate (28% increase) into incidence rates for HPV-positive (225% increase) and HPV-negative oropharynx cancers (50% decrease). Through this analysis, they were able to show that the overall increase of oropharynx cancers in the US in recent years arises exclusively from a rise in the incidence of HPV-positive oropharynx cancers. Looking at the incidence trends for HPV-positive oropharynx cancers separated by gender, incidence rates for HPV-positive oropharynx cancers increased substantially over time in men while the increase for women has been slight if at all. This shows that HPV-positive oropharynx cancers in the US primarily occur in men. If these rising incidence trends were to continue into the future, the projected incidence rates indicate that soon HPV-positive oropharynx cancers would be the most common HPV-associated cancer in the US. HPV-positive oropharynx cancers are also slated to become the most common head and neck cancers in the US by 2030, with the vast majority of the burden in men [Chaturvedi, *JCO* 2011].

Very similar to the higher incidence of oropharynx cancers in the US, the prevalence of oral HPV infection is significantly higher in men (10.5%) than it is in women (3.1%). This is true for infection with any of the 37 HPV types that are generally tested for in the oral samples, and it is true for HPV16 infection as well, which causes the vast majority of the oropharynx cancers. Oral HPV infections are primarily related to sexual activity. The prevalence of oral HPV infection changes with an increasing number of lifetime sexual partners for any type of sex and specifically for oral sex. With an increase in lifetime number of sex partners, oral HPV prevalence increases strongly in the US population. In both men and women, oral HPV is extremely rare in the absence of sexual activity. This indicates that in both genders, oral HPV infections are primarily acquired and are attributable to sexual activity [Gillison, *JAMA* 2012; Chaturvedi, *Cancer Res* 2015].

Men in the US do tend to report a higher number of sexual partners. When adjusted for just the excess of oral HPV infections in men, these behaviors explain a small proportion of approximately 18% of male excess of oral HPV infections. Neither a different mode of transmission of oral HPV infection nor sexual behaviors seem to explain this male excess of oral HPV [Chaturvedi, *Cancer Res* 2015; D'Souza, PLOS One 2014].

This male predominance of oral HPV appears to arise from stronger associations of sexual behaviors with infection prevalence in men when compared with women. With each additional sexual partner among women, infection prevalence increases but plateaus at around 10 lifetime sexual partners. Contrasting that with what is observed for men, with each additional sexual partner the prevalence of oral HPV infection increases steeply compared with women. This increase tends to plateau at about 25 sexual partners compared to 10 among women. Men might be uniquely susceptible to acquiring oral HPV infection because the same behaviors are having a disproportionately greater impact on oral HPV prevalence in men compared to women [Chaturvedi, *Cancer Res* 2015].

While the reasons for this unique male susceptibility are not entirely known at this point, one hypothesis is that men are more immunologically susceptible in general to HPV infection. Consistent with this hypothesis, lower rates of seroprevalence are seen in males versus females in the US population. In terms of seroprevalence of one or more of serotypes included in the

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9vHPV vaccine, seroprevalence data in the pre-vaccine era before the introduction of the vaccine in the US, at any given age group, men have lower seroprevalence rates compared to women[1]. This lower seroprevalence arises from lower rates of seroconversion after genital HPV infection in males versus females, which is potentially related to differences in site of infection of mucosal epithelium in females and keratinized epithelium in males where the immune system does not have ready access to the virus and does not enable a strong immune response. The hypothesis here is that this robust immune response to genital infection in women is somehow protecting them against oral HPV infection[2]. Consistent with this hypothesis, specifically for oral HPV infection, oral HPV viral load is a surrogate for host immune control of the virus and is significantly higher in males with prevalent infection than in females with prevalent infection[3] [[1]Liu, JID 2016; [2]Edelstein, JID 2011; [3]Chaturvedi, JID 2013].

Perhaps as a result of these immunologic differences between men and women, very different age-specific HPV prevalence patterns tend to be observed in females and males. Genital HPV infection in women peaks in the mid-20s and a continuing decline is observed at older ages. By contrast, genital HPV infections in men do not decline at older ages. There tends to be an increase in men and then somewhat of a plateau at older ages. In terms of oral HPV prevalence, a very atypical bimodal prevalence pattern is observed with an initial peak in the mid-20s, a decline, and a later peak that is equal to or even higher than the first peak at around ages 55 to 60 years. The reasons or this atypical bimodal pattern are not entirely known at this time. An eventual hypothesis could include acquisition of new infections at older ages, reactivations of latent infections due to age-related immune senescence at older ages, or a birth cohort effect. The reality could be a combination of all of these hypotheses. Suffice it to say that an age-related decline is not observed in the prevalence of HPV infections at any site in men. The disease-relevance of infections acquired at different ages is unknown but is of great interest [Lewis, *JID* 2017; Gillison, *JAMA* 2012].

Modeling studies based on natural history data show that up to 75% of all cervical cancers are caused by infections women acquire prior to age 30. Unfortunately for males, there are no natural or modeling studies to show what the disease relevance is specifically for the infections acquired at older ages. In terms of natural history and pathogenesis, over the past few decades, large natural history studies of cervical cancers have been conducted worldwide. However, there have been very few natural history studies of oral HPV infections and the development of HPV-positive oropharynx cancer. Therefore, the steps intervening the initial establishment of infection and the later development of HPV-positive oropharynx cancers are largely unknown. What is currently known are risk factors for oral HPV infection and HPV-positive oropharynx cancers, good estimates of oral HPV prevalence, and limited estimates of oral HPV incidence and persistence. There are many unknowns in terms of the natural history of this disease. Most importantly, there is not yet an identified HPV-induced precancerous lesion in the oropharynx. As noted, the time from initial establishment of infection to development of cancer is unknown. Again, the disease-relevance of infections acquired at older ages remains unknown.

In terms of the hypothesis for the increase in HPV-positive oropharynx cancers in recent years in the US, the understanding of the natural history of oral HPV infections and HPV-positive oropharynx cancers is still in the nascent stage. Given that HPV infection is the cause of this increase and that oral HPV infections are primarily sexually acquired, the prevailing hypothesis in the field is that changes in sexual behaviors in the birth cohorts that went through the sexual revolution in the US have led to increased exposure to oral HPV infections and this increased exposure is now manifesting as an increase in HPV-positive oropharynx cancers. For men, the

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same sexual behaviors could have a disproportionately greater impact on oral HPV infection in men. This is thought to be a reason for the rising incidence currently being observed in men.

Regarding what can be done in terms of screening and prevention of this disease, secondary prevention through screening is not currently feasible for this disease because an HPV-induced pre-cancerous lesion has not yet been identified. Even if an HPV-induced pre-cancerous lesion was identified, many questions remain unanswered. The methods for screening are not known, nor are treatments known for risk-mitigation in screen-positives. There are also no estimates for the cost-effectiveness of population-based screening. Given all of these unanswered questions, screening with oral HPV tests is not recommended for this disease [Lingen, *J Am Dent Assoc* 2017].

The inability to screen and prevent in a secondary fashion for this disease underscores the importance of the potential for HPV vaccination. There are some data in the literature that support high efficacy of the vaccines against oral HPV infections. Results from the NCI Costa Rica Vaccine Trial in young women showed a substantial reduction in oral HPV infection in vaccinated women approximately 4 years after receipt of 3 doses of vaccination compared to the control group, with an efficacy estimate of approximately 93% [Herrero, PLOS One 2013].

Looking at the US population of young adults 18 through 33 years of age, self-reported data from National Health and Nutrition Examination Survey (NHANES) about 4 years after receipt of at least 1 dose of vaccine a reduction is observed in HPV prevalence in vaccinated men and women. The reduction in women did not reach statistical significance perhaps given the very sparse sample size in this group. However, there is strong and significant evidence of reduction in oral HPV prevalence among men for the 4 vaccine types included in the quadrivalent vaccine [Chaturvedi, JCO 2017].

In summary, HPV is the cause of rising oropharynx cancer incidence in recent years in the US, and male predominance of oral HPV infection and HPV-positive oropharynx cancer in the US. Given that screening and early detection of HPV-positive oropharynx cancer is not currently feasible and given that the vast majority of HPV-positive oropharynx cancers are caused by HPV16 infection, HPV vaccination of young individuals presents the most promising prevention strategy at this time.

Discussion Points

Dr. Hayes (ACNM) asked whether Dr. Chaturvedi has any stratified data on sexual preference to determine whether the oral HPV rate was higher in MSM or women who have sex with women (WSW).

Dr. Chaturvedi replied that these are self-reported data they have examined within NHANES, which should be taken into consideration in the interpretation of the results. With that in mind, they did not see vast differences in prevalence in heterosexual men compared to MSM. They did see approximately equal oral HPV prevalence in these two subgroups. They see something different in women. They tend to see very high rates of infection in WSW compared to heterosexual women. There is a contrast in how the prevalence compares across the sites. These data are not potentially adjusted for the reported infection status of the partner, which could contribute to some of these differences as well.

Dr. Riley asked whether dysplasia occurs in the oropharynx.

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Dr. Chaturvedi indicated that there are a few reported cases. For example, if there is a cancer in the left tonsil, some evidence of dysplasia has been seen in the contralateral tonsil. As yet, there is not a lesion in terms of being detectable through some visualization modality. Some studies have tried to do an analog of Pap smear through cytology of the tonsils, but those studies have consistently failed to show a detectable pre-cancerous lesion.

Dr. Hunter commented that it was not clear to him based on the indications in the data how ACIP would incorporate oropharyngeal data of any kind into its recommendations. It seemed like they were already starting with the data that make the difference in that they were starting with HPV in areas that can be detected in the vagina and which he assumed is the source for the oropharyngeal cancer in men. He thought if they focused on the data they know, they would make the right decisions for men in the long-run.

Dr. Chaturvedi emphasized that oropharyngeal cancer is not an indication at this time, which is somewhat problematic and deferred to Dr. Markowitz for further information about this question.

Dr. Markowitz added that while she was not clear on exactly what Dr. Hunter was asking , it is true that there is no indication for prevention of oropharyngeal cancer partly because it has not been possible to conduct clinical trials because there is no pre-cancer lesion. However, this presentation was shown to illustrate and discuss the burden of disease in males and to give some background to broaden the understanding of the burden of HPV-associated disease in the US. While she agreed that they could not use these data specifically, the recommendations have stated that it is likely that vaccination will prevent all HPV-attributable disease.

Dr. Stephens observed that the 90% association with HPV is interesting and asked whether Dr. Chaturvedi would comment further on why he may think that might be different for oropharyngeal versus cervical cancer.

Dr. Chaturvedi responded that the reasons are not entirely clear at this time. In the cervix HPV16 is about 50%, 16/18 together are about 70% of the attributable fraction, and the remainder of the high-risk types account for the cancers. Looking outside the cervix at extra cervical HPV-associated cancers, for some reason HPV16 predominates. This is also true for anal cancer where the vast majority of the HPV-positive cancers are caused by HPV16 infection. Based on the results from several studies, when an oropharyngeal cancer is caused by HPV infection, it tends to be because of HPV16 infection. He was not aware of a clear biological explanation of why that is other than that HPV16 is thought to be the most carcinogenic of all of the HPV types.

Dr. Hahn (CSTE) wondered with the late onset in males shown if there was any evidence that they are acquiring HPV16 later and, therefore, vaccinating males later might have a benefit.

Dr. Chaturvedi reiterated that there are no natural history studies to say what the disease potential of infections acquired at later ages is, so all they can do is go back to the cervical cancer model which may or may not entirely apply to the oropharynx. Looking at cervical acquisition and the development of cervical cancer, it is known that most cervical infections that do lead to cancer are acquired early. He feels that natural history studies are needed for the oropharynx to understand the hazard of the acquisition of the infection at older ages and the hazard of incident infections to potentially progress to cancer. One surrogate that has been used in all of their HPV work is HPV persistence as an intermediate endpoint. Until this information is available, he does not think conclusions can be drawn about the disease

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relevance at older ages. If they cannot conclude that, it will not be possible to make conclusions about the potential for vaccination in the older years at this time.

Dr. Romero asked whether HPV16 is still predominant in laryngeal papillomatosis.

Dr. Chaturvedi responded that laryngeal papillomatosis is caused by HPV types 6 and 11, which cause warts.

Day 1: Public Comment

Andrea Woodruff
Interested Citizen

I just wanted to say that considering that ACIP is increasingly voting for non-FDA approved off-label use of various vaccines, you should also be ensuring that the patient or parent knows about this in writing at the time that the vaccine is administered, and that the information is going to be used for trial purposes. My understanding is that the information is going to go into a database for trial purposes, so make sure that the patient knows that this is the ACIP recommendation but not FDA approved information going in for trial purposes. It just seems like it would be a better idea to preserve the integrity of the recommendations if we are just very clear what's what.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Messonnier indicated that as discussed following the last ACIP vote on SHINGRIX, events around that vaccine have been assessed closely. There has been a series of reports regarding administrative errors. The previous shingles vaccine had a different route of administration and different operations. Some of the reports are of the vaccine being mis-administered subcutaneously (SQ) as opposed to intramuscularly (IM), which is how it is licensed. There has been inappropriate freezing of the vaccine, and reports of providers not telling patients they need to return for a second dose. These are the early days. These same types of challenges have arisen in the past when a second vaccine is licensed that differs from the first. CDC will be pushing out a variety of educational materials. The pharmaceutical company is also working on these same issues. She just wanted to everyone to be aware that CDC is concerned about this, and to implore everyone to do everything they can to amplify the message and the importance of getting this right.

Centers for Medicare and Medicaid Services (CMS)

No report provided.

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Department of Defense (DoD)

Written report provided:

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

The Adenovirus Vaccine Program was successfully instituted into an Officer Candidate School in January 2018 following an outbreak of Adenovirus among these trainees. This is the first application of the Adenovirus Vaccine Program outside of DoD's enlisted recruitment population. Surveillance and serological studies are in process.

DoD has completed all of Japanese Encephalitis vaccine FDA-required post-licensure studies and is awaiting FDA comment. Significant interest in intramural immunization projects with a focus on military-relevance/readiness continues to occur throughout the field.

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

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

Publications:

Authored by IHB Staff:

- McClenathan BM, Stewart DA, Spooner CE, et al. Metabolites as biomarkers of adverse reactions following vaccination: A pilot study using nuclear magnetic resonance metabolomics. Vaccine. 2017 Mar 1:35(9):1238-1245.
- Dumas EK, Gross T, Larabee J, Pate L, Cuthbertson H, Charlton S, Hallis B, Engler RJM, Collins LC Jr, Spooner CE, Chen H, Ballard J, James JA, Farris AD.. Anthrax Vaccine Precipitated induces Edema Toxin-neutralizing, Edema Factor-specific antibodies in human recipients. Clin Vaccine Immunol. 2017 Sep 6.

Funded by IHB Intramural Studies Program:

- Khodr ZG, Bukowinski AT, Gumbs GR, Conlin AMS. Tetanus, diphtheria, and acellular pertussis vaccination during pregnancy and reduced risk of infant acute respiratory infections. Vaccine. 2017;35(42):5603-5610. Intramural Studies Program funded.
- Hang J, Zavaljevski N, Yang Y, et al. Composition and variation of respiratory microbiota in healthy military personnel. PLoS ONE. 2017;12(12):e0188461. Intramural Studies Program funded.
- Conlin AMS, Sevick CJ, Gumbs GR, Khodr ZG, Bukowinski AT. Safety of inadvertent anthrax vaccination during pregnancy: An analysis of birth defects in the U.S. military population, 2003-2010. Vaccine. 2017;35(34):4414-4420. Intramural Studies Program funded.

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- Khodr ZG, Bukowinski AT, Gumbs GR, Conlin AMS. Tetanus, diphtheria, and acellular pertussis vaccination during pregnancy and reduced risk of infant acute respiratory infections. Vaccine. 2017;35(42):5603-5610. Intramural Studies Program funded.
- Pittman PR, Barrera-Oro JG, Xiaofei, et al. Time course of the early antibody response to the priming doses of anthrax vaccine adsorbed. Under review at Military Medicine. Intramural Studies Program funded.

Food and Drug Administration (FDA)

Dr. Sun reported that since the last ACIP meeting in October 2017, FDA approved the HEPLISAV-B™ vaccine using the novel adjuvant CpG, which is a novel TLR9 agonist for persons 19 years of age and older. In addition, FDA approved Fluarix® Quadrivalent for children 6 through 35 months of age. As mentioned earlier, FDA convened a VRBPAC meeting in November 2017 specifically addressing the issue of the Pfizer *S. aureus* vaccine and how safety and efficacy for a specific population could be generalizable to all elective orthopedic surgeries. The VRBPAC Northern Hemisphere 2018-2019 strain selection meeting will be convened on March 1, 2018.

Health Resources and Services Administration (HRSA)

Dr. Nair reported that HRSA is continuing to see a number of claims in the National Vaccine Injury Compensation Program (VICP) for the fiscal year (FY) ending September 30, 2017. There were 1243 claims filed, with $252 million awarded to petitioners and nearly $30 million awarded to attorneys for fees and costs that were compensated and claims that were dismissed. For FY2018 he had data that were current as of November 29, 2017. At that point, $31 million had been awarded to petitioners and $5.7 million had been awarded to attorneys. Detailed information is posted on the HRSA website.

Indian Health Service (IHS)

Written report provided:

1. *Influenza Vaccine Coverage*: IHS conducts weekly surveillance for influenza-like-illness and influenza vaccine coverage. As of 2/3/2018, 321,317 doses of influenza vaccine were administered to patients seen at an IHS/Tribal/Urban health facility. Influenza-like-illness (ILI) activity in IHS is decreasing but remains elevated at 4.3%, above the IHS baseline of 1.67%. Eleven IHS regions are reporting elevated ILI activity. Influenza vaccine coverage among children 6 months – 17 was 34.4%; coverage among adults 18 years and older was 32.9%.

2. *IHS Pharmacy Survey*: The IHS Immunization program, in partnership with the IHS Pharmacy program, is conducting a survey of pharmacies located in IHS healthcare facilities to assess the role of pharmacists in the provision of adult and adolescent immunizations, and the implementation of the Standards for Adult Immunization Practice in IHS pharmacies. Information will be used to identify best practices and strategies to increase pharmacy—based immunization activities in IHS facilities.

3. *HHS Region VI National Adult Immunization Plan-Stakeholder Engagement Meeting, Jan. 18th, 2018, Irving, Texas*: IHS participated in this meeting and presented information on IHS efforts to implement the NVAC/CDC Standards for Adult Immunization Practice in

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IHS/Tribal/Urban health facilities and current initiatives to improve access to adult immunizations in American Indian/Alaska Native communities.

National Institutes of Health (NIH)

No report provided.

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

No report provided.

US Department of Veterans Affairs (DVA)

Dr. Kim reported that VA released a policy in September 2017 that requires HCP to participate in the influenza prevention program by getting an influenza vaccine or declining vaccination and wearing a mask throughout the influenza season. VA is currently implementing this policy. More than 211,000 VA employees are documented as having received the influenza vaccine as of February 3, 2018. More than 1.7 million influenza vaccinations have been administered in outpatient settings within Veterans Health Administration (VHA) facilities since August 2017. In addition, VA is continuing its partnership with Walgreen's. There are more than 100,000 enrolled veterans who are documented to have received an influenza vaccine from Walgreen's this influenza season. VA is updating its Clinical Preventive Guidance on Herpes Zoster Administration to align with the recently published ACIP recommendation. The recombinant adjuvanted zoster vaccine was added to the VA formulary late last year.

Discussion Points

Dr. Fryhofer (ACP) indicated that they have had difficulty ordering the shingles vaccines, as two of the websites are down. There is one available source, but it is 20% higher. She said it is a surprise that this happened.

Pneumococcal Vaccines

Introduction

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

Dr. Lee reminded everyone that the Pneumococcal Vaccines WG's terms of reference are to:

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

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As a reminder, ACIP recommended PCV13 for use routinely in adults ≥65 years of age in August 2014. At that time, the short-term thought was that the recommendation for universal PCV13 use in this age group was warranted. There was a recognition that the long-term, continued herd effects from the childhood vaccination program might limit the utility of a universal recommendation for older adults. There was uncertainty about the magnitude of indirect effects as well as the burden of vaccine-preventable non-bacteremic pneumococcal pneumonia and that additional work was needed. The recommendation was to re-evaluate the decision to routinely use PCV13 among adults ≥65 years of age.

A research agenda was laid out that focused on monitoring invasive pneumococcal disease (IPD) and non-bacteremic pneumococcal pneumonia (NBPP) among adults ≥65 years of age; examine the impact of indirect effects on pneumococcal disease trends in PCV13-naïve adults 19 through 64 years old without PCV13 indications; and evaluate the impact of direct and indirect effects on pneumococcal disease among adults ≥65 years of age.

During the October 2017 ACIP meeting, the WG updated ACIP on changes in carriage and IPD among adults ≥65 years of age. Carriage rates were documented to be very low at 1.8% overall and 0.2% for PCV13 serotypes. IPD caused by PCV13 serotypes declined by 40% after PCV13 was introduced in children and annual incidence rates plateaued from 2014 through 2016. At that time, the outline of the research agenda was presented to inform potential policy change.

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

- ❑ PCV13 effectiveness against IPD among adults ≥65 years old
- ❑ PCV13 direct and indirect effects among adults ≥65 years old
- ❑ PCV13 effectiveness against pneumococcal pneumonia among US adults and coverage estimates
- ❑ Estimating burden of pneumococcal pneumonia among U.S. adults and progress of the research agenda to inform potential policy change

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

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

Pneumococcal VE against Invasive Disease among Adults ≥65 Years of Age

Tamara Pilishvili, PhD, MPH
Respiratory Diseases Branch
National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Pilishvili shared the results of studies evaluating PCV13 effectiveness against IPD among adults. PCV13 efficacy against IPD was demonstrated in a large clinical trial, Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA), in which the efficacy was measured at 75% with a 41% to 91% confidence interval against PCV13-type IPD among adults 65 years or older. Effectiveness of PCV13 alone or PCV13 given in series with PPSV23 in the

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general population of US adults 65 years or older has not been demonstrated. Therefore, evaluation of the effectiveness is crucial to inform future policy decisions.

With this in mind, two case-control evaluations were conducted in parallel using slightly different methodologies. Dr. Pilishvili outlined the methodologies and shared the results of each, in addition to comparing the results across both studies. The objective was to evaluate PCV13 effectiveness against PCV13-type IPD among adults ≥65 years of age. For Study 1, population-based controls were selected and vaccination and medical histories for cases and controls were assessed through provider record review. Study 2 was conducted in collaboration with CMS. Controls were selected from Medicare part B beneficiaries and vaccination and medical histories for both cases and controls were obtained through CMS records. As a reminder of the timeline of the vaccine introduction as it relates to the reference period for which the vaccination histories are being obtained, PCV13 was introduced for children in 2010, the PCV13 recommendation was made for adults ≥19 years of age with immunocompromising conditions in 2012, and PCV13 was recommended for adults ≥65 years of age in 2014.

Regarding the methods for Study 1, IPD cases among adults ≥65 years of age were identified through Active Bacterial Core Surveillance (ABCs). Those with pneumococcal isolates available for serotyping were eligible for enrollment. Controls were identified using the commercial database ReferenceUSAGov. The goal was to enroll 4 controls per case matched on age group and Zip Code of residence. Phone interviews were conducted for cases and controls in which all medical care encounters in the last 6 years were identified, as well as their current and past medical care providers. Information was assessed through interviews on the presence of underlying conditions, previous hospitalizations, and household exposures to smoking. For medical and vaccination history, contact was made with all providers identified through the case and control interview process, including pharmacies and vaccine registries when available. Vaccine doses received within 14 days of the case culture date were excluded from analysis.

For the analysis, underlying medical conditions were grouped as *Chronic Medical Conditions* (diabetes; chronic heart, lung, or liver disease; alcoholism; cigarette smoking) and *Immunocompromising Conditions* (HIV, hematologic cancer, generalized malignancy, immunosuppressive therapy, sickle cell disease, asplenia). VE was measured using conditional logistics regression adjusted for the presence of underlying conditions and race. VE was estimated as one minus the odds ratio. VE was measured against various groups of serotypes, but VE against PCV13 types as a group was the primary objective.

In terms of the characteristics of cases and controls, 267 cases and over 1000 matched controls have been enrolled to date. Enrollment began in October 2015 and is still ongoing. The median age of cases and controls is approximately 75 years. There was a higher proportion of black and other races among cases than controls, and there was similar distribution of gender between cases and controls. One or more chronic medical conditions were present among 83% of cases versus 60% of controls, and 60% of cases versus 32% of controls had at least one immunocompromising condition. Regarding vaccination status, a higher proportion of controls (29%) than cases (23%) received a single dose of PCV13 only. PPSV23 alone was received by a higher portion of cases (22%) than controls (20%), and both vaccines were received by a higher proportion of cases (27%) than controls (25%).

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Looking at the distribution of serotypes of enrolled cases compared to the same timeframe for ABCs cases identified, there is a similar distribution of serotypes. Serotype 3 is the single most common PCV13-type at 16% for enrolled cases versus 13% for ABCs cases. Other PCV13 serotypes (19A, 7F, 19F) were identified among enrolled and ABCs cases at 7% each. Serotype 06C was identified in about 4% of enrolled cases compared to 3% of ABCs cases. In some of the analyses, Serotype 06C was grouped with PCV13 serotypes, given that it has shown some cross-protection with the 6A antigen in PCV13.

The following table presents effectiveness by vaccine type and serotype group:

Effectiveness by vaccine type and serotype group

	N case-control sets	PCV13 only		Any PCV13	
All IPD	267	**37%**	**(2, 60)**	24%	(-9, 47)
PCV13-type	62	**65%**	**(16, 86)**	**61%**	**(20, 81)**
PCV13-type + 06C	72	**65%**	**(19, 85)**	**54%**	**(12, 76)**
PPSV23-unique types	94	27%	(-48,64)	26%	(-34, 59)
All PPSV23 types	110	**44%**	**(4, 68)**	**40%**	**(6, 62)**
Non-Vaccine types	99	13%	(-90, 60)	-13%	(-121, 42)

Conditional logistic regression
Analyses adjusted for race and presence of underlying medical conditions

The cells that are highlighted in white is where any effectiveness would be expected and VE in bold are the ones for which the confidence intervals do not cross the null value. VE against all IPD was measured at 37% against all IPD types and 65% against PCV13 types. When serotype 06C was included, the estimate did not change, and the confidence intervals are slightly narrower. Effectiveness was 44% against all PPSV serotypes. PCV13 types are included in the PPSV serotypes with the exception of 6A, so there is some effect expected because PCV13 types are contained in that group. There is no effectiveness against serotypes that are unique to the polysaccharide vaccine for PCV13 and against non-vaccine serotypes. Looking at VE for any PCV13 dose received (with or without PPSV23), the results were similar though slightly lower VE estimates, and the confidence intervals overlapped.

For Study 2, the starting point was again cases of IPD among adults ≥65 years old identified through ABCs. These cases were linked to CMS Medicare Part B data based on demographic, geographic, and clinical variables. After creating a linkage and identifying these cases, controls were identified from CMS Medicare Part B beneficiaries. Controls were matched on age group, Census tract of residence, and length of enrollment in Medicare Part B. All eligible controls within Census tract of the case were included in the analyses. Vaccinations and medical records were obtained through CMS data and doses received within 14 days of the case culture date were excluded from analysis.

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Again, underlying medical conditions were classified as *Chronic Medical Conditions* (diabetes; chronic heart, lung, or liver disease, alcoholism, cigarette smoking); and *Immunocompromising Conditions* (HIV, hematologic cancer, generalized malignancy, immunosuppressive therapy, sickle cell disease, asplenia). Conditional logistics regression was used to estimate VE, adjusted for presence of underlying conditions and race. Again, VE was estimated as one minus the odds ratio. VE against PCV13-type IPD was the primary objective.

For this analysis, it was possible to include retrospective data, so the enrollment started with the cases with culture dates from January 2015. The investigators were able to include 2 years of cases from ABCs and link them to CMS Medicare Part B beneficiaries. A total of 699 cases and over 10,000 matched controls were included. The median age was somewhat higher than in Study 1 at about 78 years. As in the previous study, there is a higher number of cases than controls of black or other races and a similar distribution of gender. There also was a higher proportion of cases with chronic conditions at 88% compared to 58% among controls, while 54% of cases versus 32% of controls had at least one immunocompromising condition. For vaccination status, overall coverage based on Medicare Part B data was lower. As far as the differences between cases and controls, the pattern was similar in that a high proportion of controls and cases had received a single dose of PCV13 and no difference was observed between cases and controls in terms of the percentage receiving both PCV13 and PPSV23.

The distribution of serotypes also was compared for cases that were included in the analysis versus cases that were identified through ABCs during the same time period. There is a very similar distribution, so there is no selection in terms of which cases were included in the analysis versus identified through surveillance. Again, Serotype 3 is the most prevalent vaccine serotype. Effectiveness against all IPD was measured at 24% and the confidence intervals did not cross the null. Effectiveness was 36% for PCV13-types as a group, but the confidence interval includes the null value. When serotype 06C was included, effectiveness was 47% with a significant confidence interval. Against all PPSV types combined (PCV13 types included), effectiveness was 26% and the confidence interval was not significant.

The following table compares the Study 1 and 2 evaluations side-by-side:

Effectiveness of PCV13 comparing two studies

	ABCs (10/1/15 - to present)			CMS (1/1/2015-12/31/2016)		
	N sets	VE (95%CI)		N sets	VE (95%CI)	
All IPD	267	**37%**	**(2, 60)**	699	**24%**	**(2, 41)**
PCV13-type	62	**65%**	**(16, 86)**	136	36%	(-18, 65)
PCV13-type + 06C	72	**65%**	**(19, 85)**	164	**47%**	**(4, 71)**
PPSV23-unique types	94	27%	(-48,64)	214	22%	(-22, 50)
All PPSV23-type	110	**44%**	**(4, 68)**	350	26%	(-5, 48)
Non-Vaccine types	99	13%	(-90, 60)	247	13%	(-36, 44)

Conditional logistic regression
Analyses adjusted for race and presence of underlying medical conditions

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Overall, the results were similar for the two studies. The point estimates for CMS analyses were lower but the confidence intervals do overlap, with the exception of VE against PPSV Serotypes which was much lower for CMS study, and not significant.

In conclusion, PCV13 was shown to be moderately effective in preventing IPD caused by PCV13-types in Study 1 with 65% VE (16, 86%), which was significant, and Study 2 with 36% VE (-18, 65%), which was not significant. VE estimated similar when Serotype 6C IPD was included, which offers evidence of cross-protection. PCV13 was not effective against PPSV23-unique and non-vaccine type IPD, but had no reason to be effective. Estimates in both studies were slightly lower compared to VE from the clinical trial of 75% efficacy (95% CI 41, 91%). However, the populations are different. As a reminder, the immunocompromised individuals were excluded from the CAPiTA study. Also, Study 1 and Study 2 had a higher proportion of adults with chronic conditions compared to the trial. At this point, it is not possible to evaluate VE estimates for PPSV23 or for PCV13 and PPSV23 given in series. Enrollment and analyses are ongoing, so those secondary objectives will be addressed. There are plans to assess VE for PCV13 and PPSV23 given in series, VE for PPSV23 against PPSV23-type IPD, and age group-specific VE to determine whether there is any difference among adults 65 through 75 years of age versus adults 75 years or older.

Estimating PCV13 Direct and Indirect Effects on IPD among Adults >65 Years of Age

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Dr. Pilishvili indicated that this study was proposed at the time the recommendation was made. When the vaccine was introduced, indirect effects were being observed for PCV13 use in children. The question ACIP posed and many had on their mind was how to understand the contribution of direct effects from PCV13 used in adults versus continued indirect effects in adults due to pediatric use of the vaccine. As a reminder, the vaccine was introduced for adults ≥65 years of age in 2014. During the period 2010 through 2014 is when adults experienced only indirect effects. From 2014 to the present, the timeframe of interest, there have been continued indirect effects due to pediatric use of PCV13 among children plus the direct effects from PCV13 use among adults.
The objectives for estimating PCV13 indirect and direct effects in adults ≥65 years are to: 1) estimate IPD incidence expected through indirect effects only (i.e., in the absence of PCV13 recommendation for ≥65-year-old adults in 2014); and 2) estimate the contribution of direct PCV13 effects from the observed (total effects) vs expected (indirect effects only) IPD incidence.

The following figure graphically demonstrates using hypothetical data what we are trying to measure. The blue solid line represents actual IPD incidence rates in adults 65 years and older. The assumption is that the observed trends during 2010-2014 are influenced by indirect effects from PCV13 in children. Based on this, it is possible to project what the IPD incidence would have been if PCV13 was not introduced in 2014, shown in the green dotted line:

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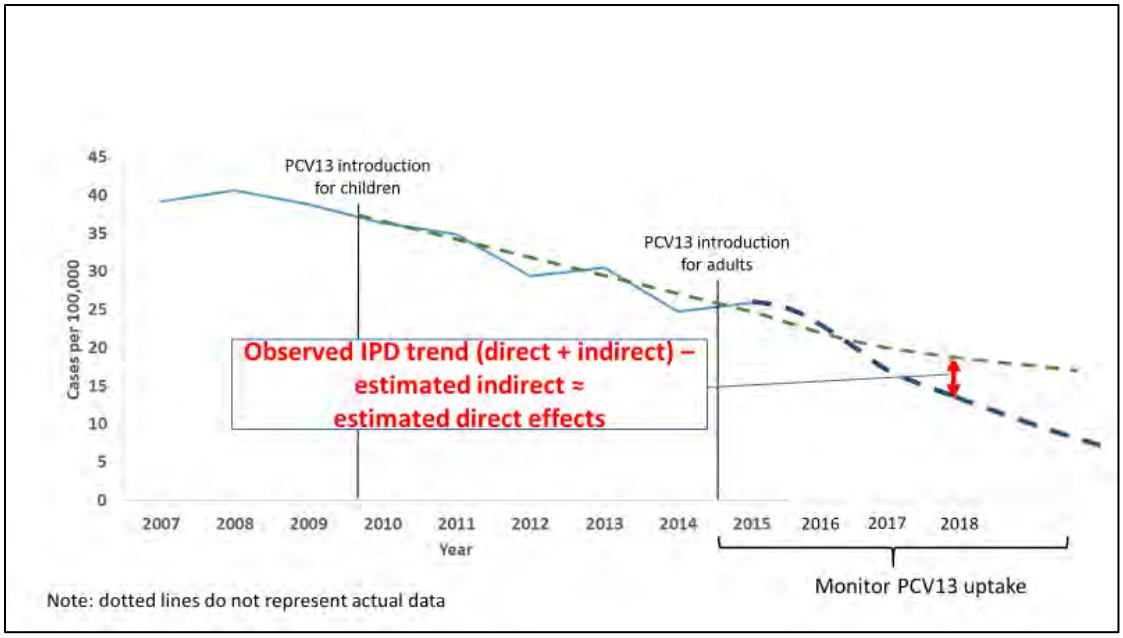

The observed IPD incidence post-2014, shown in the dark blue dotted line, reflected both direct and indirect effects of PCV13. Based on these observed and estimated IPD trends, the direct effects from PCV13 introduction can be estimated. The changes in vaccine coverage over the years must be accounted for.

There are limitations to this approach. Assuming that linear trends for indirect effects will continue to be observed is not appropriate to project indefinitely, because of what is known so far based on the post-PCV7 vaccine experience and the indirect effects observed post-PCV13. Most of the reductions occurred in the first years followed by somewhat of a plateau effect during subsequent years. The issue with this simplified approach is that there are only about 4 years' worth of data before PCV13 introduction in 2014 with which to project future indirect effect trends. Therefore, projections on indirect effects will be less accurate over time and the confidence intervals would become wider.

Realizing that assuming linear trends for indirect effects represents a very simplified approach, an alternative assumption was made and two different mathematical models were built. First, the contribution of direct and indirect effects on disease trends was estimated among adults ≥65 years of age using data on IPD incidence among adults ≥65 years, adults 50 through 64 years old, and PCV13 uptake and controlling for seasonality. The second approach was simpler. The indirect effects in adults ≥65 years of age was predicted using only the pre-PCV13 data to understand the relationship between disease rates in adults 50 through 64 years of and adults ≥65 years.

The first approach is called the "All-or-Nothing Model" because it assumes that the proportion θ (theta) of the vaccinated are not protected from disease at all and are susceptible, the white group in the following figure, while (1-θ) are 100% protected, the green group:

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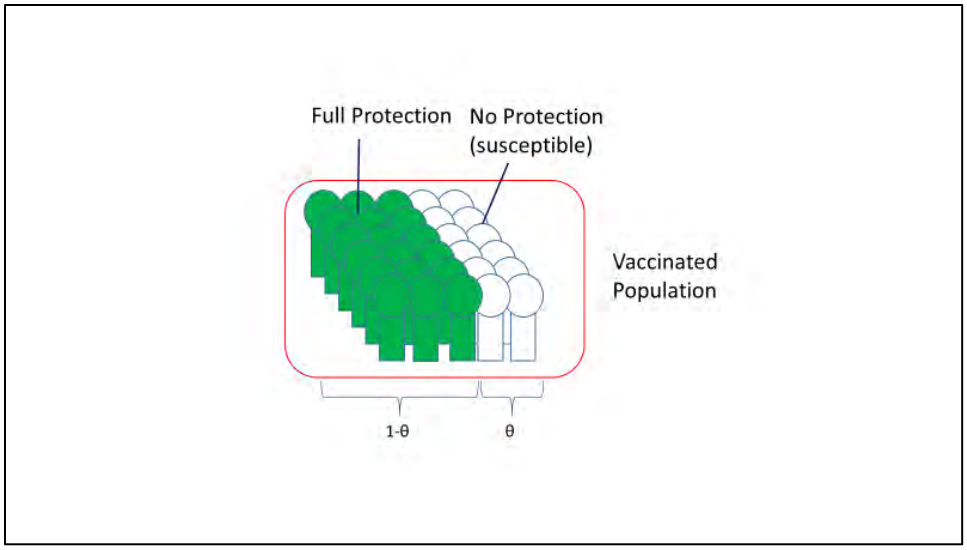
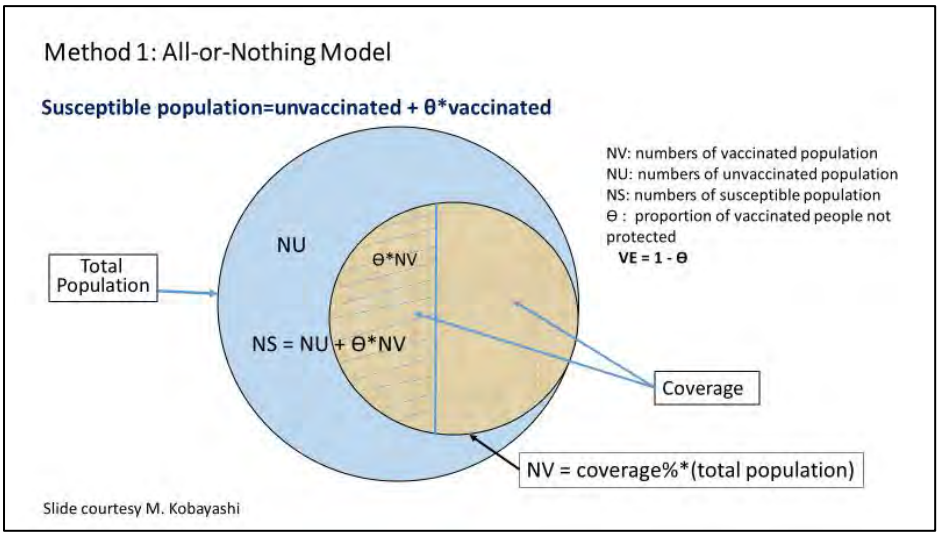


In this instance, if θ equals 1, there is no protection from the vaccine because everyone is unprotected, and adults are experiencing only indirect effects. It is assumed that unvaccinated populations continue to experience indirect effects only. To demonstrate based on this assumption how the size of the susceptible population would be estimated, the susceptible population (blue portion) = an unvaccinated population + θ x a vaccinated population (beige portion):



Pre-vaccine incidence was used to inform what the changes in the susceptible population would be. Poisson regression was used to model the rates among the susceptible population, which represents indirect effects. B (beta) in the Poisson regression formula is the indirect effect. Unlike using just pre-vaccine data, post-vaccine observed data were utilized as well. This allows for updating the estimate given beta, or indirect effects, to estimate theta. Given theta, the new susceptible population can be estimated, which for estimation of the new beta. These two steps will continue until the model converges and direct and indirect effects can be estimated. This gives more power to the predictions. Here is the model:

$$NS = NU + \Theta * NV$$
$$\log(PCV13type\ rate\ j) = \beta 0 + \beta i * Xi\ j + \log(NS\ j)$$

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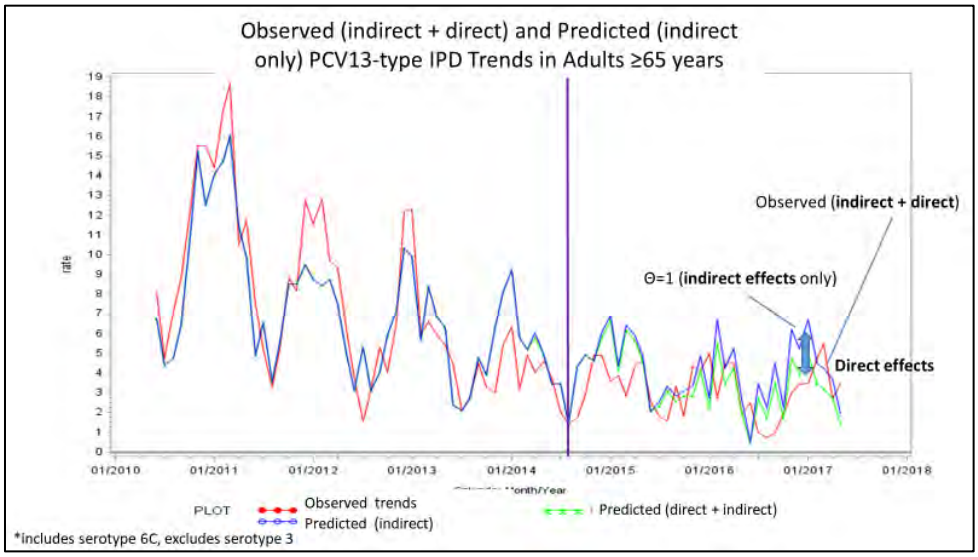
After the model converges, direct and indirect effects can be estimated. Based on the model, what is plotted in this graph is the predicted number of cases through indirect effects only, which is the blue line:



The red line represents observed total effects of indirect + direct PCV13-type IPD trends in adults ≥65 years of age. The objective is to measure the difference between the blue and red lines, which would be attributed to the direct effects of the vaccine use in adults.

During the period of time from vaccine introduction August 2014 through May 2017, there were 907 observed cases (direct + indirect). Using the model, it was predicted that there would be approximately 924 cases in the absence of vaccine. The difference between the two is 17 (-89, 10,712), but the confidence interval is very wide. That is because there were very low case numbers and a lot of uncertainty in this model. This is only for the ABCs population during the entire time period. Projecting these estimates to the US population, it was predicted that during the same period about 192 cases were prevented through direct effects. That translates to approximately 100 cases prevented annually, again with a lot of uncertainty and very wide confidence intervals.

These results essentially suggested that there are minimal changes to PCV13-type disease post 2014. To determine what was occurring in the background, serotype specific changes were examined. Serotype 3 kept coming up as the most prevalent type, with no impact being observed at the population level. Therefore, serotype 3 was removed from the analysis. This resulted in a prediction of more cases prevented during the same time period of 579 (-219, 1523), but with very wide confidence intervals and a lot of uncertainty.

The second method takes the more simplistic approach. The observed rates in adults ≥65 years of age are shown in red and observed rates in adults 50 through 64 years of age are shown in lime:

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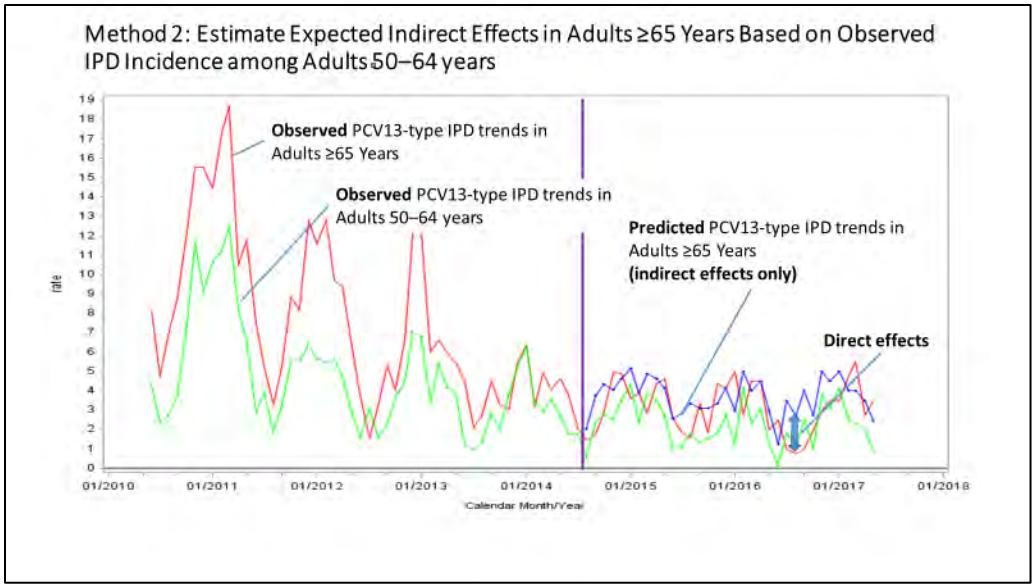

The observed rates to the left of the purple vertical line are pre-vaccine indirect effects only. Using pre-vaccine data, indirect effects in adults ≥65 years of age post-2014 were predicted based on the relationship to rates in 50 through 64 years of age presented in the green line. If the observed (total effects) are added, the difference between predicted indirect and total effects can be attributed to direct effects. The findings were similar to the first model, with the total cases prevented and wide confidence intervals using this method as well. Removal of serotype 3 again resulted in no changes in trends over time, but there was a larger impact on other PCV13 serotypes but with very wide confidence intervals again, with approximately 750 cases prevented during this period in the US population.

In conclusion, both of the models estimated that there are no additional indirect effects predicted in the absence of the PCV13 adult recommendation. There are limited indirect effects estimated for IPD caused by PCV13 serotypes, excluding type 3. There are limited direct effects observed in a setting of approximately 40% PCV13 uptake based on various estimates. However, confidence limits are very wide and include the null value—ranging from some effect to no effect. Predictions are based on small numbers of PCV13 type cases remaining following observed indirect effects of PCV13 pediatric use. IPD represents a small portion of the overall adult disease burden. Similar analyses are ongoing to estimate PCV13 direct versus indirect effects on all-cause pneumonia as well.

Discussion Points

Dr. Bennett said she thought it was fair to say that they looked for a “needle in a haystack” and actually found something, recognizing that this is very difficult.

Dr. Atmar noted that by removing serotype 3 it appeared that there could be more cases of PVC13 strains being protected against. He wondered whether this meant that even though serotype 3 is in the vaccine, it is replacing the other strains.

Dr. Pilishvili said that it would be an overstatement at this point to say that serotype 3 is acting as a replacement serotype, but it certainly is not behaving like any of the vaccine serotypes in terms of reductions. The goal with the effectiveness studies is to enroll additional cases and

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there is more serotype 3, so they hope to assess effectiveness at the individual level also. As far as the trends at the population level, it is essentially a flat line.

Dr. Szilagyi said it looked to him based on the logistic regression that the VE was markedly affected by chronic diseases and being immunocompromised, because the actual vaccination rates were very close. In addition, he wondered what the vaccination rate was among adults with chronic disease or who are immunocompromised in the second study and whether the direct effect might be larger for that subgroup.

Dr. Pilishvili indicated that depending upon the data, in the general population coverage is approximately 40% among those ≥65 years of age and older. The estimates that she has seen for adults with chronic conditions is focused on younger adults with indications, and she was not sure if they have information on adults ≥65 years of age and older with chronic conditions. These estimates were provided by colleagues at Pfizer. If their data allows it, they should be able to estimate that for adults ≥65 years of age and older with chronic conditions to determine whether there is a difference.

Dr. Bennett said that while she knew they controlled for the presence of chronic conditions and immunocompromising conditions, she wondered whether they assessed the analyses separately stratified by those.

Dr. Pilishvili said they tried to assess that, but because of the numbers the confidence intervals are wide, so there was no statistical power to evaluate effect modification.

Dr. Belongia said his understanding was that the first two case-control analyses with two different control groups was an in-progress analysis and the study was not complete, and he inquired as to the overall endpoint He asked what the overall endpoint in terms of sample size, power, and completion data.

Dr. Pilishvili indicated that based on the sample size calculations in a setting of 30% coverage, approximately 45 to 46 cases would be needed in order to estimate VE against PCV13 types. However, this has not been recalculated and it is important to take into account those sample size calculations do not take into account that vaccine coverage changes over time, and conditional logistic regression is being used such that only discordant sets on vaccination status will be contributing. Earlier on with lower coverage, there might be more concordance and later more discordance. They believe that through another winter of enrollment, there will be sufficient numbers to examine the additional endpoints. They believe that they have sufficient numbers of PCV13 types to believe the estimates they are seeing.

Dr. Stephens requested further information regarding the data specific to serotype 3 in terms of whether the studies of vaccine failures are primarily of serotype 3.

Dr. Pilishvili replied for serotype 3, there are immunogenicity studies that suggest that the response may not be as good against that serotype. There are studies in pediatric populations as well that show that it is not quite as effective. They have not assessed serotype 3 from the standpoint of vaccine failures among adults, but among cases serotype 3 is the most prevalent serotype. It is the most prevalent of the serotypes causing disease as well among vaccinated and unvaccinated. Vaccine failures for serotype 3 are observed in pediatric studies.

Dr. Lee requested the time period for which the controls were sampled for the two case-control studies.

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Dr. Pilishvili replied that the controls are sampled simultaneously with cases, but are matched on age to cases. The reference period is then matched to case culture date. The case culture date for corresponding controls is where the look back period begins for controls as well. They are interviewed with respect to that time period. Vaccination status is also assessed with respect to that period.

Ms. Pellegrini asked whether they were able to assess severity of disease in terms of whether there was hospitalization or hospitalizations were shorter.

Dr. Pilishvili responded that they have not assessed this yet, but will be able to do so eventually. As part of the first case-control study, they have information regarding prior and current hospitalization information. They are also asking questions regarding functional status of these adults, which is a subsequent analysis.

Dr. Atmar asked whether they would be able to assess effectiveness over time since PCV13 became available as more cases are enrolled in the study to address the question of direct versus indirect effects, as well as whether there were greater effects early on that over time became either larger or smaller.

Dr. Pilishvili replied that they should be able to do this, and it is a question they are exploring, because the enrollment started much earlier for the CMS study when coverage was lower. There are slightly different estimates between the two studies, so they want to limit it to the time period of the second study to see how they compare.

Effectiveness of PCV13 in US Adults

John M. McLaughlin, PhD
Global Epidemiology Lead for Pneumococcal Vaccines
Pfizer Vaccines

Dr. McLaughlin presented data that Pfizer has been working to collect in collaboration with the University of Louisville for approximately the last half of the decade. The presentation focused on real-world VE of PCV13 against vaccine-type community-acquired pneumonia (VT-CAP) based on a case-control study using a test-negative design in US adults nested in a large population-based surveillance site in Louisville, Kentucky. This study was similar to the influenza studies conducted in adults presented during the influenza session. In addition, the presentation focused on whether it is possible to disentangle the direct effects of the vaccine from indirect effects that might be stemming from the pediatric immunization program. To try to answer this question, PCV13 uptake was compared in two groups of adults contrasted with the burden of VT-CAP. The two groups are adults ≥65 years in age who were routinely recommended to receive the vaccine after September 2014 and adults 18 through 64 years of age who have essentially served as a control group in many ways who are immunocompetent and have other underlying chronic medical conditions and are currently only recommended to receive polysaccharide vaccine. It is important to underscore that for all of these analyses, CAP was assessed as it was the primary unmet medical need for PCV13 based on licensure and recommendation.

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In terms of background, the efficacy of PCV13 against hospitalized VT-CAP was previously demonstrated in a large RCT, CAPiTA, which enrolled almost 85,000 adults and found statistically significant efficacy of this vaccine against VT-CAP of 45.6% [95.2%CI: 21.8−62.5%]). However, VE against VT-CAP has not been shown in any study following introduction of PCV13 into a routine adult immunization program. The US is one of the few places it is possible to conduct a study like this, which is what Pfizer set out to do in collaboration with the University of Louisville. Specifically, the objective of the study was to determine real-world PCV13 VE against VT-CAP among adults aged ≥65 years of age following routine introduction in the US.

A recent publication in *Clinical Infectious Diseases* (*CID*) titled, "Adults Hospitalized with Pneumonia in the United States: Incidence, Epidemiology, and Mortality" outlines the early phases of the Louisville data. Essentially, this was a large population-based surveillance study that enrolled all adults ≥18 years of age living in Louisville, Kentucky who were hospitalized with CAP. The study was conducted in 9 adult acute-care hospitals throughout Louisville, Kentucky that represented a full catchment area. The timeframe for the study was September 7, 2013 through September 30, 2016. Important to note is that the study includes time periods before the ACIP recommendation in adults ≥65 years of age and after the recommendation. Also important about this study is that it collected urine for all enrolled patients, which allowed for the use of the Pfizer PCV13 serotype-specific urinary antigen detection (UAD) assay. The UAD assay can essentially tell whether PCV13 serotypes caused the hospitalized case of CAP. One of the first major findings in this study was that it found a much higher incidence rate of CAP than in previous studies. For example, the Louisville study suggested that the incidence rate of CAP in the population ≥65 years of age was roughly 2300/100,000[1]. Contrast with the earlier publication of CDC's Etiology of Pneumonia in the Community (EPIC) study, the estimate using very similar methodology and age standardization of instruments rates in that same age group was only 900/100,000[2] [[1]Ramirez et al. *Clin Infect Dis*, 2017;65(11):1806–1812, publication reports June 1, 2014 − May 31, 2016; [2] Jain S, et al. *N Engl J Med.* 2015;372:835-845].

There originally were many questions about why there was a discrepancy between these two estimates in two prospective studies that were relatively similar in how they enrolled patients. Thus, a lot of time was spent trying to determine why there was discordance between the two studies. Ultimately, they determined that it was the difference in selection criteria between the two studies in terms of two specific selection criteria: 1) patients with healthcare-associated pneumonia (HCAP) who had interaction with the healthcare system in the last 90 days, and 2) immunocompromised patients. What was remarkable was that if the same selection criteria were applied to the Louisville study that used EPIC (which exclude HCAP and immunocompromised), the Louisville study got almost an identical number to the EPIC study. Thus, it became clear that the HCAP and immunocompromised patient explained the discrepancy between the two studies.

In terms of where the nested real-world effectiveness test-negative design (TND) study among adults ≥65 years of age sat within the broader Louisville study, the timeframe for the analysis was April 1, 2015 through April 30, 2016. The definition of "pneumonia" in the Louisville study was that patients had to have: 1) ≥2 clinical criteria for pneumonia (fever, hypothermia, chills or rigors, pleuritic chest pain, cough, sputum production, dyspnea, tachypnea, malaise, abnormal auscultatory findings suggestive of pneumonia); and 2) radiographic evidence of pneumonia (infiltrate consistent with CAP as read by the treating healthcare provider or radiologist of a chest radiograph and/or a CT image). Exclusion criteria were patients with hospital-acquired pneumonia (HAP, hospitalization within previous 48 hours); patients who did not have a final diagnosis of pneumonia at discharge; and patients who did not supply a urine sample for

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laboratory testing. Another layer of selection criteria was applied to the specific TND, restricting the analysis to patients who were ≥65 years of age since that is the group for whom the recommendation was made and among whom there would be vaccine uptake, and those who provided additional consent to have their pneumococcal vaccination history confirmed by health insurance records. Only two types of patients were excluded, those whose health insurer could not be reached and those who received a pneumococcal vaccine ≤30 days prior to the urine sample, given a recent publication suggesting that there could be a false positive in the UAD if vaccination occurred too shortly before the test. This criterion was just to be conservative.

In the TND, all patients were hospitalized with CAP and cases were essentially any patient in which a PCV13 serotype was detected by positive culture or Pfizer UAD. Controls in the primary analysis were essentially everyone else. A sensitivity analysis was also performed in which the case definition remained the same, and the control group was divided into two separate groups to make sure that there was no impact of how controls were defined on the analysis. In the first sensitivity analysis, controls were defined as non-PCV13-type pneumococcal CAP. In the second sensitivity analysis, controls were the inverse of that or patients with no PCV serotypes identified and were non-pneumococcal CAP patients. There were almost 4200 adults ≥18 years of age and older hospitalized with CAP during the timeframe of the TND analysis. The analysis was restricted to adults ≥65 years of age, which left 2348 hospitalizations among adults ≥65 years of age. In terms of the exclusion criteria, 208 patients without pneumococcal vaccination status and 106 patients who had a pneumococcal vaccination ≤30 days from urine sample collection were excluded. The Louisville team did an amazing job ascertaining vaccination status, excluding less than 10% for whom vaccination status was not confirmed. This resulted in a final analysis population of 2034 CAP hospitalizations among patients ≥65 years of age.

In terms of the characteristics of the final analysis population, this is an older population with a median age of 76 years and more than a third of them were ≥80 years of age. That is not surprising given that these are all patients who are hospitalized with CAP. Of these patients, 46% were immunocompromised and 42% were immunocompetent with other underlying comorbid conditions (COPD 52.6%, CAD 35.4%, CHF 31.9%, and diabetes 32.2%). The proportions of some of the comorbid conditions are higher than the total at-risk number, given that the proportions include adults who are both at-risk and immunocompromised. The median length of stay for these patients was almost a week, and the mortality rate ranged between 7% and 13% depending upon whether it was measured as in-hospital mortality or mortality within 30 days. Regarding vaccine coverage for these patients, average PCV13 uptake was 14.2% in the last 5 years. The proportion who received PPV23 in the last 5 years was 21.2% and the proportion who received PCV13 and PCV23 in the last 5 years was 3%. The self-reported influenza vaccination receipt within the last year was 68% for these patients. The estimate of vaccine uptake was comparable to the most recent *MMWR*[1] estimate of 15% to 20% in September/October 2015, the TND study midpoint [[1]Black CL, Williams WW, Warnock R, Pilishvili T, Kim D, Kelman JA. *MMWR Morb Mortal Wkly Rep* 2017; **66**(27): 728-33].

Looking at the 2034 CAP hospitalizations among adults ≥65 years of age, PCV13 serotypes were identified in 68 patients. This left 1966 test-negative controls among whom PCV13 serotypes were not identified. Pfizer UAD and BinaxNOW® were performed for all patients since that was part of the inclusion criteria, and culture (primarily blood) was available for 93.7% of cases. Of the 68 cases, 66 were identified by the PCV13-specific UAD, 8 were identified by culture, and only 2 were identified by culture alone. A couple of things to note based on this, UAD increased detection of PCV13 serotype 6 times compared to culture alone. Compared to blood culture alone, it was 11 times. One of the key takeaways from this is that even though the

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UAD was designed to help understand effectiveness and efficacy as an epidemiological tool, it really showed that the idea of 3:1 non-bacteremic to IPD ratio may actually be underestimating as this study saw a ratio closer to 10:1.

Regarding cases and controls by vaccination status, there are two things to note. The first is that there were very few cases of PCV13-type disease among people who were vaccinated, with only 3 cases among vaccinated persons. The second is that the proportion of cases vaccinated was less than the proportion of controls who were vaccinated. This translates to an odds ratio of 0.272 that is statistically significant. Calculating VE as 1-odds ratio as is standard, the VE estimate was 72.8% (95%CI: 12.8− 91.5%) effective against hospitalized vaccine-type CAP with a confidence interval that does not cross zero.

VE was modified by confounding for all of the variables of interest and whether it was similar if the analysis was restricted to non-bacteremic pneumonia only. No matter what the crude estimates were adjusted for, the point estimates were very consistent throughout and did not change. The crude model served as the final model because there was no evidence of confounding in any of the models. The estimates for non-bacteremic effectiveness were very similar and all were statistically significant. This is not surprising given that 92% of all of the cases in this analysis were non-bacteremic.

A sensitivity analysis of how cases and controls were defined showed no difference in the results as shown in the following table:

Characteristic	Primary	Sensitivity 1	Sensitivity 2
Control Def.	all non-PCV13-type CAP	non-PCV13-type pneumococcal CAP	non-pneumococcal CAP
Cases, n	68	68	68
Controls, n	1966	96	1870
Crude VE, %	72.8 (12.8−91.5)	64.3 (-33.1−90.4)	73.1 (13.9−91.6)
Adj. VE Range, %	71.1 to 73.3	60.3 to 69.2	71.5 to 73.8

This analysis was underpowered because the UAD that increased the sensitivity for detection is not available for other non-PCV serotypes, so the analysis was limited to culture and BinaxNOW® for controls.

In summary, the VE study showed that the vaccine is effective against hospitalized CAP in older adults in a population that includes immunocompromised patients and HCAP patients. The VE estimate was robust to adjust for confounding for all of the variables, which is a testament to TNDs and their ability to help mitigate some of that type of bias. It was also robust to how controls were defined.

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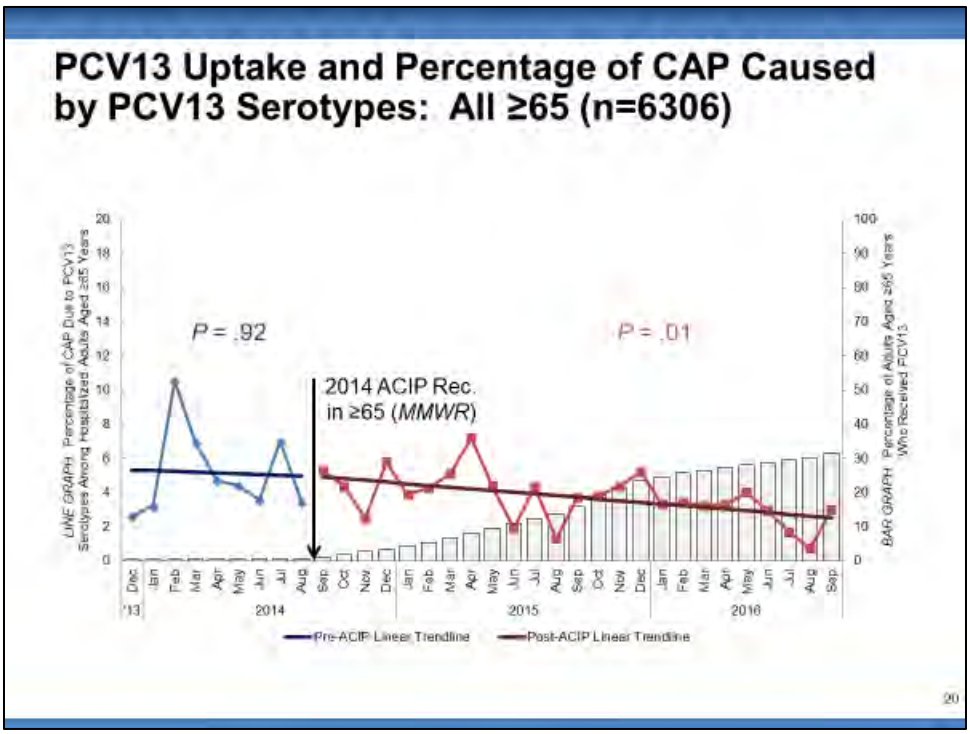
The next thing Pfizer wanted to assess was whether direct effects could be teased apart from indirect effects. Because of the Louisville population-based study allowed for assessment of incidence, while the vaccine history data for this population allowed for the assessment of VE. The surveillance of CAP that also collected urine samples on these patients and looked at the proportion of disease that was vaccine-type was bigger than just Louisville. It includes a lot of sites throughout the US and over 12,000 patients hospitalized with CAP, which is the group of patients who will be studied to determine what proportion of all-cause VT-CAP. This was contrasted with PCV13 uptake data that was presented during previous ACIP meetings, which essentially looked at QuintilesIMS Health claims data for PCV13. Uptake of PCV13 among all patients ≥65 years of age and older (n=6306) based on administrative claims data over the time period that is pre- and post-ACIP recommendation demonstrates that the recommendation had a big impact on people getting vaccinated. It is important to note that these coverage estimates are almost identical to the CDC *MMWR* report. The proportion of all-cause VT-CAP was overlaid over the coverage estimates, which is demonstrated in the following graphic:



The blue line represents the time period before the ACIP recommendation, while the red represents the time period after the ACIP recommendation. The important takeaway is that before the ACIP recommendation, the proportion of disease that is vaccine-type is approximately 4% to 6%, which is consistent with EPIC estimates that used the UAD in an earlier timeframe. The proportion of CAP due to PCV13 serotypes begins to decline in people ≥65 years of age, corresponding with the uptake of the vaccine. That was statistically significant with a p-value of .01.

The next question regarded whether these were direct effects of the vaccine or indirect effects. The way to answer that question was to compare this to another group for whom uptake was much lower where the vaccine was not recommended. This was done by assessing the at-risk population 18 through 64 years of age who are recommended to receive only polysaccharide vaccine as shown in the following graphic:

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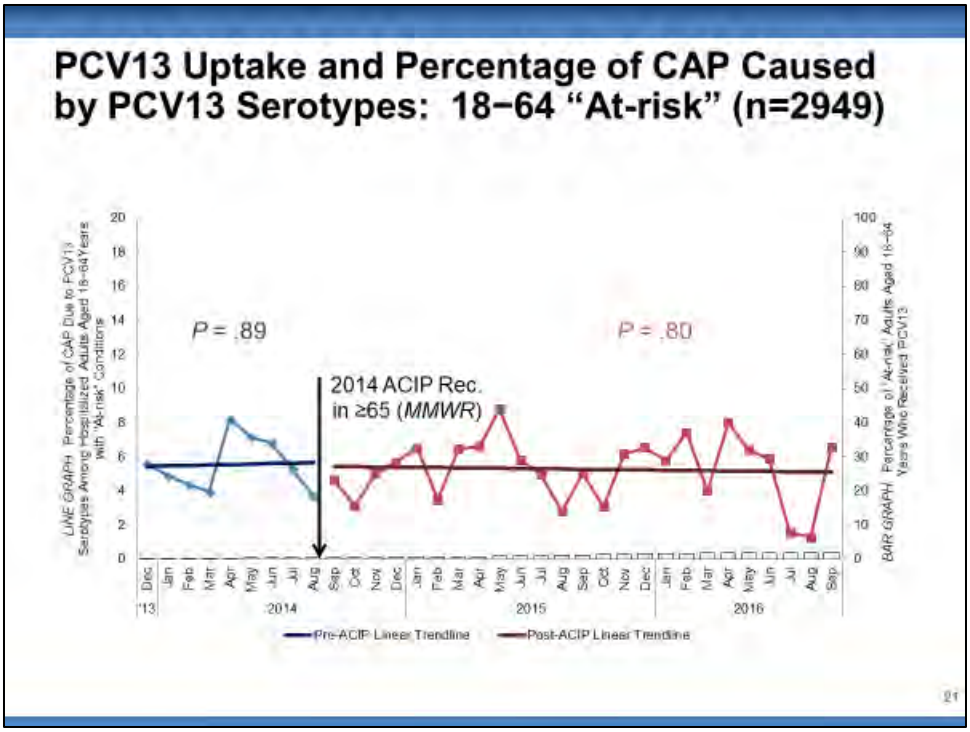

Not surprisingly, the uptake in the gray bars is very low. Comparing the proportion of all-cause CAP that is vaccine-type before and after ACIP recommendation, the two trend lines are flat, remain between the 4% to 6%, and not decreasing as was seen in the ≥65 population. This was the first hint at the idea that the vaccine was having an impact within the group with higher vaccine uptake.

In conclusion, the vaccine has real-world effectiveness in a population that included HCAP and immunocompromised adults. This was done in the same study that also showed that the burden of CAP is higher than other studies that included HCAP and immunocompromised patients. Though serotype-specific results were not presented, disease in 40% of the patients in this study was caused by serotype 3. The initial estimates of serotype 3 showed VE, though the point estimates were not statistically significant. This is consistent with estimates in the pediatric data that have shown effectiveness against serotype 3. Results from CAPiTA and this study has positive point estimates against serotype 3 of roughly 50%, though the study was underpowered. It appears that there are limited indirect effects against serotype 3, so the force of infection is increasing. This means that serotype 3 may be acting as a replacement serotype and that there is some level of direct effectiveness in adults. Comparing PCV13 uptake to the proportion of all-cause CAP that is vaccine-type, there is a clear difference in the vaccinated and unvaccinated groups. Following the PCV13 recommendation in adults ≥65 years of age, PCV13 uptake has increased and corresponds to reductions in VT-CAP. Where PCV13 is not used (e.g., 18 through 64 years of age "at-risk"), VT-CAP has not decreased despite pediatric PCV13 use and indirect effects and has plateaued at a consistent level. PCV13 serotypes still cause around 3% to 5% of all CAP in unvaccinated adults. It is not clear whether this is even a meaningful amount of disease. Accounting for the overall incidence rate of roughly 2300/100,000 in adults ≥65 years of age and multiply that by the 3% to 5%, that still means there is an incidence rate of PCV13-type CAP of 69 to 115/100,000 among adults ≥65 years of age. If that is translated to the 49 million adults who are ≥65 years of age in this country, that is

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153,000 to 255,000 hospitalizations and 9,900 to 32,400 deaths over a 5-year time horizon when this vaccine has been shown to be effective.

Discussion Points

Dr. Hunter indicated that when he was practicing clinical hospital medicine between 2005 and 2010, the urine testing they were using for pneumonia was not very clinically effective in his opinion in how it was used in Milwaukee. He inquired as to whether anyone could comment on the urine testing Pfizer is using and whether that is more clinically effective and could be used to make population-level decisions.

Dr. McLaughlin responded that the assay used in their studies seemed to increase the sensitivity of detection of pneumococcal serotypes compared to blood culture or blood culture alone somewhere between 6 to 10 times. It is an important tool.

Dr. Stephens requested information about the sensitivity and specificity of the UAD in normal populations where this has been a concern. High colonization rates will sometimes result in positivity.

Dr. McLaughlin replied that in the most recent EPIC publication, the sensitivity and specificity of the assay was assessed. They found 95% sensitivity and 100% specificity using the gold standard of IPD. They also confirmed previous studies for validation of the assay.

Dr. Atmar asked whether nasopharyngeal carriage results in a positive UAD test.

Dr. McLaughlin responded that a baseline adjustment is made for any carriages seen in a control population. For all of the UAD studies, control patients were enrolled and had a baseline detection done. If any positivity is seen, the cutoffs essentially can be adjusted. That has been built into the assays since the beginning.

Dr. Lee observed that it might be helpful to remove the immunocompromised population since those people presumably receive vaccine anyway and focus on the population of interest, and asked whether Pfizer was able to assess that.

Dr. McLaughlin responded that they did do this, but were restricted by the fact only 3 patients were vaccinated who also had a failure. Regardless of how the results were stratified, the point estimates were consistent throughout at between 60% to 70%.

Dr. Belongia requested clarification regarding what was included the fully adjusted model.

Dr. McLaughlin replied that the fully adjusted model included everything shown on the list.

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Estimating Burden of Pneumococcal Pneumonia among Adults in the US: Progress of the Research Agenda to Inform Potential Policy Change

Almea Matanock, MD
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Dr. Matanock discussed estimating pneumococcal pneumonia burden among US adults, as well as progress on the research agenda for a potential policy change. As has been noted, pneumococcal conjugate vaccines have dramatically reduced IPD in adults through indirect effects. ACIP recommended routine use of PCV13 in series with PPSV23 for adults aged ≥65 years in 2014. Many factors went into making this decision, including PCV13's effectiveness against IPD including pneumonia with bacteremia and PCV13's demonstrated efficacy against vaccine-type NBPP as noted from the CAPiTA trial presented by Dr. Pilishvili. Based on this, the following questions were raised:

- What is the burden of NBPP?
- What is the impact of PCV13 on NBPP for adults ≥65 years old?

S. pneumoniae is a common cause of CAP. A meta-analysis assessing pre-pediatric PCV13 introduction estimated *S. pneumoniae* to cause 27% of CAP[1]. However, figuring out CAP incidence attributable to *S. pneumoniae* is very difficult because blood culture has low sensitivity and is thought to detect about 25% of pneumococcal pneumonia cases. Additionally, the commercially available pneumococcal urinary antigen test (UAT) that has a pooled sensitivity of 74% to 75% and specificity of 95% to 97%[2, 3] is not universally available or routinely used by all providers [[1]Said M.A., et al (2013). Estimating the burden of pneumococcal pneumonia among adults... PloS one. 8(4):e60273. Epub 2013 Apr 2; [2]Horita, N., et al (2013). Sensitivity and specificity of the Streptococcus pneumoniae urinary antigen test… Respirology 18(8): 1177-83; and [3]Sinclair, A., et al (2013). Systematic review and meta-analysis of a urine-based pneumococcal antigen test… J Clin Microbiol 51(7): 2303-2310]. It is important to note that the commercially available pneumococcal UAT referred to in this presentation differs from the SSUAD just presented by Pfizer, which can determine serotype.

To put some studies into context, those with an adult incidence reported are notched on the following graphic:

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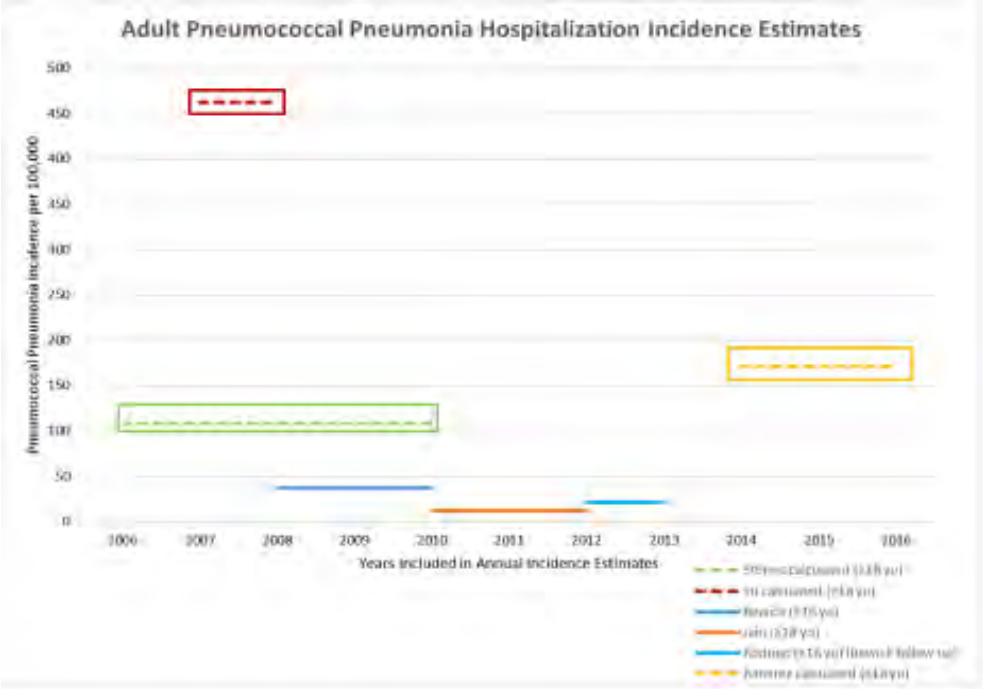

The hashed lines are studies that reported a pneumonia incidence and for which Dr. Matanock calculated a pneumococcal proportion using the 27% estimate. All lines represent measured pneumococcal pneumonia. Going chronologically through this graphic, Storms using discharge codes for VSD sites had a calculated pneumococcal pneumonia incidence of 108/100,000. Yu also using discharge codes but from US Medicare Part A beneficiaries, so a population in which younger adults would have been eligible only if they were disabled or had another qualifying condition, Dr. Matanock calculated a pneumococcal pneumonia incidence of 462/100,000. Bewick measured a pneumococcal pneumonia incidence of 37/100,000 in 2008-2010 using culture and a serotype-specific UAT for UK adults admitted with pneumonia. A follow-up study published by Rodrigo had an incidence of 21/100,000 post-pediatric PCV introduction using the same population and methods. Jain measured a pneumococcal pneumonia incidence of 12/100,000 in the EPIC study using culture, PCR, and UAT, which was 5% of CAP in this study. Lastly, Ramirez from the previous study calculated pneumococcal pneumonia incidence as 27% of CAP at 171/100,000 for all adults.

Given that background, a Surveillance for Non-invasive Pneumococcal Pneumonia (SNiPP) was set up to describe non-invasive pneumococcal pneumonia among adults, estimate the disease burden of non-invasive pneumococcal pneumonia, and eventually examine the potential impact of the 2014 ACIP recommendation for routine PCV13 among adults 65 years and older. Dr. Matanock focused only on the first two objectives for this presentation. SNiPP is built into the ABCs. Cases are defined as adults ≥18 years hospitalized with clinically- or radiographically-confirmed pneumonia and a positive pneumococcal UAT. Cases are excluded if they have IPD or another positive UAT within 30 days. SNiPP has been running prospectively since 2015, with retrospective data collection to 2013. This presentation focused on the pre-PCV13 period among adults ≥65 years of age from 2013 to 2014.

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Of the UAT-positive cases captured by SNiPP during this time period, half were ≥65 years old, most were diagnosed within 1 day of admission, almost all had radiographically-confirmed pneumonia, and a third were admitted to the ICU. Because it is known that not all suspected pneumococcal pneumonia cases are tested by UAT, the UAT case count is adjusted by the proportion tested by UAT at that hospital (Adjustment A). This information is obtained from hospital discharge records and clinical laboratories. Additionally, it is known that not all hospitals use UAT. To address this, UAT case counts are adjusted by the proportion of pneumonia in the catchment area that was seen at hospitals offering UAT (Adjustment B). This information is obtained from hospital discharge records and county level discharge data.

A sample of hospitals within the catchment area are selected. Currently included in this presentation are 22 hospitals. At each of these hospitals, a random selection of 20 pneumonia discharges per age group per month is made. Pneumonia discharges are defined similarly to the studies before by a first discharge code of pneumonia or empyema or a first discharge code of sepsis with pneumonia or empyema elsewhere. The pneumonia discharges in the catchment area are seen at hospitals offering pneumococcal UAT. There are 37 hospitals now included from 7 urban areas (CO, CT, GA, MD, NY, and 2 TN). These represent public, private teaching, university, small, and large hospitals. However, the majority (70%) of the hospitals are medium sized at 200 to 500 beds per hospital.

During 2013-2014, sites reported between 9 and 550 UAT-positive cases as show in the following table:

Location	Reported UAT Positive Cases	Hospitals with UAT Positive Cases		Average 2013–2014 Population (Total 10,000,148)
		% Pneumonia Tested by UAT (n 22 hospitals)	% Catchment Area Pneumonia (n 37 hospitals)	
CO	121	32%	11%	1,984,144
CT	282	47%	63%	1,421,074
GA	42	13%	17%	2,908,215
MD	551	72%	83%	1,137,326
NY	131	60%	42%	588,107
TN_1	9	2%	34%	1,220,755
TN_2	29	14%	36%	740,530
Average	**166**	**32%**	**41%**	

In part, this wide range is due to testing practices. On average, 32% of pneumonia discharges are tested by UAT during their hospitalization, but the range is from 2% to 72%. The average percent of pneumonia discharges seen at hospitals offering UAT is 41% with a range of 11% to 83%.

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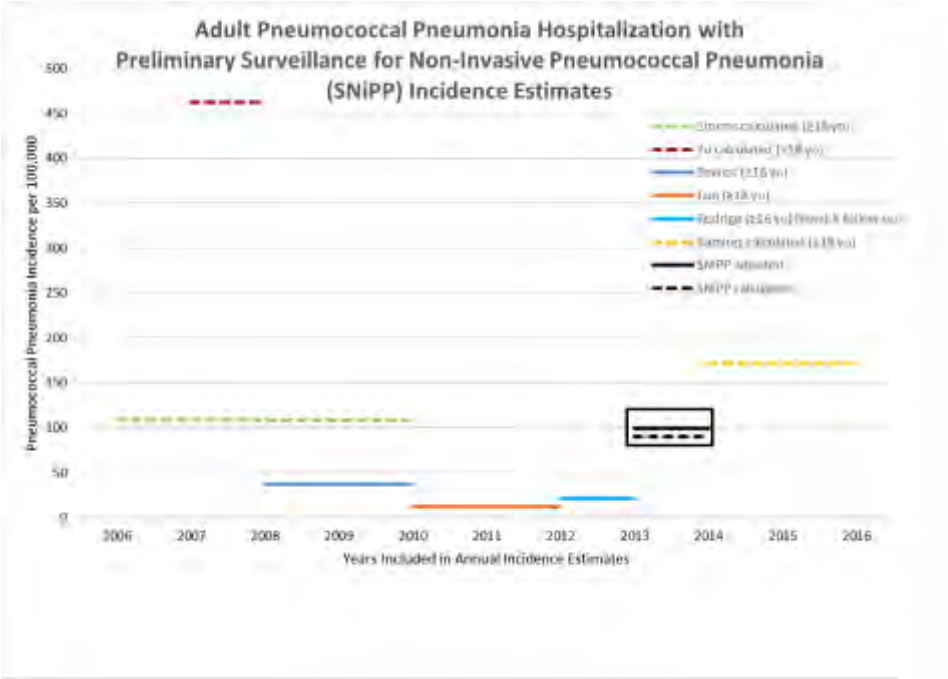
The crude incidence based on reported UAT-positive NBPP cases only would be 6 cases/100,000. A very preliminary annual incidence estimate using the described adjustments results in 99 cases/100,000. Because such a difference has been observed in UAT testing practices, the examined incidence by percent of pneumonia tested by UAT was examined. As the percent increases from 10% to 50%, there are fewer hospitals included but the incidence stays relative stable between 79 to 97 cases/100,000.

There are several limitations in SNiPP, including missing data from hospitals and laboratories. As is the case with many previous studies, SNiPP is reliant on administrative codes (ICD) for adjustments. A sample of hospitals and a sample of pneumonia discharges within these hospitals are used to determine the proportion of pneumonia tested by UAT, and there is variability in the testing practices by hospital and site. Because of these limitations, the investigators wanted to check their incidence estimates using all pneumonia discharge codes similar to the calculations Dr. Matanock made for the background literature. Taking all pneumonia discharges from the SNiPP catchment area, there are 440 pneumonia cases/100,000. Assuming that 27% of CAP is *S. pneumoniae*, there are 120 pneumococcal pneumonia cases/100,000. From the meta-analysis, it can be estimated that NBPP represents three-quarters of all pneumococcal pneumonia which is 90 NBPP cases/100,000 as compared to 99 case/100,000 using the adjustments. Putting this into perspective with the other studies, the two estimates are now added in black to the earlier table:



Several next steps are planned, including the following:

- ❑ Complete data collection and cleaning
- ❑ Model the proportion of patients with pneumonia discharge diagnoses tested by UAT (Adjustment A) for hospitals not sampled
- ❑ Determine the age-adjusted annual incidence
- ❑ Compare incidence in 2013-2014 to 2015-2016 to look at PCV13 impact
- ❑ Consider any thoughts ACIP has on ways of improving surveillance for NBPP

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Regarding progress on the research agenda for potential policy change, Dr. Matanock reiterated the questions that have been raised:

- ❑ In light of indirect effects observed, what is the impact of direct effects of PCV13 on pneumococcal disease among adults ≥65 years of age?
- ❑ What benefits would be expected from continued PCV13 use among adults ≥65 years old?

Focusing on adults ≥65 years of age, the evidence presented to date is that pneumococcal carriage amongst adults ≥65 years of age is very low with PCV13 carriage 0.2% in 2015-2016. PCV13 coverage among adults ≥65 years of age is approximately 40%. Coverage is lower amongst adults 19 through 64 years of age, but varies by indication. Amongst adults 18 through 64 years of age, coverage in 2017 was 34% amongst those who are HIV-positive and 20% amongst those with hematologic or metastatic cancer.

PCV13-type IPD declined among all age groups. IPD incidence among adults ≥65 years of age plateaued in 2014-2016. Modeled direct and indirect PCV13 effects on IPD in adults ≥65 years of age projected relatively few cases prevented as shown earlier. It has been noted that serotype 3 IPD does not follow the same pattern as other PCV13-types. The following table puts into perspective the VE that has been presented:

Evidence Presented to Date

Vaccine effectiveness (VE) against PCV13-type* IPD

Study	Population	VE	(95% Confidence Interval)
CAPiTA	Randomized control trial Dutch adults ≥65 years old	75%	(41–91)
CDC Traditional Methods	IPD cases identified through ABCs matched with population-based controls	65%	(19–85)
CDC CMS	Medicare part B IPD cases matched with controls	47%	(4–71)

* CDC Traditional Methods and CDC CMS VE includes serotype 6C

VE against PCV13-type pneumococcal pneumonia

Study	Population	VE	(95% Confidence Interval)
CAPiTA	Randomized control trial Dutch adults ≥65 years old	45%	(14–65)
Louisville Pneumonia Study	Test negative design in a cohort U.S. adults ≥65 years old	73%	(13–92)

During upcoming ACIP meetings, the WG plans to continue to provide updates about PCV13 impact on pneumonia from SNiPP and other ongoing studies. Models will be run to estimate the public health impact and cost-effectiveness of different policy options including no PCV13 for adults ≥65 years of age and expanding indications for adults <65 years of age.

In conclusion, Dr. Matanock asked what additional information the committee will need to help determine whether continued PCV13 use in adults ≥65 years of age is warranted.

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Discussion Points

Dr. Hunter said his understanding was that the vote in 2014 to vaccinate adults for PCV13 was in part based on a cost-effectiveness analysis that heavily weighted NBPP. He inquired as to whether there had been a change in the cost of the vaccine since that time, and whether consideration would be given to redoing the cost analysis.

Dr. Matanock responded that the cost-effectiveness analysis would be updated. When she said "modeling public health impact" she meant that it goes beyond just the cost-effectiveness, but that will be included in the modeling. It will be updated with new information about pricing, as well as pneumonia incidence and impact.

Dr. Bennett added that when the original cost-effectiveness analysis was done, the biggest factor was the disappearance of vaccine serotype disease. The cost-effectiveness was projected out through 2019.

Dr. Lee commented that the estimate of 27% for PCV13 would be the highest estimate, because the proportion of CAP attributable to pneumonia infection and the PCV13 types specifically was substantially lower at from 3% to 5% of what was shown during this session.

Dr. Matanock acknowledged this important point, stressing that the presentation only gave overall adult estimates for SNiPP, she limited what was presented to overall adults. However, it is known that the incidence is higher amongst older age groups. From previous studies, it is also thought that the proportion does change in older age groups versus younger age groups. They will give the fuller presentation when possible.

Dr. Quach (NACI) asked whether there was any understanding in the SNiPP study of the practices for ordering UAT. Because it might not be completely random, there could be some selection bias. Just adjusting the way it is being done may not be sufficient.

Dr. Matanock said they are working on and will present what is known about the variation in UAT testing practice. This is a consideration, but how this is impacting the numbers is not yet fully understood.

Dr. Bennett asked what the possibility would be for serotype-specific UAT being commercially available in the near future.

Dr. Matanock replied that so far, the UATs that are serotype-specific look only at vaccine serotypes. Of course, that is of interest, but it also would be of interest to know the other, non-vaccine serotypes are causing pneumonia and how they have been impacted by vaccine introduction.

Dr. Messonnier emphasized that they needed to be careful in interpreting the Pfizer assay, which is set up for surveillance and is usually important from a public health impact perspective. Whether it would be important for clinical decision-making is actually a very different evaluation.

Dr. Brady (AAP) noted that the mean ages for pneumonias were in the 70s, and he wondered whether someone who is immunized at age 65 would maintain adequate immunological protection and if any efforts had or would be made to assess duration of protection.

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Dr. Matanock responded that duration of protection was assessed out 4 years in the CAPiTA trial.

Dr. Whitney (SME) added that she did not think CDC had a great way to assess this with its methodology, and thought it might be a better question for Pfizer.

Dr. Stephens asked whether conjugate is given earlier and then boosted with the polysaccharide. He thought some of the questions regarding timing and the relationship to those 65 years of age and older perhaps not responding as well should be addressed.

Vaccines and Other Biologics for Prevention and Treatment of HAIs

Anthony Fiore, MD, MPH
Chief, Epidemiologic Research and Innovations Branch
Division of Healthcare Quality Promotion
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Centers for Disease Control and Prevention

Dr. Fiore provided a presentation on some of the exciting work being done on vaccines and other biologics to prevent healthcare-associated infections (HAIs), including the following information:

- A brief overview of some of the challenges faced with prevention of HAI and the ambitious reduction goals set out over the past several years under the National Action Plan (NAP) for Combating Antibiotic-Resistant Bacteria (CARB)
- The increasing interest in the potential role for vaccines in prevention and control of these infections
- Specific vaccines undergoing later phase human trials, including *Staphylococcus aureus* (*S. aureus*) and *Clostridium difficile* (*C. diff)* vaccines by Pfizer
- A monoclonal antibody by Merck that currently is licensed for use in prevention of recurrent *C. diff* (bezlotoxumab; Zinplava™)
- Ongoing and potential CDC and public health contributions to HAI vaccine development, evaluation, and program implementation

CDC's Antibiotic Resistance Threats in the United States report released in 2013 provided some initial estimates of the magnitude and cost of 10 different antibiotic resistant infections. Dr. Fiore displayed the graphic associated with two of the most prominent, *C. diff* and *methicillin-resistant S. aureus* (*MRSA*). There are 250,000 *C. diff* infections (CDIs), at least 14,000 deaths, and $1 billion in excess medical costs per year and this is deemed an urgent threat. MRSA is a subset of all *S. aureus* infectious and is very important in the community and in healthcare settings. There are over 80,000 severe MRSA infections, 11,000 deaths, and hundreds of thousands of overall *S. aureus*-associated infections per year. The NAP targets to prevent HAIs are shown in this table:

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Measure	Data Source	Baseline Years	2013 Target	Progress By 2014	Targets for 2020
Reduce **central-line associated bloodstream infections (CLABSI)** in ICU and ward-located patients	CDC/ NHSN	2006-2008	50% reduction or .50 SIR	50% reduction or .50 SIR	**50% reduction from 2015 baseline**
Reduce **catheter-associated urinary tract infections (CAUTI)** in ICU and ward-located patients	CDC/ NHSN	2009	25% reduction or .75 SIR	no change	**25% reduction from 2015 baseline**
Reduce the incidence of **invasive healthcare-associated methicillin-resistant Staphylococcus aureus (MRSA)** infections	CDC/EIP/ ABC	2007-2008	50% reduction	36% reduction	**50% reduction from 2015 baseline**
Reduce **facility-onset methicillin-resistant Staphylococcus aureus (MRSA)** in facility-wide healthcare	CDC/ NHSN	2010-2011	25% reduction or .75 SIR	13% reduction or .87 SIR	**50% reduction from 2015 baseline**
Reduce **facility-onset Clostridium difficile infections** in facility-wide healthcare	CDC/ NHSN	2010-2011	30% reduction or .70 SIR	8% reduction or .92 SIR	**30% reduction from 2015 baseline**
Reduce the rate of **Clostridium difficile hospitalizations**	AHRQ/ HCUP	2008	30% reduction	18% increase	**30% reduction from 2015 baseline**
Reduce **Surgical Site Infection (SSI)** admission and readmission	CDC/ NHSN	2006-2008	25% reduction or .75 SIR	18% reduction or .82 SIR (2012)	**30% reduction from 2015 baseline**

The NAP set a very ambitious goal of reducing *C. diff* facility-onset infections by 30% and related hospitalizations by 30%. The goal is a 50% reduction in facility-onset MRSA and the incidence of invasive HAIs. There are also goals for reductions of infections such as central line-associated bloodstream infections (CLABSIs) of 50% and surgical site infections (SSIs) of 30%, which are largely driven by *S. aureus* infections [https://health.gov/hcq/prevent-hai-measures.asp].

Data from EIP for 2012-2015 show that crude rates of healthcare-associated CDI are decreasing, although slowly and perhaps plateauing. With current interventions and much increased investments in antibiotic resistance control and health care safety that have occurred over the past few years, it is believed that this can be driven down further. Certainly, supplementary interventions such as a vaccine would be most welcomed. For MRSA, the story is similar based on EIP data from 2009-2015 from 6 sites. There has been major progress since 2005 in preventing MRSA bacteremia due to declines in hospital-onset and healthcare-associated bacteremia. However, declines are slowing in these areas. There has been little or no decline in community-associated MRSA bacteremia.

The role for vaccines certainly would be complementary to existing strategies to combat HAIs and antimicrobial resistance. These strategies are anticipated to be successful in continuing to drive down rates of HAIs, but not every infection can be prevented with infection control and antibiotic stewardship. As ACIP knows, vaccines are a proven successful strategy in terms of direct and indirect disease prevention. Vaccines are effective regardless of mechanism or prevalence of antibiotic resistance. There is some potential to reduce antibiotic use by reducing overall vaccine-preventable bacterial infections, reducing broad spectrum use aimed at highly resistant strains, and indirect effect for vaccines directed against other drivers of antibiotic use (influenza, RSV, GBS). Obviously, reducing the number of infections would reduce exposure to antibiotics. There is also potential to reduce opportunities for exchange of resistance elements among bacteria, including cross species.

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Many advisory bodies have advocated for the use of vaccines to address antibiotic resistance in HAIs, such as those listed here:

- Trans-Atlantic Task Force on Antimicrobial Resistance (TATFAR) 2014:
  - "Develop a transatlantic strategy to facilitate vaccine development for HAIs"
- National Vaccine Advisory Committee (NVAC) 2016:
  - "…incentives proposed to stimulate antibiotic development must also be evaluated for their utility to accelerate the development of vaccines…"
- Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) (Vaccine Incentives Workgroup, 2017):
  - "Provide additional funding for the development of new product pipelines for vaccines that prevent viral or bacterial syndromes that drive antibiotic use"
  - "Optimize the interactions among sponsors, regulatory agencies (such as FDA), and use policy committees (e.g., the ACIP)"
  - "Incentivize the uptake of vaccines by influencing behavior, such as reimbursement to ensure 'first-dollar coverage'"

There are technical challenges associated with HAI vaccine development. These are not necessarily unique to HAIs, but they certainly are very prominent in development of vaccines against these challenging pathogens. Natural infection typically does not protect against subsequent infection. There is often no established immune correlate of protection and demonstrating an antibody response does not necessarily predict that there is going to be protection. Animal models have not proven to be predictive in many of the vaccine trials. There is probably going to be a need for multiple antigens. The toxins that some of these pathogens produce are quite complex. Human trials require large at-risk populations.

There is some evidence, at least for *C. diff,* that protection is possible though the evidence is indirect. For example, there is the recently approved human monoclonal bezlotoxumab from Merck. This is a human monoclonal antibody that had an indication approved in 2017 for prevention of recurrent infection for adult patients at risk. This is given as an intravenous (IV) dose treatment. It binds to toxin B and does not impact the initial clinical cure, but in the fairly large study, it did show a reduced risk of recurrence of about 38% during the 12-week follow-up period, which is a time when a lot of the recurrent *C. diff* occurs. Protection of at least some of the population with the monoclonal suggests that protective immunity against CDI is, in fact, possible. There are other monoclonals directed against other HAI pathogens, Gram-negative bacteria, and *S. aureus* that are in development. Most of these are in early Phase 1 or Phase 2 trials, and clinicaltrials.gov lists several of them that are currently in development.

In terms of a couple of the candidate vaccines, Pfizer's investigational *C. diff* induces neutralizing antibodies against *C. diff* toxins. The experience with bezlotoxumab suggests that neutralizing antibodies against *C. diff* toxins are sufficient to prevent *C. diff* infection. This is a bivalent vaccine consisting of genetically engineered Toxins A and B along with an alum adjuvant. It induced high levels of neutralizing antibodies in the Phase 1 and 2 trials and neutralizes toxins from over 95% of clinically relevant *C. diff* strains globally. Responses were established following a 0/1/6-month schedule in the Phase 2 study in humans, and they are currently in the middle of a Phase 3 with 16,000 patients projected to be enrolled looking at the

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usual Phase 3 safety endpoints of safety, tolerability, and efficacy in adults ≥50 years of age. A range of people will be included, but certainly there will be many who have various chronic conditions or immunologic deficiencies that are common in the older age groups.

It is important to note that there has not always been success with *C. diff* vaccines. Recently, Sanofi's *Cdiffense* vaccine that was a purified Toxin A and B was shown to be immunogenic in healthy volunteers. However, in a Phase 2b/3 trial late last year, it was discontinued due to low efficacy.

The SA4Ag vaccine from Pfizer took the multiple antigen approach and includes the capsular polysaccharides CP5 and CP8, which account for approximately 75% to 80% of invasive infections, conjugated to the carrier protein CRM197; mutated recombinant clumping factor A (rmClfA, lacks plasma fibrinogen-binding activity); and a manganese transporter protein C (MntC), which is important for uptake. This has been shown in several studies to have rapid and robust humoral immune response lasting over 6 months. There has been evidence of opsonophagocytic bacterial killing responses, suggesting some degree of induced T-cell dependent immunity and there may be some cellular response also. The Phase 2b/3 trial in which it would be given as a single dose to pre-operative patients getting elective spinal surgery is now enrolling and anticipates an enrollment of 6000 subjects 18 to 85 years of age, with the vaccine dose being given 10 to 60 days before the operation. This could affect a lot of people as an estimated 9.7 million spinal procedures are projected to occur during the study timeframe of 2021-2030 and *S. aureus* causes over 50% of orthopedic SSIs. This could have a significant impact on SSIs and potentially on invasive MRSA and *S. aureus* infections.

S. aureus vaccines have also been a challenge. StaphVAX from Nabi consisted of capsular polysaccharides CP5 and CP8 conjugated to non-toxic recombinant *Pseudomonas aeruginosa* exotoxin A. This was protective in animal challenge models and immunogenic in healthy volunteers. However, it failed its Phase 2b/3 trial among patients with ESRD and development has been discontinued. More recently, V710 by Merck in which the iron surface determinant B (IsdB) was used as the antigen was protective in animal challenge models and immunogenic in healthy volunteers, but failed its 2b/3 trial in cardiothoracic surgery patients with low efficacy and even increased mortality among the patients who developed *S. aureus* infections. While causality has not been fully explained, development has been discontinued.

Several of the vaccines and monoclonal antibody products that are in Phase 2 development are listed in this table:

Vaccine or Biologic	Target	HAI(s)
NVD3a (NovaDigm)	*Candida* agglutinin and *S. aureus* adhesion protein	Vulvovaginal candidiasis Surgical site infection
VLA84 (Valneva)	*C. difficile*	Primary prevention
Antibody (multiple companies)	*S. aureus*	Infection, pneumonia
Antibody (multiple companies)	*P. aeruginosa*	Pneumonia

Source: Pew Trust 2017. http://www.pewtrusts.org/en/multimedia/data-visualizations/2017/nontraditional-products-for-bacterial-infections-in-clinical-development

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In addition to technical challenges, there will be programmatic challenges. For example, usual delivery models that are based on universal age-based vaccination will sometimes not apply. The approved indication often will be narrow (e.g., elective orthopedic surgery, post antibiotic, limited age group, chronic disease risk factors, et cetera). Vaccination programs may have to rely on settings that are less experienced with delivering vaccinations (e.g., outpatient surgery, transitions of care such as between the hospital and a nursing home, et cetera). Immunogenicity is likely to be reduced among persons at risk, though the vaccine trials will include some of those people so there should be some knowledge of this going into a program once a vaccine is licensed. There is unknown potential for interaction between other treatments (e.g., monoclonals, polypharmacy) and vaccines. Obviously, these patients receive a lot of other medications that must be kept in mind. In addition, economic analyses are needed.

In terms of what CDC and public health have been doing and can do to contribute to HAI vaccine development and evaluation, epidemiologic studies can help to identify populations and settings for trials and model potential impact. CDC conducts a lot of risk factor and healthcare encounter types of studies, and has been expanding its work in linking data sources to follow patients across healthcare encounters over the course of months and years to understand their antibiotic exposures, subsequent illnesses they acquire, et cetera. One example is work that CDC's James Baggs led in which EIP data were merged with hospital discharge data in New York to develop a predictive risk score for subsequent *C. diff* infection. This risk score worked quite well and has been validated in a validation dataset. However, what is interesting is that one cannot conduct vaccine studies in only high-risk populations, given that the anticipated sample size would never be reached based on the expected attack rate in that group. Numerous relatively healthy people will have to be included in such trials [J Baggs, et al. Vaccine 2015;33:6241-9].

With the Antibiotic Resistance Solutions Initiative, a great deal of funding was provided to CDC and other federal agencies. Much of the CDC funding is being allocated to states. In the Epidemiology and Laboratory Capacity (ELC) for Infectious Diseases Cooperative Agreements, all of the states receive these funds. One focus of these grants has been to better link public health and healthcare settings. Some results of this infrastructure building have already been observed, with more results anticipated over the coming years. CDC's Prevention Epicenters program, now with 11 epicenters across the US, will continue to be an important source of information on risk factors and transmission in healthcare settings. These academic centers are funded by CDC to perform cutting edge research on HAIs. CDC collects diverse isolates of important HAI pathogens through the EIP, which conducts population-based surveillance based on laboratory-confirmed infections in 10 sites across the US.

CDC's laboratory is making diverse bacterial isolates available. One example is the CDC & FDA Antibiotic Resistance Isolate Bank. CDC receives isolates now from many sources (e.g., health departments, laboratories, outbreak and surveillance activities). Many isolates are being received, particularly from CDC's Antimicrobial Resistance Laboratory Network that is funded through the ELC grants. EIP provides isolates from outbreaks. CDC is able to make panels that manufacturers have found useful in the development of diagnostics and antibiotics, and potentially could find useful for vaccine development to examine things like antigenic diversity. CDC curated 14 panels from its 450,000+ isolate collection, has shared 55,000 isolates since July 2015 with 571 unique customers, and has processed 637 orders. In addition, large surveillance systems are already established at CDC that could be used for post-approval effectiveness and safety assessments within EIP, NHSN, and ISO.

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In conclusion, Dr. Fiore explained that the reason CDC was bringing this to ACIP's attention during this meeting was because they wanted to suggest that an HAI Vaccine WG be established. The best-case scenario for vaccine licensure is probably 2 to 3 years in the future. However, as has been a theme in this presentation, CDC thinks that HAI vaccines and HAI vaccine programs will be different in many respects from currently licensed vaccines in adult schedules. Careful and deliberate discussion will be needed, and merit consideration of forming an HAI Vaccines WG as early as late 2018 to hear from manufacturers and other sources how these vaccines might be used.

Discussion Points

Dr. Messonnier welcomed Dr. Fiore back to ACIP, noting that he had served as a long-time ACIP influenza lead. She requested that he talk about how he envisioned the Healthcare Infection Control Practices Advisory Committee (HICPAC) and ACIP recommendations coming together in this space.

Dr. Fiore responded that HICPAC has not had an opportunity to think about vaccines very much, and he did not know how much had been presented to them in the past on vaccines. However, supplementation with members from HICPAC to any ACIP WG would be really important because those members will understand the healthcare settings where some of this vaccination will occur and the groups that will be needed for vaccination. It seems that they would want members of each WG cross-represented, and HICPAC may also want to develop a related WG.

Dr. Lee expressed her excitement that these two worlds are colliding. Implementation in terms of the public health infrastructure tends to be through separate paths or sometimes different people. It would be great to think about not only how to harmonize these recommendations with HICPAC, but also how to collaborate on the HAI and immunization delivery sides to be able to achieve what they would like to do. Dr. Fiore agreed completely.

Dr. Bennett said she also thought this was very exciting and supported creating a WG sooner rather than later. Adequate surveillance systems should be in place in order to evaluate impact moving forward.

Dr. Hunter said he was thinking about how this would play out on the local or state level with public health, because he has observed in the City of Milwaukee Health Department that the Epidemiologists rely on the Infection Preventionists (IPs) within healthcare systems. IPs are the ones who do the brunt of the work on this, so this is another level to consider in terms of implementation.

Dr. Moore added that many states have an HAI program. Tennessee has the luxury of having the second largest HAI program outside of CDC, so they work very closely with HAI folks at the state level who also in turn are very tightly connected to IPs across the states. These kinds of implementations would work smoothly with immunization collaborating with HAI at the state level, and supporting IPs as is done with other issues such a measles outbreak occurring in a healthcare facility or as is done in every influenza season. She thinks that investments have been made at the state level and in HAI that will pay off for implementing this.

Dr. Sun (FDA) emphasized that FDA is engaged in very pointed discussions with the sponsors regarding many of the programmatic challenges that Dr. Fiore pointed out with respect to HAI vaccines. For example, FDA convened a VRBPAC meeting in November 2017 specifically

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addressing the issue of the Pfizer *S. aureus* vaccine and how safety and efficacy for a specific population could be generalizable to all elective orthopedic surgeries.

Meningococcal Vaccines

Introduction

David S. Stephens, MD
Chair, Meningococcal Work Group
Advisory Committee on Immunization Practices

Dr. Stephens reported that the activities of the Meningococcal Vaccines WG have involved reviewing the WG terms of references; updated data on meningococcal disease epidemiology among college students, infants, and young children; newly available data for MenB vaccines regarding antibody persistence and response to a booster dose and safety and immunogenicity of MenB vaccines in children aged <10 years; and the GRADE evidence for booster doses of MenB vaccine for persons at increased risk.

In terms of future activities, a GRADE evaluation is being planned for MenB vaccine booster doses pending data availability. A full session is being planned on MenB booster doses in persons aged ≥10 years at increased risk for meningococcal disease pending data availability. In late 2018/early 2019, a publication is planned of Consolidated ACIP Recommendations and a Report on Meningococcal Vaccines for MenACWY and MenB vaccines.

The agenda for this session focused on the epidemiology of meningococcal disease among college students in the US for 2014-2016. This was an informational session only.

Epidemiology of Meningococcal Disease Among College Students, US 2014-2016

Sarah Meyer, MD MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Meyer presented on the epidemiology of meningococcal disease among college students in the US from 2014 to 2016. In the 1990s, college freshman living in residence halls were identified as being at increased risk for meningococcal disease. During this time period, meningococcal disease and outbreaks in young adults were primarily due to serogroup C. ACIP recommended routine quadrivalent meningococcal conjugate (MenACWY) vaccine in 2005 for all adolescents aged 11 through 12 years, along with persons at increased risk for meningococcal disease, including unvaccinated college freshman living in residence halls. In 2010, a booster dose at age 16 years was recommended. In the past 20 years, the overall incidence of meningococcal disease in the US has declined 10-fold, and serogroup B is now the primary cause of meningococcal disease and outbreaks in young adults.

Two serogroup B meningococcal (MenB) vaccines are currently licensed in the US: MenB-4C (Bexsero®) and MenB-FHbp (Trumenba®), both administered as a multi-dose series. In 2015, ACIP recommended that a MenB vaccine series may be administered to adolescents and young adults aged 16 through 23 years to provide short-term protection against most

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strains of MenB. The preferred age for MenB vaccination is 16 to 18 years. This is a Category B recommendation.

Data presented to ACIP in June 2015 during the MenB vaccine policy deliberations demonstrated that the estimated incidence of MenB among college students aged 18 through 23 years was low at 0.09 cases/100,000 population and was similar to that of non-college students during 2009-2013. However, the data were limited as cases and incidence in college students were estimated using multiple sources, given that no national-level data were available. At this time, CDC shared plans to improve surveillance and report updated findings to ACIP on the incidence of MenB in college students once additional data became available.

In 2014-2015, enhanced meningococcal disease surveillance activities were implemented to collect additional data, including college student status, and isolates on cases submitted to NNDSS. Enhanced surveillance activities are currently conducted in 45 states, covering 98% of the US population. Thus, in light of improved surveillance, CDC conducted an analysis to reassess the epidemiology of meningococcal disease among college students aged 18 through 24 years during 2014-2016. The objective of this presentation was to update ACIP on the incidence and risk of MenB in college students and review additional considerations for MenB vaccination in this group.

All cases reported to NNDSS during 2014-2016 were reviewed. Cases aged 18 through 24 years were classified as college students or non-college students based on information collected through enhanced meningococcal disease surveillance activities. For cases with missing college student status or cases from states not participating in enhanced surveillance activities, college status was ascertained by state health departments through review of case investigation records. Population denominators were obtained from the 2015 National Center for Education Statistics (NCES) Integrated Postsecondary Education Data System (IPEDS) Fall Enrollment Survey and the US Census Bureau.

Before describing the epidemiology of meningococcal disease in college students, Dr. Meyer first reviewed the overall epidemiology of disease in the US. Incidence of meningococcal disease has steadily declined in the past 20 years, reaching reported lows during 2014-2016, with an incidence of 0.12-0.14 cases/100,000 population. She focused on 2014-2016 for the rest of the presentation. While the incidence of meningococcal disease in adolescents and young adults is overall low, a peak in the incidence of MenB, is observed between the ages of 18 to 20 years. In contrast, the incidence of disease due to serogroups C, W, and Y remains low in this age group. Among the 1178 cases reported to NNDSS during 2014-2016, 166 (14%) of cases occurred in persons aged 18 through 24 years. College status was known in 162 (98%) of these cases comprised of 83 college students and 79 non-college students.

Compared to non-college students, college student cases were younger, with approximately 60% of cases reported in 18 through 19-year olds, with a greater proportion due to serogroup B accounting for nearly 3-quarters of college student cases. Overall, 12.5% of cases in this age group died, with a similar case-fatality rate in college students and non-college students. Overall, an average of 54 cases of meningococcal disease due to any serogroup was reported annually among 18- through 24-year olds in the US, for an average annual incidence of 0.17 cases/100,000. The highest incidence of disease was reported in 18- through 19-year olds, followed by 20- through 21-year olds and 22- through 24-year olds. Serogroup B accounts for the majority of disease in this age group, and the incidence of disease due to serogroups C, W, or Y combined is very low.

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Next, the incidence of meningococcal disease was assessed by college student status and the relative risk of disease was estimated in college students compared to non-college students. An average of 20 cases of MenB were reported annually among college students, with an incidence of 0.17 cases/100,000 population and a relative risk of 3.5. The incidence was highest in college students aged 18 through 19 years at 0.28 cases/100,000 population with a relative risk of 3.1. While the incidence was lower among college students aged 20 through 21 years at 0.18 cases/100,000 population, the relative risk was higher at 4.1. The incidence of MenB in 22- through 24-year olds was similarly low among college students and non-college students. In all age groups, the incidence of meningococcal disease due to serogroups C, W, or Y combined was very low and was similar in college students and non-college students. By year of age, the estimated incidence of MenB was highest among 18- through 20-year-old college students. Incidence of serogroup B disease in non-college students was highest among 18-year olds and was lower in all other ages. The estimated incidence of serogroups C, W, and Y combined was low for all ages irrespective of college student status.

During 2014-2016, 6 outbreaks of MenB were reported on college campuses. The size of these outbreaks ranged from 2 to 6 cases, with an undergraduate population size ranging from approximately 4000 to 35,000. Mass vaccination with a MenB vaccine series was implemented in response to all of these outbreaks. Serogroup B college outbreaks continued to occur in 2017, with 2 additional clusters or outbreaks reported. Overall, 32% of all serogroup B cases in college students were outbreak-associated. The highest proportion of outbreak-associated cases was observed in 18- through 19-year olds at 38%, followed by 20- through 21-year olds at 23%. Only one serogroup B case was reported in college students aged 22 through 24 years, and this case was not outbreak-associated.

In order to assess the impact of outbreaks on the increased risk of MenB in college students, any subsequent outbreak-associated cases were excluded from the analysis of 18- through 21-year olds. In other words, for this analysis, all sporadic cases as well as the first case associated with each outbreak were kept in order to estimate the incidence and risk of disease in the absence of outbreaks. While the magnitude of the relative risk was lower, the same trends were observed in increased incidence among college students after exclusion of subsequent outbreak-associated cases with an overall relative risk of 2.8.

In summary, the incidence of MenB in college students is low; however, college students aged 18 through 21 years are at increased risk compared to non-college students. In contrast, the incidence of serogroups C, W, and Y combined is lower, and is similar in both college students and non-college students, likely at least in part due to the success of the adolescent MenACWY vaccine program. Serogroup B college outbreaks are an important factor, though the risk remains elevated among college students even when excluding outbreak-associated cases.

In addition to the data presented during this session, the WG has continued to review data on MenB vaccines as it has become available, much of which has been previously shared with ACIP. To summarize the key considerations for use of MenB vaccines in college students, the WG discussed the burden of disease and population at risk; challenges with mass vaccination during outbreak response; effectiveness and duration of protection of MenB vaccines; molecular features of serogroup B isolates and expected strain coverage by MenB vaccines; cost-effectiveness of MenB vaccines in college students; and awareness and use of MenB vaccines under the existing Category B recommendation.

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Overall, the burden of MenB in college students is low. An average of 20 cases and 2 to 4 outbreaks have been reported annually in recent years. No additional data on potential risk factors (such as year in school, housing, participation in fraternities or sororities) is currently available, though collection of this information is planned. However, as the incidence of MenB is uniformly elevated among students aged 18 through 20 years, freshman may not be at particularly increased risk. Finally, in 2015, nearly 9 million students aged 18 through 21 years were enrolled in college.

Meningococcal disease outbreaks on college campuses create significant anxiety and major logistical and financial challenges. While MenB vaccine is recommended by ACIP during outbreaks of serogroup B disease, achieving high uptake has been difficult, especially at large universities with over 20,000 undergraduates. The estimated first dose coverage following initial mass vaccination efforts at 6 large universities has been less than 60%, with even lower coverage for second or third doses. Outbreak response through mass vaccination may become more challenging if MenB vaccine uptake under the Category B recommendation increases, given the potential complexity of determining the number of doses a student has previously received, which vaccine product, et cetera.

There are currently no effectiveness data available in the US or for adolescents, though 2-dose vaccine effectiveness among UK infants was 83% in the first year following vaccination.[1] However, data in adolescents suggest waning of antibodies after vaccination with MenB vaccines as early as 12 months after completion of the primary series. Finally, evaluations conducted to-date show little-to-no impact of MenB vaccines on serogroup B carriage, suggesting that herd protection is unlikely[2,3,4] [[1] Parikh SH, et al. Lancet 2017; [2] McNamara L, et al. JID 2017; [3] Soeters H, et al. CID 2017; [4] Read R, et al. Lancet 2014].

Another consideration is the molecular epidemiology of serogroup B disease in college students, as well as the expected strain coverage of MenB vaccines in this population. Overall, serogroup B meningococcal strains in college students are genetically diverse. Among the 34 isolates from 2014-2016 that were analyzed by whole genome sequencing (WGS), 16 sequence types were identified. The 6 serogroup B college outbreaks were due to 5 different sequence types. MenB vaccines are expected to cover a wide range of circulating strains in the US, but will not prevent all cases. The expected strain coverage of MenB vaccines in college students is not determined. However, 16 (47%) of isolates in this analysis possessed one or more MenB vaccine variants included in MenB-4C or MenB-FHbp and others may still be covered by MenB vaccines through cross-reactivity. No information is available on gene expression or isolate susceptibility to vaccine antigen-induced antibodies.

In terms of the cost-effectiveness of MenB vaccines in college students, the analysis previously shared with ACIP was updated with 2014-2016 MenB incidence data. Despite higher, more accurate incidence estimates, similar conclusions were reached. If the focus is just on vaccination in college students, an estimated 11 cases and 1 death could be prevented each year. The NNV to prevent one case is 305,000 and to prevent one death is nearly 2.8 million. The cost per QALY saved is $9.6 million dollars.

Another potential consideration is awareness and use of MenB vaccines under the existing category B recommendation. There are currently gaps in awareness of MenB vaccines among parents and providers. Among parents of adolescents aged 16 through 19 years, 43% report being aware of MenB vaccines. Among these, 69% became aware through their child's healthcare provider.[1] However, in another study only 70% of pediatricians and 21% of family practitioners reported being "very aware" of MenB vaccines.[2] Uptake of MenB vaccines among

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adolescents and young adults is estimated to be low. Coverage of at least one dose of MenB vaccine among 16- through 18-year olds is estimated at less than 10%.[3] Uptake in college students is unknown; however, only 2% of colleges specifically require MenB vaccine and only 24% stock MenB vaccine[4] [[1] Pfizer Parental Awareness and Utilization of Meningococcal Serogroup B Vaccines Survey (unpublished); [2] Vaccine Policy Collaborative Initiative, PI Alison Kempe MD MPH (unpublished); [3] CDC unpublished data; [4] American College Health Association/CDC (unpublished)].

The WG's interpretation of the data presented is that although the risk of MenB is increased among college students, the number of preventable cases is low and the NNV to prevent a case is high. The limited duration of protection of MenB vaccines and the lack of evidence for impact on carriage may limit the ability to protect college students through the period of greatest risk. The WG feels that in practice, MenB vaccination should occur as close to college entry as possible for those students who choose to get vaccinated. While achieving high coverage of MenB vaccine during college outbreaks has been challenging, routine vaccination of all college students also would be difficult. Finally, awareness and uptake of MenB vaccines is currently low. The WG does not propose any changes to the current MenB vaccine recommendations. However, the WG suggests that CDC provide more guidance around clinical decision-making during pre-college health visits to help students, parents, and providers make an informed decision.

In closing, Dr. Meyer posed the following questions to ACIP for input:

- ❑ Does ACIP agree with the WG interpretation?
- ❑ And are there additional data ACIP would like to review?

Discussion Points

Dr. Belongia asked how "college students" were defined for this analysis in terms of whether community and technical colleges were included.

Dr. Meyer responded that in terms of the cases, "college students" is a self-defined variable in the surveillance system and would include 2-year colleges, 4-year colleges, technical schools, et cetera. The denominator is comprised of anyone who is in an academic program including 2-year students, 4-year students, vocational students, et cetera.

Dr. Bennett asked whether they were able to separate residential versus non-residential college students in the data.

Dr. Meyer replied that at this point, they are not able to do so. However, they are planning to collect that information on cases in order to further define the types of college students who are getting disease.

Dr. Bernstein asked whether the 2% of colleges that require vaccination previously had outbreaks or what the reasons were for instituting a requirement.

Dr. Meyer said that while they do not have this information, they could probably examine those data more in-depth. Some of the data collected as part of this survey included whether there was a previous outbreak at the university or previous outbreaks in that area. They found that quite a few schools reported that there was an outbreak in their area, but it is not clear whether that was in the state, region, et cetera.

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Dr. Cohn inquired as to whether the number of cases per year for 2014, 2015, and 2016 was stable or changed over those three years.

Dr. Meyer indicated that the number was pretty stable between 2015 and 2016 and was somewhat lower in 2014. There were no outbreaks during 2014, which is the year they began collecting this information. She was not sure they could describe a trend between those three years, but would say that it has been pretty stable for the last two years.

Dr. Riley noted that as a mother of a college student, the discussion regarding individual risk factors was very difficult to have. She has information because she sits on this committee, but the discussion with the pediatrician in trying to figure out the risk for her individual child who is on a sports team was very unsatisfying. While it sounded like a good idea, the flip side regards the potential for side effects. Now that there have been several outbreaks, she wondered whether there is more information about side effects from the vaccine and if this is also something they should be concerned about. She remembered when the vote was taken that the concern was that there were side effects, and people also were concerned about how long immunity would last.

Dr. Meyer responded that meningococcal disease is very rare in the US, but it is also very serious. She agreed that the conversations are challenging and expressed her hope that in the coming months more information would be available on the characteristics of sporadic and outbreak cases. Currently, only anecdotal reports are available from the various outbreaks. That information needs to be assembled along with cases that were not involved as part of an outbreak. A number of evaluations have been conducted on safety that are now published that assessed SAEs following vaccination through mass vaccination efforts. Overall, there were no serious concerns. Side effects have been mild and included fever, sore arm, et cetera.

Dr. Bennett observed that it is difficult to parse out risk factors when the numbers of cases are so small. It might be helpful to look at modes of transmission rather than individual risk factors perhaps through a network analysis to try to figure out how transmission occurs.

Dr. Messonnier noted that there have been numerous studies regarding the risk factors for meningococcal disease in college and high school students, as well as numerous network studies focused on transmission patterns and populations. The risk factors are always the same—things that transmit secretions. Having a conversation with a pediatrician about what a student will do while away at college is exceedingly difficult. CDC will continue to endeavor to gather more information, but it is not likely that anything they can gather will make this a simple conversation.

Dr. Bennett noted that the issue has to do with recommendations to pediatricians about how to have these conversations, which might be a conversation without the parent in the room.

Ms. Pellegrini asked whether CDC has plans for the future to try to incorporate some type of measure that will reflect how many of the students who survive have significant long-term health consequences. This is important and is currently not captured. Instead, there is a binary of “survived” or “did not survive.” Given how devastating this disease can be, capturing long-term health effects seems to be an important part of understanding the burden.

Dr. Meyer indicated that there is a wide body of evidence that describes some of the sequelae outcomes, but they have discussed ways they could better understand this issue with more updated data.

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Dr. Stephens noted that there is about 20% morbidity associated with invasive meningococcal disease. There are numerous studies, which address long-term cognitive issues as well.

Dr. Frey requested clarity regarding whether those who developed meningococcal were not vaccinated.

Dr. Meyer replied that the majority received MenACWY vaccine and very few received at least one MenB, but that was not in a case of serogroup B.

Dr. Bernstein asked whether the 16-year-old platform may be somewhat early given waning immunity and when they might be sharing bodily secretions.

Dr. Meyer responded that they continue to review data on waning immunity and duration of protection. The 16 through 18-year-old preferred age is why the WG suggested that CDC provide more discussion and guidance regarding the pre-college health visit. It may not change the preferred language, but those who are going off to school can have those discussions with their pediatricians to determine when the best time might be for them to get vaccinated if that is what they choose to do.

Dr. Rockwell (AAFP) pointed out that secretion sharing starts very early and it is cultural. Her two children, raised by physicians, still share cups, glasses, and water bottles. When they are with a group of friends, children trust each other and share drinks. That is pretty universal unless someone is a germaphobe.

Dr. Even (ACHA) said that it is complicated to try to explain to her colleagues why ACIP does not have a generalized recommendation. One thing that stood out to her as a member of the WG is that herd immunity has not been demonstrated.

Dr. Meyer pointed out that in Australia, a very large carriage study is being conducted to try to examine this issue with many thousands of students enrolled. Those data will be reviewed with the WG when it becomes available.

Japanese Encephalitis Vaccine

Introduction

Chip Walter, MD
Chair, ACIP Flavivirus Vaccines WG

Dr. Walter reminded everyone that Flavivirus Vaccines WG's objectives with respect to JE are to: 1) review the newly available safety and immunogenicity data for JE vaccine; 2) review the epidemiology and risk of JE in travelers; 3) review ACIP recommendations for use of JE vaccine in consideration of updated safety, immunogenicity, and traveler risk data; and 4) update the *MMWR Recommendations and Reports* last published in 2010. Given some of the questions raised during the last ACIP meeting, the presentations during this session focused on a review of JE epidemiology and vaccine, as well as the WG's activities and plans.

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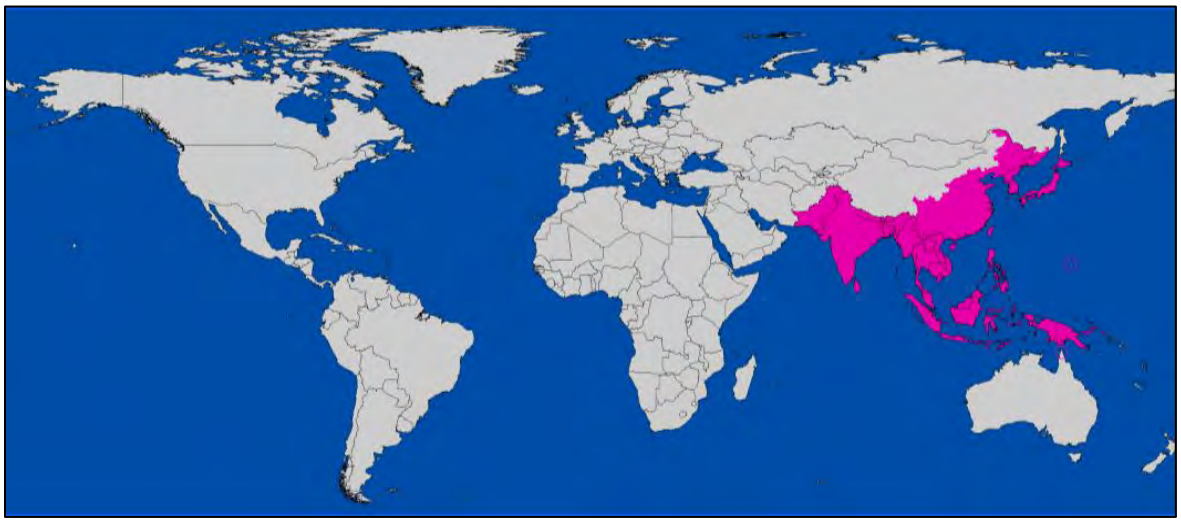
Review of JE and WG Plans

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 reminded everyone that JE is caused by a mosquito-borne flavivirus that is the leading vaccine-preventable cause of encephalitis in Asia. *Culex tritaeniorhynchus* mosquitoes are the primary JE virus vectors. They are evening- and nighttime-biting mosquitoes, usually feed outdoors, and commonly breed in rice fields.

JE virus is maintained in an enzootic cycle between mosquitoes and amplifying vertebrate hosts, primarily pigs and wading birds. The virus is transmitted to humans through the bite of an infected mosquito. Humans are dead-end hosts for JE virus because they do not usually develop a level or duration of viremia sufficient to infect mosquitoes. Therefore, infected travelers pose little risk for introducing the virus into the US or other non-endemic areas. Because of the ongoing circulation of JE virus in the environment, non-immune travelers to JE-endemic countries can be at risk for JE virus infection, even if JE cases are not reported among the local population because of high vaccine coverage or natural immunity. The approximate global distribution of JE virus is shown on the following map:



JE virus occurs only in Asia and parts of the Western Pacific; however, more than 3 billion people live in JE-endemic countries.

Most JE virus infections in humans are asymptomatic with less than 1% of infected people developing neurological disease. However, when disease does occur it is often severe. Overall, about 20% to 30% of patients die and 30% to 50% of survivors have significant neurologic, cognitive, or behavioral sequelae. There is no specific antiviral therapy, and treatment consists of supportive care [Vaughn DW, Hoke CH. Epidemiol Rev 1992].

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Based on a recent estimate, there are about 68,000 JE cases annually in Asia with an overall incidence in all age groups of approximately 1.8 cases/100 000 population. The highest risk for infection is in rural agricultural areas where all elements of the JE transmission cycle are present. The seasonality of disease varies by region. In most temperate areas of Asia, JE virus transmission is seasonal. Human disease usually peaks in summer and fall, sometimes with large outbreaks. In the sub-tropics and tropics, sporadic cases may occur year-round but there is often a peak during the rainy season. Because of the ongoing risk for the local population, national vaccination programs have been implemented in some endemic countries [Campbell GL, et al. Bull World Health Organ 2011].

For most travelers to Asia, the risk for JE is very low but varies based on travel destination, duration, season, and activities. Overall incidence is estimated to be less than 1 case per million travelers. In the US in 25-year period following first licensure of JE vaccine in 1992, 12 travel-associated cases were reported, or less than 1 case reported per year [Hills et al. CDC Yellow Book 2018].

The inactivated Vero cell culture-derived JE vaccine manufactured by Valneva, Ixiaro®, is the only JE vaccine currently licensed and available in the US. The vaccine was licensed for adults 17 years of age and older in 2009. The licensure was subsequently extended to children ages 2 months and older in 2013. There are no efficacy data for Ixiaro®, but the vaccine was licensed based on its ability to induce JE virus neutralizing antibodies as a surrogate for protection. The vaccine demonstrated a good immunogenicity and reactogenicity profile in pre-licensure clinical trials, and no safety concerns have been identified to date in post-licensure surveillance. The vaccine costs approximately $600 for the 2-dose primary series.
When making recommendations regarding the use of JE vaccine, there are many factors HCPs need to consider. These include that the risk of JE disease for most travelers is very low. However, the risk varies based on travel location, duration, season, and activities. JE is a severe disease with substantial morbidity and mortality, and there is no specific treatment. A safe and effective vaccine is available, but the vaccine costs about $600 for a 2-dose primary series and rare SAEs can occur. Finally, from a public health perspective, vaccination of travelers is not reported to prevent importation or spread of JE virus as humans are a dead-end host for JE virus.

In terms of the existing ACIP recommendations for prevention of JE among travelers, providers should discuss with all travelers to JE-endemic countries the risks of JE disease and the importance of taking precautions to avoid mosquito bites and thus to reduce risk of JE and other vector-borne diseases. JE vaccine is recommended for longer term travelers who will live in or visit endemic areas for one month or longer during the JE virus transmission season, including expatriates and recurrent travelers who will be based in an urban area but are likely to visit rural areas during the transmission season. JE vaccine should be considered for short-term travelers to endemic areas during JE virus transmission season if they plan to travel outside of an urban area and have an itinerary or activities that increase the risk of JE virus exposure or if their itinerary is uncertain or there is an outbreak. JE vaccine is not recommended for short-term travelers whose visit is restricted to urban areas or times outside of transmission season [CDC. *MMWR* 2010].

As a reminder, the JE Vaccine WG was reformed in March 2015. As noted earlier, the WG's objectives 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*.

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Presentations to ACIP since the WG was reformed have included new safety data, including a review of AEs reported to VAERS over a 4-year period from 2012 to 2016 and a presentation on post-marketing AE surveillance among US military personnel. Several presentations on updated vaccine immunogenicity data also have been given, including immunogenicity in adults ≥65 years of age, the accelerated 0- and 7-day dosing schedule, concomitant administration of JE vaccine with rabies vaccine, and duration of protection following a primary series in adults and data regarding the need for a booster dose in children. Finally, an updated review was given of the epidemiology and risk of JE in US travelers.

Current WG activities are focused on finalizing a JE vaccine cost-effectiveness analysis. To provide some background to this analysis, JE vaccination has been shown to be cost-effective or cost-saving for local populations in JE endemic countries where disease incidence is higher and substantially lower cost vaccines are used. No JE vaccine cost-effectiveness studies have been conducted among travelers. Given the low incidence of disease among travelers and the high cost of vaccine, it is not expected that a JE vaccine would be cost-effective for travelers. However, the rationale for conducting a JE vaccine cost-effectiveness analysis is to provide perspective on the NNV and cost per case averted and to compare the relative costs of vaccination for travelers with different itineraries and disease risk.

To complete the remaining ACIP JE Vaccine WG objectives, the following items will be addressed during upcoming ACIP meetings:

- ❑ Presentation of the cost-effectiveness analysis
- ❑ Review of the ACIP recommendations for use of JE vaccine in consideration of the updated safety, immunogenicity, and traveler risk data
- ❑ 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 & Reports*

Finally, for ACIP's awareness, there are two JE vaccine submissions currently under review at FDA: 1) FDA is assessing the safety and effectiveness of a booster dose in children; and 2) data for the accelerated primary schedule are under review.

Discussion Points

Dr. Belongia asked whether it was correct to say that under the vast majority of circumstances, the cost of the vaccine in the US would be borne by the traveler.

Dr. Hills responded that based on the information they have, in most cases the cost of the vaccine would be borne by the traveler. There are some companies that will pay for their staff, but it is not believed to be covered by insurance in most cases.

Dr. Romero asked whether the ACIP recommendations define what constitutes "short-term" and "long-term" intervals of exposure, or if it is left up to the traveler and physician.

Dr. Hills replied that "longer term" is a month or longer and shorter-term is less than a month. The consideration component of the recommendations relates to shorter-term travel with risk activities.

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Vaccine Supply

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

During this session, Dr. Santoli presented an update on HepA and HepB vaccine supplies. During 2017, large outbreaks of HepA among adults in several US cities resulted in increased demand for vaccine and resulted in constrained supplies of vaccine. In response, CDC staff have taken the following actions:

- ❑ Worked directly with public health officials in affected jurisdictions to provide guidance about how best to target vaccine in response to local epidemiology
- ❑ Collaborated with manufacturers to understand options for managing supplies in the private sector and for increasing national supply
- ❑ Implemented ordering controls in the public sector to support affected jurisdictions and maintain an equitable distribution of vaccine in unaffected jurisdictions
- ❑ Increased vaccine availability on CDC's adult vaccine contracts to support the management of ongoing and future outbreaks, as well as routine vaccination activities

As available vaccine supplies have increased and progress has been made regarding the ongoing outbreaks, the public-sector vaccine supply strategy has evolved. First, support for affected jurisdictions is ongoing in terms of technical assistance and vaccine supply as part of the outbreak responses. Second, increased levels of vaccine supply have been made available for unaffected jurisdictions to facilitate routine vaccination activities and make modest amounts of vaccine available for small scale outbreak response without awardees having to consult CDC. In addition, CDC and vaccine manufacturers are continuing to carefully monitor ongoing demand and usage of adult HepA vaccine. Of note, there currently are no constraints on TWINRIX®, which is the combination HepA/HepB vaccine, or the pediatric HepA vaccine supply.

Merck is not currently distributing its adult HepB vaccine and will not be distributing the vaccine through the end of 2018. However, the dialysis formulation of HepB vaccine is available. GSK has sufficient supplies of their adult HepB vaccine to address the anticipated gap in Merck's adult HepB vaccine supply. However, preferences for a specific presentation (i.e., vial versus syringe) may not be met uniformly during this period.

Merck is not currently distributing its pediatric HepB vaccine, but anticipates resuming distribution in the beginning of April 2018. GSK has sufficient supplies of pediatric HepB vaccine to address the anticipated gap in Merck's pediatric HepB vaccine supply during this period. Similar to the adult vaccines, preferences for a specific presentation (i.e., vial versus syringe) may not be met uniformly during this time.

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

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Discussion Points

Dr. Cohn requested an update on the MMR VFC resolution.

Dr. Santoli replied that to return to an earlier question that was raised, the VFC resolution for MMR and varicella vaccines does include the use of MMR vaccine for those 6 months of age and older in the setting of an outbreak and in preparation for international travel.

Day 2: Public Comment

Krystle Beauchamp Grindley
Meningococcal Disease Survivor
National Meningitis Association Advocate

Good morning. My name is Krystle Beauchamp Grindley and I am survivor of meningococcal disease and an advocate with the National Meningitis Association (NMA). In 2003, I contracted meningococcal disease as a college junior at the University of New Orleans at a time when the meningococcal vaccine was not mandatory for college students in the State of Louisiana. In a few short hours, I went from being an excited college student to a very scared, very sick patient uncertain of my future. I was hospitalized for several weeks and although my road to recovery was long and I suffered permanent hearing loss, liver damage, muscle paralysis, and other lifelong consequences of the disease, I'm truly one of the lucky ones because we know that many who contract meningococcal disease ultimately die from it and many others will have amputated limbs, brain damage, and other serious complications.

My parents were strong advocates for my health and when I was a teenager, they made me get my routine immunizations every time they were up for me to get them, but I did however, skip the meningococcal vaccine. It was not routinely recommended to me at the time when I went to get my vaccines, so I did not receive it. That's a decision that ultimately regretted. I convinced myself that meningococcal disease was something that no one really got, and certainly something that I would never contract. But my story and the stories of countless others prove otherwise. Many teens feel invincible like I did at the time, but they're not. This is why I think that a permissive recommendation on a potentially life-saving vaccine just isn't strong enough. My experience with meningococcal disease showed me what a crucial role healthcare professionals play in helping individuals make personal health decisions. If a healthcare professional had made a strong recommendation for me for the meningococcal vaccines and told me that they weren't negotiable, my outcome may have been a lot different.

My experience also has driven home the importance of vaccines as tools for personal and public health. I advocate on a daily basis for adolescents and young adults to get vaccinated against meningococcal disease, and I am equally as passionate making sure that folks in my community get vaccinated for their influenza vaccines as well. Not only do we need to protect ourselves, but we have an obligation to protect those that may be immunocompromised as well. As an NMA advocate, I look at our map of meningococcal disease of outbreaks on college campuses, and I've brought a few that are outside, and I look at this map and am alarmed. The number of cases, particularly meningitis B on college campuses just keeps on growing. We need to prioritize the administration of both kinds of vaccines to help protect all of us from meningococcal disease. Thank you.

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Dr. Scott Halstead
Uniformed Services University of Health Services (RET)

Good afternoon. Just a couple of remarks on risk of Japanese encephalitis to complement Susan Hills remarks. I realize that looking at a map of the globe, the purple area didn't look so big, but this really is one of the very largest global zoonosis. It is important to think of Japanese encephalitis as a zoonosis. I studied zoonosis in Japan prior to development of vaccines. People were largely immune when they became adults, and that indicates that probably the transmission rate every year was between 10% and 15%. Since those days, people have both moved into cities and also there have been vaccines. So, we can't use human incidence as a measure of the intensity of this zoonosis.

Japanese encephalitis really resembles West Nile in that not only is this a zoonotic disease of birds, but it's widespread in a large number of other species. For example, when I was in Japan we found that every amphibian and reptile and even bats were infected. The dimensions of the zoonosis and the niches it occupies are really quite profound. Given this risk, the fact that Asia is highly populated and visited and really is without any monitoring—there is nobody really monitoring the dimensions of the zoonosis, which of course varies from area-to-area, year-to-year, and season-to-season—it really is prudent to provide immunization protection to people that enter into this sort of unknown zoonotic adventure if you will.

I'm a little bit concerned about the sort of hands-off approach to a vaccine recommendation for travelers, because I think that almost everybody who travels outside of a shepherded group and goes to Asia, you know, people say "seasonal." It's true in Northern Asia there is seasonality. But in Southeast Asia, there is not much seasonality. So, people are visiting these countries who wander away from urban areas. They don't have to go very far to actually be in zoonotic areas. The *Culex tritaeniorhynchus* is a rice paddy breeding mosquito. It's a very efficient transitional mosquito because it both intersects with the zoonotic cycle and with the human cycle.

I'm very encouraged that we have an effective, safe, and efficient Japanese encephalitis vaccine. But my suspicion frankly is that a single course of vaccine will actually last a lifetime, because you know what you're doing with Japanese encephalitis is protecting the brain. To do that, the virus has to enter the body, replicate, and then become viremic as far as we know. So, this gives the body a chance if you have immunological memory to provide an antibody barrier. I think this is a breakthrough vaccine that's efficient and non-reactogenic. We out to be more proactive perhaps in trying to get this vaccine into people's arms. I realize that the historical rate of encephalitis among visitors outside of Asia is quite low, but this zoonosis is not going anywhere. It's going to be there forever, and I think we need to think long-term. Thank you.

Dr. Bennett thanked Dr. Halstead for reminding them that the world is small and that they need to think about this carefully.

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Dr. Leonard Friedland
Vice President, Director Scientific Affairs and Public Health
Vaccines North America at GSK

Thank you very much. Dr. Leonard Friedland from GSK vaccines. I would like to take the opportunity to provide public comment in two topics that were discussed today, meningococcus and zoster. I'll start with meningococcus. It's a very important area that we really understand all of the data. Just a few comments on duration and around waning immunity. Much more data is being generated with all of the meningococcal vaccines at GSK. We have data now of persistence at 2 years, at 4 years, at 7 years which we look forward to reviewing with the committee. I think it's important to mention that when we look at immunogenicity, we're reporting antibody levels. But it's become quite clear that hSBA (human complement serum bactericidal antibody) underestimates immunity to meningococcus, and I think we really need to understand how the body responds immunologically to MenB vaccines. So, what is protective? With regard to coverage, I want to mention that GSK worked with CDC and published a recent paper demonstrating that BEXSERO® vaccine provides 91% coverage against strains circulating in the United States in a recent publication in November 2017. Also, it's important to mention around safety, there was a comment on safety, the post-marketing experience for BEXSERO® is very similar to that in the clinical trials. In the United Kingdom where the vaccine is being used routinely for infants, there are over 2 million infants that have now received the vaccine. There is a very large and growing safety database. Lastly on meningococcus around the carriage study that was mentioned, 56,000 adolescents 15 to 18 years old are being studied in Australia to investigate carriage for MenB vaccination, BEXSERO® particularly.

Now on to zoster if I may just briefly. Dr. Fryhofer, just to respond to your comments, SHINGRIX® can be ordered in different ways through wholesalers, through distributors, and through a GSK direct ordering site called GSK.com. GSK.com went through an SAP implementation. We notified all of our customers that the site would be down for a short period of time. Just yesterday, all customers on GSK Direct were notified that the site will be back up on Monday and so what you're referring to is for those who ordered directly from GSK, we will be back up on Monday. The websites are all up and running and providing information. Around information, thank you Dr. Messonnier for pointing out to all of our professional society partners how important it is to get out the right information around proper dosing, storage, administration, and reconstitution of SHINGRIX®. So, thank you very much for socializing that information so that people get this vaccine the proper way and can benefit. Thank you.

Frankie Milley
Meningitis Angels

Hi. I am Frankie Milley. My only child died with meningococcal disease at the age of 18. He had just graduated high school, just reached his pro golf career, and on Father's Day became ill with a fever and an earache and 14 hours later he laid on an emergency room table with blood literally coming from every orifice of his body. The Medical Examiner told me had Ryan lived, he would have been blind, deaf, his adrenal glands had ruptured, his kidneys had ruptured, he would have lost all 4 extremities.

Ryan was a golfer. He loved to dance. He was an amazing young man. He wanted to own his own golf club and call it "Hackwood." Since Ryan's death, I've spend the last almost 20 years now trying to make sure that other families don't have to go through what we did. Some of the kids that we work with have no legs, no arms, they've lost their faces, they've had kidney transplants, they take 26 plus pills a day just to replace what the adrenal glands are supposed

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to be doing, they have severe mental illness, suffer learning disabilities, their families are going bankrupt, they end in divorce, suicide—it's horrible. When you throw percentage rates around, you need to remember that 1% was a real person. He was my only child. This disease took away my right to ever be a grandparent, to be the parent of a loving son, and to have his comfort in my old age.

I've worked with this committee and spoken to this committee over the years and I want to commend you, because this is often a thankless job that you do and it's not recognized the work that this committee does in this country and around the world. I'm proud to stand here today with you guys. Because of what you did with MenC4 years ago, we are seeing a decline. Kids aren't dying anymore from this, but they are dying and they are still having it, but it's a lot better. We've seen the carriage rate go down immensely. I have to talk to those moms that are in an emergency room, or those dads. I have to listen to those parents who call me all hours of the night telling me that their child is so mentally ill and they can't get the help they need. I know with all of my heart that this committee moving forward is going to do the right thing when it comes to this disease because you do your homework and you're willing to listen. You're willing to listen to us all before you make those decisions. I commend you and I look forward to a time when I don't have to do this anymore. I'm 65. I'm ready to go sit on the lake and retire and not have to talk about Ryan dying every day of my life. But, I do want to thank you. You guys rock.

Dr. Bennett thanked Ms. Milley and commended the work that she does as well.

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Certification

Upon reviewing the foregoing version of the February 21-22, 2018 ACIP meeting minutes, Dr. Nancy Bennett, ACIP Chair, certified that to the best of her knowledge, they are accurate and complete. Her original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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Appendix A: ACIP Membership Roster

January 11, 2018

Department of Health and Human Services
Centers for Disease Control and Prevention
Advisory Committee on Immunization Practices
November 27, 2017 – June 30, 2018

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

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

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

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

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

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EZEANOLUE, Echezona, MD, MPH
Professor of Pediatrics and Public Health
Department of Epidemiology and Biostatistics
Director, Global Health and Implementation Research Initiatives
University of Nevada Las
Vegas, NV
Term: 07/01/2015-06/30/2019

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

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

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

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

PELLEGRINI, Cynthia
Senior Vice President
Public Policy and Government Affairs
March of Dimes
Washington, DC
Term: 07/01/2013-06/30/2018

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RILEY, Laura E., MD
Associate Professor, Obstetrics, Gynecology and Reproductive Medicine
Harvard Medical School
Maternal Fetal Medicine
Massachusetts General Hospital
Boston, MA
Term: 07/01/2014-06/30/2018

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Appendix B: Public Comment Letters Submitted

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,

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Advisory Committee on Immunization Practices (ACIP)
Secretariat 1600 Clifton Road, N.E., Mailstop A27
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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.

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