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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
October 24-25, 2018
Atlanta, Georgia

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Final - October 16, 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
October 24-25, 2018

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
Wednesday, October 24			
8:00	**Welcome & Introductions**		Dr. Amanda Cohn (ACIP Executive Secretary; CDC)
8:30	**Hepatitis A Vaccines - . Paul Weidle**		
	Introduction	Information & Discussion	Dr. Kelly Moore (ACIP, WG Chair)
	Background		Dr. Noele Nelson (CDC/NCHHSTP)
	Homelessness as a risk group: Evidence to Recommendation Framework and GRADE		Dr. Mona Doshani (CDC/NCHHSTP)
	Public comment		
	Recommendation vote	**Vote**	Dr. Noele Nelson (CDC/NCHHSTP)
	VFC vote	**VFC Vote**	Dr. Jeanne Santoli (CDC/NCIRD)
10:15	***Break***		
10:30	**Pneumococcal Vaccines - Tamara Pilishvili**		
	Introduction	Information & Discussion	Dr. Grace Lee (ACIP, WG Chair)
	PCV13 Impact on IPD and serotype distribution for the remaining disease burden		Dr. Tamara Pilishvili (CDC/NCIRD)
	Incidence of non-Invasive Pneumococcal Pneumonia before and after PCV13 recommendation for adults ≥65yo		Mr. Ryan Gierke (CDC/NCIRD)
	U.S. trends in pneumonia hospitalizations		Dr. Fernanda Lessa (CDC/NCIRD)
	Economic analysis of PCV13 for adults ≥65 year old		Dr. Charles Stoecker (Tulane University School of Public Health and Tropical Medicine)
	Preliminary EtR and GRADE. Summary and timeline		Dr. Almea Matanock (CDC/NCIRD)
12:15	***Lunch***		
1:30	**Adult Immunization Schedule - Melinda Wharton**		
	Introduction	Information & Discussion	Dr. Paul Hunter (ACIP, WG Chair)
	Proposed 2019 adult immunization schedule		Dr. David Kim (CDC/NCIRD)
2:20	**Child/Adolescent Immunization Schedule - Melinda Wharton**		
	Introduction	Information & Discussion	Dr. Henry Bernstein (ACIP, WG Chair)
	Proposed 2019 child and adolescent immunization schedule		Dr. Candice Robinson (CDC/NCIRD)
	Public comment		
	Immunization schedules recommendations vote	**Vote**	Drs. David Kim and Candice Robinson (CDC/NCIRD)
3:00	***Break***		
3:15	**Japanese Encephalitis - Marc Fischer**		
	Introduction	Information & Discussion	Dr. Chip Walter (WG chair)
	JE vaccine Evidence to Recommendations		Dr. Susan Hills (CDC/NCEZID)
	JE-VC accelerated schedule recommendation for adults		Dr. Susan Hills (CDC/NCEZID)
	JE-VC pediatric booster and booster dose recommendations		Dr. Susan Hills (CDC/NCEZID)
	Conclusions and next steps		Dr. Susan Hills (CDC/NCEZID)
4:15	**Anthrax - Henry Walke, Jarad Schiffer**		
	Introduction	Information	Dr. David Stephens (ACIP, WG Chair)
	NuThrax®		Dr. Paul- Andre de Lame, Mr. Jeff Shearer (Emergent BioSolutions)
	Anthrax antitoxin for PEP		Dr. William Bower (CDC/NCEZID)
5:00	**Vaccine Supply**		
5:05	**Public Comment**		
5:20	**Adjourn**		

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Thursday, October 25

8:00	**Agency Updates & Unfinished Business**		
	CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NIH, NVPO	Information	Dr. Nancy Messonnier (CDC/NCIRD); *Ex Officio* Members
8:30	**Human Papillomavirus - Elizabeth Unger**		
	Introduction		Dr. Peter Szilagyi (ACIP, WG Chair)
	Vaccine safety update - no association with primary ovarian insufficiency		Ms. Julianne Gee (CDC/NCEZID)
	Background - Expanded age indication for 9vHPV	Information & Discussion	Dr. Lauri Markowitz (CDC/NCIRD)
	GRADE		Dr. Elissa Meites (CDC/NCIRD)
	Impact and economic analyses		Dr. Harrell Chesson (CDC/NCHHSTP)
	Recommendation options		Dr. Lauri Markowitz (CDC/NCIRD)
10:15	***Break***		
10:45	**General Recommendations**		
	Introduction		Dr. Paul Hunter (ACIP, WG Chair)
	Background and posted changes since April 2017	Information & Discussion	Dr. Andrew Kroger (CDC/NCIRD)
	Vaccine Administration – Vaccinators with conditions that are contraindications or precautions		Dr. Andrew Kroger (CDC/NCIRD)
11:15	**Influenza - Alicia Fry**		
	Introduction		Dr. Chip Walter
	Influenza vaccine effectiveness in preventing influenza-associated hospitalizations during pregnancy	Information & Discussion	Dr. Mark Thompson (CDC/NCIRD)
	Fluzone Quadrivalent 0.5-mL dose for children aged 6 through 35 Months		Dr. Monica Mercer (Sanofi Pasteur)
12:15	**Rabies**		
	Workgroup update	Information	Dr. Sharon Frey (ACIP, WG Chair)
12:20	**Meningococcal**		
	Workgroup Update	Information	Dr. David Stephens (ACIP, WG Chair)
12:25	**Pertussis - Susan Hariri**		
	Introduction to Work Group		Dr. Henry Bernstein (ACIP, WG Chair)
	Background to current ACIP recommendations (Td and Tdap) and policy considerations for Tdap revaccination	Information	Dr. Fiona Havers (CDC/NCIRD)
	Adacel revaccination safety and immunogenicity		Dr. David Greenberg (Sanofi Pasteur)
	Boostrix revaccination safety and immunogenicity		Dr. Leonard Silverstein (GSK)
1:30	**Public Comment**		
1:45	**Adjourn**		

Acronyms

9vHPV	9-Valent Human Papillomavirus Vaccine
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
IPD	Invasive pneumococcal disease
JE-VC	Vero cell culture-derived Japanese encephalitis vaccine
NCHHSTP	National Center for HIV, Hepatitis, STD and TB Prevention [of CDC/OID]
NCIRD	National Center for Immunization & Respiratory Diseases [of CDC/OID]
NCEZID	National Center for Emerging and Zoonotic Diseases [of CDC/OID]
NVPO	National Vaccine Program Office
PEP	Post-exposure prophylaxis
PCV13	13-valent pneumococcal conjugate vaccine
Td	Tetanus and diphtheria vaccine
Tdap	Tetanus, diphtheria, and pertussis vaccine
VFC	Vaccines for Children
WG	Work Group

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Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
AAR	After Action Report
ABCs	Active Bacterial Core Surveillance
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACOG	American Congress of Obstetricians and Gynecologists
ACP	American College of Physicians
ADHD	Attention-Deficit/Hyperactivity Disorder
ADVISE	Agent-based Dynamic model for Vaccination and Screening Evaluation
AE	Adverse Events
AESI	Adverse Events of Special Interest
AFM	Acute Flaccid Myelitis
AHIP	America's Health Insurance Plans
AI/AN	American Indian/Alaskan Native
AIGIV	Anthrax Immune Globulin Intravenous
AIM	Association of Immunization Managers
AIS	Adult Immunization Status
Anti-HAV	Serum Antibody to Hepatitis A Virus
Anti-HBsAg	Hepatitis B Surface Antigen
Anti-PA IgG	Anti-Protective Antigen Immunoglobulin G
AOA	American Osteopathic Association
APhA	American Pharmacists Association
aQIV	Adjuvanted Quadrivalent Influenza vaccine
ARFI	Acute Respiratory or Febrile Illness
ARI	Acute Respiratory Illness
ASD	Autism Spectrum Disorder
ASTHO	Association of State and Territorial Health Officers
AVA	Anthrax Vaccine Adsorbed
B. anthracis	*Bacillus anthracis*
BAA	Broad Agency Announcement
BAO	Bemidji Area Office
BLA	Biologics License Application
CAP	Community-Acquired Pneumonia
CAPiTA	Community-Acquired Pneumonia Immunization Trial in Adults
CDC	Centers for Disease Control and Prevention
CDSi	Clinical Decision Support for Immunization
CIN2+	Cervical Intraepithelial Neoplasia Grade 2 or Worse
CIVICs	Collaborative Influenza Vaccine Innovation Centers
CLD	Chronic Liver Disease
CMC	Chronic Medical Condition
CME	Continuing Medical Education
CMS	Center for Medicare and Medicaid Services
CNS	Central Nervous System
COI	Conflict of Interest
COID	Committee on Infectious Diseases (AAP)
COPD	Chronic Obstructive Pulmonary Disease

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CPI	Consumer Price Index
CSELS	Center for Surveillance, Epidemiology, and Laboratory Science
CSF	Cerebrospinal Fluid
CSTE	Council of State and Territorial Epidemiologists
CVD	Cardiovascular Disease
DC	District of Columbia
DFO	Designated Federal Official
DHA	Defense Health Agency
DHA-IHB	DHA Immunization Healthcare Branch
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DTaP	Diphtheria and Tetanus Toxoid and Pertussis
DVA	Department of Veterans Affairs
ECBT	Every Child by Two
ED	Emergency Department
EHR	Electronic Health Record
EIS	Epidemic Intelligence Service
EMA	European Medicines Agency
EMR	Electronic Medical Record
EtR	Evidence to Recommendation
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FHA	Filamentous Hemagglutinin
FIM	Fimbriae
FOA	Funding Opportunity Announcement
FPL	Federal Poverty Level
FQHC	Federally Qualified Health Center
FSH	Follicle Stimulating Hormone
FUTURE	Females United to Unilaterally Reduce Endo/Ectocervical Disease Study
GAVI	Global Alliance for Vaccines and Immunisation
GBS	Guillain-Barré Syndrome
GCC	(Tom Harkin) Global Communications Center
GID	Global Immunization Division
GLITEC	Great Lakes Inter-Tribal Epidemiology Center
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titers
GP	Guinea Pigs
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HAV	Hepatitis A Virus
HBIG	Hepatitis B Immune Globulin
HCAP	Healthcare-Associated Pneumonia
HCH	Health Care for the Homeless
HCP	Healthcare Personnel / Providers
HCW	Healthcare Workers
HEDIS	Healthcare Effectiveness Data and Information Set
HEMU	Health Economics Modeling Unit
HepA	Hepatitis A

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HepB	Hepatitis B
HHS	(Department of) Health and Human Services
HI	Hemagglutinin Inhibition
Hib	Haemophilus Influenzae Type B
HIC	High Income Country
HIE	Health Information Exchange
HIV	Human Immunodeficiency Virus
HMIS	Homeless Management Information System
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
HUD	(Department of) Housing and Urban Development
IAC	Immunization Action Coalition
ICD	International Classification of Diseases
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
IDSA	Infectious Disease Society of America
Ig	Immunoglobulin
IHS	Indian Health Service
IIS	Immunization Information Systems
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
ILINet	Influenza-like Illness Surveillance Network
IM	Intramuscular
IOM	Institute of Medicine
IPD	Invasive Pneumococcal Disease
ISTM	International Society of Travel Medicine
ITK	Immunization Tool Kit
ITT	Intention-To-Treat
IV	Intravenously
IVE	Influenza Vaccine Effectiveness
IVIG	Intravenous Immunoglobulin
JE	Japanese Encephalitis
JE-MB	Inactivated Mouse Brain-Derived JE Vaccine
JE-VC	Inactivated Vero Cell Culture-Derived JE Vaccine
KPNW	Kaiser Permanente Northwest
LAIV	Live Attenuated Influenza Vaccine
LD_{50}	Median Lethal Dose
LG	Leadership Group
LIC	Low Income Country
LMICs	Low and Middle-Income Countries
LTFU	Long-Term Follow-Up
MAE	Medically Attended Adverse Event
M-CHAT™	Modified Checklist for Autism in Toddlers™
MDRO	Multi-Drug Resistant Organism
MenB	Meningococcal B
MHS	Military Health System
MIC	Middle Income Country
MIPS	Merit-Based Incentive Payment System
MMR	Measles, Mumps and Rubella

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MMWR	*Morbidity and Mortality Weekly Report*
MSM	Men Who Have Sex With Men
MSSP	Medicare Shared Savings Program
MUC List	Measures Under Consideration List
MVC	Michigan for Vaccine Choice
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization
NAPNAP	National Association of Pediatric Nurse Practitioners
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCHS	National Center of Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases
NCIRS	National Centre for Immunisation Research & Surveillance
NCVIA	National Childhood Vaccine Injury Act
NF	Neutralizing Factor
NFID	National Foundation for Infectious Diseases
NHANES	National Health and Nutrition Examination Survey
NHF	National Health Federation
NHIS	*National Health Interview Survey*
NHP	Non-Human Primate
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIS	National Inpatient Sample
NIS-Child	National Immunization Survey-Child
NMA	National Meningitis Association
NNDSS	National Notifiable Diseases Surveillance System
NNV	Number Needed to Vaccinate
NP	Nasopharyngeal
NPRM	Notice of Proposed Rulemaking
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
NVT	Non-Vaccine Types
OASH	Office of the Assistant Secretary for Health
OB-GYN	Obstetrician-Gynecologist
OHAIDP	Office of HIV/AIDS and Infectious Disease Policy
OID	Office of Infectious Disease
OP	Oropharyngeal
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PEP	Post-Exposure Prophylaxis
PICO	Population, Intervention, Comparison, Outcomes
PIDS	Pediatric Infectious Disease Society
PK	Pharmacokinetics
POF	Premature Ovarian Failure
POI	Primary Ovarian Insufficiency
PPQ	Pre-Production Quality
PR	Puerto Rico
PrEP	Pre-Exposure Prophylaxis

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PREVENT	Pregnancy Influenza Vaccine Effectiveness Network
PRN	Pertactin
PRNT	Plaque Reduction Neutralization Test
PT	Pertussis Toxoid
PWUD	People Who Use Drugs
QALY	Quality-Adjusted Life-Year
QIV	Quadrivalent Influenza Vaccine
QRP	Quality Reporting Program
RCT	Randomized Controlled Trial
RR	Relative Risk
RRP	Recurrent Respiratory Papillomatosis
rRT-PCR	Real-Time Reverse Transcription Polymerase Chain Reaction
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
RZV	Recombinant Zoster Vaccine
S. pneumoniae	*Streptococcus pneumoniae*
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
SCM	Synthetic Control Method
SIDS	Sudden Infant Death Syndrome
SME	Subject Matter Expert
SMI	Street Medicine Institute
SNiPP	Surveillance for Non-invasive Pneumococcal Pneumonia
SOMNIA	Systematic Observational Method for Narcolepsy and Influenza Immunization Assessment
SQ	Subcutaneous
TB	Tuberculosis
TBE	Tick-Borne Encephalitis
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis
TIV	Trivalent Influenza Vaccine
TNA	Toxin-Neutralizing Antibody
TND	Test Negative Design
UAD	Urinary Antigen Detection
UAT	Urinary Antigen Test
UK	United Kingdom
US	United States
US Flu VE	US Influenza Vaccine Effectiveness Network
USICH	United States Interagency Council on Homelessness
USPHS	US Public Health Service
USPRT	Updating Sequential Probability Ratio Test
UTD	Up-To-Date
VA	(US Department of) Veteran's Affairs
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VE	Vaccine Effectiveness

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VFC	Vaccines For Children
VICP	Vaccine Injury Compensation Program
VIS	Vaccine Information Statement
VIS	Vaccine Information Sheet
VSD	Vaccine Safety Datalink
VT	Vaccine Type
VT-CAP	Vaccine-Type Community-Acquired Pneumonia
VTEUs	Vaccine and Treatment Evaluation Units
WG	Work Group
WHO	World Health Organization
YF	Yellow Fever
ZVL	Zoster Vaccine Live

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

José Romero, MD, FAAP
ACIP Incoming Chair

Amanda Cohn, MD
Executive Secretary, ACIP / CDC

Dr. Cohn called to order the October 2018 Advisory Committee on Immunization Practices (ACIP) and welcomed those present. She indicated that they are awaiting final approval of new incoming ACIP members and the new incoming Chair. Therefore, as the Designated Federal Official (DFO), Dr. Cohn chaired the October 2018 ACIP meeting with Dr. Romero's assistance. She confirmed that 11 voting members were in attendance, which constituted a quorum.

Dr. Cohn indicated that the proceedings of the 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 recognized others in the room who were to be present throughout the duration of the meeting to assist with various meeting functions: Ms. Stephanie Thomas and Ms. Natalie Greene.

She noted that handouts of the presentations were distributed to the voting ACIP members and were made available for others on the tables outside of the auditorium. Slides presented during this meeting will be posted on the ACIP website approximately two weeks after the meeting concludes after being made visually accessible to all viewers, including the visually disabled. The live webcast will be posted within four weeks following the meeting, and the meeting minutes will be available on the website within approximately 90 days following the meeting. The minutes from the June 2019 meeting are now available on the website.

The next ACIP meeting will be convened at the Centers for Disease Control and Prevention (CDC) on Wednesday and Thursday, February 27-28, 2019. Registration for all meeting attendees is required and may be completed online at www.cdc.gov/acip. The registration deadline for Non-United States (US) citizens is January 30, 2019 and for US citizens registration closes February 15, 2019. 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. Cohn said she was pleased to announce that there is a new ACIP website, which was launched on October 23, 2018. Hopefully, everyone will find this new website easier to navigate and will be able to find information about ACIP more readily. This site includes a new section on ACIP Work Groups (WG), and will be adding information to that section over the next several months regarding each WG's terms of references and members.

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Dr. Cohn announced and welcomed the following new *Ex Officio* and liaison members and member substitutions for this meeting:

Ex-Officio Members

- ❑ New Member: Doran Fink, MD representing the Food and Drug Administration (FDA)
- ❑ Substitute: Lori Hoffman Hōgg, MS, RN, CNS, AOCN, representing the Veterans Administration (VA)
- ❑ Substitute: Tammy Beckham, DVM, PhD representing National Vaccine Program Office (NVPO)

Liaison Representatives

- ❑ New Member: Jason Goldman, MD representing the American College of Physicians (ACP)
- ❑ Substitute: Matthew Tunis, PhD representing the National Advisory Committee on Immunization (NACI)

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 under 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. The ACIP members were provided with copies of several letters that were submitted prior to this meeting.

Dr. Cohn announced that as part of ACIP's continuous improvement process, some changes will be made to the public comment process beginning with the February 2019 meeting. These changes are intended to ensure that members of the public have ample opportunity to provide written and/or in-person comments and to make the comment process clearer. Regarding changes to in-person public comments, 30-minutes will be reserved at the end of each ACIP meeting day. It is no longer necessary to register online prior to the meeting. Attendees may register for in-person comments at the meeting and comments will be made in order of registration, time permitting. At the end of the 30-minute period, no additional public comments will be taken. This is more than the amount of time utilized over the last few years, so it should be ample. Additional fixed times will be reserved for in-person comment prior to votes. Written comments should be submitted to the new CDC.gov mailbox to receive all written comments. The current 1-page maximum length requirement will be changed to a 5-page maximum. Written comments will be accepted before, during, and immediately after meetings. Comments submitted up to 48 hours in advance of a meeting start time will be provided to ACIP members prior to meeting. Comments submitted within 24 hours of the meeting end will be included in the record. This information will be included in the *Federal Register*.

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

Detailed instructions for submission of names of potential candidates to serve as ACIP members may be found on the ACIP website and inquiries may be emailed to acip@cdc.gov The deadline for consideration of ACIP applications for the Term of July 1, 2020-June 30, 2024 is July 1, 2019. The membership process begins about a year in advance of each new term.

Dr. Cohn conducted a roll call to determine whether any ACIP members had COIs. No conflicts were declared.

Hepatitis Vaccines

Introduction

Kelly L. Moore, MD, MPH
Chair, Hepatitis Vaccines Work Group

Dr. Moore indicated that the terms of reference for the Hepatitis WG with respect to hepatitis A are to: 1) update the HepA vaccine recommendations that ACIP originally published in 2006 [ACIP Routine Recommendation for Hepatitis A Vaccine, *MMWR* 2006 May 19;55(RR-7):1-23]; and 2) address homelessness as an indication for routine immunization against HepA.

Between February 2018 and October 2018, four meetings of the WG focused on homelessness as an indication for routine vaccination. The WG discussed HepA vaccination and homelessness in San Diego County, California and the experience they have had since 2016-2018. In addition, the WG heard presentations about and discussed the Evidence to Recommendation (EtR) and Grading of Recommendation Assessment, Development and Evaluation (GRADE) frameworks.

Dr. Moore indicated that during this ACIP meeting, members would hear a background presentation on homelessness as an indication for routine HepA vaccination, a presentation on homelessness as a risk group, and public comment followed by a recommendation and vote.

In terms of next steps, the WG has an upcoming publication on November 2, 2018. This Morbidity and Mortality Weekly Report (MMWR) Policy Note publication will update the ACIP recommendations for use of the HepA vaccine for post-exposure prophylaxis and for pre-exposure prophylaxis for international travel. During a future meeting, the WG will present to

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ACIP the full updated HAV vaccine statement for a vote. In addition, the WG will continue its deliberations on adult hepatitis B (HepB) vaccination topics.

Background

Noele Nelson, MD, PhD, MPH
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Centers for Disease Control and Prevention

Dr. Nelson presented background information on: HAV epidemiology, HepA vaccines, HAV ongoing outbreaks, a study of HAV among homeless in San Diego, and Homelessness in general.

Data collection for HAV started in 1966. The highest number of HAV cases reported was in 1971, about 60,000 cases at a rate of about 30 cases per 100,000 population. Vaccine was recommended in 1996. From 1996-2011, there was a 95.5% decrease in reported cases. The number of reported cases has fluctuated slightly since 2011, primarily due to outbreaks. In 2016, there were 2007 reported cases [National Notifiable Diseases Surveillance System (NNDSS); Armstrong GL. *Pediatrics* 2007;119:e22-9].

Rates of reported HAV reached a low point in 2014 for all age groups except those aged 10-19 years, for which the low point occurred in 2015. Rates increased for all age groups from 2015 through 2016, except for those aged 0-9 whose rates remained stable. When comparing the 2016 HAV rates of all age groups, persons aged 20-29 years and 30-39 years had the highest rate at 0.9 cases/100,000 population and persons aged 0-9 years had the lowest rate at 0.1 cases/100,000 population [NNDSS; http://www.healthypeople.gov/2020/ topicsobjectives2020/ pdfs/Immunization.pdf].

The prevalence of antibody to hepatitis A virus (anti-HAV) by age group for 2009-2010 is based on data from the National Health and Nutrition Examination Survey (NHANES). Compared to previous surveys, significant increases occurred in the proportion of children with protection for ages 6-11 years and 12-19 years, most likely due to vaccination. However, significant decreases occurred in the proportion of adults with protection for ages 40-60 years and older. Overall, the prevalence of antibody among US residents is about 26.5% indicating that <1/3 of the US population had protection against HAV infection in 2009-2010 [National Health and Nutrition Examination Survey (NHANES); Murphy TV et al. Progress Toward Eliminating Hepatitis A Disease in the United States. MMWR Suppl. 2016 Feb 12;65(1):29-41].

Two inactivated single-antigen HepA vaccines are licensed in the US, [1]HAVRIX® in 1995 and [2]VAQTA® in 1996. In a clinical trial, the efficacy of VAQTA® in protecting against clinical HepA was 100% among >1000 New York children 2 to 16 years of age who received one dose while living in a community with a high HAV disease rate. The efficacy of HAVRIX® in protecting against clinical HepA was 94% among >38,000 Thai children 1 to 16 years of age who received two doses 1 month apart while living in villages with high HAV disease rates. A combined HepA/HepB vaccine, TWINRIX®, is also available in the US [[1]Innis BL, et al. *JAMA* 1994;271:1328–34; [2]Werzberger, A et al. *New Engl J Medicine*. 1992;327:453–7].

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In pre-licensure trials, adverse reactions to HAVRIX®, VAQTA®, and TWINRIX® were mostly injection site reactions and mild systemic reactions. The most frequent side effects are soreness or erythema at the injection site, fever, headache, and malaise. Multiple studies demonstrate no serious adverse event (SAEs) definitively attributed to inactivated vaccine. Post-marketing surveillance for adverse events (AEs) following receipt of HepA vaccines has been performed primarily by two systems in the US, the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD). No unusual or unexpected safety patterns were observed for any of the HepA vaccines licensed in the US [Vaccine Information Statement (VIS) https://www.cdc.gov/vaccines/hcp/vis/vis-statements/hep-a.html *MMWR* 2006;55(RR-7).

HepA vaccination was introduced incrementally in the US from 1996-1999. In 1996, vaccine was recommended for children at age 2 years in communities with high rates of disease and children through teen years in outbreaks. In 1999, vaccine was recommended for children at age 2 years of age in 11 states with average annual HepA vaccine rates of 2 times the national average (>=20 cases/100,000 pop). Vaccine was considered in 6 states with rates above the national average (>=10 cases/100,000 population). In addition, groups at increased risk of HAV infection or severe HAV disease were recommended to receive HepA vaccine, including: Travelers, Men Who Have Sex with Men (MSM), Users of Injection and Non-Injection Drugs, Persons with Clotting-Factor Disorders, Persons who Work with Non-Human Primates (NHP), Persons Who Anticipate Close Personal Contact with an International Adoptee, and Persons with Chronic Liver Disease (CLD). During this meeting, WG deliberations regarding adding homelessness as an indication for vaccination will be presented [*MMWR* 1996;45(RR-15); *MMWR* 1999;48(RR-12); *MMWR* 2006;55(RR-7)].

The single antigen HepA vaccine is recommended to be administered as a 2-dose series at least 6 months apart. Anti-HAV has been shown to persist in vaccine recipients for at least 20 years in adults administered inactivated vaccine as children with a 3-dose schedule.[1] Subsequent studies have shown that a 3-dose series is equivalent to the 2-dose schedule given today. At least 20-year anti-HAV persistence was demonstrated among adults vaccinated with a 2-dose schedule as adults.[2] Detectable antibodies are estimated to persist for 40 years or longer based on mathematical modeling and anti-HAV kinetic studies.[2,3] Protection following natural infection is lifelong and may also be following vaccination. Anti-HAV after a single dose of HepA vaccine can persist for almost 11 years.[4] A single dose of HepA vaccine was shown to promote HAV-specific cellular immunity similar to that induced by natural infection[5] [[1]Plumb ID, et al. *J Viral Hepat*. 2017 Jul;24(7):608-612.; [2]Theeten H, et al. *Vaccine*. 2015 Oct 13;33(42):5723-7; [3]Hens N, et al. *Vaccine* 2014;32(13): 1507-1513; [4]Ott J.J. and Wiersma S.T., *Int. J. Infect. Dis*., vol. 17, no. 11, pp. e939-44, Nov. 2013; and [5]Melgaço JG, et al. *Vaccine*. 2015 Jul 31;33(32):3813-20].

The ≥2 dose HepA vaccine coverage for Children was 60.6% for children age 19-35 months. This 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. The ≥1 dose coverage was 86.1% for children age 19-35 months.[1] Similar vaccine coverage was recently published for 2017. The ≥2 doses vaccine coverage for adolescents age 13-17 years was 64.4% and the 1 dose coverage was 73.9%.[2] The ≥2 doses vaccine coverage for Adults was much lower at 9.5% for adults ≥19 years, 13.4% for adults 19-49 years, 19% for travelers, and 24% among those with CLD; and 5.4% for adults ≥50 years [[1]Hill HA, et al. MMWR 2017;66:1171–1177; [2]Nelson NP, et al. *Vaccine* 2018. Mar 14;36(12):1650-1659 ; [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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Prior to 2016 there had not been a large, multistate HepA outbreak in the US since the 2013 outbreak associated with frozen pomegranate arils and there had not been a large person-to-person community-wide outbreak since 2003. In 2016, two outbreaks associated with contaminated food items imported from HAV-endemic countries occurred, followed by community wide person-to-person outbreaks that continue to this day. Over 7000 outbreak cases have been reported in this time, staff have been sent to multiple states, and the Division of Viral Hepatitis (DVH) laboratory has sequenced over 2500 specimens [Craig AS, et al. *Am J Med Sci* 2007; Collier MG, et al. *Lancet Infect Dis* 2014.; Foster et al. *MMWR* 2018].

Why is this happening now? In the past, large community outbreaks were associated with asymptomatic children infecting the adults who cared for them who then transmitted the virus to other adults. With the widespread adoption of the universal childhood vaccination recommendations, asymptomatic children are no longer the main drivers of outbreaks. Although the overall incidence rate of HAV infection has decreased within all age groups, most adults are not immune because they have not been vaccinated and were not infected naturally. Therefore, susceptible adults are exposed through contaminated food or through behaviors that increase risk of infection. Older individuals are more likely to be symptomatic and experience severe disease and adverse outcomes such as hospitalization, fulminant liver failure, and death. For the at-risk adults for whom vaccination recommendations do exist, uptake is low [Collier M, et al. *Hepatology* 2015., Ly KN, Klevens RM. *J Infect Dis* 2015; Epson E, et al. *Public Health*, 2015; and Murphy TV, et al. *MMWR Suppl* 2016].

Dr. Nelson showed the DVH's Outbreak Website Map depicting the 12 states that are currently considered part of the state-specific HAV outbreak: Arkansas, California, Indiana, Kentucky, Michigan, Missouri, Ohio, Utah, and West Virginia. Massachusetts and North Carolina were recently added [https://www.cdc.gov/hepatitis/outbreaks/2017March-HepatitisA.htm].

Looking at the case counts of HAV in the outbreaks among persons who report drug use and/or homelessness in multiple states based on mostly publicly available data through 10/19/2018, the total number of cases in the affected states was approximately 7500. Among those, 58% were hospitalized and there were 74 deaths. In comparison, in the multistate HAV outbreak associated with pomegranate arils in 2013, there were 162 cases in 10 states, with 44% hospitalization and no deaths. The death rate for this outbreak is very high, which is likely due to hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infection and the poor immune and health status of the persons infected [https://www.cdc.gov/hepatitis/outbreaks/2017March-HepatitisA.htm].

In terms of the affected states that have provided numbers of homeless persons infected with HAV, the methods used to generate homeless counts and the availability of risk factor information varies among states. Homeless persons have made up a large percentage of the cases, particularly in California. Considering the total HAV homeless cases (including cases with injection or non-injection drug use), over 40% of cases are in San Diego and Utah and over 10% of cases are in Michigan, West Virginia, Tennessee, and Kentucky among the states that report risk factor information. Massachusetts reports 58% homelessness among outbreak associated cases. The percentages are lower when looking at HAV homeless cases alone, with 7.5% in Utah and 15% in San Diego [https://www.cdc.gov/ hepatitis/outbreaks/2017March-HepatitisA.htm].

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There has been increased morbidity and mortality reported in these outbreaks. HAV-related hospitalizations were increasing prior to 2016, from 7% in 1999 to 46% in 2015. Hospitalizations related to the outbreaks during 2016 to 2018 ranged from 25% in the foodborne outbreak associated with frozen scallops to 81% in the Michigan outbreak associated with drug use and homelessness. All age mortality for HAV infection is typically less than 1%. The case mortality in outbreaks associated with homelessness and drug use is around 3%. Currently, 3% to 13% of cases are co-infected with HBV and 17% to 61% are co-infected with HCV. The increased mortality is likely due to acute or chronic infection of an already damaged liver. There is no indication that there is increased virulence in the circulating outbreak strains [Ly et al. *J Infect Dis*. 2015; https://www.cdc.gov/hepatitis/statistics/2015surveillance/pdfs/2015HepSurveillanceRpt.pdf; CDC *MMWR* pending publication].

Little is known about HAV virus immunity among homeless populations in the US. HAV infection is found at a high frequency among persons who use drugs in these outbreaks. Given that HAV is transmitted primarily by the fecal-oral route, close contact and poor hygiene conditions are likely to play the principal role in driving these outbreaks [Hennessey KA, et al. *Public Health Reports*. 2009; Villano et al. Clinical Infectious Diseases. 1997; MMWR 1996;45(No. RR-15):1—30].

How do we stop these outbreaks? Reduction in new cases can be obtained and sustained by maintaining a high level of population immunity through vaccination. Historically, the spread of HAV was controlled through vaccinating contacts of cases. This approach has been shown to be limited in the recent outbreaks as persons are frequently unaware of exposure and cases may be reported to public health authorities too late for post-exposure prophylaxis (PEP) to be effective. CDC is recommending proactive vaccination of groups at highest risk in specialized venues since outreach to people who use drugs (PWUD) and the homeless can be challenging for many reasons, including mistrust of government and limited access to routine medical care. Ideally, these groups should be identified and targeted early in the outbreak, but this can be logistically difficult and costly, so primary prevention, ensuring vaccination of these groups before outbreaks occur, is definitely preferable [McMahon et. al. *Arch Pediatr Adolesc Med* 1996; Craig et al. *Clinical Infectious Diseases.*1998].

In 2017, the large outbreaks of HAV among adults in several US cities resulted in increased demand for vaccine, resulting in constrained supplies of vaccine. In response, CDC: 1) worked directly with public health officials in affected jurisdictions to provide guidance about targeting vaccine in response to local epidemiology; 2) collaborated with manufacturers to understand options for managing supplies in the private sector and increasing national supply; 3) implemented ordering controls in the public sector; and 4) increased vaccine availability on CDC's adult vaccine contracts. As available vaccine supplies have increased and progress has been made regarding ongoing outbreaks, the public sector vaccine supply strategy has evolved. Additional vaccine has been made available for unaffected jurisdictions to facilitate routine vaccination activities. While manufacturers have supply to meet current demand, CDC and vaccine manufacturers continue to monitor ongoing demand for and usage of adult HepA vaccine closely [https://www.cdc.gov/vaccines/hcp/clinical-resources/shortages.html#note1].

Regarding the outbreak response in San Diego, there were 2538 total HepA vaccination events of which 833 were Points of Dispensing events, 80 were Mobile Van events, and 1625 were Foot Team events. A total of 121,921 HepA vaccinations were administered in San Diego County from March 6, 2017 to January 23, 2018. An estimated 103,000 of the total at-risk population were vaccinated, and there were 8335 jail vaccinations through January 23, 2018

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[https://www.sandiegocounty.gov/content/dam/sdc/cosd/SanDiegoHepatitisAOutbreak-2017-18-AfterActionReport.pdf].

A study conducted in San Diego by Dr. Corey Peak and Dr. Eric McDonald analyzed homelessness as a risk factor. HAV transmission was assessed using a test-negative case-control study design, while elevated disease severity was assessed by a cohort study. The conclusions from this study were that vaccine indication was unrecognized for >25% of patients reporting homelessness, meaning than >25% of patients reporting homelessness did not already have a recommended risk group for vaccination. Homelessness was independently associated with a 2-3 times higher odds of infection with HAV and a 2-4 times higher odds of severe outcomes of HAV infection, specifically hospitalization or death. A number of limitations were noted in these analyses, including the incomplete list of co-morbidities, such as CLD, and that people who are homeless may be preferentially hospitalized.

The costs of the ongoing outbreaks are unknown at this time. However, San Diego County spent about $12.5 million as of the end of April 2018 on the outbreak response. Other states have spent millions of dollars as well. For example, Michigan has spent about $7.1 million so far on its HAV outbreak response, which does not yet fully include staff time for individuals who work outside of the immediate preparedness area. Additionally, it does not include any costs incurred directly by the local health departments prior to having received HepA vaccine funding. In Kentucky, Louisville has spent $2.1 million and has had numerous staff working on the outbreak full time for about 9 months. Many of the local health departments have invested significant amounts of staff time in responding to the outbreak locally. At the state level, Kentucky has had a large number of staff spending 20% to 100% of their time on the outbreak since November 2017. Many staff are not working extra time, but are instead setting aside their other public health duties during the outbreak. Hospitalization expenses and diversion of human and financial resources from other activities have occurred in many affected jurisdictions. People who are homeless and drug users are involved in propagating the outbreak, even if all of the costs are not associated with the homelessness.

There are many definitions for “homelessness,” but there is not one “official” definition. Different agencies use different definitions of homelessness, which affect how various programs determine eligibility for individuals and families at the state and local levels. Health centers funded by the US Department of Health and Human Services (HHS) use the HHS definition in providing services:

> A homeless individual is defined in section 330(h)(5)(A) as “an individual who lacks housing (without regard to whether the individual is a member of a family), including an individual whose primary residence during the night is a supervised public or private facility (e.g., shelters) that provides temporary living accommodations, and an individual who is a resident in transitional housing.” A homeless person is an individual without permanent housing who may live on the streets; stay in a shelter, mission, single room occupancy facilities, abandoned building or vehicle; or in any other unstable or non-permanent situation. [Section 330 of the Public Health Service Act (42 U.S.C., 254b)]

The number of homeless persons is determined by the Department of Housing and Urban Development (HUD). Data from the HUD 2017 Annual Homeless Assessment Report showed that on a single night in January 2017, state and local planning agencies reported that 553,742 people were homeless. This represents an overall 0.7% increase from 2016. Most homeless persons (N=360,867) were located in emergency shelters or transitional housing programs, while 192,875 persons were unsheltered [https://www.hud.gov/press/press_releases_media_

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advisories/2017/HUDNo_17-109].

Homeless persons are categorized as individuals, people in families with children, unaccompanied homeless youth, veterans, and chronically homeless individuals and are further characterized as sheltered or unsheltered. In the states currently experiencing outbreaks, individuals represent the majority of persons who are homeless and sheltered are a larger percent (up to 90%) than unsheltered except for California where 68% are unsheltered and 32% are sheltered. In terms of the total number for the US, the majority of homeless are individuals and sheltered (65%) [The U.S. Department of Health and Human Services; https://www.hudexchange.info/ resources/documents/2017-AHAR-Part-1.pdf].

People experiencing homelessness experience diseases at higher rates than domiciled persons, including higher rates of chronic conditions, acute illnesses, and behavioral health issues. Conditions are more difficult to treat for a person experiencing homelessness. Problems with health sometimes leads to homelessness, and homelessness leads to and exacerbates health issues. Persons who are homeless experience greater barriers to accessing care due to lack of a stable address, difficulty with transportation, being uninsured or on public insurance, and the need to prioritize basic survival (food, shelter, safety) before health care.

How do homeless access health services? The National Health Care for the Homeless Council is a membership organization that provides training and technical assistance to 300 Health Care for the Homeless (HCH) Federally Qualified Health Centers (FQHCs) and 90 Medical Respite Programs. Medical Respite Programs provide homeless individuals a safe place to recover from acute injury or illness. The National Health Care for the Homeless Council also shares best practices among the community, conducts research, and advocates for policies to eliminate homelessness. There is at least one HCH program in each state, the District of Columbia (DC), and Puerto Rico (PR). HCH programs meet all the requirements of FQHCs and must conduct outreach and provide or have strong linkages to mental health and substance abuse services. In 2018, over 300 sites delivered care to over 850,000 individuals. HCH programs provide primary care, behavioral health, and support services to people who are homeless regardless of their insurance status or ability to pay. There are also requirements for outreach, such as shelter-based care and mobile clinics. HCH programs have Street Clinics in over 30 metropolitan areas. The Street Medicine Institute (SMI) facilitates and enhances the direct provision of health care to the unsheltered homeless where they live.

In terms of health insurance and healthcare for the homeless, 90% of HCH clients earn <100% of the Federal Poverty Level (FPL) and 64% are insured. In 2016, 295 HCH programs provided care to 934,174 patients. Of these, 51% have Medicaid, 4% have Medicare and Medicaid, 4% have Medicare, 5% have private insurance, and 36% are uninsured. Only 25% are uninsured in expansion states. For the uninsured, referral to specialty care is limited. However, basic services are provided. There has been a decrease in the uninsured since Medicaid expansion. There is wide variation in outreach and enrollment activities across states. Medicaid is the largest source of insurance for HCH patients overall. As states continue working to reduce health care disparities and improve health, access to comprehensive health insurance remains a key factor in access to care [National Health Care for the Homeless Council].

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How would routine vaccination of homeless persons for HepA vaccine be implemented? Vaccination would be integrated into clinics that serve the homeless (FQHCs, CHCs, shelters, mobile clinics, and street clinics). This would provide a familiar setting for many homeless persons. Providers would be experienced in caring for persons who are homeless. There would be opportunities for education in these settings, and they would provide access to other preventive and health services.

While the exact number of persons who need to be vaccinated to stop transmission or halt an outbreak is not known, a few studies have explored this question. In a study in Israel of trends in disease incidence after the implementation of universal HepA vaccination among children, with <10% of the rest of the Israeli population immunized during the study period, the overall incidence of hepatitis A declined by nearly 90%. Among children 5 to 14 years of age, an estimated 81% decline in incidence occurred at a time when vaccination coverage had reached 25%.[1] A vaccine demonstration project conducted in Butte County, California from 1995–2000, the incidence of reported HepA cases dropped by 93% despite immunization coverage of only 60%.[2] A study in Alaska suggested that 80% vaccine coverage is needed to control an outbreak. It is important to note that the susceptible population in that case was a rural population, not persons from a specific risk group.[3] It is challenging to determine herd immunity thresholds for routine vaccination among specific risk populations (e.g., Homeless, PWUD, MSM).However, these studies have shown that at low rates of routine vaccination, transmission can be slowed [[1]Chodick, 2008; [2]Averhoff, 2001; [3]McMahon, 1996].

Regarding the cost to vaccinate the homeless population, a cost effectiveness analysis was not done for homelessness as an indication for vaccination. However, states are in the process of assessing the costs for the ongoing outbreaks mentioned earlier. This assessment includes vaccination of injection and non-injection drugs users as already recommended risk groups. Vaccine administration fees range from a few dollars up to $20 based on the best available information. Vaccine refusal rates for influenza and HepA in homeless shelters in San Diego ranged from 15% to 20%. Refusal rates have been observed, anecdotally, to be higher in jails and EDs. Recall that approximately 550,000 persons in one night who experienced homelessness in 2017, including youth and Veterans. A very basic calculation of $550,000 X $30 (price of single dose) = $16,500,000. $550,000 X $60 (for both doses) = $33,000,000, including a small administration fee. Given that uptake will not be 100% and not all homeless will be vaccinated at the same time, that cost would be distributed over time. Another consideration is that the homeless population is dynamic, with people entering and leaving the risk population with an ongoing need for protection. The chronic homeless population is much smaller at about 87,000 than the single night total. In addition, a proportion of those 87,000 people might already have another indication for HepA vaccine such as drug use. In an outbreak response, the costs associated including health care expenses and deferred activities is substantial, such as in the $12.5 million example for San Diego.

In summary, HepA vaccine is largely responsible for the marked reduction in HepA cases. An increasing proportion of adults in the US are susceptible to HAV due to low 2-dose vaccination coverage, decreases in anti-HAV seroprevalence in older adults (≥ 40 years), and reduced exposure. Ongoing outbreaks demonstrate a shifting epidemiology with person-person transmission among unvaccinated vulnerable populations (e.g., homeless). Community outbreaks of HAV are often prolonged and challenging to control. Vaccination is the cornerstone of outbreak control of community outbreaks. Outreach and vaccination of persons at-risk in targeted venues is effective outbreak control. However, routine vaccination of HAV risk groups is critical for outbreak prevention.

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Homelessness as a Risk Group: EtR Framework and GRADE

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Dr. Doshani walked through the EtR framework for homelessness as an indication for HepA vaccination. The components of the framework include the following:

- ❑ Policy question
- ❑ Background
- ❑ Evidence retrieval

- ❑ Criteria
    1. Is the problem a public health priority?
    2. How substantial are the desirable anticipated effects?
    3. How substantial are the undesirable anticipated effects?
    4. Do the desirable effects outweigh the undesirable effects?
    5. What is the overall certainty of the evidence for critical outcomes? GRADE
    6. Does the target population feel that the desirable effects are large relative to the undesirable effects ?
    7. Is there important uncertainty about or variability in how much people value the main outcomes?
    8. Is the option acceptable to stakeholders?
    9. Is the option a reasonable and efficient allocation of resources?
    10. Is the option feasible to implement?

- ❑ Balance of consequences (summarization of findings)
- ❑ ACIP recommendation

The policy question is, “Should routine inactivated two-dose HepA vaccination be recommended for protection against HepA among persons experiencing homelessness?” To address this, the WG assessed the population, intervention, controls, and outcomes (PICO). In this case, the population is homeless people of all ages. The intervention is inactivated HepA vaccine administered as a two-dose series. The control group is unvaccinated homeless individuals. The outcomes include benefits and harms, which are as follows:

Benefits
- ❑ Reduction in disease burden (HAV-related disease and fulminant HAV-related disease)
- ❑ Protection against HAV-related disease (efficacy, immunogenicity)

Harms
- ❑ Local reactions: injection site pain/tenderness, erythema, fever, malaise, headache, loss of appetite, drowsiness, irritability
- ❑ Systemic adverse events: anaphylaxis, transient purpura, interference with other vaccines

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As a reminder, approximately 3 million persons in the US are homeless in a given year. This represents 1% of the population. Rates of homelessness have been increasing for the last decade. Men, women, and children of all ages and ethnicities are affected. In 2017, in a single night more than 553,742 people experienced homelessness in the US [HUD, 2017]. Of these, 65% were staying in emergency shelters, transitional housing programs, and safe havens and 35% were staying in unsheltered locations. A study by Gambatese et al in 2013 indicated that individuals experiencing homelessness have an increased risk of mortality ranging from 1.5 to 11.5 times higher than the risk in the general population.

Community health centers provide comprehensive preventive and primary health services and serve as a basic platform to provide vaccination to meet the specific needs of persons experiencing homelessness. The National Healthcare for the Homeless Council is an organization comprised of a network of physicians, nurses, social workers, and advocates all sharing a mission to eliminate homelessness. In 2018, this council presented on the importance of the Medicaid expansion to 34 states and mentioned that 3 additional states are planning to expand Medicaid coverage. This will provide an opportunity to increase HepA vaccine coverage and access to care and treatment services among the homeless.

Studies have shown that congregate living conditions increase the risk of HAV transmission among the homeless, which can result in outbreaks[1].Vaccinations are critical to the prevention of disease in such individuals. The majority of homeless adults have no protection from vaccine-preventable diseases due to limited access to healthcare and low rates of insurance coverage. HepA vaccine has proven to be effective. Studies have shown that vaccine-induced antibodies persist for more than 20 years in adults and detectable antibodies have been estimated to persist for 40 years or longer based on mathematical modeling and anti-HAV kinetic studies[2] [[1]Tjon et al, 2005; [2]Theeten et al, 2015].

Even though evidence suggests that appropriate street- and shelter-based interventions for targeted populations are the most efficient methods for mass vaccination of the homeless, a study by Badiaga in 2009 mentions that national public health programs specific to the homeless are required and strongly recommends systematic vaccination against HAV along with hepatitis B virus (HBV), influenza, streptococcus pneumonia, and diphtheria. A study by Smith in 2016 and medical societies such as the American Academy of Family Physicians (AAFP) state that vaccines are a cornerstone in preventing spread of infectious diseases and in the prevention of future disease in the homeless population. Smith further states that maximizing the immunization rate among the homeless is critical in order to prevent outbreaks in shelters and for the greater community at large.

This table displays some of the seroprevalence studies that the WG found:

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Characteristics of Included Sero-Prevalance Studies

Author, year, location	No of subjects	Population	Seroprevalence
Hennessey, 2009 San Francisco	N=1138 6% aged < 35 years 67% aged 35-45 years 23% aged >45 years	Homeless	Anti-HAV positivity associated with years of homelessness <=1 year: 46% ; 2-4 years: 50% and >=5 years: 61%
Poulos, 2007 Sydney	N-=189 Mean age: 42 years	Homeless at Haymarket Foundation Clinic (FQHC)	48% positive for anti-HAV
Ochnio, 2001 Vancouver	N=111 Mean age: 19.6 years Inclusion criteria: • Age=<25 years • Spending at least 8 hours on the street	4 locations: 2 street outreach clinics, needle exchange facility and STD clinic • Street youth (all) • Street youth who are IDU's • Street youth who are not MSM or IDU	 6.3% positive for anti-HAV 9.5% positive for anti-HAV 3.1% positive for anti-HAV
Villar, 2013 Brazil	N=160 Mean age:18-25 years	Crack users	78.8% positive for anti-HAV
Kose, 2017 Turkey	N=187 Age range: 6-18 years	Street urchins	34% positive for anti-HAV
Roy, 2002 Montreal, Canada	N=427 Age range 14-25 years	Street youth	4.7 % positive for anti-HAV

Dr. Doshani emphasized that very little information was available among homeless populations. She highlighted the Hennessey study, which was conducted in San Francisco. This study examined 1138 homeless individuals of whom 6% were <35 years of age, 67% were 35-45 years of age, and 23% were >45 years of age. This was the only published study that identified homelessness as an independent risk factor. It looked at anti-HAV positivity associated with years of homelessness and found that positivity was 46% for those who were homeless ≤1 year, 50% for those who were homeless 2-4 years, and 61% for those who were homeless ≥5 years.

In terms of the evidence retrieval, the systematic review of data for HepA vaccine and homelessness included a search of PubMed, Medline, and EMBASE from January 1, 2000 through April 25, 2018. Search terms included: ((Hepatitis OR HepA OR hepatovirus) AND vaccin*) OR HAV OR vaqta OR avaxim OR epaxal OR havpur OR havrix OR nothav AND Homeless* OR street people OR (living ADJ2 street*). Articles on animals were excluded, there were no language restrictions on initial searches, and articles were included from any country. The search resulted in the identification of 582 abstracts, from which 288 duplicate abstracts and 21 abstracts dated prior to 2000 were excluded. A total of 273 unique abstracts were reviewed, 238 of which were excluded due to irrelevance. A full article review was conducted of the remaining 35. Of these, 31 articles were excluded given that they included no primary data, did not address the population of interest, focused on vaccines not licensed in the US, and the data could not be abstracted. The remaining 4 studies were included in the GRADE analysis.

The WG then looked at 10 criteria, each with two components: Judgements and Research Evidence. Dr. Doshani reviewed the judgments and research evidence to support those judgements for each criterion.

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Criterion 1: Is the problem a public health priority?

JUDGEMENTS:

☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ **Yes** ☐ Varies

RESEARCH EVIDENCE:

- Homeless people face many barriers to accessing healthcare systems. These factors contribute to increasing the spread of infections.

- Implementing efficient strategies to prevent the spread of communicable infections among the homeless is a public health priority [Hwang , 2001].

- Homelessness is associated with enormous health inequalities, including shorter life expectancy, higher morbidity, and greater usage of acute hospital services [Kushel et al, 2002].

- Compared with the general US population, homeless persons are three to six times more likely to become ill compared to the general population. Hospitalization rates are four times higher, and they are three to four times more likely to die at a younger age [National Health Care for the Homeless Council].

- Overuse of ED services leads to higher costs for treatment among the homeless. A quarter to one third of homeless individuals are hospitalized during a given year and 3 times more likely to utilize the ED than the general population [Bharel, 2013; CDC-NHIS ED visits, 2010].

- Vaccinations are important public health measures for infectious disease control, yet are often not accessible to some of the most vulnerable adults.

- Insurance coverage varies by states; however, Medicaid expansion in 34 states and 3 additional states may provide an opportunity to make available routine vaccination coverage and access to care among persons experiencing homelessness.

- Furthermore, outbreak investigations among persons who report drug use and/or homelessness in the US have shown that:

  - Homeless people are often at high risk for HAV infection due to overcrowded and unsanitary living conditions, and should receive active immunization against HepA.

  - During a large outbreak in San Diego County, more than one-fourth of the homeless were not covered by the current indications for vaccination. Homeless persons were at higher risk of infection and higher risk of severe outcomes from infection. Of the approximately 600 reported cases, homelessness was identified as an independent risk factor for HAV transmission in 163 cases [Peak et al, 2018: unpublished].

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- Among persons experiencing homelessness in Maricopa county, Arizona, Iverson mentions that expeditious vaccination slowed the spread of a hepatitis A outbreak [Iverson et al, 2017].

- In a HAV outbreak in Bristol (UK), there were a total of 123 cases among the homeless, of whom 4 patients died and 39 were hospitalized [Syed et al, 2003].

- Case counts of HAV among persons who report drug use and/or homelessness from multiple states as of 10/19/2018 reflect the number of deaths and hospitalizations that have resulted due to the multi-state HAV outbreak that is occurring.

- A study in California by Kushel et al published in 2018 addresses the root cause of the HAV outbreak in the homeless. The study discusses the importance of vaccinating and educating the homeless in order to contain the outbreak, and states that more needs to be done to address the underlying cause.

Criterion 2: How substantial are the desirable anticipated effects? (e.g., the beneficial effects of vaccination)

JUDGEMENTS:

☐ Minimal ☐ Small ☐ Moderate ☒ **Large** ☐ Don't know ☐ Varies

RESEARCH EVIDENCE:

- Vaccination programs are an important component of public health initiatives and preventive medicine:

  - HepA vaccine has been shown to be highly effective and is a well-understood vaccine.

  - 2 doses of inactivated HepA vaccine induce protective efficacies of >90%.

  - The effectiveness of inactivated HepA vaccines in large-scale immunization programs in North American populations resulted in a 94% to 97% reduction in the incidence of acute HAV within 6-10 years [WHO position statement, July 2012].

- HepA vaccination has been shown to be effective in ending and controlling outbreaks in the homeless population as well. A vaccination program with more than 90,000 doses distributed was the key to ending an outbreak of HAV in Southern California among the homeless [Nelson, R, 2018].

- A study published by Poulos et al in 2010 stated that completion rates were reasonable in a vaccination program among the homeless in Sydney, Australia. The study concluded that if vaccination was offered as part of standard care to the homeless, as opposed to part of a research project, uptake rates would have been higher among this clinic population.

- A study published by Tjon et al in 2005 of an outbreak of HAV among the homeless and drug users in Rotterdam, Netherlands mentioned that contact tracing was very difficult in this hard to reach group. Therefore, a mass immunization campaign was carried out over a 2-week period. This campaign successfully vaccinated 83% (1515/1800) of the homeless people and was effective in stopping the outbreak.

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- A study by Weatherill et al in 2004 demonstrated that immunizations can be successfully delivered to a high-risk inner city population in non-traditional settings. During a 5-week HepA and B vaccination blitz in the year 2000, a total of 3,542 persons were immunized. Of these, 58% received both vaccines, resulting in reduction of reported cases of HAV.

Criterion 3: How substantial are the undesirable anticipated effects? (e.g., SAEs)

JUDGEMENTS:
☒ **Minimal** ☐ Small ☐ Moderate ☐ Large ☐ Don't know ☐ Varies

RESEARCH EVIDENCE:
- HepA vaccines is considered to be highly immunogenic, safe, and effective.

- Studies by WHO and the Institute of Medicine (IOM) found no SAEs to be causally linked to HepA vaccine. HepA vaccine has been recommended to reduce HAV case fatalities as well.

- The studies that the WG found available reported no SAEs:

  - A study by James et al in 2009 that assess AEs reported no vaccination reactions.

  - A study by Tjon et al in 2005 during the 2004 HAV outbreak in Rotterdam, Netherland indicated that 4 homeless people became jaundiced despite vaccination. The authors felt that this suggested that these individuals were likely already infected at the time of vaccination.

Criterion 4: Do the desirable effects outweigh the undesirable effects?

JUDGEMENTS:
☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ **Yes** ☐ Varies

RESEARCH EVIDENCE:
- It is known that HepA vaccine is highly immunogenic, provides lasting protection in healthy individuals, and generates protective levels of antibodies in patients with CLD or impaired immunity.

- Analysis of data accrued for over 2 years from the VAERS from 1995-1996 showed only 428 AEs following administration of at least 6 million doses. Only 93 SAEs were reported, which reaffirms the safety of HepA vaccine [Niu et al, 1998].

- Another study looked at post-licensure evaluation of the safety of VAQTA® in children and adults in which more than 49,000 doses of HepA vaccine were administered. This study showed no health problems linked to vaccination [Black et al, 2004].

- An article published by Andre et al in 2002 mentions that a review of 104 clinical studies in 27 countries where over 50,000 subjects were given 120,000 doses of HepA vaccine showed that about 50% who received the vaccines reported no symptoms. Among those who reported side effects, the main side effect was a mild and transient local soreness at the site of injection, which resolved spontaneously.

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***Criterion 5: What is the overall certainty of the evidence for critical outcomes?* (*GRADE*):**

- The WG conducted a GRADE analysis that examined 4 studies. The outcomes were divided into two categories: 1) Benefits: Reduction in disease burden; and 2) Harms: Any SAEs. Both of these were deemed to be of critical importance.

- For the first outcome, the WG found 1 study from Poulos that was published in 2010 in Australia. This was a clinical trial in which 201 homeless individuals whose mean age was 42 years. A single dose of HAVRIX® 1440 IU was administered at a federally funded clinic, the Haymark Foundation Clinic. There was no comparison group and the main outcome observed was that the outbreak was controlled; however, there was no mention on the reduction of cases or percent of HAV cases seen after vaccination.

- For the second outcome of harms, 4 studies were identified:

  - The first study by Poulos from Australia in 2010 did not mention AEs.

  - The second study by James in 2009 in Boston, Massachusetts was an observational study. In this study, 122 homeless substance users and incarcerated persons over 21 years of age were given a HepA vaccine in the ED. The vaccine name and dosage are unknown, and there was no comparison group. There were no reported SAEs.

  - The third study by Tjon in Rotterdam, Netherlands published in 2005 was an observational study in which 1515 homeless individuals whose mean age was 42 years were immunized with HepA vaccine. The name of the vaccine and dosage are unknown, and there was no comparison group. The main outcomes observed included 4 jaundice cases that were reported after vaccination. The authors stated that this was probably due to vaccine failure and that the persons may already have been infected at the time of vaccination.

  - The fourth study by Weatherill published in 2004 in Vancouver, Canada was an observational study in which 3542 vulnerable adults whose mean age was 46 years and of whom most were males (76%) were immunized with HAVRIX®. The dose was unknown and there is no comparison group. In early 2000, no AEs were reported. In the Fall of 2000, multiple vaccines (influenza, pneumococcal, and HepA) were administered together and 3 cases of anaphylaxis and 8 cases of oculo-respiratory syndrome were reported.

As a reminder, the evidence types for GRADE are as shown in the following table:

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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- In terms of the evidence types for benefits and harms determined by the WG in the GRADE analysis:

  - For the outcome of reduction in disease burden, there was only 1 study in Australia. Even though it was a clinical trial, there was no comparison group and there was a serious risk of bias, inconsistency, indirectness, and imprecision. Hence, the WG downgraded it to Evidence Type 4. Because there was only one study and no data were available on the comparison group, the WG was unable to determine estimates of effect and was not able to complete the GRADE analysis in determining the overall quality of evidence.

  - For the outcome of AEs, there were 3 observational studies and 1 clinical trial. The studies were weak and did not have comparison groups. Hence, the Evidence Type was downgraded to 4. The overall quality of evidence was rated as very low using the judgment criteria, given that the WG was unable to compare the estimates of effects across the studies. There were no confidence intervals or relative risk information to make this determination.

  - Regarding the limitations of the GRADE analysis, the clinical trial study had limitations in detailed design and execution and no comparison/control groups were present. The observational studies had severe limitations, and some studies did not report any quantitative data. There was only one study on the immunogenicity of the vaccine in the homeless population, but it was a non-US population. The studies did not look at homelessness as a risk factor in isolation.

Criterion 6: Does the target population feel that the desirable effects are large relative to the undesirable effects?

JUDGEMENTS:

☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ **Varies**

RESEARCH EVIDENCE:

- Even though limited evidence is available among the homeless population about their perceptions on comparative health benefits and risks of vaccination, expert opinion by the ACIP WG members and medical societies put forward that routine ongoing vaccination by providers with established relationships will be better accepted than vaccination by unfamiliar public health professionals during a crisis.

- This was seen in an article by Duncan et al in 2018 that stated that many homeless individuals who were encountered during vaccination efforts expressed distrust of vaccines and the vaccinators; whereas, others believed they could keep themselves clean and therefore were not at risk. An article by Metcalfe & Sexton in 2014 discussed similar findings (e.g., mistrust of healthcare providers, fear of needles, belief that illness may result from immunizations).

- However, a survey on opinions and behaviors related to vaccine providers by Grabenstein et al in 2002 demonstrated that individuals vaccinated at traditional sites such as physician offices and public health clinics felt the vaccine provider had more experience and they trusted them more as opposed to non-traditional settings. This also was supported in a study by Poulos et all in 2010 that identified that the clinic chosen had a well-established

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history of acceptance and utilization by the homeless group. Hence suggesting that familiar surroundings and provider trust are important factors to increase vaccine coverage among the homeless.

Criterion 7: Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENTS:

☐ No ☐ Probably No ☒ Uncertain ☐ Probably Yes ☐ Yes ☐ Varies

RESEARCH EVIDENCE:

- ❑ Not many studies specific to the homeless on valuing the protection of disease are available.
- ❑ Several studies have shown that persons experiencing homelessness have high rates of hospitalizations and deaths. Thus, making necessary vaccines both available and accessible to highly vulnerable homeless is a critical public health issue.
- ❑ As a reminder, the Poulos et al study from 2010 showed that completion rates were reasonable, and the identified clinic chosen had a well-established history of acceptance and utilization by the homeless group.

Criterion 8: Is the option acceptable to stakeholders?

JUDGEMENTS:

☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies

RESEARCH EVIDENCE:

- ❑ Recent HAV outbreak investigations among persons who report drug use and/or homelessness in all 10 states were supported by stakeholders and raised awareness of homelessness among local officials.
- ❑ An article by Duncan et al in 2018 looked at a HAV outbreak in San Diego County among disproportionately affected homeless individuals (53%) and illicit drug users (68%) in which community clinics vaccinated 7521 adults in 7 months. There was strong support from executive leaders and public health officials that resulted in partnerships with public health nurses who took HepA vaccine to homeless encampments.
- ❑ A study by Nelson in 2018 mentioned a budget being passed in Seattle that increased homelessness spending to $67 million, which was a 60% increase over the previous 4 years.
- ❑ A study by James et al in 2009 demonstrated that EDs made a significant contribution in stemming a HepA outbreak in Boston. Strong leadership and buy-in from ED personnel and hospital stakeholders were credited for the program's success.
- ❑ A study by Thorburn et al in 2001 that looked at drug users and food handlers, in which the homeless population was combined with the drug user population, reported that the Washington State legislature appropriated $300,000 for a vaccination campaign in jurisdictions experiencing a HAV epidemic due to drug user and food handlers.

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Criterion 9: Is the option a reasonable and efficient allocation of resources?

JUDGEMENTS:

☐ No ☐ Probably No ☐ Uncertain ☒ Probably Yes ☐ Yes ☐ Varies

RESEARCH EVIDENCE:

- After Action Reports (AARs) of HepA outbreak investigations that are currently occurring in the US show that outbreak campaigns entail major medical cost, productivity losses, disruption of other public health services, diversion of public health resources, and extensive human resources. The cost of responding to the HAV outbreak was approximately $12.5 million in San Diego County as of the end of April 2018. Costs of routine immunization through clinics serving the homeless are likely to be lower per capita than the costs of large, rapid outbreak response vaccination campaigns.

- During the multi-state HAV outbreak in 2013, a study by Epson et al published in 2016 stated that outbreak-related hospitalizations associated with chronic medical conditions resulted in substantial healthcare usage and lost productivity.

- A study by Bialek et al in 2014 mentioned that routine childhood and catch-up vaccination was a cost-saving measure from a societal perspective in communities experiencing period outbreaks such as American Indian reservations and Alaskan villages.

- A national study by Ku et al published in 2010 of ED use showed that among individuals experiencing homelessness, overuse of emergency services leads to higher treatment costs. Homeless individuals were more likely to be transported to the hospital via an ambulance, further increasing treatment costs.

- A systematic review and meta-analysis by Van der Hilst et al in 2009 stated that the cost of liver transplantation could rise to $163,438, which could be prevented if individuals are immunized with HepA vaccine.

- Vaccination based on housing status may be simpler than vaccination based on disclosure of behavioral risk factors such as MSM and persons injecting drugs. However, an adult immunization coverage assessment by Walter et al in 2016 showed that <10% of adults aged ≥19 years with an indication of HepA vaccination had been vaccinated.

- A study by O'Conner et al in 1999 demonstrated that even though HepA vaccine is licensed in the US only for certain high-risk groups, cost-effectiveness data cost on its indications are limited.

Criteria 10: Is the option feasible to implement?

JUDGEMENTS:

☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ **Yes** ☐ Varies

RESEARCH EVIDENCE:

- Health departments, EDs, community health centers, and primary health clinics are examples of effective venues for conducting immunization campaigns against vaccine-preventable diseases.

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- Providers demonstrate ingenuity and perseverance in ensuring that uninsured adults have access to vaccine and vaccination services.

- An Association of State and Territorial Health Officers (ASTHO) reported in 2016 identifying strategies on vaccinating uninsured adults stated that integrating immunization assessment, screening, and vaccination into the routine clinic flow is important for programs to achieve success.

- Organizations like the National Health Care for the Homeless Council are working to make healthcare for the homeless more accessible and are advocating for more states to increase Medicaid expansion. As noted early, 34 states have expanded Medicaid, leading to increases in coverage and access to care among persons experiencing homelessness.

- A study by Nyamathi et al in 2009 investigated the feasibility of an HepA/HepB vaccination program among homeless adults in Los Angeles County. The effectiveness of a nurse-case-managed intervention compared with two standard programs on completion of HepA/HepB vaccine series was evaluated. This study concluded that the use of vaccination programs incorporating nurse case management and tracking is critical in supporting adherence to completion of a 6-month HepA/HepB vaccine.

- The James et al study in 2009 in Boston demonstrated that targeted vaccination of homeless, substance users, and incarcerated persons ages >21 years in the ED following an HAV outbreak is feasible.

- The Poulos et al study in 2010 in Sydney suggested that a successful vaccination program can be mounted in the homeless population. Completion rates were reasonable, and the authors stated that if vaccination was part of a standard care as opposed to part of a research project, uptake rates would have been higher among the clinic population.

- Regarding feasibility with other vaccines, the WG found some studies addressing uptake of other vaccines among the homeless:

  - In 2014, Story et al published the results of a cross-sectional survey conducted at 27 homeless hostels among 190 homeless persons in London, UK looking at the 2011-2012 influenza season. This study concluded that influenza vaccine uptake was lower than national levels for all clinical risk groups identified.

  - In 2018, Weisman et all examined zoster, tetanus, and pneumococcal vaccines. This was a retrospective observational study at a federally-funded clinic in New York City. This study reported higher uptake of vaccines among the homeless versus the general population, suggesting that homeless adults are accepting of routine vaccination.

In summary, the WG reached consensus regarding routine inactivated 2-dose HepA vaccination for protection against HAV among persons experiencing homelessness. When the WG examined the balance of consequences, they found that the desirable consequences of routinely vaccinating homeless individuals for protection against HAV versus vaccinating during an outbreak clearly outweigh undesirable consequences such as hospitalizations and deaths in most settings. Hence, the WG supports the intervention and concludes that the benefit that is

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achieved by vaccinating homeless individuals is significant, and the cost and risk of vaccinating the homeless is much lower than not vaccinating homeless individuals.

Discussion Points

Dr. Szilagyi said it struck him that the major issues with this population would be feasibility and practicality. Regarding Medicaid expansion, it is threatened with work requirements in 3 states and 7 to 9 states having already applied for work requirements. This is the population who may lose their Medicaid. He also inquired as to whether anything is known about HepA vaccination rates among the 40,000 youth who are homeless across the US, and whether HepB vaccination status is known among the homeless population. He emphasized that tracking is going to be very important in terms of whether there are state Immunization Information Systems (IISs) or some other way of tracking the homeless population, many of whom will not remember whether they have been vaccinated.

Dr. Doshani replied that they could not find any data specific to the 40,000 homeless youth across the US, and that HepB vaccination among the homeless was not a focus of this evaluation.

Dr. Nelson added the WG identified tracking as a concern. Tracking potentially could be improved with state IIISs as those improve over time.

Dr. Walter asked whether there are any data on the proportion of people who are homeless who admit to being homeless. This is an important issue for providers in clinics in terms of recognizing who may or may not be homeless when caring for them.

Dr. Nelson indicated that the survey that is conducted on one night every year offers the best indication of how many people are homeless at one given time, but she did not know whether this was in terms of whether they admit to it or are merely observed.

Dr. Hunter emphasized that people do not qualify for the Medicaid work requirement would become uninsured and would be covered by 317 funding, which must be done through a local health department.

Dr. Szilagyi added that while they would be covered for vaccine under 317,the feasibility issue would remain.

Dr. Stephens requested further details about the variability in herd protection. There seemed to be a significant herd protection effect with 10% coverage in some populations, but other populations required 80% protection.

Dr. Nelson clarified that the 80% protection was with regard to stopping an outbreak, while the other studies showed that 10% implementation of routine vaccination resulted in a decrease in incidence of cases.

Dr. Messonnier stressed that CDC completely concurs that tracking will be a problem. There are no systems in place at the local, state, or federal levels that are going to solve this problem. It also is true, based on most data, that a single dose is sufficient to stop an outbreak. When ACIP makes this type of recommendations where there are complicated issues pertaining to implementation, it is possible to make a recommendation and then provide some context and

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then rely upon CDC to provide clinical guidance to help state health departments, which will have to decide how to implement such a program.

Dr. Moore added that 42 or more of the IISs are lifelong registries at this point. As part of the outbreak response in the multi-state outbreak, there has been a much greater emphasis on reporting HepA doses administered to adults as part of the outbreak across the US. This has demonstrated to many people the benefits of reporting adult immunization in registries and checking that prior to immunization. Her state and others have used that tool to reduce unnecessary excess immunization in outbreak responses, so there is hope as state health departments and partners in clinical settings are working on this.

In terms of the definition of “homelessness,” Dr. Bernstein observed that 3 of the 4 studies in the GRADE evaluation were outside of the US. He wondered whether their definitions were comparable to the US definition. The average age in the studies outside of the US was 46, while it was 21 in the small US study.

Dr. Doshani indicated that the age criteria were similar in the seroprevalence studies. They have not looked at the definition of “homelessness” from the international perspective, but there are different definitions for “homeless” even within the US.

Dr. Fryhofer (AMA) applauded the WG’s evidence-based definition of homelessness as a risk factor for HAV. The AMA has a new initiative dedicated to health equity, eliminating health disparities, encouraging more research and data collection, influencing determinants of health, and identifying tools to help physicians identify at-risk individuals. This recommendation is specifically in line with new AMA policies to improve the health and wellbeing of people facing homelessness. Certainly, the increase in HAV infection is a good example of how social determinants (e.g., how people live, work, play) affect people’s health and how HepA vaccination can make a difference. In terms of tracking, the background data offered some data about 1-dose efficacy. She wondered whether there are any more details or references on effectiveness after one dose. There is concern that perhaps some of these patients will not complete the 2-dose series, so consideration must be given to how to address that.

Dr. Nelson replied that the study she presented was from Ott et al in 2011. There is not another study that looks at long-term protection after 1 dose. However, based on modeling and experience of low vaccine failures, they do believe that 1-dose protection is likely much longer than the 11 years she presented, and is potentially even lifelong.

Dr. Netoskie (AHIP) said he was curious about the population that may have been recently homeless or intermittently is homeless but not at the time they are evaluated, and whether they should be considered at-risk and part of this population.

Dr. Nelson indicated that the WG assessed homeless in terms of all of the definitions of homelessness (transient, sheltered, unsheltered, chronic, et cetera), so all of the groupings she showed on the slide from HUD should be considered as homeless and potentially at-risk.

Dr. Duchin (NACCHO) expressed support for the recommendation to administer HepA vaccine proactively to homeless persons. He also wondered whether anything is known about sheltered versus unsheltered homeless. In Seattle in King County, approximately 12,000 persons are homeless and half of them are living unsheltered. This is a very large number and is more than most states. They are concerned about the spread of HAV and other infectious diseases. They have had outbreaks of Shigella and Bartonella and have HIV among the homeless population

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who do not inject drugs. He stressed that providers need to take into consideration the risk for homelessness in terms of someone who is transiently housed but has been chronically homeless or has risk factors for homeless. For example, sexual minorities have a higher prevalence of homelessness. About 20% of people who are transgender will experience homelessness during their lifetime. He also would like to see more guidance for EDs on how they can more effectively administer vaccinations to homeless persons, given that many homeless persons seek care in EDs and this is quire challenging for EDs.

Dr. Kimberlin (AAP Redbook) expressed concern about the variability in the definitions of "homelessness." A family whose primary bread winner loses their job, is kicked out of their apartment, and crash on a neighbor's couch for 3 weeks is homeless. That is not the same as someone who is on the streets and spending the night in shelters. This is a very broad group of people who find themselves in certain circumstances in life, and it is not clear whether the proposed recommendation applies across that entire spectrum. The concern seems to be people who are living on the streets.

Dr. Nelson indicated that the main drivers for transmission found in these outbreaks has been persons who are in close contact to one another and poor hygiene. They certainly could consider a recommendation that focuses on persons who are clearly homeless. However, it is hard for providers to make the distinction between someone who claims to be homeless who is transient, staying on someone else's couch, or staying on the street. The other concern regards people who move from couch to couch but are engaging in other activities, such as drug use. There could be additional risk factors as well.

Regarding the concern about transient homelessness, Dr. Frey pointed out that even for the people who are sleeping on their family's or neighbor's couches, it is not possible to know how long someone's period of homelessness will truly last.

Dr. Moore indicated that the WG discussed the fact that there are variable definitions of "homelessness" and that within those definitions, certain populations will be more at-risk and more vulnerable than others. However, it was felt that using an HHS standard definition that was broad and allowed for clinical judgment to be exercised would be most valuable, especially given that the focus of implementation of a recommendation like this would likely be on clinics that routinely provide service to the homeless through HRSA funding and other mechanisms. The implementation focus around that often would reach those who are most likely to be homeless for the longer term. Someone who is homeless for 3 weeks is unlikely to come to medical attention as needing a vaccine. For practical purposes, the WG felt that the broader standard definition that is widely accepted would be the most useful here.

Dr. Messonnier emphasized that CDC values and works toward precise, simple recommendations. She asked whether it was the intention of the WG and the ACIP statement to provide more of this context. In other recommendations, ACIP has been precise about whose responsibility it is. For example, the mumps recommendation put the responsibility squarely upon health departments.

Dr. Moore replied that the WG's discussion did address inclusion of context to put the focus on implementers of routine care to the homeless. As far as the detailed guidance in the recommendation, ACIP can elaborate on that. It is a very good question that people will have. The WG recognized that transient/unstable housing is very difficult to predict for anyone, so guidance can be provided in the note regarding who is considered to be at most risk and most critical to receive vaccine.

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Dr. Sapna Bamrah Morris indicated that she currently is serving as Incident Manager for the HAV multi-state outbreaks, has a background in working for healthcare for the homeless, and serves as a subject matter expert (SME) on this topic for the Center. She indicated that HHS and HUD have aligned their definitions, making them very close. For a few years, they have been using relatively the same definition. HUD manages a federal Homeless Management Information System (HMIS), so there is very good tracking of homeless individuals. While that is not necessarily tied to immunization registries, there is a lot more sophisticated tracking of people who are reporting homeless than is otherwise apparent to most people. Given that most people who are reporting homelessness are homeless less than a year, they can look at the point in time count, which is about 550,000 per year. But looking at the individuals who experience homelessness in a given year, it is closer to 1.1 million to 1.5 million. Of course, those numbers are variable but it is possible to de-duplicate and look at individuals who experience homelessness. In terms of chronic and sheltered versus unsheltered homelessness, one could argue that unsheltered have a risk because of the lack of access to hygiene and care, but sheltered also have a risk. They see a lot of infectious disease spread in congregate settings with very few bathrooms, shared air space, et cetera. She works a lot in tuberculosis (TB) on this topic, and there are tremendous problems in sheltered communities in terms of infectious disease spread, particularly among those who live in encampments. There is a special WG that is working with the United States Interagency Council on Homelessness (USICH) on hygiene improvements and decreasing infectious disease in encampments. In terms of how clinics for the homeless deliver care, people do not tend to have a problem reporting their homelessness. Lack of reporting homelessness is more common in EDs or other clinical settings. By broadening the questions to ask people how many addresses someone has had in a year, there has not been a problem. There have been a lot of recommendations through the USICH to use that as a further definition. The care that is delivered in the 300 HCHs across the country is tremendously robust. They acquire their vaccine supply through their clinic's ordering system, so they vary it based on what their population needs are. In terms of the Medicaid expansion concern, ordering can be adjusted through other mechanisms such as 317 to obtain the supply needed for their populations.

Considerations for Use of Hepatitis A Vaccines for Routine Vaccination of the Homeless

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 discussed the considerations for use of HepA vaccines for routine vaccination of the homeless. As a reminder, the policy question is, "Should routine inactivated HepA vaccination be recommended for protection against HepA among persons experiencing homelessness? The following is the current ACIP recommended risk groups, with the proposal to include homelessness to the list [*MMWR* 1996;45(RR-15); *MMWR* 1999;48(RR-12); *MMWR* 2006;55(RR-7)]:

- ACIP Hepatitis A Vaccine Recommendations
  Groups at increased risk of HAV or severe HAV disease
  - Travelers
  - Men who have sex with men
  - Users of injection and non-injection drugs
  - Persons with clotting-factor disorders

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- Persons who work with nonhuman primates
- Persons who anticipate close personal contact with an international adoptee
- Persons with chronic liver disease
- Homelessness

The GRADE analysis showed an Evidence Type 4 for reduction in disease burden and Evidence Type 4 for AEs, with very low overall quality of evidence for AEs. The framework showed that desirable consequences clearly outweigh undesirable consequences in most settings. In terms of whether routine inactivated 2-dose HepA vaccination should be recommended for protection against HAV among persons experiencing homelessness, the WG recommended the intervention. In terms of WG considerations, the Hepatitis Vaccines WG convened for 4 teleconference meetings on this topic and has reached consensus regarding the proposed update to the hepatitis vaccine statement regarding homelessness as a risk group for HepA vaccination.

The WG's considerations regarding homelessness as an independent indication for HepA vaccination were that homelessness might be a proxy for high rates of known risk factors (e.g., CLD, drug use); however, these risk factors might be more difficult to identify than homelessness itself. In San Diego, a currently recommended indication for vaccination was not found for >25% of homeless cases reporting risk factors.

Regarding risk of infection and severe manifestations among the homeless, the WG's considerations were that homeless are more vulnerable due to poor hygienic conditions and overcrowding. Once HAV is in the homeless community, it spreads because of poor sanitation, poor hygiene, and congregated living conditions. Homeless have an increased risk of severe disease, hospitalization, and death. Vaccinations are critical to the prevention of disease outbreaks and epidemics among individuals experiencing homelessness because of their poor living conditions that are conducive to HAV transmission.

The WG's considerations for routine 2-dose HepA single-antigen vaccination were that the FDA licensed schedule and ACIP HepA vaccine routine recommendations include 2-dose vaccination. If homelessness is included as an ACIP indication for vaccination, vaccination is more likely to be considered by homeless service providers. There is evidence that homeless in San Diego are returning to care for a second dose. One-dose single-antigen vaccine is highly effective in that it provides up to 11 years of protection and might provide life-time immunity. However, considering the immune and health status of homeless, 2 doses is optimal for long-term immunity. The homeless population is not stable and move from place to place. For example, the California outbreak is genotypically linked to the outbreaks in Utah, Kentucky, and other states. Therefore, it is important to take a national approach to vaccinating homeless. Integrating vaccination into services for the homeless over time will reduce the at-risk population and, therefore, will reduce the risk of large-scale outbreaks. This will result in an increase in herd immunity among the homeless population over time. Vaccine administration record-keeping was a work group concern, given that it is a challenge for all adult immunization. However, it was felt that increasing the use of IIS for adults and future advances in interoperability will address this concern and should not be a reason not to vaccinate routinely. Of note, TWINRIX® is an option for vaccination of the homeless. However, the WG's considerations for routine 2-dose HepA single-antigen vaccination were that the FDA licensed schedule and ACIP HepA vaccine routine recommendations include 2-dose vaccination.

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In terms of pre-exposure prophylaxis versus PEP in outbreak settings, the WG's considerations were that vaccinating homeless in an outbreak setting is very challenging. The resources involved are enormous, the population is hard to reach, and the efforts required to vaccinate are vast. Vaccination of homeless in outbreak situations results in vaccine hesitancy due to the emergency situation, unanticipated event, rushed health care, and limited time for education and understanding of the situation. Effective post-exposure vaccination is difficult, including obtaining exposure history and coordinating vaccination within 2 weeks. It is difficult to control outbreaks among homeless quickly. The longer it takes to vaccinate, the higher the probability of breakthrough cases and spread to other jurisdictions. Routine vaccination is a more feasible approach to reach homeless persons over time through homeless outreach organizations. This can occur through gradual implementation. Barriers to vaccination might be mitigated with a routine recommendation. There will be more opportunities to reach people in settings where they are comfortable with greater use of homeless advocacy groups. A routine recommendation would allow for vaccination of homeless by trusted providers who serve the homeless in familiar settings.

The WG's considerations regarding individual homeless persons were that it is important to recognize the individual homeless person, because they are at higher risk than other groups. High hospitalization and fatality rates in these outbreaks occur on an individual level. People experiencing homelessness have difficulty implementing recommended non-vaccine strategies to protect themselves from exposure (e.g., clean toilet facilities, ability to wash their hands regularly). For this reason, they depend more heavily on vaccination for protection from HAV infection. Due to limited access to healthcare and state-to-state variation in access to insurance coverage, homeless adults can be more vulnerable than other adults to vaccine-preventable diseases.

In terms of cost, the WG's considerations were that these outbreaks have demonstrated the enormous cost and difficulty associated with trying to do widespread immunization of a large vulnerable population in a short amount of time. High hospitalization rates among vulnerable populations drive up costs. The costs per capita of integrating vaccination into routine care is cheaper and much less disruptive than vaccination solely as part of outbreak response. Outbreak response has caused substantial diversion of human and financial resources from other activities in many affected jurisdictions.

The WG consensus is that homelessness should be an indication for Hep A vaccination. Homeless persons could benefit from a specific recommendation for routine HepA vaccination. Recent outbreaks have demonstrated that individuals who are experiencing homelessness have an increased risk of serious illness with HAV infection and face barriers to implementation of alternative strategies to prevent exposure, such as strict hand hygiene, due to their living conditions. A routine recommendation would allow homeless persons to be vaccinated using the services and facilities that already provide established healthcare for the homeless population. Routine HepA vaccination of the homeless would allow for integration of vaccination into these services over time toward reducing the HAV infection risk of this vulnerable population and reducing the risk of large-scale outbreaks.

The pros and cons of homelessness as an indication for vaccination versus no indication for homelessness are as follows:

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Pros

- ❑ Protection of a vulnerable population
- ❑ Providers are more likely to administer vaccine to homeless persons if homelessness is an ACIP recommended indication for vaccination
- ❑ Vaccination of homeless persons would reduce an at risk population and therefore reduce the risk of large-scale outbreak, and increase the herd immunity among the homeless population over time
- ❑ Vaccinating homeless persons in an outbreak setting and controlling an outbreak among homeless is challenging compared to integrating services into a familiar setting
- ❑ Routine vaccination is likely less costly than vaccination as part of an outbreak response

Cons

- ❑ Vaccine administration record-keeping
- ❑ Limited published data exist on hepatitis A or on HepA vaccination that specifically focuses on persons who are homeless
- ❑ Routine vaccination of homeless who do not utilize health services might not be feasible

The WG proposed the following recommendation language for a vote:

> *All persons aged 1 year and older experiencing homelessness should be routinely immunized against hepatitis A.*

Discussion Points

Dr. Lee made a motion to accept the recommendation, which Dr. Moore seconded. The floor was then opened for Public Comment pertinent to HepA vaccination.

Dr. Cohn indicated that a written comment was provided from Dr. Wilma Wooten from San Diego, which would be appended to the official meeting minutes.

Public Comment

May Morgan, MD
Chief Medical Officer
Mercy Care

Good morning. I am May Morgan. I'm the Chief Medical Officer for Mercy Care, which is a community health center that focuses on health care for the homeless. Pretty much my comments have already been stated and have been covered during the session. I just wanted to add that for anybody who is concerned that there is not a network in place, there are several community health centers in the Atlanta area that provide services for the homeless. We are the primary provider. Out of the 45,000 visits we had last year, there were 1600 unique visits. About 65% to 68% of that population were homeless. Because we are a Health Resources and Services Administration (HRSA)-funded agency, not only is general health care expected, but also preventive care. So, we have procedures that are in place that address that. We not only work at community health centers and with the other community health centers in the area, we also work with the health departments, the safety net hospital, and have a Health Information Exchange (HIE) where many of us can see each other's health records. This state also has a registry for immunization documentation. Two issues. I think if this is voted on, what it does is give heightened awareness to providers; whereas, we do prevention. You hear a lot about Hepatitis B, and we often use TWINRIX® to address both issues. We also have a high Hepatitis

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C population where vaccination is indicated as well. I've been doing this for 12 years. My biggest issue, and I've always focused on preventive care, is the cost that is associated with it. We do get a little bit of break for purchasing vaccines; however, the focus has been on those that are already recommended on a regular basis. If we did have an outbreak, it would just be difficult to rise to the occasion and address that issue. So, I think cost just across the board is something else that needs to be considered as well. I think with this being a recommended vaccine, then we can tap some of the resources that are not available currently. Thank you.

Jamie Lynn Juarez
Concerned Parent
President, Hope, Inc. Academy

Thank you everyone in attendance and online. I wrote this on the cusp, so hopefully I do okay. I would first like to address the variables related to homelessness and children and our veterans especially. Of course, thank you to our military. It's personal to me. My dad was Airborne in Vietnam and my mom graduated in 1978 from the Air Force Academy. She is currently one of the highest ranking women in aviation. So, thank you to our military. I'd like to include that I didn't see statistics, especially in San Diego where I am from in Southern California, where there is a 45% increase in homelessness in our veterans there. I think that that data is pretty relevant when it comes to issues like this. My concern in particular here is the ethical obligations to the benefits and harms data that was presented. It appears that a lot of this data lacks independent versus dependent variable analysis, especially when you combine Hepatitis A in conjunction with other vaccinations. We looked at the vaccinations in combination. There are over 440 ingredients in these vaccinations according to the schedule, so I think it's pretty relevant when we're looking at data that we include those types of looking into that, especially when it comes to longitudinal data. I didn't see any of the studies showing any longitudinal data. They were mostly observational, and I think that's a big concern when it comes to the recommendations by the committee. In response to the data that looked at youth, I think that is data on youth. I think it's relevant when looking at the school districts and particular social service programs. So, I think that the question asked about data and youth is relevant and I'm disheartened by the fact that that wasn't included. And then lastly, of course, we need to look at the World Health Organization (WHO) Code of Conduct, because I do believe that there is a lot of irresponsibility in the way that we're conducting these studies and looking at the meta-analysis approaches. Thank you.

Denise Marie Aguilar
Concerned Citizen
National Health Federation

My name is Denise and I am from California where we have these large outbreaks. These large outbreaks are partly because there are no facilities for homeless people to go to. We have only one facility, and for a large population of 300,000 in a city, this is a problem. From the numbers that I saw, it was going to cost $28 and some cents per dose of vaccine. I would just like to know has anybody ever looked at the cost of putting in bathrooms and sanitation practices in these neighborhoods instead of a mass vaccination. It seems that from the one study that was done and the multiple studies that sanitation practices would be a better fit than mass vaccination for people who are not trackable. These are homeless people. It's impossible. They move around, so how are you going to actually implement something like this. So, that's my concern.

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Motion/Vote: Routine HepA Vaccination for Homeless Populations

Dr. Lee made a motion to accept the recommendation for routine vaccination of all persons aged 1 year and older experiencing homelessness as proposed, which Dr. Moore seconded. The motion carried with 11 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

11 Favored: Atmar, Bernstein, Ezeanolue, Frey, Hunter, Lee, Moore, Romero, Stephens, Szilagyi, Walter
0 Opposed: N/A
0 Abstained: N/A

VFC Resolution

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

Dr. Santoli indicated that the purpose of this resolution was to correct and streamline language related to catch-up vaccination, noting that the only change was to combine the 2 catch-up sentences and adding "through 18 years of age" at the end of the recommended vaccine schedule.

Eligible Groups

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

The recommended vaccine schedule wording will 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 **through 18 years of age**.

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.

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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 remains unchanged:

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

Selected Special Categories remains unchanged:

- ❑ 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.

- ❑ 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.

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

<u>Recommended Dosage</u>
Refer to product package inserts.

<u>Contraindications and Precautions</u>

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

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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 is included:

[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.]

Motion/Vote: VFC Resolution

Dr. Frey made a motion to accept the VFC Resolution as proposed, which Dr. Szilagyi seconded. The motion carried with 11 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

11 Favored: Atmar, Bernstein, Ezeanolue, Frey, Hunter, Lee, Moore, Romero, Stephens, Szilagyi, Walter
0 Opposed: N/A
0 Abstained: N/A

Pneumococcal Vaccines

Introduction

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

Dr. Lee reminded everyone that the Pneumococcal Vaccines WG's terms of reference are to:

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

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ACIP recommended 7-valent pneumococcal conjugate vaccine (PCV) for children in 2000, followed by 13-valent (PCV13) in 2010. In 2012-2013, ACIP recommended PCV13 for adults and then children with immunocompromising conditions. In 2014, ACIP recommended PCV13 in series with PPSV23 for adults ≥65 years of age. Presently, the WG is re-evaluating the use of PCV13 in adults ≥65 years of age. When ACIP recommended PCV13 in series with PPSV23 for adults ≥65 years of age in 2014, the thinking was that it was warranted in the short-term. A major factor in this decision was the estimate PCV13-type pneumonia burden among older adults that could be prevented with this recommendation. . However, the long-term public health benefits at that time were expected to be limited, because of the anticipated continued indirect effects from the pediatric PCV13 program. Therefore, the recommendation was made in 2014 with a commitment to re-evaluate this policy 4 years later and revise it as needed. The WG is still in the process of re-evaluating this recommendation. During this process, the WG has been: 1) monitoring pneumococcal disease, including both invasive disease and non-invasive pneumonia among adults ≥65 years; 2) evaluating the impact of direct and indirect effects on pneumococcal disease among adults ≥65 years; and 3) continuing to monitor vaccine safety.

As a reminder of how complex ACIP's recommendations can be in terms of implementation, the WG is focused on the red box in the right upper half of the following table and looking at the PCV13 recommendation for those ≥65 years in immunocompetent patients with and without chronic health conditions. The WG is not re-considering the recommendation for immunocompromised persons, persons with functional or anatomic asplenia, Cochlear implants, or cerebrospinal fluid (CSF) leaks:

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

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

*This PPSV23 column only refers to adults 19 through 64 years of age. All adults 65 years of age or older should receive one dose of PPSV23 6 or more years after any prior dose of PPSV23, regardless of previous history of vaccination with pneumococcal vaccine. No additional doses of PPSV23 should be administered following the dose administered at 65 years of age or older.
†Including congestive heart failure and cardiomyopathies
‡Including chronic obstructive pulmonary disease, emphysema, and asthma
§Includes B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease)
¶Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy

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

- ❑ PCV13 impact on IPD and serotype distribution for the remaining disease burden with a focus on adults ≥65 years old
- ❑ Incidence of non-invasive pneumococcal pneumonia among adults ≥65 years old

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- Impact of introduction of infant vaccination with PCV13 on pneumonia and IPD in the United States, 2005–2014

- Economic analysis of continuing a recommendation to immunize with PCV13 for adults ≥65 years in the context of continuing herd immunity from the childhood immunization program

- Preliminary Evidence to Recommendations for the ongoing review of the PCV13 recommendation for adults ≥65 years old

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

- Which domains of the EtR framework warrant additional exploration regarding continued use of PCV13 in immunocompetent adults ≥65 years?

  - Benefit, Risks
  - Values
  - Acceptability
  - Resource Use
  - Feasibility

Impact of PCV13 on Invasive Pneumococcal Disease (IPD) Burden and the Serotype Distribution in the US

Tamara Pilishvili, PhD MPH
Respiratory Diseases Branch
National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Pilishvili indicated that the focus of her presentation was to update ACIP on the impact of PCV13 introduction for children and then adults on IPD. This update has been provided almost every year, and the current update includes surveillance data through 2017. She also planned to focus on the remaining disease burden and describe the serotype for that remaining burden after several years of PCV13 use in the US. She indicated that the date she would be presenting was from the Active Bacterial Core Surveillance (ABCs) system, which is a laboratory- and population-based surveillance system that is ongoing at 10 US sites. An IPD case was defined as isolation of pneumococcus from a normally sterile site. Isolates are serotyped by Quellung or polymerase chain reaction (PCR) at a reference laboratory.

For this analysis, Dr. Pilishvili indicated that the serotypes were grouped by PCV13 serotypes, which are the serotypes contained in PCV13 plus serotype 6C as it has shown cross-protection from the 6A antigen in the vaccine, and non-vaccine types (NVT), which includes all other serotypes that are not included in PCV13. US Census Bureau race-bridged post-Census population estimates were used as denominators, and the analysis examined overall and serotype-specific IPD incidence rates/100,000.

Looking at the IPD rates among children <5 years of age from 2007-2017, shortly after PCV13 was introduced in 2010, reductions were observed in overall disease and PCV13 + 6C. From 2013 through 2017, the remaining vaccine serotype disease group has leveled off and no additional reduction has been observed. However, the burden of disease is very low at less than

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2 cases/100,000. In terms of NVT, no changes or evidence of disease replacement due to these serotypes have been observed. Looking at adults ≥65 for this same timeframe, between 2010 and 2014 when the vaccine was introduced for adults, indirect effects from pediatric vaccine reduced overall vaccine-type disease dramatically. After 2014, the disease rates leveled off. Since the vaccine was introduced for adults, no population-level impact has been observed from this vaccine. Similar to children, there is no evidence of serotype replacement for NVT.

In terms of which vaccine serotypes contributed to these reductions, most of the reductions among children are due to 19A and 7F. There was some evidence to suggest that reductions were occurring in serotype 3, but the rates remained the same from 2013 through 2017 and have not changed. One of the PCV7 serotypes, 19F, has persisted and even increased slightly. The picture is similar for adults ≥65 years of age, but with greater variability in the distribution of serotypes. The reductions are driven by serotypes 19A and 7F. There is no evidence of impact on serotype 3 when looking at combined indirect and direct effects at the population level.

Serotype 3 has raised questions about what is occurring in terms of seeing no impact. Some studies have suggested that there are some direct effects, but an impact has not been observed at the population-level. Therefore, CDC wanted to examine the ABCs data further to look at longer trends due to serotype 3. Traditionally, CDC has assessed the impact on serotype-specific disease by looking at the time periods before and after vaccine introduction to measure the impact. They decided to assess serotype 3 in a different way by letting the data tell when the changes occurred. For the time period 1998-2017, a joinpoints analysis was used to let the data identify the point of inflection in the rates. In children, there was a slight increase in serotype 3 disease preceding PCV7 introduction. The slope changed at some point in 2003 and the confidence interval for this change in slope was between 2000-2008. This was before PCV13 introduction. Reductions in serotype 3 have continued through 2017. However, looking at just the time period before and after PCV13 introduction this trend would not have been apparent. The data suggest that there might have been additional benefits from PCV13 introduction, but the trends going down for serotype 3 really began before PCV13 was introduced. The picture is similar for adults.

In terms of disease caused by the serotypes in the PCV13 era, serotypes 3 and 19A remained in the top 10 among children <5 years of age in 2016-2017. Because 19A at the baseline contributed to a large burden, Dr. Pilishvili excluded it to show what the trends over time looked like among the remaining top nine serotypes. Some serotypes increased and some have decreased, but there has not been a consistently emerging NVT. Regarding the remaining disease burden, each serotype contributes to a relatively small disease burden. The two most common serotypes in 2016 and 2017 were 33F and 23B, which contributed to about 16% of IPD.

Dr. Pilishvili conducted an exercise with a hypothetical PCV15 vaccine in children, emphasizing that none of the hypothetical vaccines she referred to exist or are in the pipeline. Instead, the hypothetical vaccines were based on the rank order of serotypes. A hypothetical PCV15 vaccine comprised of PCV13 + 2 NVT administered in children would result in a total preventable burden of <2 cases/100,000 with an estimated 260 US cases. For a hypothetical PCV20 vaccine comprised of PCV13 + 7 NVT (33F, 23B, 22F, 15C, 35B, 15A, 38) administered in children, the preventable disease burden would be 3 cases/100,000 with an estimated 700 US cases. The 7 top NVT in this scenario comprised 48% of IPD in 2016-2017.

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Doing the same for adults, the top 7 ranking pediatric serotypes in adults are 33F, 23B, 22F, 15C, 35B, 15A, and 38. These serotypes accounted for 35% of IPD in 2016-2017 among adults. Using a hypothetical PCV20 pediatric vaccine that is comprised of PCV13 + the 7 pediatric NVTs in children, preventable burden through indirect effects would be about 11 cases/100,000 with an estimated 10,000 US cases. That is, a 60% to 70% reduction would be expected through indirect PCV effects. This time, the hypothetical PCV20 is comprised of PCV13 + the top ranking 7 adult NVTs in adults that accounted for 42% of IPD in 2016-2017 (22F, 35B, 23A, 15A, 33F, 11A, 9N). The preventable burden would be 9 cases/100,000 with an estimate 12,000 US cases. That is, a 30% reduction would be expected through direct effects taking into account the current 45% vaccine coverage and 60% vaccine effectiveness (VE).

In conclusion, overall IPD incidence was significantly lower in 2016-2017 following PCV13 introduction for children. The reductions were driven by serotypes 19A, 7F, and 6C cross-protection of 6A. There were no changes in type 3 IPD during 2007-2017, and rates have plateaued since 2014. PCV13 direct effects on IPD among adults ≥65 years of age were likely very limited during this observation period, and there is no evidence of serotype replacement. New PCVs covering the top 7 NVT pediatric strains would target a relatively small IPD burden in children of approximately 3 cases/100,000. The same PCV for children has the potential of reducing a large disease burden among adults ≥65 years of age through indirect effects.

Estimating The Impact of 13-Valent Pneumococcal Conjugate Vaccine (PCV13) on Pneumococcal Pneumonia Among US Adults

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Mr. Gierke discussed CDC's efforts to estimate the impact of PCV13 on pneumococcal pneumonia among adults in the US. *Streptococcus pneumonia* (pneumococcus) is a common etiology of all-cause pneumonia among adults. However, the true burden of disease is unknown due to the limitations of available diagnostic tests. The ratio of bacteremic to non-bacteremic pneumococcal pneumonia has been estimated to be around 1 to 4, but this was estimated before PCV13 introduction[1]. Blood cultures have low sensitivity. A commercially available pneumococcal urine antigen test (UAT) has a sensitivity of about 75% and is not routinely used by all health care providers [2, 3] [[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].

Pneumococcal conjugate vaccine use among children has dramatically reduced IPD in adults through indirect effects. Additionally, studies have documented reductions in pneumonia hospitalizations among children through direct effects and adults through indirect effects after introduction of conjugate vaccine in children[1,2]. PCV13 demonstrated efficacy/effectiveness against PCV13-type pneumococcal pneumonia among older adults[3, 4] [[1]Alicino C., et al (2017). The impact of PCV10 and PCV13 on hospitalization for pneumonia in children... Vaccine 35:5776–5785; [2]Tsaban G., et al (2017). Indirect (herd) protection, following pneumococcal conjugated vaccines introduction... Vaccine. 35:2882–2891; [3]Bonten M, et al (2015). Polysaccharide Conjugate Vaccine against Pneumococcal Pneumonia in Adults. N Engl J Med. 372:1114–25; and [4] McLaughlin, J. M., et al (2018). Effectiveness of PCV13 Against Hospitalization for Community-Acquired Pneumonia in Older US Adults: .. Clin Infect Dis.].

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Given the uncertainties around the true burden pneumococcal pneumonia, and the importance of this outcome for future PCV policy decisions for adults 65 and older, CDC established Surveillance for Non-invasive Pneumococcal Pneumonia (SNiPP). The objectives of SNiPP are to: 1) estimate the burden of non-invasive pneumococcal pneumonia; and 2) evaluate the impact of the 2014 ACIP recommendation for routine use of PCV13 among adults 65 years of age and older. SNiPP case ascertainment is built into the ABCs system. Cases are defined as adults 18 years of age or older who were hospitalized with clinically- or radiographically-confirmed pneumonia and have a positive pneumococcal UAT. Cases were excluded if they had IPD, had a prior positive UAT within the past 30 days, or were not a resident of the catchment area. Data collection has been prospective since 2015, with retrospective data collection dating back to 2013. This provides 2 distinct time periods from 2013-2014 before the age-based recommendations for PCV13 in adults 65 and older, referred to as the pre-PCV13 time period, and the post-PCV13 period from 2015-2016 after the recommendation. The SNiPP catchment area has 10 sites across the US that are primarily in urban areas (Oregon, California, Colorado, Minnesota, New York, Connecticut, Maryland, 2 sites in Tennessee, and Georgia). The average annual population under surveillance is 16 million.

In terms of the basic demographics for UAT-positive cases for 2013-2016, when comparing cases in the pre- and post-time periods, a similar distribution of age, race, gender, and ethnicity was found. In terms of the distribution of characteristics related to the diagnosis and treatment for reported UAT-positive cases, a similar proportion of pre- versus post-PCV13 time period cases had community onset, chest x-ray confirmation, and intensive care unit (ICU) admissions. There were no differences in the median length of stay, proportion who died, or proportions with immunocompromising and chronic medical conditions (CMCs). A slightly higher percentage of cases during pre-PCV period compared to the post-PCV period received pneumococcal vaccine during hospital admission.

In order to estimate the incidence rates of pneumococcal pneumonia, it was necessary to make several adjustments to the UAT case counts. It is known that not all pneumonia cases are tested by pneumococcal UAT, so the UAT-positive case count was adjusted by the proportion of pneumonia tested by UAT. It is also known that not all hospitals perform pneumococcal UAT, so the UAT-positive case count was adjusted by the proportion of pneumonia in the catchment area who were seen at hospitals offering UAT. In addition, it is known that UAT is not 100% sensitive. Therefore, based on available literature, it was estimated that pneumococcal UAT sensitivity is approximately 75% and further adjusted the case count by test sensitivity.

Regarding the data collected and how incidence is estimated from the defined catchment area hospitals, sites obtain the total number of all-cause pneumonia discharges from all catchment area hospitals. All-cause pneumonia is defined as a patent with pneumonia or empyema as their primary discharge diagnosis International Classification of Diseases (ICD) code, or with septicemia as their primary diagnosis discharge ICD code plus a pneumonia or empyema discharge diagnosis in any position. Dr. Gierke noted that for brevity, this definition is what he would be referring to when saying “pneumonia.” From this total number of pneumonia discharges in the catchment area, select hospitals pull a random sample of pneumonia discharges by month and age group, and collect information on UAT testing status among these patients. This provides the proportion of pneumonia tested by UAT. A model is used to estimate the proportion of positive UAT cases, and this proportion is applied to the total pneumonia in the catchment area to calculate the total number of pneumococcal pneumonia cases in the catchment area.

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The first step was to model the proportion of pneumonia tested by UAT as an outcome using a fixed effects logistic regression model. Inputs included the sampled number of pneumonia cases and number of pneumonia tested within the sample. Additional predictors in the model were year, age group, select hospital characteristics (size, case mix index, payment scheme, teaching and university affiliation), and site. Interactions were tested for and the following interactions remained in the model: site*year, site*age group, year*age group. The model output was annual percentage of pneumonia tested by UAT by age group, year, and hospital. The next step was to model the percent of pneumonia positive by UAT. A generalized linear mixed effects model was used with the following inputs: number of UAT positive cases and percent of pneumonia tested, which was estimated from the logistic regression model. Additional predictors in the model were year and age groups as fixed effects and hospital and site as random effects. Interactions were tested for, and none were found to be significant. The model output was annual percent of pneumonia positive by UAT, which was aggregated for all hospitals and sites included in the model by age group and year.

This model made the assumptions that UAT testing among pneumonia cases is assumed to be random after stratifying by hospital, age group, and year. The effects of hospital characteristic are assumed to be random, but they follow a common normal distribution. Testing practices from hospitals reporting UAT cases follow a similar distribution as those not reporting. The final steps in the adjustment calculations were to multiply the estimated percent positive UAT obtained from the generalized mixed linear model by the total number of pneumonia cases in the catchment area. Finally, the case counts were inflated to account for an estimated UAT sensitivity of 75%.

The estimated incidence of non-invasive pneumonia per 100,000 with 95% confidence interval was calculated using the adjusted cases count at the numerator and the total catchment area population as the denominator. In the pre-2013 time period, adults ≥65 years of age had the highest incidence of non-invasive disease, followed by adults 50 through 64 years of age, and finally adults 18 through 49 years of age. Comparing the incidence in the pre- and post-time period, reductions were observed in non-invasive disease among all ages in the post-PCV13 time period.

In terms of annual non-invasive pneumococcal pneumonia incidence by year for 2013-2016, adults age 65 and older had the largest reductions. Using the pre-post PCV13 incidence estimates, reductions were observed in non-invasive disease of 35% among adults ≥65 years of age, 12% among adults 50 through 64 years of age, and 35% among adults 18 through 49 years of age. The rate reductions in adults aged ≥65 years of age and 18 through 64 years of age were statistically significant. However, the majority of these reductions occurred in the years between 2013 to 2014, before the PCV13 recommendations in adults. These are likely the result of continued indirect effects of PCV13 vaccination in children. Comparing 2014 to 2016 among all ages, the rate ratio is 0.95 with a non-significant p-value of .53. Therefore, it appears that there are not any significant changes in these later years.

CDC wanted to compare whether the changes seen for non-invasive pneumococcal pneumonia are consistent with the trends in invasive disease. Comparing the changes in non-invasive pneumonia with bacteremic pneumonia during 2013-2016 from SNiPP and the incidence of invasive pneumococcal pneumonia from ABCs for the same time period among the same age groups, non-invasive pneumonia incidence is 3 to 7 times higher than IPD. Changes in the incidence of invasive and non-invasive pneumococcal pneumonia appear to follow a similar pattern, with the majority of declines observed in 2013-2014. No additional reductions in disease are observed after the 2014 recommendations for PCV13 use in adults ≥65 years of age.

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The findings have the following limitations. UAT testing practices at hospitals are likely not at random. Adjusted incidence is based on ICD codes for pneumonia, and coding practices may change over time among hospitals and sites. There are relatively short time periods for both pre- and post-PCV13 data. The serotype distribution of UAT positive cases is unknown, so it is not possible to determine the burden of vaccine-type pneumonia. It is possible that increases in non-vaccine type pneumonia are minimizing the reductions observed. Finally, the direct effects cannot be estimated without the pneumococcal vaccination status of cases.

In conclusion, pneumococcal pneumonia continues to contribute to a high burden of disease among adults. The most dramatic decreases in pneumococcal pneumonia were observed before 2014. These reductions were likely driven by continued indirect effects from PCV13 use among children. No additional reductions were seen after 2014, and the changes in the incidence of pneumococcal pneumonia are similar to those observed in IPD during 2013-2016.

Discussion Points

Dr. Frey requested clarity regarding whether the incidence of non-invasive is increasing while the incidence of invasive pneumonia is decreasing simply because the vaccine is partially protective (i.e. prevents more severe disease).

Mr. Gierke replied that given the short time period, it is difficult to draw conclusions. The 2014-2016 comparison for non-invasive disease was not significant, so it is not clear that this is an actual increase. They will have to wait to see whether it continues to down.

Dr. Lee wondered whether there is sufficient information available on a yearly basis such that this could be treated more as a time series analysis as opposed to pre/post.

Mr. Gierke indicated that they would like to do this, but are still working on the modeling and have not gotten to that point yet.

Dr. Atmar wondered about the annual impact of the size and extent of the influenza outbreaks each year on the variability observed from year to year on invasive and non-invasive pneumonia.

Mr. Gierke indicated that they have not assessed any other diseases at this point, but this is something they can look into.

Dr. Pilishvili added that they have tried to look at this in previous IPD analyses. For example, 2009 was known to be a bad year. Therefore, they had to remove 2009 from all of the comparisons because there was a spike in disease. Going forward, they could probably utilize a time series approach. With more data points, they probably could examine the contribution of different influenza seasons to the pneumococcal disease trends being observed.

Dr. Walter said he was trying to tease out the 2013-2014 decrease and looking at the time sequence for change in policies, and what was indirect benefit and potentially direct benefit from the change in 2012-2013 for immunizing people with immunocompromising conditions.

Mr. Gierke said he thought that recommendation pertained to a very small number of cases and would not likely be influencing the change, which is driven primarily by the indirect effects from children.

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With regard to the comments about the effectiveness of vaccine against non-invasive pneumonia, Dr. Luis Jodar (Chief Medical Officer, Pfizer Vaccines) indicated that there are convincing data that the vaccine is protective against vaccine-type non-invasive pneumonia. This was shown in the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) study, which is a randomized double-blind controlled efficacy trial with 80,000 participants, as well as another effectiveness trial that was presented to ACIP. As Mr. Gierke mentioned, the time period from 2015-2016 has to show the uptake of PCV. It is important to remember that the recommendation was not made until August 2014, so uptake was low. In addition, the UAT does not discriminate between the 13 serotypes, so it is not fair to say that the vaccine does not work against the 13 serotypes.

Dr. Cohn clarified that she did not believe a comment was made that the vaccine does not work against these serotypes.

US Trends in Pneumonia Hospitalizations

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Dr. Lessa presented on the impact of the introduction of infant vaccination with PCV13 on pneumonia and IPD in the US from 2005–2014. This work is the result of a major collaboration between CDC, academic partners, and departments of health. Decreases in pneumonia and IPD hospitalizations were observed in the US in both vaccinated and unvaccinated populations after pediatric PCV7 introduction in 2000[1, 2, 3]. The rise of non-vaccine serotypes, especially 19A, led to the switch from PCV7 to PCV13 in the US in 2010 [[1]Grijalva CG et al. Lancet 2007; [2]Zhou F et al Arch Pediatric and Adolescent Medicine 2007; [3]Simonsen L et al. MBio. 2011 Jan 25;2(1):e00309-10].

The objective of this analysis was to determine if PCV13 introduction in 2010 resulted in further declines in pneumonia and IPD hospitalization rates in the US given the additional serotype protection. To address this question, statewide hospitalization data were utilized from 23 US states. A total of 73.4 million hospitalizations were analyzed from the pre-PCV13 period, defined as January 1, 2005 through June 30, 2009, and a total of 69.7 million hospitalizations in the post-PCV13 period, defined as July 1, 2010 through December 31, 2014. No data were included after 2014 to allow for measurement of indirect effects of PCV13 use in children among US adults.

Three outcomes were evaluated that were defined by ICD 9 codes: all-cause pneumonia, pneumococcal pneumonia and IPD. Hospitalizations not meeting the case definition were grouped into categories using a classification software based upon their clinical similarities to one another to serve as control conditions. A synthetic control method (SCM) was utilized, which was developed by Google for market research and has been evaluated for use with population-based data to measure vaccine impact. This method provides a data-driven way to select a combination of control conditions to better adjust for unmeasured confounders present when analyzing administrative data, such as changes in healthcare utilization or in the underlying health of the population. Data were analyzed for each outcome stratified by age. The null model was a simple time-series of monthly incidence controlling for seasonality. The SCM was a time-series model accounting for a composite synthetic control instead of a single control disease. A rate ratio of <1.0 was considered vaccine impact.

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In terms of the results, all-cause pneumonia represented about 15% of all hospitalizations for the younger age groups and about 10% to 12% for the older age groups. Hospitalizations coded as pneumococcal pneumonia were very uncommon, representing less than 0.4% in this dataset. Regarding the rate ratios and the 95% credible intervals per year post-PCV13 introduction for the null model and the SCM using all-cause pneumonia as the outcome of interest, declines were observed in all-cause pneumonia for children <2 and 2 through 4 years of age in 2011 and 2012, respectively. No declines were observed for children 5 through 17 years of age, with the exception of 2014 when adjusting for controls. For adults, no declines were observed in all-cause pneumonia after pediatric PCV13 introduction.

Declines on pneumococcal pneumonia hospitalizations were observed across all pediatric age groups, with declines ranging from 25% to 60% in some years post-PCV13 introduction. Declines in pneumococcal pneumonia also were observed for adults, with the exception of groups ≥75 years of age where the credible intervals of the synthetic control model crossed one for 2013 and 2014.

Declines were observed in IPD for children <2 years from 2010 forward. In children 2 through 4 years of age, there was no decline during the year of vaccine introduction. There was no declines in the first year after vaccine introduction for children 5 through 17 years of age, but declines were observed afterwards. For adults, the age groups 40 through 64 and ≥75 years did not experience any declines after adjusting for confounders.

Overall, from June 2010 through December 2014, the cumulative number of cases of all-cause pneumonia prevented among children was over 38,000 in the age group <2 and over 17,000 for the age group 2 through 4 years. For pneumococcal pneumonia, the number of cases averted ranged from 743 for children <2 years to over 5000 in adults. For adults ≥75 years of age, there were over 6000 pneumococcal pneumonia hospitalizations averted by 2013 with a credible interval that did not cross zero. For IPD, the total number of cases averted in the post-PCV13 period across the 23 states ranged from 335 in children to over 1200 in adults.

In summary, declines in all-cause pneumonia were observed only in children <5 years of age after PCV13 introduction. Pneumococcal pneumonia hospitalizations declined in all age groups, with the exception of adults ≥75 years of age for whom no declines were observed in 2013 and 2014. There was no decline in IPD hospitalizations for the groups 40 through 64 years and ≥75 years.

There are several limitations in this data analysis. Even though a robust methodology was used to try to overcome some of the limitations, changes in hospital coding practices during the analysis period may affect trends over time. The outcome of all-cause pneumonia is very sensitive and includes healthcare-associated pneumonia hospitalizations. Administrative data likely underestimate the specific outcomes related to pneumococcal disease. Comparison of the US ABCs with administrative data revealed under-reporting of IPD, especially for adults.

In conclusion, the lack of a measurable impact on all-cause pneumonia in persons ≥5 years of age is likely related to the use of a non-specific outcome. Only a small fraction of all-cause pneumonia is vaccine-type pneumococcal pneumonia. Also, PCV7 was in place for a decade prior to PCV13 introduction. Therefore, small benefits already are expected for all-cause pneumonia. Direct and indirect effects were observed for pneumococcal pneumonia and IPD hospitalizations after switching to PCV13. There was no decline in IPD hospitalizations among age groups 40 through 64 years of age and ≥75 years of age when adjusting for confounders. A

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comparison with ABCs IPD data shows under-reporting of IPD in administrative hospitalization data. The wide credible intervals should be further explored. It is possible that the relatively low weight of control conditions suggests low correlation of these conditions with the pneumonia pre-PCV trend and, therefore, may not be the best control conditions.

Economic Analysis PCV13 in Adults ≥65 Years of Age

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Tulane University
School of Public Health and Tropical Medicine

Dr. Stoecker presented the economic analysis of sustaining the current recommendation for PCV13 use among adults ≥65 years of age in the context of continued indirect effects from the pediatric PCV13 program. The study question was to evaluate the cost-effectiveness of continuing to recommend PCV13 at age 65 for all adults to determine how well the direct protection offered by PCV13 matches the current and projected disease burden, and incorporate updated estimates of indirect (herd) impacts from the pediatric immunization program. The analysis evaluated the program cost versus changes in medical and non-medical costs and changes in disease, and aggregated disease endpoints into quality-adjusted life years (QALYs).

The intervention examined regarded whether to continue the age-based recommendations for PCV13 at 65 introduced in 2014 to administer PPSV23 to those with underlying medical conditions 19-64 and PCV13 at age 65 years followed by PPSV23 ≥ 1 year later (or when at least 5 years have passed since previous dose). Prior analyses indicated that vaccinating immunocompromised individuals is cost-saving; therefore, they were excluded from this model and the vaccine recommendation from 2012 will stand for this group. The comparison strategy included PPSV23 for those with underlying medical conditions 19-64 years of age and a strategy that included the PPSV23 recommendation only at age 65 years. That is, removing PCV13 at age 65. Again, individuals with immunocompromising conditions were removed from the model.

This cohort model tracked individuals who were 65 years of age in 2019 through life expectancy or until age 100, incorporated disease rates prior to the 2014 PCV13 recommendation for adults aged 65 years and older with PCV13, and projected indirect impacts from pediatric PCV13 immunization program ahead through lifetime of cohort. All outcomes and costs were discounted by 3% and all costs are presented in 2017 dollars. The cohort was comprised of 2,676,090 adults at age 65 of whom 43.8% had CMC (e.g., chronic heart disease, chronic lung disease, diabetes mellitus, alcoholism, and CLD). The incremental cost-effectiveness ratio of the two recommendations was calculated, and the change in costs were divided by the change in QALYs. The analysis was conducted from the societal perspective. The following disease outcomes were tracked:

- ❑ Cases of IPD
- ❑ Cases of inpatient non-invasive pneumococcal pneumonia (henceforth “pneumonia”)
- ❑ Cases of outpatient pneumonia
- ❑ Deaths due to IPD
- ❑ Deaths due to pneumonia
- ❑ QALY
- ❑ Life Years

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The model was run once for Schedule A (PCV13 given in series with PPSV23, the current policy) and again for Schedule B (PPSV23 alone, the comparison strategy). Individuals could be vaccinated or unvaccinated and have one of three different disease states (IPD, pneumonia, or no pneumococcal disease). Those with IPD could have had an inpatient visit or potentially death; those with pneumonia could have had an inpatient visit, outpatient visit, or potentially also death; and those with no pneumococcal disease. The inputs for IPD disease burden were taken from ABCs data prior to the direct vaccine recommendation for adults at age 65. The model was broken down into healthy and those with CMCs. The rates for IPD were 15/100,000 for the healthy and 36/100,000 for population with CMCs. There was about a 14% fatality rate among both of those populations. Serotype 3 represented 12% of the total IPD disease, which was almost half of the vaccine serotype disease in the 2013-2014 data.

In terms of the inputs for pneumonia disease burden, the lower bound of all-cause pneumonia disease burden came from Jain et al. 2015, while the upper bounds came from Ramirez et al. The base case used the midpoint between those two. These bounds were then decomposed into healthy and CMC-specific rates using the ratio of disease in these two groups from Weycker et al. The case fatality rate for pneumonia was 3.9% in the base case, which was taken from the National Inpatient Sample (NIS) 2014. The outpatient all-cause pneumonia rate came from Nelson et al. 2008, while the percent of pneumonia due to PCV13 serotypes came from Pfizer data. The base case was from a Pfizer study from October 2013-September 2014, with some confidence intervals constructed around that for a lower bound from data from October 2015-September 2016) and an upper bound constructed to be symmetrical.

Vaccine effectiveness (VE) was estimated separately by serotypes, given that serotype 3 seems to behave differently. VE against IPD came from a CDC case-control study that was indicted to be 67% (11,88) effective against serotype 3. In base case, it was assumed to be 0% (0.26) effective but sensitivity was conducted around that[1]. Against pneumonia, the estimate of 41.1% (12.7, 60.7) for the healthy was drawn from the original CAPITA trial[2] and the 32.5% (3.9, 53) estimate for the CMC group was drawn from a post-hoc analysis[3]. For the effectiveness of PCV13 against pneumonia, this was broken down by serotype. It was assumed to be 0 (0,45) in the base case[2]. PPSV23 was assumed to be as effective against IPD as PCV13 at 67% (37, 73) with confidence intervals constructed from a meta-analysis[4]. PPSV23 was assumed not to be effective against pneumonia in the base case based on several meta-analyses[4, 5, 6], with sensitivity analyses conducted with much higher effectiveness [[1]Pilishvili et al. ISPPD2018 abstract; [2]Bonten NEJM 2015 (CAPITA); [3]Suaya Vaccine 2018; [4]Falkenhorst et al. 2017; [5]Schiffner-Rohe 2016; 6Tin Tin Htar 2017].

For the indirect effects from the pediatric immunization program, it was assumed in the base case that there was a 4.1% (95% CI = 0, 7%) reduction in serotype disease per year for serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 23F, 6C. This was applied to both pneumonia and IPD, and no further indirect effects were assumed on 19F and 3. These results were taken from a study that was presented to ACIP in February 2018.

The coverage rate for PPSV23 of 61.3% (59.9%, 62.7%) was drawn from the National Health Interview Survey (NHIS) published in the *MMWR* in 2016. The lower bound of coverage of 40% (39.6, 41%) for PCV13 was drawn from CMS coverage data, while the upper bound was drawn from Pfizer IMS Claims data from September 2017.

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For vaccine price, the assumption was made that PCV13 costs about $200 per dose, which is about 95% of the average wholesale price (AWP); about $100 per dose for PPSV23[1]; $26.61 per dose for vaccine administration averaged across all Medicare Administrative Contractors; and about $30 for travel and time cost derived from prior work and inflated for 2017 dollars for consistency[3] [[1]Medicare Part B, December 2017; [2]Medicare Reimbursement Rate 2017; [3]Maciosek et al 2006 *Am J Prev Med*]. Costs to treat an episode of disease were derived from Medicare Claims, 2010-2015, and inflated to 2017 dollars with the Consumer Price Index (CPI). IPD costs about $21,000, inpatient pneumonia about $11,000, and outpatient pneumonia about $300.

These disease endpoints were aggregated into a single metric using QALY decrements, which indicate how much of a healthy life year someone loses when they contract this disease. Two sets of QALY decrements, healthy life lost in days and implied average duration of illness in days. The base case estimates were derived from several studies that tried to elicit these values from patients. Base case IPD was estimated to cost 0.008665 of a healthy life year, which is equivalent to 3.2 days of healthy life lost and an implied duration of a case of IPD of 21 days using the assumption that a case of IPD is about 85% of a health day[1]. These numbers were discounted according to how the baseline health the person was, so a person with CMCs or an older person would have a lower baseline utility level, which would achieve a lower decrement[2] [[1]Melagaro & Edmunds 2004 *Vaccine*; [2]Vold et al 2000 *Clin Infect Dis*].

For alternative larger utility decrements, inputs were included from a different study that used decrement about 10 times higher. In this instance, base case IPD was estimated to cost 0.074521 of a healthy life year, which is equivalent to 27.2 days of healthy life lost and an implied duration of a case of IPD of 181 days using the assumption that a case of IPD is about 85% of a health day[1]. These numbers were discounted according to how the baseline health the person was, so a person with CMCs or an older person would have a lower baseline utility level, which would achieve a lower decrement[2] [[1]Sisk et al 2003 *Ann Intern Med*; [2]Vold et al 2000 *Clin Infect Dis*].

In terms of the immunity conferred by the two vaccines, there were two scenarios for PCV13. Scenario 1, there was no decline in VE between age 65 and 70 and then a linear decline to zero between ages 65 and 85. Scenario 2 had a slower waning starting at age 65 and declining by 10% every 5 years. For PPSV23, it was assumed that all protection disappears within 15 years after vaccination with decline in effectiveness starting at vaccination, a linear decline to 50% of initial decline over the first 5 years, a linear decline to 30% of initial decline over the next 5 years, and a linear decline to 0% of initial decline over the next 5 years.

With regard to the base case results, 82 discounted cases of IPD would be prevented over the lifetime of this cohort. That represents a number <1% of the total cases of IPD across this cohort. About 1770 inpatient pneumonia cases would be prevented of the lifetime of this cohort, again representing <1% of the total cases in this cohort. The total cost would be $401 million, which is comprised of $423 million to vaccinate this cohort combined with a savings of $22 million in direct medical costs. The cost per QALY would be $648,845 (277,338; 1,951,526) in the base case.

Four one-way sensitivity analyses were performed. In the base case, it was assumed that PPSV23 was ineffective against pneumonia. In the sensitivity analysis, it was assumed to be 44% effective, which is as effective as the per protocol effectiveness of the conjugate vaccine against pneumonia. For PCV versus serotype 3 disease based on a case-control study and measurement of serotype rates, it was assumed to be zero in the base case. In the sensitivity

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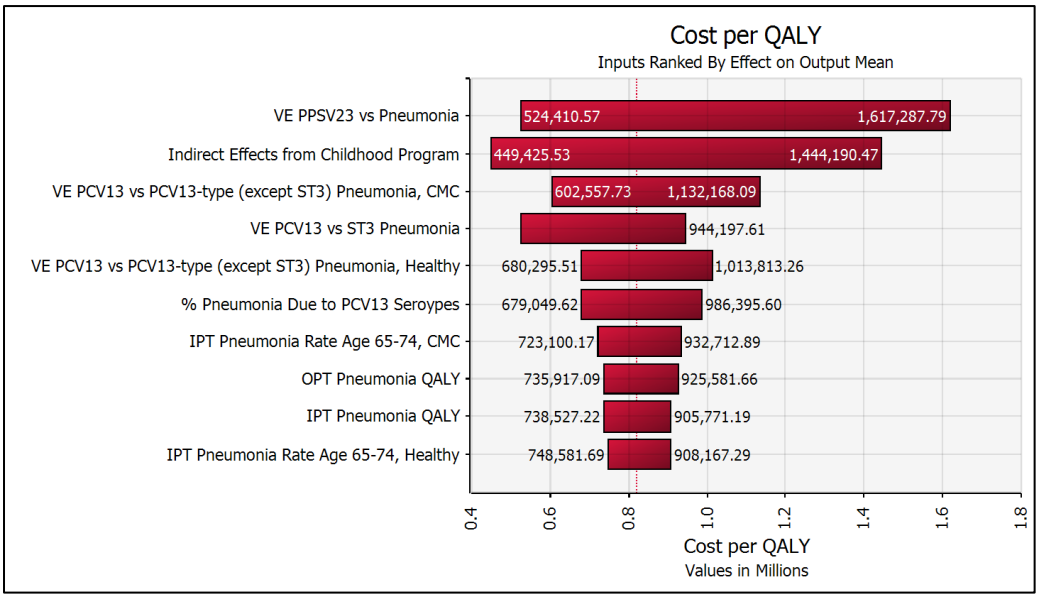
analysis, it was assumed to be at the highest ranges of 26% versus IPD and 45% versus pneumonia. Sensitivity analyses also were performed around the QALY decrements. For the base case, the smaller decrements were utilized: IPD = 0.009 (3 days of perfect health), IPT Pneumonia = 0.006 (2 days), and OPT Pneumonia = 0.004 (1 day). For the sensitivity analyses, much larger QALY decrements were utilized: IPD = 0.075 (27 days of perfect health), IPT Pneumonia = 0.052 (19 days), and OPT Pneumonia = 0.034 (13 days). In the base case, the linear decline to zero between 70-85 years of age was used for PCV13 waning; whereas, the sensitivity analysis used 10% every 5 years. Based on the first two one-way, the cost/QALY would be about $650,000. If the polysaccharide vaccine is assumed to be highly effective against pneumonia, the cost per QALY would be $3.7 million/QALY. However, if PCV is assumed to be effective against serotype 3 at 26% versus IPD and 45% versus pneumonia, the cost/QALY is about $250,000. Looking at the larger QALY decrements, the change was not huge at a cost of about $650,000 to about $560,000. Changing the assumptions about how PCV13 wanes also did not have a very large impact on the cost-effectiveness ratio either.

The model is run 50,000 times to generate multivariate sensitivity analyses and inputs are drawn at random from the distributions. For about 80% of those runs, the cost is some amount less than $1 million/QALY. About 50% of the runs cost some number less than $600,000/QALY. Less than 1% of those runs cost some number less than $200,000/QALY. Here is tornado diagram from the multivariate sensitivity analyses, which shows the relative importance of the assumptions about various inputs into the model:



The width of the bar indicates the impact, with the most important number being the VE of the polysaccharide versus pneumonia. As that number increases, the cost-effectiveness ratio increases. The way to read these bars is that when a number is in either the top or bottom 10% of the possible values for that number, this would be the mean cost-effectiveness ratio for those runs. For instance, when the model draws VE against the poly saccharide vaccine in the 90 percentile and above for that VE, the mean cost-effectiveness ratio among those draws would be $1.6 million/QALY. The next most important input is the impact of the indirect effects from the childhood program. The rest of the inputs deal with pneumonia, indicating that the pneumonia results seem to be driving this model.

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Comparing the results presented in 2014 and the 2018 results, the 2014 analysis after converting to 2017 dollars indicated that the cost/QALY of recommending the conjugate vaccine at age 65 was about $65,000. At the time, it was project that this would rise to nearly $300,000/QALY by 2019. The 2018 analysis just presented indicates that in the base case, the cost would be about $650,000/QALY by 2019. After using some updated numbers, the cost per QALY has increased substantially. In terms of the chief differences between the impacts of the 2014 and 2018 studies, the 2018 study assumes that the indirect effects are about half the size. In the 2014 analysis, it was assumed that the indirect effects were about 7% per year. In the 2018 analysis, the indirect effects were assumed to be about 4.1% per year. The 7% was based on experience from the 7-valent conjugate vaccine, while the 4.1% was based on modeling using actual data since vaccine introduction. The 2018 study assumed that PCV13 is ineffective against serotype 3 in the base case, which was based on a case-control study and observations of disease burden over time. The burden of PCV13-type pneumonia disease was assumed to be half the size in the 2018 study, with the base case assuming burden to be 5.1%. In the 2014 model, the base case assumed the burden to be 10% based on the CAPiTA. The lower incidence was based on a population more relevant to the US. In the 2018 analyses, pneumonia burden was decomposed by risk status using the third study to indicate that the CMC population has a rate about 3 times as high as a healthy population.

Discussion Points

Dr. Raul Isturiz (VP and Regional Head, Pfizer Vaccines Medical) said he wanted to make a comment about one fundamental assumption that was made in this analysis. The lack of effectiveness of PCV13 against serotype 3 disease is probably not accurate. The protectiveness of PCV13 against serotype 3 is not zero in pediatric or adult disease. He shared 4 pieces of data to substantiate this. A meta-analysis just published about all available evidence in Europe and the CDC case-control study published in 2016 estimated the effectiveness against serotype 3 disease to be upwards of 50%. There are three adult pneumococcal pneumonia studies (CAPiTA, Louisville test-negative design study, and a smaller study in Argentina), all of which showed about 50% efficacy of PCV13 vaccine against serotype 3 disease in older adults. In the US, the situation is very interesting. In a different analysis from the one Dr. Pilishvili presented, it can clearly be seen that since the introduction of PCV13 in the childhood program in the US, there has been a steady decrease in cases of serotype 3 IPD of about 60 cases per year for a total of about 480 cases in the last 7 years. At the same time, this has not happened in adults. The disease burden has remained about the same or has increased slightly. There must be a difference, because children <5 years of age have been vaccinated and it is notable that PCV13 does not heavily impact nasopharyngeal carriage of serotype 3. That may explain the lesser perceived efficacy in the population. It is interesting that in countries that do not use PCV13, the increase in serotype 3 increase has been dramatic. This suggests that if PCV13 is not given to adults, the disease burden would be even higher. All-in-all, the available data for effectiveness show direct impact of PCV13 vaccine against serotype 3. This is very important, because the assumption of limited effectiveness of PCV13 has a tremendous impact on the cost/QALY. Using zero in the base case is wrong and misleading.

Dr. Eddy Bresnitz (Merck) commended Dr. Stoecker for the tremendous analysis. A similar comment but on the other side, which would not change the cost-effectiveness analysis as a base case, is the assumption that there is zero effectiveness for PPV23 for non-bacteremic pneumococcal pneumonia. Dr. Stoecker cited the meta-analyses, including Falkenhorst, which was a very comprehensive review. There have been a number of studies published over the last few years since 2014 that basically show that vaccine effectiveness against non-bacteremic pneumococcal pneumonia is not zero. One could argue what it really should be. The sensitivity

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analysis shows that this makes the cost-effectiveness analysis worse. He urged that when the GRADE analysis is presented in February 2019, there is some discussion about those additional studies published since 2014 and some assessment. The methodology is different in these studies, but they do have some value.

Dr. Peter McIntyre (National Centre for Immunisation Research & Surveillance (NCIRS) in Australia) indicated that he is not affiliated with a vaccine company. Consistent with other data, the SNiPP data indicated that about 80% of the identified pneumonia cases occurred in individuals with underlying conditions. The model includes only the incidence amongst those with underlying conditions being double those without; whereas, the proportion occurring in those with underlying conditions suggest that it is somewhat greater than that. That has implications for vaccine policy decisions. In regard to waning, the single best study of efficacy of PPSV23 against IPD found that almost all of the effect had waned within 2 years. Therefore, the waning assumptions may be overly generous. As a general comment, it seems extraordinary there are 2 vaccines that have been in production for more than 20 years and in many cases much longer than that, but the list prices quoted of $200 and $100 respectively seemed quite extraordinary in relation to other vaccines that have been in production for similar periods of time.

In response to the 80%, Dr. Stoecker indicated that they assumed that 66% of pneumonia occurs in the CMC population. That is roughly consistent.

Preliminary EtR and GRADE: Summary and Timetable

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

Dr. Matanock summarized the evidence presented thus far before further discussion. In 2012, ACIP recommended PCV13 in series with PPSV23 for adults ≥19 years old with immunocompromising conditions, asplenia, cochlear implants, or CSF leaks. In 2014, ACIP added an age-based recommendation for PCV13 in series with the previously recommended PPSV23 for all PCV13-naïve adults ≥65 years old. At that time, a commitment was made to re-evaluate and revise this recommendation as needed, for which the time had come.

The current policy question for consideration is, “Should PCV13 be administered routinely to all immunocompetent adults aged ≥65 years given sustained indirect effects?” For the PICO question, the population is immunocompetent adults ≥65 years of age. The intervention is PCV13 at ≥65 years old in series with PPSV23 in the context of indirect effects. The comparison is PPSV23 alone at ≥65 years old. The outcomes are pneumococcal disease and PCV13 safety.

The guide for assembling the evidence is the EtR Framework. During this presentation, Dr. Matanock focused on the statement of problem in terms of why this is a public health priority and the burden of disease. She recapped what has been reviewed so far with regard to the benefits and harms in terms of PCV13 use amongst adults ≥65 years of age. The EtR Framework for the statement of the problem and the benefits and harms were reviewed using GRADE.

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For the GRADE process, the outcomes of IPD, non-invasive pneumococcal pneumonia, and PCV13 safety were reviewed. To measure these outcomes, population trends in disease outcomes, indirect PCV13 effects, and direct PCV13 effects were assessed. In terms of the statement of the problem, IPD incidence has dramatically declined since pediatric PCV13 introduction in 2010. Annual rates of PCV13-type IPD have gone from 14/100,000 in 2010 to 5/100,000 in 2014. This represents a 40% decline. Rates have plateaued since 2014 as Dr. Pilishvili presented. Mortality has not changed since the introduction of PCV13 for pediatrics. Currently, >50% of the remaining PCV13 IPD is caused by serotype 3. Non-PCV13 types have been relatively stable during the time period 2007-2017.

A model that used ABCs IPD rates before and after the 2014 recommendation for older adults to try to separate out direct and indirect effects was presented to ACIP in February 2018. When looking at all PCV-type IPD, including 6C, there were an estimated 192 projected US cases prevented through PCV13 direct effects. This was not statistically significant. Excluding serotype 3, the projected 579 US cases prevented through direct effects are significant.

Looking at direct effects of vaccine efficacy and effectiveness against PCV13-type IPD, only one study was available in 2014 from Bonten. Since then, information was presented to ACIP on two case-control trials. The CAPiTA RCT from Bonten et al estimated an efficacy of 75% against PCV13-type IPD. Using ABCs data with two different methods for obtaining controls, PCV effectiveness against IPD was estimated to be 47% to 59% [[1]Bonten, M. J., et al. (2015). Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med 372(12): 1114-1125].

The majority of the disease burden in older adults is due to non-invasive pneumococcal pneumonia, and the incidence is more difficult to measure than for IPD because there are less standard diagnostic methods. Many studies take a broad approach to measuring pneumonia by looking at all-cause pneumonia, which is estimated to be 630–2,300/100,000. The range is bounded by the Jain[1] and Ramirez[3] studies, in both of which cases of pneumonia were verified by clinical; whereas the other three studies in the middle of this range used ICD codes. Differences in inclusion criteria, primarily of patients with immunocompromising conditions and recent healthcare exposure are included. The ICD codes that define pneumonia likely read to this wide range. When measured with serotype-specific UAT, approximately 5% of all-cause pneumonia in adults ≥65 years of age is caused by PCV13 serotypes[2]. In-hospital case fatality for pneumonia is between 4% to 9%[2]. Again, this is likely dependent upon the patient population [[1] Jain et. al. lowest, Ramirez et. al. highest, also includes Griffin et. al., Hayes et. al., and Simonsen et al; [2]McLaughlin et. al. and Hammitt et al June 2018 ACIP pneumococcal session presentation; [3]Huang reanalysis (unpublished) lowest, [9]Griffin et. al. highest, also includes Huang et. al., Rodrigo et. al., Ramirez et. al., and Hayes et al].

Several studies have measured pneumococcal pneumonia specifically. In a Pfizer-funded study, Simonson used specific pneumococcal pneumonia-related discharge codes. For this reason, they may have under-estimated the incidence since there are likely patients with pneumococcal pneumonia who are discharged with a less specific pneumonia code. The remaining four studies measured pneumococcal pneumonia based on clinical diagnosis. The CAPiTA trial (Bonten) included the incidence of invasive and non-invasive pneumococcal pneumonia amongst vaccinated and unvaccinated patients, but excluded immunocompromised persons. Rodrigo et al measured pneumococcal pneumonia using blood culture, serotype non-specific UAT, and a 14 serotype specific UAT amongst adults admitted with radiographically-confirmed pneumonia to 2 large hospitals in the UK. Healthcare patterns are different in the UK, making comparisons less direct. However, their estimates are close to those of the other studies. Jain et

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al, which excludes both patients admitted in the past month and those with immunocompromising conditions had a low incidence. That estimate was doubled based on a re-analysis of the urine specimens using Pfizer's serotype specific pneumococcal UAT as reported in Wunderink et al, which double the number of cases detected. The results from SNiPP presented earlier in the session, which do not include/exclude previous admissions or immunocompromised individuals, are slightly higher. They include not only adjustments for UAT testing practices, but also include an adjustment for the UAT test sensitivity. Again, this is the clinically available non-serotype specific UAT. Not presented here are the pneumococcal-specific incidence estimates from the Louisville cohort presented by Dr. David Swerdlow during the June 2018 meeting. This study includes only PCV-type pneumonia incidence, not all pneumococcal pneumonia. Some ratios of distribution in IPD can be applied and discussed further, but Dr. Matanock indicated that this is why she did not include this.

In terms of IPD, indirect effects have been observed in most studies which examined rates after pediatric PCV introduction but before 2014. Most studies showed modest declines in all-cause pneumonia after pediatric PCV introduction, but before the 2014 recommendation[1]. The largest effects are seen with more specific codes such as lobar pneumonia[2] and appear to be less consistent in older ages[3]. As presented earlier in the CDC surveillance data, non-invasive pneumococcal pneumonia among those ≥65 years and older decreased between January 2013 and December 2016 during which a 35% relative reduction (95%CI: 14, 49) was observed. This is driven by the decline from 2013 to 2014[4] [[1] Tsaban et. al.; [2] Simonsen et. al., Lessa et. al. October 2018 ACIP; [3] Lessa et. al. presented Oct 2018 ACIP; [4] Gierke et. al. presented Oct 2018 ACIP].

After the 2014 recommendations for older adults, two studies looking at combined indirect and direct effects have been presented to ACIP thus far. The first was presented during the June 2018 ACIP meeting, which showed that PCV13-type pneumonia among those ≥65 years of age decreased by 31% (95%CI: 8.3, 43.9) between June 2014 and May 2016[1]. In SNiPP, non-invasive pneumococcal pneumonia among ≥65 year olds was observed to be decreasing. Post-2014, the time of total effects of the combined direct and indirect effects, a statistically significant decrease in incidence has not been observed[2] [[1] Swerdlow et. al. Jun 2018 ACIP; [2] Gierke et al. presented Oct 2018 ACIP].

Looking at the direct effects through vaccine efficacy and effectiveness against PCV13-type pneumonia, the Bonten study was available in 2014. The CAPiTA RCT estimated efficacy of 45% against PCV-type pneumonia[1]. Since then, a cohort study using a test negative design estimated effectiveness to be 73%[2]. This is the same population that is included in the upper bound of all-cause pneumonia estimates in Ramirez et al [[1]Bonten, M. J., et al. (2015). Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med 372(12): 1114-1125; [2]McLaughlin, J. M., et al. (2018). Effectiveness of 13-Valent Pneumococcal Conjugate Vaccine Against Hospitalization for Community-Acquired Pneumonia in Older US Adults: A Test-Negative Design. Clin Infect Dis. dio 10.1093/cid/ciy312].

For safety, the study submitted for licensing to the FDA showed no difference between treatment groups in serious events, including death[1]. No deaths were considered to be vaccine-related. Since the ACIP recommendation in 2014, an evaluation of VAERS data has been presented and published, as well as a cohort from 6 VSD sites. Neither of these studies detected concerning safety signals [2, 3] [[1]US Food and Drug Administration. *Vaccines and Related Biological Products Advisory Committee (VRBPAC) adult indication briefing document: Prevnar 13.* Silver Spring, MD2011. a. No difference between the treatment groups as measured by risk difference per 1000 (95% CI), b. No deaths were considered vaccine related;

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[2]Haber, P., et al. (2016). Post-licensure surveillance of 13-valent pneumococcal conjugate vaccine (PCV13) in adults aged 19years old in the United States, Vaccine Adverse Event Reporting System (VAERS), June 1, 2012-December 31, 2015. Vaccine 34(50): 6330-6334; [3]Tseng, H. F., et al. (2018). Pneumococcal Conjugate Vaccine Safety in Elderly Adults. Open Forum Infect Dis 5(6): ofy100. c. anaphylaxis relative risk 1.32, but not statistically significant (95%CI 0.2-5.8). All others <1].

The elements still to be addressed in the EtR framework include a summary of additional economic analyses, which are forthcoming alongside Dr. Stoecker's model presented during this session, and these EtR elements:

- ❑ Values and preferences of target population
- ❑ Acceptability to stakeholders
- ❑ Resource use
  - ➢ Health economic analyses
- ❑ Feasibility
  - ➢ Implementation considerations

In terms of the tentative timeline, a completed GRADE analysis is anticipated to be ready for the February 2019 meeting, including the results of outstanding pneumonia studies and a completed EtR Framework. A vote is anticipated in either February or June 2019 depending upon ACIP's feedback and deliberations.

In conclusion, Dr. Matanock reminded everyone that the policy question under consideration is, "Should PCV13 be administered routinely to all immunocompetent adults aged ≥65 years in a setting of sustained PCV13 indirect effects?" She asked ACIP to consider the following question for this discussion and going forward:

Which domains of the EtR framework warrant additional exploration regarding continued use of PCV13 in immunocompetent adults ≥65 years?

- ❑ Benefit, risks
- ❑ Values
- ❑ Acceptability
- ❑ Resource use
- ❑ Feasibility

Discussion Points

Dr. Atmar pointed out that generally speaking, part of the framework is to reach a conclusion about benefits and harms. ACIP will ultimately have to deliberate that component, but he wondered whether the WG had any preliminary discussions about assessments to date and/or what data the WG is awaiting to make such an assessment.

Dr. Lee replied that it has been a challenge, in part because there is so much uncertainty, particularly with regard to pneumonia burden and the proportion due to PCV13 serotypes. The harms have been more straightforward. In addition to that, thinking about the effectiveness of these vaccines on the pneumonia burden reduction and disentangling the direct versus indirect effects has been a challenge. The WG is careening toward that conversation, and some of the challenge will be ensuring that they have consensus. They hope during the next ACIP meeting

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to be able to share a clearer sense of the degree of uncertainty, as well as the benefit/risk balance.

Dr. Hunter added that all of the controversy and discussion in the WG has been very educational. As his role within local governmental public health is translating public health policy into clinical practice, it is going to be quite a challenge to explain all of this to clinicians. He thinks the way to prepare clinicians for understanding the issue it to emphasize the dramatic and terrific indirect effects that have occurred already by vaccinating children. They should be educating everyone about that publicly and widely.

To set the stage, Dr. Messonnier said that CDC recognizes that this is a complicated decision and is why they are so happy to have ACIP wrestling with it with them. Part of the intentionality with the way this is presented is to give ACIP time to mull it over. The WG obviously sits with this a lot longer and a lot more directly, but part of the pace question is for ACIP members to think about what they are seeing and how quickly they are seeing it. They have to have in the back of their minds all of the data the WG has presented over the course of the past year. They have struggled with how much data to present at a single time to make sure that it is fresh in their minds as they try to wrestle with an issue that is going to require judgment. In this situation, the evidence is not all consistent. She invited everyone to provide any advice for the WG and CDC leads about additional information and context that would help, which they certainly would appreciate.

Dr. Romero said that for more clarity, it would be helpful to have more information about the impact of serotype 3. There is a spectrum—a spread of nothing to 13% to 14%. Somewhere in between lies the truth. A better handle on that would aid him in coming to a decision.

Dr. Lee replied that the degree of uncertainly around some of the estimates is why they have struggled. She commended Dr. Stoecker for doing a phenomenal job of accommodating the range of opinions on the WG calls over time to try to come up with a base case estimate. It is difficult to know what the exact right answer is, but the purpose of the sensitivity analyses for the WG was to be able to understand how much that really impacts the understanding of burden that is preventable in addition to cost-effectiveness.

In response to an inquiry posed about whether there would be more data from later years on direct effects, Dr. Matanock said there are plans to look at pneumonia discharges post-2014 and trying to tease out the direct effect. There was discussion about perhaps looking further out at the SNiPP that Dr. Gierke presented during this session. Other than that, she was not aware of any upcoming information on direct effects.

Dr. Schmader (AGS) pointed out that everyone knows that the health states of individuals 65 years of age and above are widely heterogeneous from fit to frail and dependent to independent, so it is hard to generalize. He emphasized the importance of keeping that principle in mind when interpreting epidemiology data and impact of the vaccine on outcomes. At one level, it would be very useful to routinely report older age groups in the incidence data as 80 year olds are different from 60 years. He congratulated Dr. Lessa for showing 75 years of age and above. The WG also should consider whether the vaccine will have a beneficial impact on subgroups. Perhaps this is useful in frail and functionally impaired individuals or vice versa.

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Dr. Ezeanolue asked whether he heard correctly that after the 2014 recommendation, the uptake of the recommendation was about 40% and if that has remained steady since 2014.

Dr. Matanock replied that she did not have the exact number with her, there has been a gradual and continued increase. However, the slope of the curve may not be as great as it was in 2016.

Dr. Bresnitz (Medical Director, Merck) asked whether the WG would be presenting an update on the data on real world series completion to date, which informs the discussion as well in terms of policy-making.

Dr. Matanock indicated that they could include that information for the February 2019 meeting.

Dr. Moore thought it would be helpful to know about anything in the pipeline with regard to PCV13 and whether to continue its use that ACIP should be considering.

Dr. Luis Jodar (Chief Medical Officer, Pfizer Vaccines) reported that Pfizer is developing a 20-valent vaccine. They have interactions with CDC on progress on the clinical development program, through which they will make decisions about presenting that in February 2019 as well so the ACIP members have the context on when next generation pneumococcal conjugate vaccines are likely to be available.

Dr. Bresnitz (Medical Director, Merck) reported that Merck is working on an expanded PCV15 serotype vaccine.

Dr. Cohn said it was her sense from ACIP was that they felt that they may need additional time to deliberate past February 2019, depending upon the data presented.

Adult Immunization Schedule

Introduction

Paul Hunter, MD
Chair, Adult Immunization Work Group
Advisory Committee on Immunization Practices

Dr. Hunter began by thanking Dr. Laura Riley on behalf of the WG. She was an ACIP voting member from 2014 to 2018 and chaired the Adult Immunization WG from 2016 to 2018. As Vice Chair of Obstetrics and Medical Director of Labor and Delivery at Massachusetts General Hospital, she championed immunizations for pregnant women and frequently reminded ACIP colleagues to try to make vaccination work for the busy clinician. She is even busier herself now with her recent appointments as Chair of the Department of Obstetrics and Gynecology at Weill Cornell Medicine and Chief of Obstetrics at New York-Presbyterian/Weill Cornell Medical Center.

The ACIP Adult Immunization WG meets monthly to update the adult immunization schedule each year. Each adult immunization schedule update, along with the child and adolescent immunization schedule update, represents current, approved ACIP policy and is designed for clinicians to implement in clinical practice with individual patients. As with other ACIP

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recommendations, the adult immunization schedule is forwarded to the CDC Director for approval. In addition, the adult schedule is sent to the following partner professional medical organizations for approval:

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

The approved adult immunization schedule is then posted on the ACIP website and an announcement of its availability is published in the *MMWR* in early February. The adult immunization schedule also is published in its entirety in the *Annals of Internal Medicine* in February. Few ACIP updates in adult immunization were published since the 2018 adult schedule was recommended by the ACIP and approved in October 2017. Adjuvanted hepatitis B vaccine was voted on in February and published in the *MMWR* in April. The Tdap summary published in April did not change any recommendations for adults, although there were a few changes for children and adolescents. As usual, the annual influenza recommendation was voted on in June and published in August. This included the vote from February bringing back live attenuated influenza vaccine (LAIV) as an option this season. The addition of homelessness as an indication for HepA that was just voted on will be incorporated in the adult schedule when it is published in February 2019.

Several formatting changes were proposed to increase the usability of the schedule in clinical practice. The 2018 adult immunization schedule was formally evaluated for usability over the past year and a half. The evaluation process consisted of conducting in-depth interviews of health care professionals who reported routinely using the adult immunization schedule. The appearance of the graphics and text of the schedule were redesigned based on these interviews. Feedback on this new design was collected from healthcare professionals by conducting a survey to assess their reactions and preferences. In addition, the WG and CDC SMEs reviewed the current “no recommendation” white spaces in the adult schedule. These white spaces occur for several vaccines in the pregnancy column in Figure 2 of the 2018 adult schedule. This column has been updated in the draft 2019 adult schedule.

Several vaccination recommendations overlap between the adult and child and adolescent schedules. The Adult Immunization WG collaborated closely with the Child and Adolescent Immunization WG, SMEs, and others to harmonize the language and graphics for these recommendations.

During the remainder of this session, Dr. David Kim provided a summary of the usability testing on the 2018 adult schedule, an update on the pregnancy column in Figure 2 of the 2018 adult schedule, a summary of the effort to harmonize the adult schedule with the child and adolescent schedule, and the proposed draft 2019 adult immunization schedule to highlight the major changes.

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Adult Immunization Schedule

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

Dr. Kim provided updates in the ACIP recommendations pertinent to the adult schedule, noting that he would spend the bulk of his time going over the schedule evaluation project that was recently completed. Although the evaluation project started as a usability test of the adult immunization schedule, it later also included a review and changes for the child and adolescent schedule.

The ACIP assembled the first adult schedule in 2002 and it has been updated annually since then. Though frequently cited for being useful, the adult schedule has been criticized for being difficult to read due to a number of reasons. In response, in 2016, an ad hoc evaluation was conducted on the adult schedule to improve its usability by integrating principles of human factors and ergonomics[1]. Extensive additional updates were done on the footnotes of the 2017 and 2018 adult schedules to standardize and simplify the text. These efforts were presented to the ACIP in past meetings. Over the past year and a half, a formal evaluation was conducted of the 2018 adult immunization schedule for usability[2]. That project was completed just two months ago [[1]Chen D et al. Improving the U.S. adult immunization schedule by applying usability principles. Proceed Human Factors Ergonom Soc Ann Meet 2018;62:1316–1320; [2]Porter-Novelli Public Services, Inc. Contract number 200–2015–F–88117].

The purpose of the evaluation project was to determine how providers use the adult schedule to guide their clinical immunization practices and identify improvements to increase its usability. The plan centered around three activities: 1) in-depth, qualitative interviews conducted with health care providers who reported being familiar with the adult schedule; 2) redesign of the adult schedule based on their feedback; and 3) administration of a survey to providers to get their reactions and preferences. Dr. Kim described the results of each of these activities.

A total of 48 in-depth interviews were conducted with internists, family physicians, physician assistants and nurse practitioners, nurses, medical assistants, and pharmacists. They were screened for their familiarity with the adult schedule (i.e., they reported using the adult schedule at least once per week). These interviews, each lasting an hour, included how they used the adult schedule as they worked through case-based patient scenarios. Among other findings, it was determined that most providers who professed to being expert users of the adult schedule actually did not know how to use it. Most reported using Figure 1, the table of immunization recommendations by age, and that was it. Few reported using Figure 2, the immunization recommendations by medical condition and other indications. Few reported using the footnotes to help guide their immunization practice.

Dr. Kim said that an ex-champion boxer once famously said, “Everybody has a plan until they get punched in the mouth.” Their carefully laid plan was basically bludgeoned, given that the rest of the evaluation plan was contingent on the results of the first activity. However, driven by this inspiring passage that Dr. Kim said was cherry-picked for effect from “Invictus” by the English poet William Ernest Henley, they forged ahead though they “winced and cried out loud.”

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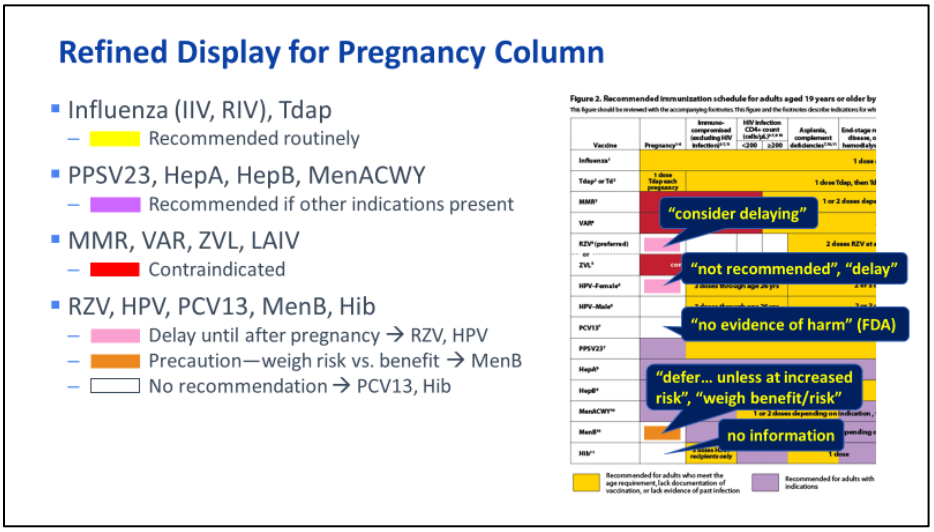
Drama aside, though they had little concrete evidence to go with, the WG developed a prototype graphic based on their collective assumptions. They kept the adult schedule's overall format and flow to maintain providers' familiarity with it. They tried a more neutral set of colors in the schedule for effect, reduced the overall amount of information on the cover page, and compartmentalized the text for easy location. They included trade names for easy reference. Given the extensive nature of the text associated with each vaccination section, they replaced "footnotes" with "notes" and re-ordered them alphabetically because they were no longer numbered. "Figures" were replaced by "Tables" though the graphics remained the same. Lastly, the Table of Contraindications and Precautions was removed from the adult schedule, and the extra space was used to make the notes easier to read.

Armed with the original 2018 schedules and redesigned draft schedules, the WG proceeded with the third activity and surveyed a panel of about 250 internists and family physicians on the adult schedule and another panel of about 250 pediatricians and family physicians on the child and adolescent schedule. The respondents were asked about their impressions and perceptions on usability. The 2018 adult schedule cover page and the redesigned cover page based on 2018 adult schedule were compared. Similar comparisons were made for the child and adolescent schedule. The survey results were similar for both the adult, and child and adolescent schedules. Overall, survey respondents preferred the redesigned cover page and original color scheme, and recommended that the font size be bigger.

The WG's past chair, Dr. Laura Riley, was and remains a strong champion for immunizing pregnant women, and advocated a simple and strong message for them. But, the graphic display for vaccines for pregnant women has a lot of white space, indicating that there are no recommendation for these vaccines. The vaccines in question on the adult schedule are: recombinant zoster, human papillomavirus, pneumococcal conjugate, serogroup B meningococcal, and *H. flu* vaccines. The WG reviewed ACIP policy statements and package inserts for these vaccines and collaborated with SMEs to look for a better way to present the information in the adult schedule. Based on available information, the WG adopted the following display for the pregnancy column on the adult schedule (and the child and adolescent schedule):



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The inactivated and recombinant influenza vaccines and Tdap are, as before, represented by yellow blocks (or recommended routinely). PPSV23, HepA, HepB, and MenACWY remain purple (or recommended if another medical condition or condition is present). The live vaccines, MMR, VAR, and ZVL, and now LAIV, are contraindicated and represented by red blocks. In the adult schedule, two new color blocks were added: pink for "delay vaccination until after pregnancy" and orange for "precaution—vaccine might be indicated if benefit of protection outweighs risk of adverse reaction." RZV and HPV were given the pink (or delay) designation. MenB, though it has a "delay" component along with "precaution," has an orange (or precaution) designation. Discussions on the use of PCV13 in pregnancy will be taken up by the Pneumococcal WG, and kept as "no recommendation" for the time being. Hib vaccines simply have no information available for pregnancy and will continue to have "no recommendation" designation.

Dr. Kim mentioned that, in June 2018, Dr. Kevin Ault, one of the new ACIP members, penned maternal immunization recommendations on behalf of the American College of Obstetricians and Gynecologists (ACOG). This is ACOG's maternal immunization summary table:

Table 1. Summary of Maternal Immunization Recommendations — **ACOG Committee Opinion, 2018**

Vaccine*	Indicated During Every Pregnancy	May Be Given During Pregnancy in Certain Populations	Contraindicated During Pregnancy	Can Be Initiated Postpartum or When Breastfeeding or Both
Inactivated influenza	X[†,1,2]			X[‡]
Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap)	X[†,3,4]			X[‡]
Pneumococcal vaccines		X[§,5,6]		X[§,5,6]
Meningococcal conjugate (MenACWY) and Meningococcal serogroup B		X[‖,7]		X[‖,7]
Hepatitis A		X[¶,8]		X[¶,8]
Hepatitis B		X[#,9,10]		X[#,9,10]
Human papillomavirus (HPV)**				X[**,11,12]
Measles–mumps–rubella			X[††,13,14]	X[††]
Varicella			X[††,13,15,16]	X[††]

*An "X" indicates that the vaccine can be given in this window. See the corresponding numbered footnote for details.

Maternal immunization. ACOG Committee Opinion No. 741. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;131:e214–217

If the summary table of ACOG recommendations is overlapped with the color scheme of the proposed adult immunization for pregnancy, they align very nicely. One difference is that the footnote for pneumococcal vaccination in the ACOG's table describes that PCV13 should be deferred in a pregnant woman unless she is at increased risk for disease and benefits of vaccination outweigh risks. On the adult schedule, a decision is pending review by the ACIP Pneumococcal WG as mentioned earlier.

A lot of effort went into standardizing and harmonizing the notes with the child and adolescent schedule. In addition to the changes mentioned earlier, the titles of the documents were shortened; the notes were organized and revised for brevity, clarity, and consistency; and the text was shortened as long as the meaning was not compromised.

The cover page features a shortened title, simple instructions on how to use the schedule, a list of vaccines, including trade names of vaccines, and compartmentalized supporting information for easy reference. Also, an additional helpful resource and reference on vaccine-preventable disease case identification and outbreak response has been added:

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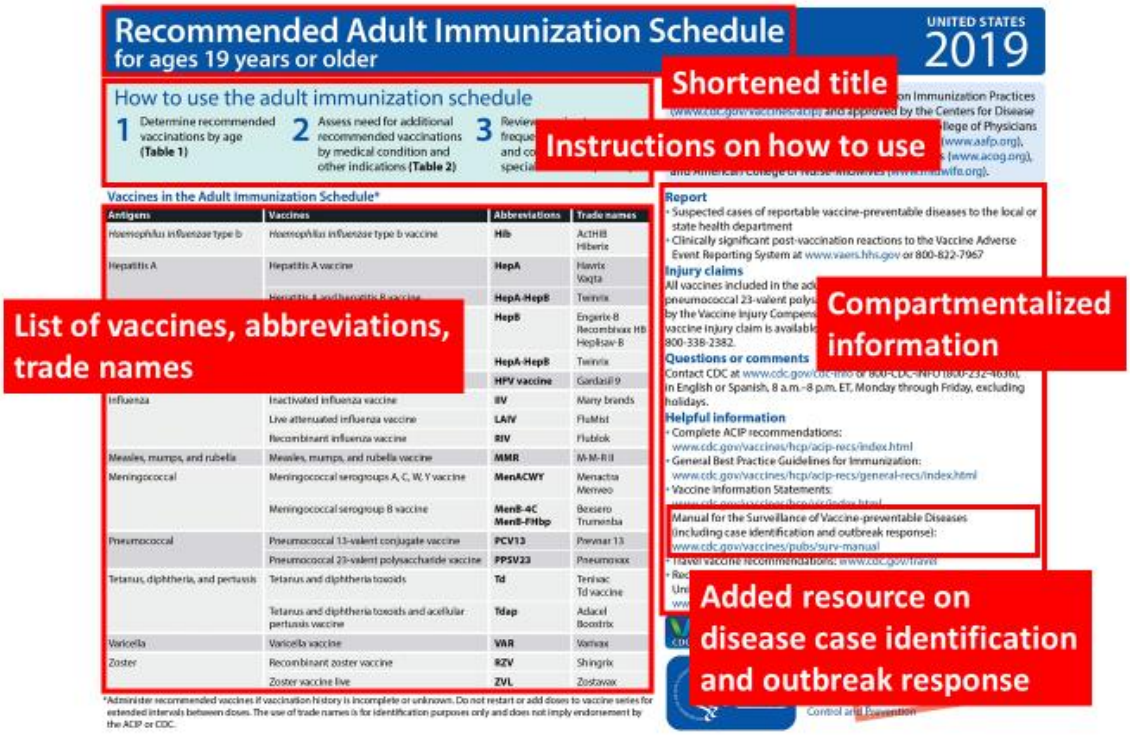
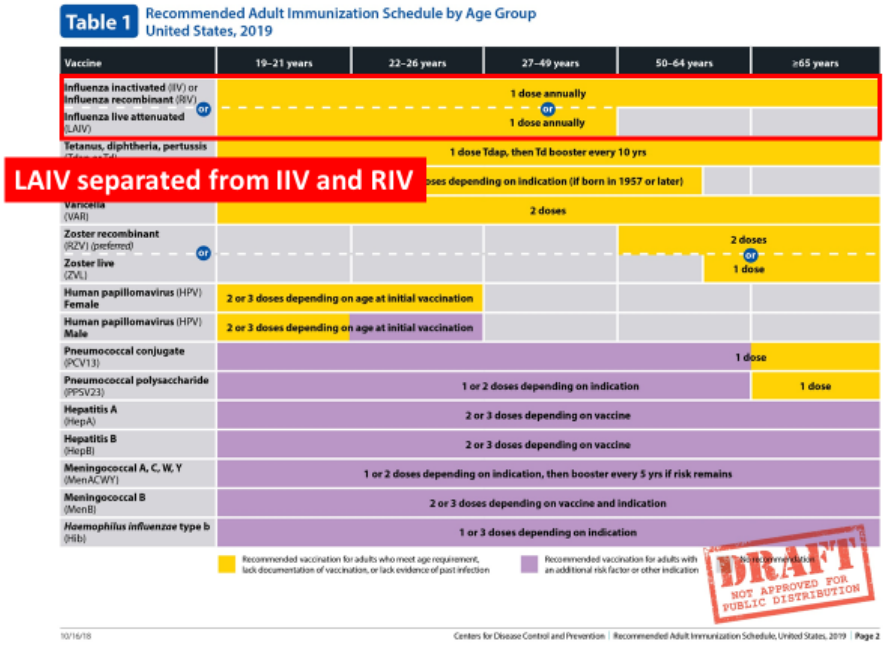


Next is Table 1, the recommended adult schedule by age. One major change in the 2019 graphic is the separation of LAIV from other influenza vaccines because it is a live vaccine:



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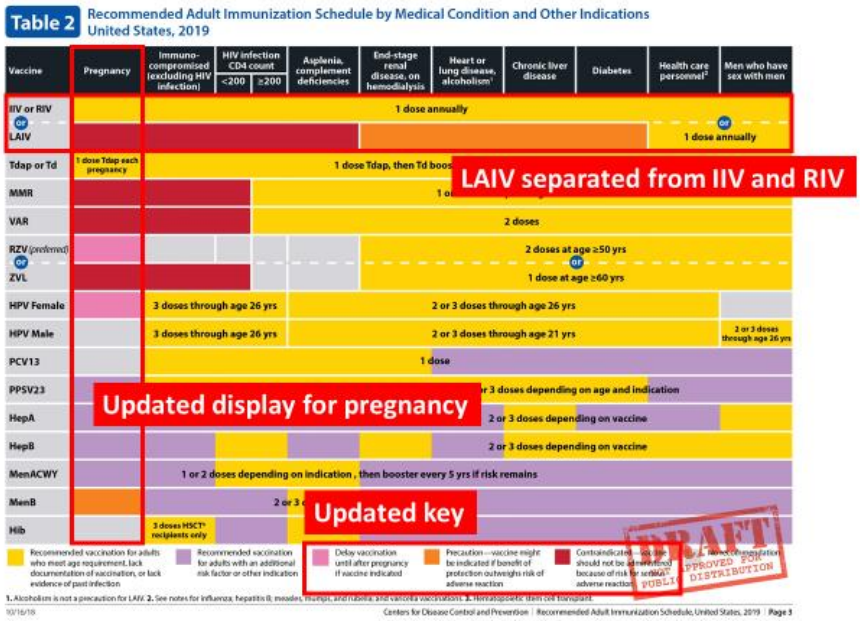
Next is Table 2, the recommended adult schedule by medical condition and other indications:



First, the keys for Table 2 have been updated to introduce the two new colors: pink for “delay vaccination until after pregnancy if the vaccine is indicated” and orange for “precaution—vaccine might be indicated if the benefit of protection outweighs risk of adverse reaction.” The key for the red “contraindicated” now includes more information to separate it from the orange “precaution” and includes the text “vaccine should not be administered because of risk for serious adverse reaction.” As in Table 1, LAIV has been teased away from other influenza vaccines. As a live vaccine, LAIV is displayed as contraindicated in pregnancy, immunocompromising conditions, including HIV infection, and asplenia. LAIV has also been designated as “precaution” for use in end-stage kidney disease; chronic heart, lung, and liver diseases; and diabetes. As described earlier, the pregnancy column in Table 2 displays updated vaccination information.

In addition to the changes in graphics, there are some content edits. In the notes section, the following content changes have been made. Because outbreak responses pertaining to vaccination are decided and coordinated by public health authorities, and vaccination service providers are likely not making outbreak response decisions, indications for vaccinating adults in outbreak settings have been removed in the adult schedule. On the first page of the notes, the use of HepA and HepB in outbreak responses have been deleted. Dr. Kim noted that a resource on vaccine-preventable disease case identification and outbreak response has been added to the cover page under “helpful information.” As was voted on earlier in the day, homelessness as an indication for HepA has been added. Next, the new 2-dose series cytosine-phosphate-guanine-adjuvanted HepB vaccine has been added to the adult schedule. For HPV vaccination, “transgender persons” through age 26 years has been added to receive a 2- or 3-dose vaccination series, depending upon the age at their series initiation. For influenza vaccination on the second page of the notes, LAIV was added back to the adult schedule as an option. Information on when not to use LAIV also was added. Like the removal of notes on the use of HepA and HepB in outbreak settings, the use of a third dose of MMR in mumps outbreaks and MenACWY and MenB in meningococcal outbreaks have been removed. As mentioned earlier,

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the use of MenB in pregnancy has been updated to “precaution—vaccine might be indicated if the benefit of protection outweighs the risk of adverse reaction.” Lastly, on the third page of the notes, the use of RZV in pregnancy has been updated to delay vaccination until after pregnancy. Also, the provider is informed that the use of RZV in severely immunocompromised adults is currently under review.

Child and Adolescent Immunization Schedule

Introduction

Henry Bernstein, DO, MHCM, FAAP
Chair, Child and Adolescent Immunization Work Group

Dr. Bernstein introduced this session on behalf of Child and Adolescent Immunization Schedule WG. He reminded everyone that the schedule is presented for a vote every fall, given that the ACIP’s approval is necessary prior to publication of the schedule in the *MMWR* in January or February of the following year. ACIP’s approval also is necessary before its partners (AAP, AAFP, and ACOG) review and approve the schedule. He emphasized that no new policy is established by the schedule. It simply reflects the recommendations already approved by ACIP. Dr. Bernstein indicated that for the remainder of this presentation, Dr. Robinson would highlight harmonization between the child/adolescent and adult schedules; edits to all tables; and content changes to the notes for HepA, HepB, IPV, MMR, meningococcal, and Tdap. These edits are intended to incorporate ACIP recommendations and *MMWR* publications that have occurred since October 2017, and improve readability and utility of the schedule. He explained that the session would conclude with discussion of the proposed edits and a vote for both the child/adolescent and adult schedules.

Child and Adolescent Immunization Schedule 2019

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

Dr. Robinson reviewed the updates for the 2019 Child and Adolescent Immunization Schedule, which was updated to reflect recommendations published or voted upon regarding influenza vaccination and the use of LAIV, HepA vaccination and homelessness as an indication for vaccination, HepB vaccination with the use of CpG-adjuvanted HepB vaccine, and Tdap vaccination regarding vaccination of persons who received Tdap at 7 through 10 years of age. Changes that impact multiple portions of the schedule include the adoption of the updated immunization schedule graphics demonstrated in the adult presentation, and minor edits throughout the notes section to improve harmonization between the Child and Adolescent and Adult Immunization Schedules.

For the cover page, the Child and Adolescent Schedule has adopted an updated title and the color scheme for this schedule is purple so that it is readily distinguishable from the adult schedule by any provider. The table of vaccine abbreviations and trade names remains on the cover, though the appearance has been updated. A box with instructions outlining how to use the schedule has been added to the cover, and there are four sections for Tables 1, 2, and 3

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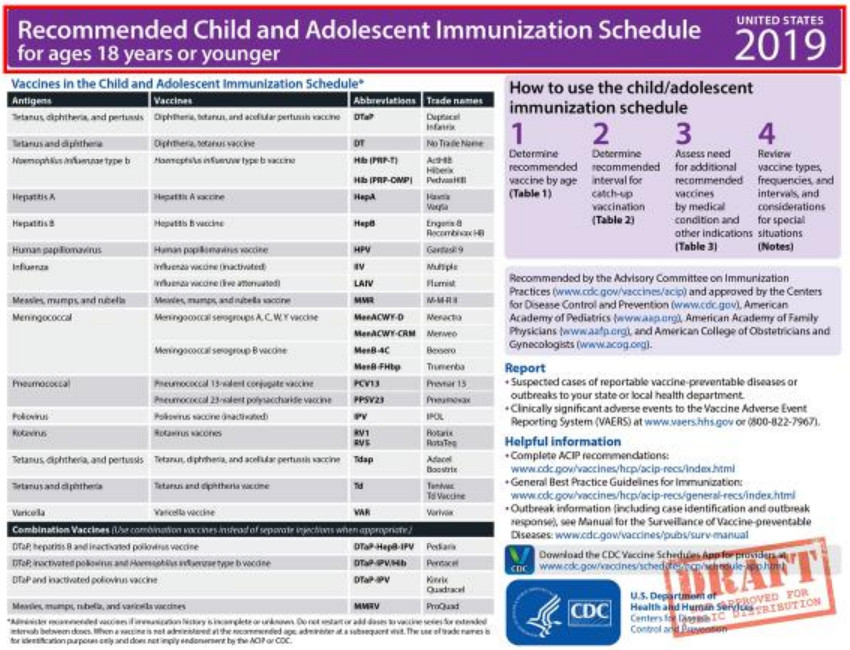
and the notes. A section with helpful information and resource links also has been added, including a link for outbreak guidance:



Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger — UNITED STATES 2019

Vaccines in the Child and Adolescent Immunization Schedule*

Antigens	Vaccines	Abbreviations	Trade names
Tetanus, diphtheria, and pertussis	Diphtheria, tetanus, and acellular pertussis vaccine	DTaP	Daptacel Infanrix
Tetanus and diphtheria	Diphtheria, tetanus vaccine	DT	No Trade Name
Haemophilus influenzae type b	*Haemophilus influenzae* type b vaccine	Hib (PRP-T) Hib (PRP-OMP)	ActHIB Hiberix PedvaxHIB
Hepatitis A	Hepatitis A vaccine	HepA	Havrix Vaqta
Hepatitis B	Hepatitis B vaccine	HepB	Engerix-B Recombivax HB
Human papillomavirus	Human papillomavirus vaccine	HPV	Gardasil 9
Influenza	Influenza vaccine (inactivated)	IIV	Multiple
	Influenza vaccine (live attenuated)	LAIV	FluMist
Measles, mumps, and rubella	Measles, mumps, and rubella vaccine	MMR	M-M-R II
Meningococcal	Meningococcal serogroups A, C, W, Y vaccine	MenACWY-D MenACWY-CRM	Menactra Menveo
	Meningococcal serogroup B vaccine	MenB-4C MenB-FHbp	Bexsero Trumenba
Pneumococcal	Pneumococcal 13-valent conjugate vaccine	PCV13	Prevnar 13
	Pneumococcal 23-valent polysaccharide vaccine	PPSV23	Pneumovax
Poliovirus	Poliovirus vaccine (inactivated)	IPV	IPOL
Rotavirus	Rotavirus vaccines	RV1 RV5	Rotarix RotaTeq
Tetanus, diphtheria, and pertussis	Tetanus, diphtheria, and acellular pertussis vaccine	Tdap	Adacel Boostrix
Tetanus and diphtheria	Tetanus and diphtheria vaccine	Td	Tenivac Td Vaccine
Varicella	Varicella vaccine	VAR	Varivax
Combination Vaccines *(Use combination vaccines instead of separate injections when appropriate.)*			
DTaP, hepatitis B and inactivated poliovirus vaccine		DTaP-HepB-IPV	Pediarix
DTaP, inactivated poliovirus and *Haemophilus influenzae* type b vaccine		DTaP-IPV/Hib	Pentacel
DTaP and inactivated poliovirus vaccine		DTaP-IPV	Kinrix Quadracel
Measles, mumps, rubella, and varicella vaccines		MMRV	ProQuad

*Administer recommended vaccines if immunization history is incomplete or unknown. Do not restart or add doses to vaccine series for extended intervals between doses. When a vaccine is not administered at the recommended age, administer at a subsequent visit. The use of trade names is for identification purposes only and does not imply endorsement by the ACIP or CDC.

How to use the child/adolescent immunization schedule

1. Determine recommended vaccine by age **(Table 1)**
2. Determine recommended interval for catch-up vaccination **(Table 2)**
3. Assess need for additional recommended vaccines by medical condition and other indications **(Table 3)**
4. Review vaccine types, frequencies, and intervals, and considerations for special situations **(Notes)**

Recommended by the Advisory Committee on Immunization Practices (www.cdc.gov/vaccines/acip) and approved by the Centers for Disease Control and Prevention (www.cdc.gov), American Academy of Pediatrics (www.aap.org), American Academy of Family Physicians (www.aafp.org), and American College of Obstetricians and Gynecologists (www.acog.org).

Report
- Suspected cases of reportable vaccine-preventable diseases or outbreaks to your state or local health department.
- Clinically significant adverse events to the Vaccine Adverse Event Reporting System (VAERS) at www.vaers.hhs.gov or (800-822-7967).

Helpful information
- Complete ACIP recommendations: www.cdc.gov/vaccines/hcp/acip-recs/index.html
- General Best Practice Guidelines for Immunization: www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html
- Outbreak information (including case identification and outbreak response), see Manual for the Surveillance of Vaccine-preventable Diseases: www.cdc.gov/vaccines/pubs/surv-manual

Download the CDC Vaccine Schedules App for providers at www.cdc.gov/vaccines/schedules/hcp/schedule-app.html

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Here is the new graphical presentation of Table 1, the routine immunization schedule:

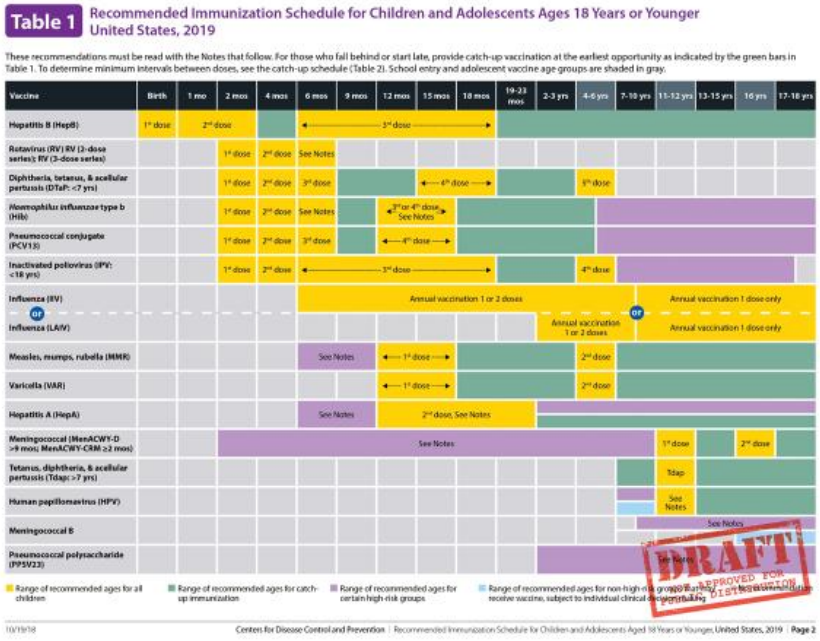

Table 1 Recommended Immunization Schedule for Children and Adolescents Ages 18 Years or Younger United States, 2019

These recommendations must be read with the Notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Table 1. To determine minimum intervals between doses, see the catch-up schedule (Table 2). School entry and adolescent vaccine age groups are shaded in gray.

Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19-23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13-15 yrs	16 yrs	17-18 yrs
Hepatitis B (HepB)	1st dose	2nd dose			3rd dose												
Rotavirus (RV) RV (2-dose series); RV (3-dose series)			1st dose	2nd dose	See Notes												
Diphtheria, tetanus, & acellular pertussis (DTaP: <7 yrs)			1st dose	2nd dose	3rd dose			4th dose				5th dose					
Haemophilus influenzae type b (Hib)			1st dose	2nd dose	See Notes		3rd or 4th dose, See Notes										
Pneumococcal conjugate (PCV13)			1st dose	2nd dose	3rd dose		4th dose										
Inactivated poliovirus (IPV: <18 yrs)			1st dose	2nd dose	3rd dose							4th dose					
Influenza (IIV)					Annual vaccination 1 or 2 doses									Annual vaccination 1 dose only			
OR														OR			
Influenza (LAIV)											Annual vaccination 1 or 2 doses			Annual vaccination 1 dose only			
Measles, mumps, rubella (MMR)					See Notes		1st dose					2nd dose					
Varicella (VAR)							1st dose					2nd dose					
Hepatitis A (HepA)					See Notes		2nd dose, See Notes										
Meningococcal (MenACWY-D >9 mos; MenACWY-CRM ≥2 mos)			See Notes											1st dose		2nd dose	
Tetanus, diphtheria, & acellular pertussis (Tdap: >7 yrs)														Tdap			
Human papillomavirus (HPV)														See Notes			
Meningococcal B														See Notes			
Pneumococcal polysaccharide (PPSV23)														See Notes			

Range of recommended ages for all children — Range of recommended ages for catch-up immunization — Range of recommended ages for certain high-risk groups — Range of recommended ages for non-high-risk groups that may receive vaccine, subject to individual clinical decision-making

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As noted by Dr. Kim earlier, the footnotes will be presented unnumbered and in alphabetical order. Therefore, the superscript notes that previously directed the user to the footnotes have been removed from Table 1. All places that previously referred to a numbered footnote now simply say, “See Notes.” Within the influenza row, LAIV has been separated from inactivated

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influenza vaccine (IIV). In the HepA row, a purple bar has been added for those 6 through 12 months of age to indicate the recommendation for use in infants who are traveling to an area of high or intermediate HepA endemicity. This mirrors the similar bar in the MMR row.

For Table 2, the catch-up table, the graphical appearance has been updated. In addition, the order of information in the Hib and pneumococcal conjugate rows has been edited for clarity. Now the criteria under which no further doses are needed is presented first, followed by recommendations for those in whom additional doses are indicated:

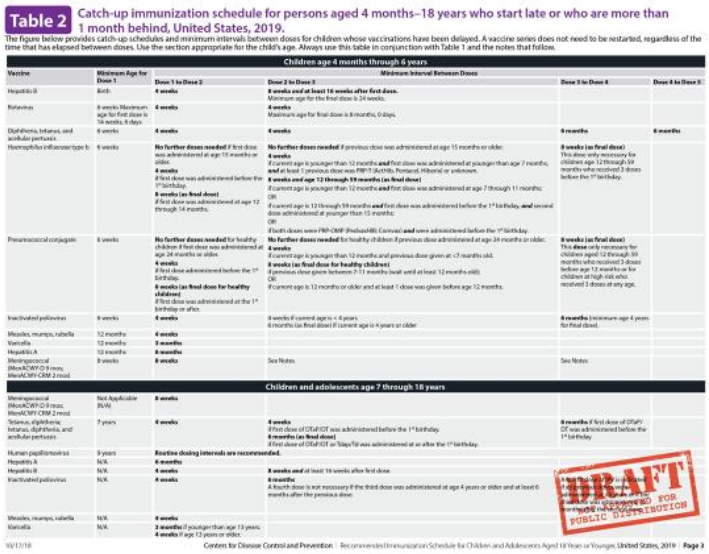

Table 2 Catch-up immunization schedule for persons aged 4 months–18 years who start late or who are more than 1 month behind, United States, 2019.

The figure below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. Always use this table in conjunction with Table 1 and the notes that follow.

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses: Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Children age 4 months through 6 years					
Hepatitis B	Birth	**4 weeks**	**8 weeks and at least 16 weeks after first dose.** Minimum age for the final dose is 24 weeks.		
Rotavirus	6 weeks Maximum age for first dose is 14 weeks, 6 days	**4 weeks**	**4 weeks** Maximum age for final dose is 8 months, 0 days.		
Diphtheria, tetanus, and acellular pertussis	6 weeks	**4 weeks**	**4 weeks**	**6 months**	**6 months**
Haemophilus influenzae type b	6 weeks	**No further doses needed** if first dose was administered at age 15 months or older. **4 weeks** if first dose was administered before the 1st birthday. **8 weeks (as final dose)** if first dose was administered at age 12 through 14 months.	**No further doses needed** if previous dose was administered at age 15 months or older. **4 weeks** if current age is younger than 12 months **and** first dose was administered at younger than age 7 months, **and** at least 1 previous dose was PRP-T (ActHib, Pentacel, Hiberix) or unknown. **4 weeks and age 12 through 59 months (as final dose)** if current age is younger than 12 months **and** first dose was administered at age 7 through 11 months; OR if current age is 12 through 59 months **and** first dose was administered before the 1st birthday, **and** second dose administered at younger than 15 months; OR if both doses were PRP-OMP (PedvaxHIB; Comvax) **and** were administered before the 1st birthday.	**8 weeks (as final dose)** This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday.	
Pneumococcal conjugate	6 weeks	**No further doses needed** for healthy children if first dose was administered at age 24 months or older. **4 weeks** if first dose administered before the 1st birthday. **8 weeks (as final dose for healthy children)** if first dose was administered at the 1st birthday or after.	**No further doses needed** for healthy children if previous dose administered at age 24 months or older. **4 weeks** if current age is younger than 12 months and previous dose given at <7 months old. **8 weeks (as final dose for healthy children)** if previous dose given between 7-11 months (wait until at least 12 months old); OR if current age is 12 months or older and at least 1 dose was given before age 12 months.	**8 weeks (as final dose)** This **dose** only necessary for children aged 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age.	
Inactivated poliovirus	6 weeks	**4 weeks**	4 weeks if current age is < 4 years. 6 months (as final dose) if current age is 4 years or older	**6 months** Minimum age 4 years for final dose.	
Measles, mumps, rubella	12 months	**4 weeks**			
Varicella	12 months	**3 months**			
Hepatitis A	12 months	**6 months**			
Meningococcal (MenACWY-D 9 mos; MenACWY-CRM 2 mos)	6 weeks	**8 weeks**	See Notes	See Notes	
Children and adolescents age 7 through 18 years					
Meningococcal (MenACWY-D 9 mos; MenACWY-CRM 2 mos)	Not Applicable (N/A)	**8 weeks**			
Tetanus, diphtheria, tetanus, diphtheria, and acellular pertussis	7 years	**4 weeks**	**4 weeks** if first dose of DTaP/DT was administered before the 1st birthday. **6 months (as final dose)** if first dose of DTaP/DT or Td/aP/Td was administered at or after the 1st birthday.	**6 months** if first dose of DTaP/DT was administered before the 1st birthday.	
Human papillomavirus	9 years	**Routine dosing intervals are recommended.**			
Hepatitis A	N/A	**6 months**			
Hepatitis B	N/A	**4 weeks**	**8 weeks and** at least 16 weeks after first dose.		
Inactivated poliovirus	N/A	**4 weeks**	**6 months** A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.		
Measles, mumps, rubella	N/A	**4 weeks**			
Varicella	N/A	**3 months** if younger than age 13 years. **4 weeks** if age 13 years or older.			

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In Table 3, vaccinations by medical indications, the Child and Adolescent Schedule has added the pink color indicating "delay vaccination until after pregnancy if vaccine indicated." This will be used in the pregnancy column for HPV vaccine on the child schedule:

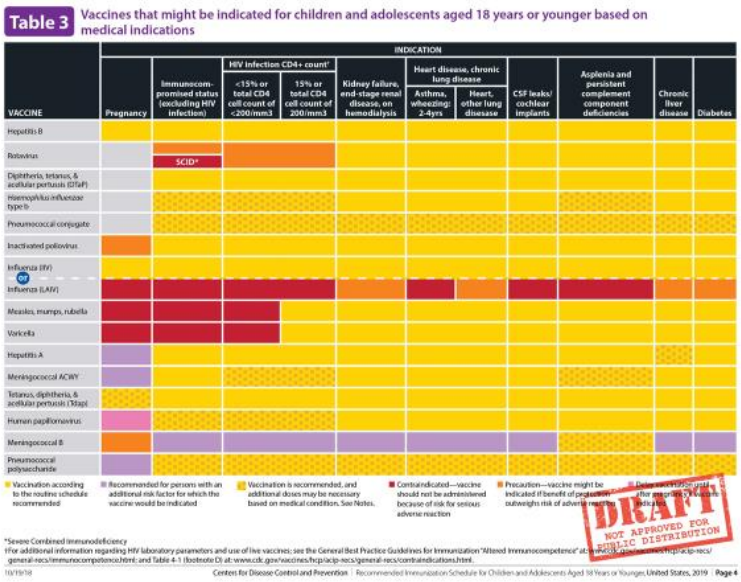

Table 3 Vaccines that might be indicated for children and adolescents aged 18 years or younger based on medical indications

VACCINE	Pregnancy	Immunocompromised status (excluding HIV infection)	HIV infection CD4+ count* <15% or total CD4 cell count of <200/mm3	HIV infection CD4+ count* 15% or total CD4 cell count of 200/mm3	Kidney failure, end-stage renal disease, on hemodialysis	Heart disease, chronic lung disease: Asthma, wheezing; 2-4yrs	Heart disease, chronic lung disease: Heart, other lung disease	CSF leaks/ cochlear implants	Asplenia and persistent complement deficiencies	Chronic liver disease	Diabetes
Hepatitis B											
Rotavirus		SCID*									
Diphtheria, tetanus, & acellular pertussis (DTaP)											
Haemophilus influenzae type b											
Pneumococcal conjugate											
Inactivated poliovirus											
Influenza (IIV) OR Influenza (LAIV)											
Measles, mumps, rubella											
Varicella											
Hepatitis A											
Meningococcal ACWY											
Tetanus, diphtheria, & acellular pertussis (Tdap)											
Human papillomavirus											
Meningococcal B											
Pneumococcal polysaccharide											

Vaccination according to the routine schedule recommended; Recommended for persons with an additional risk factor for which the vaccine would be indicated; Vaccination is recommended, and additional doses may be necessary based on medical condition. See Notes.; Contraindicated—vaccine should not be administered because of risk for serious adverse reaction; Precaution—vaccine might be indicated if benefit of protection outweighs risk of adverse reaction; Delay vaccination until after pregnancy if vaccine indicated

*Severe Combined Immunodeficiency

†For additional information regarding HIV laboratory parameters and use of live vaccines; see the General Best Practice Guidelines for Immunization "Altered Immunocompetence" at: www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html; and Table 4-1 (footnote D) at: www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html.

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The pregnancy column for rotavirus and DTaP vaccines will remain gray, as pregnancy is not applicable to the population for which these vaccines are recommendation. The pregnancy column will remain gray for Hib and pneumococcal conjugate vaccines for the reasons detailed by Dr. Kim in the adult presentation. Within the legend, descriptive text has been added next to "Contraindicated" and "Precaution." Within the influenza row, LAIV has been separated from IIV. The "Heart Disease and Chronic Lung Disease" column has been subdivided into two columns, a sub-column for asthma and wheezing in those 2 through 4 years of age and a sub-column for heart and other lung disease to demonstrate that LAIV is contraindicated in children 2 through 4 years of age with a history of asthma or wheezing, while heart and other lung diseases are a precaution to the use of LAIV.

In addition to the changes made to harmonize the language within the notes section with the Adult Immunization Schedule, there are a few content edits. First, within the HepA note , information regarding the use of combined HepA-HepB vaccine in persons 18 years of age and older has been added. A section for international travelers has been added , with recommendations for vaccination of those 6 through 11 months of age and unvaccinated persons 12 months of age or older. Homelessness has been added as an indication for vaccination. Within the HepB note , the word "all" has been added to the vaccine recommendations for the birth dose for infants born to HepBsAg-negative mothers. This was added to emphasize the recommendation for this population. The sentence now reads "1 dose within 24 hours of birth for all medically stable infants ≥2000 grams." The sentence pertaining to infants born at <2000 grams remains unchanged. Information regarding the use of CpG-adjuvanted HepB vaccine and combination HepA-HepB vaccine also has been added .

Within the inactivated poliovirus (IPV) vaccination note , a bullet has been added regarding the use of combination vaccines that contain IPV. It reads, "4 or more doses of IPV can be administered before the 4th birthday when a combination vaccine containing IPV is used. However, a dose is still required after the 4th birthday and at least 6 months after the previous dose." This mirrors similar language that appears in the HepB footnote for use of combination vaccines that contain HepB. In the influenza vaccination note , LAIV has been added where appropriate. Information regarding vaccination of persons with a history of egg allergy and information when not to use LAIV has been added. Language regarding the use of MMR vaccine in the setting of a mumps outbreak and MenACWY and MenB vaccine use in the setting of a meningococcal outbreak has been removed. Finally, in the Tdap footnote , the catch-up vaccination section has been updated to indicate that those who receive a dose of Tdap at 7 through 10 years of age "should" receive the routine dose of Tdap at 11 through 12 years of age. This is to be consistent with the Tdap recommendations published in April 2018. Additionally, a link to information regarding the use of Tdap/Td for wound prophylaxis has been added.

The graphical updates presented apply to the print version of the schedule. However, CDC also is redesigning the immunization schedule web pages. The purpose is to enhance usability for HCP and the public, and to ensure access to vaccine schedules and tools to determine what vaccines are needed. Improvements also will be made to improve readability across multiple formats, including tablets and hand-held devices. The redesign will make it easier for users to access other important immunization-related information, such as easy links to Vaccine Information Statements (VIS), vaccine administration tools, and vaccine storage and handling information. CDC also is making some changes to schedule-related products. The on-line schedule usability is being improved by allowing users to tab between schedule tables, making it easier to use the schedule in its totality online. Additionally, because adult vaccine recommendations vary based on individual needs, the adult "easy-to-read" schedule is being

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removed and instead, CDC will promote the adult vaccine assessment tool that provides vaccine recommendations based on individual conditions and needs. The childhood assessment tools also are being streamlined, allowing CDC to eliminate duplicate products.

Discussion Points

Dr. Cohn observed that both the Adult and Child/Adolescent WGs really took into consideration comments heard at ACIP a couple of years ago, and expressed gratitude for the huge effort they have made with each subsequent year to improve the usability and readability of each of these schedules.

Dr. Moore pointed out that in cases where zoster vaccine live (ZVL) is given, one may still choose to receive recombinant zoster vaccine (RZV) at a later date. Therefore, it is not truly an either/or situation. At the end of the notes section, there is a comment that those who are ≥50 years of age may be given RZV regardless of history of ZVL. However, the second statement for those ≥60 years of age does not repeat that. The nuance of the wording is somewhat confusing.

Dr. Walter thanked both WGs for all of the work they did to make the schedules look a lot more user-friendly, particularly the notes. Regarding the use of the contraindication for asplenia, CSF leaks, and Cochlear implants in the tables for LAIV, he thought the term used in the current influenza recommendation is that due to a lack of data, it is “not recommended” rather than “contraindicated.” He inquired as to how to distinguish between “not recommended” and “contraindicated.” While he understood the goal to simplify for providers, they may need to nuance that. The Influenza WG has given quite a bit of thought to this as well.

Dr. Robinson responded that they tried to keep the schedules as simple as possible. It is a broad document, but it also is very condensed. She and Dr. Kim can explore how to better indicate that on both schedules.

Dr. Kim added that one simple way to look at that is to determine whether the vaccine is or is not live vaccine. Live vaccines are referred to as being “contraindicated” specifically; whereas, in other scenarios the vaccines are not live and there is “not recommended” text.

Dr. Melinda Wharton (CDC SME) said they would look at this to determine whether there is a way to better reflect the nature of the concern other than the “contraindication” link. She agreed with Dr. Walter that this is not typically how “contraindication” is used.

Dr. Middleman (SAHM) said her understanding was that because some teenagers become pregnant, the catch-up bar for Tdap in Table 1 would be half green and half purple. Dr. Robinson indicated that this bar could be split.

Dr. Maldonado (AAP) inquired as to how outbreak information is going to be made available to providers, and whether the providers should be contacting public health agencies or vice versa.

Dr. Robinson indicated that the intention is to have the provider refer to the public health agency in the setting of an outbreak. There is a section on the cover page that instructs providers to report suspected cases of reportable vaccine-preventable diseases or outbreaks to the health department, and a link was added to the cover page for outbreak response information. The thought process was that providers should not be making these decisions regarding vaccination

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in the setting of an outbreak independently, but should be in contact and communicating with their health department when making those decisions.

Dr. Bernstein asked whether Dr. Maldonado thought it would be helpful to include something under the notes as well.

Dr. Maldonado said it was unclear to her with the already complicated schedule how often a pediatrician might contact the public health department. Perhaps another reminder would be helpful for them.

Dr. Robinson said that there is an “Additional Information” section for the Child and Adolescent Schedule where this could be re-emphasized without having to add it back to each footnote.

Dr. Moore said she thought the key was to drive folks to public health in those complex outbreak situations, but it certainly would be doable to put something in the “notes” sections reading, “For outbreaks, refer to public health” and then the reminder link to the surveillance manual. The surveillance publication from CDC is available on line to anyone, but it is tailored to public health.

Dr. Atmar said he interpreted that as meaning that if there is a suspected case of a reportable disease or a practitioner thinks there is an outbreak, they need to report it to the health department versus if they are in the midst of an outbreak how to determine whether to vaccinate. He thought it would be helpful to include that information in the notes or elsewhere.

With no further discussion, Dr. Cohn indicated that the comments would be addressed and incorporated into the final version.

Dr. Atmar moved to accept both the Adult and Child and Adolescent Immunization Schedules with incorporation of the additional suggestions at the discretion of the WG and CDC. Dr. Frey seconded the motion.

Public Comment

Priscilla Zielinski, RN
Concerned Citizen
Milledgeville Georgia

My name is Pricilla Zielinski and I’m from Milledgeville, Georgia. I’m here today because I have been in nursing for a while. I have never in my life had any knowledge, been taught any knowledge of vaccines, the side effects, the ingredients, or anything. I have taken care of people. I have taken them to get their vaccines. I’ve done so much to do with health care. My daughter—I took her in for her 4-month well check for routine vaccines. She was given Hepatitis B, DTaP, Prevnar 13®, and RotaTeq®. Instantly right after, my daughter experienced encephalitis. She screamed and screamed to the top of her lungs. She would not sleep, rest, eat, drink, nothing. She became very lethargic. I could not even see my baby for her eyes. I know my child’s heartbeat. She had completely lost herself all together. Instantly, my child died. Gone. Boom. Just like that. My child gave it all for the herd. I was told that before I came here today, that there is a lot of voting done with little or no data. I didn’t believe it. I was proved totally wrong when I came in here today. I just ask you guys to please do your research. Please, as a mother, I am begging you. I’ve seen it happen over and over again. I mean, I’m helping mothers now whose children have passed away just like mine, because there is no coroner

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mandate. They don't know what to test for. I'm having to give them stuff to take to the pathologist for certain things to test because it's not done. These children are dying. Thank you. One more thing, Hosea 4:6 "My people are destroyed from lack of knowledge." Thank you.

Patricia Neuenschwander, PNP
Pediatric Nurse Practitioner

Hello. My name is Patricia Neuenschwander. I am a Pediatric Nurse Practitioner (PNP). I have been a nurse for over 25 years. I've come here today I believe representing numerous other medical providers in our concern about the decline of our children's health. Children are this country's most valuable resource, and they are sick. They are sicker than they have ever been previously in history with chronic disease. Members of this committee are some of the most important people in the world when it comes to vaccination recommendations and vaccine safety. You influence medical providers with whatever your recommendations are. I can tell you that if you say, "Give pregnant women a flu shot," we give pregnant women a flu shot. If you say, "Add third measles, mumps, rubella (MMR)," we add a third MMR. If you say, "Change human papillomavirus (HPV) from 3 doses to 2 doses," we change to 2 doses. We follow your recommendations blindly based on the faith that you have done the research, and that you have looked into this on our behalf. We don't have time to do all of that. The Centers for Disease Control and Prevention (CDC) is supposed to be concerned about the prevention of all diseases, not just infectious diseases. I understand that your focus here is on vaccination, but we don't know how vaccinations may be contributing to the skyrocketing chronic disease we are seeing in our children. Those studies have not been done. I'm sure that you're aware the Health and Human Services (HHS) hired the Institute of Medicine (IOM) in 2011 to look at vaccine injuries. They asked them to look at 158 common injuries reported for varicella, hepatitis B, tetanus, and MMR. The IOM located science which convincingly supported a causal relationship for 14 of these serious injuries, including: pneumonia, meningitis, hepatitis, measles inclusion body encephalitis (MIBE), febrile seizures, and anaphylaxis. The review found sufficient evidence to support acceptance of a causal relationship for 4 additional serious injuries and favored rejection of a causal relationship for 5. For the other 135 vaccine injury pairs, over 86% that were reported in this review, the IOM found that the science simply had not been performed. We don't know. In addition, the current vaccine schedule has never been tested for safety of the entire schedule. The IOM was asked in 2013 to evaluate the safety of the entire schedule, which is what you're here approving today. They found that no studies have been conducted to validly assess the safety of the entire schedule, or even portions of it. That's a quote from their report.

We have witnessed a rise in chronic conditions in our children, including: asthma, eczema, autoimmune diseases, learning disability, allergies, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), seizures, developmental disorders, autism, and many others. We don't have any knowledge if vaccines may be contributing to this. US children are far more likely to die before their first birthday as infants in this country than in other developed areas of the world. Suicide is the second leading cause of death in our teens. Half report to have at least one mental, emotional, or behavioral disorder. One in 6 children have a developmental disorder. The proportion of public school children now receiving special services is 13% to 25%, which is what leads me to my request today. More and more parents are questioning vaccine safety and the safety of the schedule. I'm not sure how to respond to their concerns. They want studies on the vaccine schedule related to safety, but according to the IOM, those have not been done. They want to know if vaccines are contributing to the rise of neurodevelopmental disorders, including autism, of which only one vaccine, the MMR, out of 16 have been studied as it relates to autism. It is mystifying that there is almost no outcry in the

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medical, public health, or government circles to find answers and solutions to improve the health and wellbeing of our children. In the presentations presented today, there was an enormous amount of data on the effectiveness and cost-effectiveness of vaccination, yet little on the safety and none on long-term safety. Please consider placing some urgency on resources and priorities to evaluate the long-term safety of vaccines and the vaccine schedule so that medical providers can provide adequate published research to their patients and not just tell them, "Take the vaccines because I say so." Thank you for your consideration.

Denise Jaglowski
Retired Sleep Disorders Technologist
Concerned Citizen

Thank you. My name is Denise Jaglowski and I came here from Michigan yesterday to speak to you. I am a retired sleep disorders technologist. I did sleep studies on infants and adults. I just find it absolutely despicable that you are speaking about or even considering giving vaccines to pregnant women. I could just stop there, because it's just unbelievable that you would even imagine it. Have you ever seen your own website page that lists the vaccine excipient and media summary where you list that human and animal deoxyribonucleic acid (DNA) are in our vaccines? Have you even ever read this? This is available to parents if they would even know of it. I feel they are not even being given full informed consent to know that these lists are available—that they can ask for a vaccine package insert. For example, the flu vaccine package insert say if you get this vaccine as a pregnant person—well, first of all, "If you get the vaccine, call and let us know because you're part of our ongoing research." Apparently rats are too expensive, so we're going to just give it to the pregnant women humans directly. This is absolutely despicable. I can't believe that you're adding more and more burden to the brains of our children, and that you expect us to be a strong nation, and go forward, and be intelligent when we are so compromised. Thank you.

Jamie Heeringa
Concerned Citizen

Hi. I'm Jamie Heeringa from Grand Rapids, Michigan. I am here because I am a mother, I'm a grandmother, I'm a friend, I'm an aunt, I'm a teacher, and I'm an advocate for children's health. What is happening to our kids is so scary. I've got injured kids in my family. It's just very, very frightening. I can read, so I read the independent research that is done by very brave scientists and researchers around the world—research that the CDC should be doing. It's out there. The information is there and I can't unlearn what I have learned from all of the studying that I have been doing. All of the toxins and adjuvants in the vaccines are not proven safe to inject into a baby independently or as a group. We're compromising a growing immune system. We don't know what we're doing to it. We're super boosting unnaturally. What are the consequences? Does anybody know? There are some studies showing that children who have immunizations die earlier from other diseases. We should know this before we inject our children with this stuff. There's too many questions to be doing this kind of a schedule. Our kids are an experiment. They're guinea pigs. I think that's so unfair. We've traded off these diseases for lifetime effects on kids. These families and these kids are in prison. They're in prison for the rest of their lives some of them—the ones that are severely compromised. The study needs to be done, and the CDC should be doing this. They should be working with independent researchers, not shutting the door on it. You should not be treating our children like this without positive proof that this is all safe to do to our children. It's not there. I'm haunted by this. I can't even sleep sometimes because I'm so haunted as I learn what is happening to our kids because of our lack of information and informed consent. Who has that? If you have informed consent, you have to

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have a package insert, you have to have the ingredient label, you have to hear the doctor talk to you about that. It doesn't happen. It didn't happen for my grandkids. It doesn't happen. Doctors have to be informed. They're not. They're told to do this, and that's it. We need a better program for our kids. How are we going to continue to educate these kids? In fact, my thing is we cannot improve education, I don't care how much money you put into education, you can't improve it unless you improve the health of our children. You can't improve it. We've got sick kids who can't learn. How are we going to pay for this? Who is going to take care of these kids? Where are we heading with this? So, I'm just asking you to take this seriously and let's get down to work with some of the people that have done some of the research independently and not just shut the door on them, and figure this out for the safety and health of our children. Please.

LeeAnn Ducot
No Shots No School Not True

Hi. Thank you for having me. My speech is actually starting off with a quote from Dr. Paul Offit, who thank you very much for joining us for lunch, we really appreciate it. It was very kind of you. To quote Dr. Paul Office, "You can never really say that MMR doesn't cause autism. But frankly, when you get in front of the media, you better get used to saying it because otherwise, people hear a door being left open when there shouldn't be a door left open." Well, the door has been busted open. How? Because we recently discovered that in reality, only one vaccine and one ingredient have ever actually been evaluated for a relationship to autism. When the remaining 37 common ingredients in 15 vaccines have been blatantly ignored, you cannot definitively say that vaccines don't cause autism or any other chronic condition that 1 in 5 of our children is currently diagnosed with. I always tell my 9-year-old about integrity—that it means doing the right thing whether someone is looking or not. Well, we're looking. We're all looking. We're looking at why this committee is relying on safety studies that use adjuvants or other vaccines as placebos to downplay adverse events (AEs) between 2 control groups. We're looking at why we're giving babies vaccines for sexually transmitted diseases (STDs) on their first day of life when mom is not infected, preventing any type of baseline analysis to watch for future neurologic progression. We're looking at why we are vaccinating pregnant women when manufacturers admit no safety evaluations have been conducted on pregnant women or even humans that tiny. We're looking at why are vaccines given to fragile populations like the newborn and elderly when the recommendations are based on incomplete studies funded by the very manufacturers who are immune to liability. We're looking at why the recommendations of this committee only seem to make sense from the perspective of profitability for the pharmaceutical companies and not at all in the interest of public health. We're looking at why this committee is actively dismissing a tsunami of parents and professionals from every racial and socioeconomic demographic vehemently calling for answers, accountability, and immediate change. We're looking at the start conflicts of interest that riddle this committee and all of its influencing cohorts, including how Robert F. Kennedy, Jr. (RFK, Jr.) is demanding that the Office of Inspector General (OIG) investigate fraud and obstruction of justice committed during the Autism Omnibus Hearing of 2009 leading to the denial of over 5000 injury compensation claims. We're looking at all sorts of things. But mostly, we're looking, planning, and organizing what we're going to do about it. We'll see you back in February. Thank you so much for your time.

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Jamie Lynn Juarez
President
Hope, Inc. Academy

Hello. Thank you for having me. I'm going to read this time. I'm Jamie Lynn Juarez. I'm the mother of 4 amazing children. One is severely injured from vaccines from the particular schedule on the agenda items. He is diagnosed with severe autism, but we all know that this is really viral encephalopathy. That's why mothers like me and all of us activists together call it "The Big Lie." He also has seizures. I have two unvaccinated children. They are straight A students. They are voted number one in their division for soccer. I have another daughter that's mildly injured, recovered, and had a full academic scholarship to the University of La Verne. Like many of you on the committee and those in the room, I'm also educated. I did a PhD—my Doctorate in Education at the University of Southern California (USC) where I'm currently a candidate. We have accumulated data on thousands of victimized children by vaccine injury, school districts and social service fraud, and child abuse negligence. I'm also a licensed marriage and family therapist, behavior analysts, and credentialed school counselor in the State of California where I have testified in thousands of hearings for thousands of patients, legitimizing that we are dealing with public corruption. I'm proudly the President of Hope, Inc. Academy where I have also testified in over $30 million in settlements in a legal system that hides the truth by forced settlement agreements, committing fraud and federal crimes by lobbyists. If you would like to learn more about me, because I know that this is about the agenda item, I'm a number one best-selling author of *Hope for Autism*.

So, when it comes to the schedule, I think it's really important that we do listen to RFK, Jr. and his recent petition to the OIG at the Department of Justice (DOJ) and both Congressional and judiciary committees who investigate the alleged fraud and obstruction of justice of the two key DOJ lawyers' actions in the 2009 Vaccine Court Omnibus Autism Proceedings (OAP). My son is one of those 5000 children whose been continuously subject to issues like this schedule and not doing the real data analysis that we need. The complaint by RFK, Jr. has now been transferred to the DOJ Office of Professional Responsibility (OPR). We urge everybody here in this room and online to do the same. As you know, in the Section 1920 of the Social Security Act (SSA) that was established, you are to periodically review, and as appropriate, and revise this list for vaccine administration to children and adolescents eligible to receive vaccines through the vaccine program. But, this has not been done. What you guys are doing is not being done accurately according to the standards of research. In particular, we're not looking at methylene tetrahydrofolate reductase (MTHFR), mitochondrial dysfunction, gastrointestinal (GI) issues, or etiological sensitivities, which are growing indescribably. Parents are having their informed consent protection under the law violated. There are no pre and post studies with independent variables researched against the enormous amounts of viruses, toxins, bacteria in combination. Thank you Dr. Offit for having lunch and those discussions with us, and for agreeing that perhaps there are some adjuvants in these vaccines that are causing some of the epidemics we're looking at. We can pre-screen. We can do retrospective and prospective studies with control groups. The data is available. We have the data. Ask us for it. There are highly credible doctors and researchers that don't have bias that are independent of the pharmaceutical companies that are controlling what is happening in our country. I do want to thank President Trump and his Administration for his diligence and his assurance that he'll be looking into these things. Lastly, I just want to remind you, hopefully I'm okay on time, I'm not sure, about the WHO Code of Conduct, because we have to be looking at the funding of these studies, the data analyses that you're all doing from Pfizer, Merck, and all these companies that are funding the billions of dollars. We have to recommend products that are free of any harm and hold them accountable for liability, and we currently don't have that, as well as we're ignoring

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whistleblowers in many different arenas. Having said that, I thank you all. I do believe maybe one, maybe two, hopefully all at some point will do the right thing and really take a look at what's happening to our country. Thank you.

Jaclyn Gallion
Board Member
Informed Choice Washington

Hello. My name is Jaclyn Gallion. I'm on the Board of Informed Choice Washington. I represent thousands of parents and citizens across the State of Washington who are done following or trusting anything from this committee. You recently recommended two vaccines with new adjuvants that were never safety tested with other adjuvanted vaccines, admitting that in the real world, they would likely be administered with other vaccines, and you have no idea what sort of reaction that would cause. After your unanimous vote, you discussed safety signals that had appeared in clinical trials and you said you would be watching post-market reporting for reactions. That post-market surveillance is us—the public. We did not agree to participate in safety trials. No warnings are being given to the people receiving these new vaccines. You simply handed the American public over to the pharmaceutical companies like dispensable guinea pigs. These are just two recent examples of how you are putting our lives and our children's lives in jeopardy. It is well-known that someone with mitochondrial impairment is more likely to have a vaccine-adverse reaction that gets out of control and ends up causing severe injury, even autism. Former CDC Director, Julie Gerberding, admitted this on television (TV), and so did Dr. Kelley and Dr. Zimmerman from Johns Hopkins recently under oath, "Children with mitochondrial impairment are at risk of vaccine injury, leading to autism and other chronic disease." Does the ACIP work to ensure that nobody with mitochondrial dysfunction is vaccinated? Does the ACIP recommend screening? No. You do the opposite. You say children can be vaccinated while on antibiotics, and you ignore studies that show antibiotics are one of the many drugs that are toxic to mitochondria. You ignore studies that show acetaminophen is toxic to mitochondria. You do not warn pediatricians and parents to avoid it around the time of vaccination. Instead, when vaccination reactions occur, families are gaslighted and do not receive proper care to heal the vaccine injury. Aluminum is known to be toxic to mitochondria, but you allow multiple doses of vaccines with aluminum to be administered throughout infancy. By the time they reach their 12-month or 18-month visit, the aluminum has done its damage and the next round of vaccines sends them into a serious reaction. So, I'm here today to say "no." We are done. We are done with your recommendations, done with your guidelines, done with you selling us and our children to pharmaceutical companies. Before you vote on the immunization schedule recommendation changes, these concerns need to be taken into account. Know this—we will not be your test subjects. It is time the American people call for the separation of pharma and state. I will leave you with a quote by Dr. Stanley Plotkin, "Science never completely understands anything." Thank you.

Denise Marie Aguilar
National Health Federation

Hi. My name is Denise and I'm from California, where it is now mandated for our children to be vaccinated in order to go to school. The amount of home-schooled children in California has skyrocketed, which says a lot. I really hope the people who are on their telephones look at the parents that have traveled thousands, hundreds of miles at their own expense to come and speak to you guys. So, the best thing you guys can do is give us a little bit of respect and look at us. We have a problem on our hands, and adding more vaccines to the schedule is not a

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solution. I had to pick my daughter up. She almost killed herself from the HPV vaccine, and here you guys sit putting more vaccines on the schedule.

Brandy Vaughan
Founder
Council for Vaccine Safety

Hi everybody. It's my first time at the CDC, but I'm sure some of you know me very well. I used to work for Merck, and now I speak out against the dangers that the pharmaceutical companies don't tell you about pharmaceutical drugs and vaccines. So, when I was trained at Merck, which was a very intense training, we were told that all drugs go through a gold standard process, which is double-blind, placebo-based, long-term studies. Well, for vaccines, as most of you know in here, they don't have to go through that process because they are categorized differently. So, what's happening is we're seeing a lot of these vaccines being put on to the market and our children are test subjects. Right now, we're seeing almost half of all children with a chronic illness. If you look at the studies, the independent studies that are not funded by the pharmaceutical companies that fill this room, you will see 1000 studies, more than 1000 studies, showing the harm of the vaccines that are released on market without proper testing. So, I ask that when you're considering the immunization schedules today, that you really take a step back, because our children and adults—you know, in the US we've never been sicker. Our health is suffering. I have done a lot of research on the difference between injection and ingestion. This is something that the pharmaceutical companies will never tell you, but anything injection goes straight into the circulation. It goes to vital organs. There is a great study on aluminum which shows that 95+ percent is absorbed in the body tissues. When you eat something, when you drink something, when you inhale something, 95% of that is filtered out through our body's natural detox processes. So, anything you inject is going to be far, far more dangerous and far more potent. What's happening now is because the pharmaceutical industry—it's a saturated drug market and it's expensive. There's liability. Unfortunately, there is no liability for vaccine makers with vaccines. So, you're seeing all of these new vaccines in development, almost 300, because if they can call it a vaccine, they can a) inject the body with toxins and make them far more potent and create further health issues that sell the drugs that make them the most powerful industry in the world, and b) we're seeing them without liability and they go through the committee here. I sat this morning and I was disturbed, and I have watched this on the television on live stream before, but I was really disturbed. Doctors were asking about safety signals and when safety information is going to be available. The answer is always like 5 sentences that distract with no real answers. "Well, enough people have to be hurt by the vaccine before we will know if it's safe." "Enough people have to die from the vaccine before we'll know it's safe." It's not acceptable, because the American population pays really good tax dollars to make sure that this committee is not biased, and to make sure that this committee is putting the people of America before the profits of the pharmaceutical industry. I saw first-hand when I sold Vioxx for Merck that these agencies, including CDC and the FDA, are not doing their job anymore. So, I ask you today, when you consider these recommendations, consider all of the children, and the adults, and all the pregnant women that are going to suffer because of your vote, because there may be a lot of money backing these recommendations from the pharmaceutical industry, but you are beholden to the American people. Please, don't forget your mission. Thank you.

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Motion/Vote: Adult & Child and Adolescent Immunization Schedules

Dr. Atmar made a motion to accept both the Adult and Child and Adolescent Immunization Schedules with incorporation of the additional suggestions at the discretion of the WG and CDC. Dr. Frey seconded the motion. The motion carried with 11 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

11 Favored: Atmar, Bernstein, Ezeanolue, Frey, Hunter, Lee, Moore, Romero, Stephens, Szilagyi, Walter
0 Opposed: N/A
0 Abstained: N/A

Japanese Encephalitis Vaccine

Introduction

Chip Walter, MD
Chair, ACIP Flavivirus Vaccines WG

Dr. Walter indicated that while the Flavivirus Vaccines WG was once combined into a single WG, it has been split again into two groups: The Japanese Encephalitis (JE) Vaccine WG and the Dengue Vaccines WG. This is due to the amount of work to be done and the expertise needed for both WGs. The JE Vaccine WG will continue working to finish the updates to the JE vaccine recommendations. This work is expected to be completed in February 2019. Dr. Robert Atmar will chair the Dengue Vaccine WG, which will consider recommendations for possible use of dengue vaccine in the US and will present terms of reference and background information for the formation of that WG during the February 2019 meeting.

The JE Vaccine WG's objectives are to: 1) review newly available safety and immunogenicity data for inactivated Vero cell culture-derived JE vaccine (JE-VC); 2) review epidemiology and risk of JE in travelers; 3) review ACIP recommendations for use of JE vaccine in consideration of updated data; and 4) update *MMWR Recommendations and Reports*. WG presentations to ACIP since its inception in 2015 have included:

- Immunogenicity in adults aged ≥65 years
- Accelerated dosing schedule at 0 and 7 days
- Duration of protection
- Booster dose for children aged <17 years
- Updated epidemiology and risk of JE in US travelers
- Post-marketing safety and adverse events
- Comparative analysis of vaccination strategies
- GRADE analysis of JE vaccine for US travelers

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Dr. Walter indicated that this session would include the following presentations in anticipation of taking a final vote on the recommendations during the February 2019 meeting:

- ❑ EtR Framework for the updated JE vaccine recommendations
- ❑ Review of accelerated dosing schedule data in adults
- ❑ Review of booster dose recommendations, which strengthen the current permissive recommendation and are expanded to include children aged <17 years
- ❑ Conclusions and next steps

EtR for JE Vaccine

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Dr. Hills indicated that she would be discussing the various components that make up the EtR Framework, which include the policy question, background, public health importance, benefits and harms of vaccination, values, acceptability, resource use, feasibility, and balance and consequences; followed by the WG's proposed JE vaccine recommendations. The overarching policy question the WG addressed was, "Should JE-VC be recommended for use in persons aged 2 months and older at risk of travel-related exposure to JE virus?" In terms of the components of the PICO question, the population is persons aged 2 months and older traveling to JE risk areas in Asia; the intervention is JE-VC administered as a 2-dose primary series; the comparison is No JE vaccine recommended; and the critical outcomes are short- and long-term seroprotection, SAEs, and AEs of special interest.

Before discussing the components of the framework, Dr. Hills first provided some background information important for understanding the JE vaccine recommendations. JE is caused by a mosquito-borne flavivirus. JE occurs in most of Asia and parts of the Western Pacific, and is the leading vaccine-preventable cause of encephalitis in Asia. Most JE virus infections in humans are asymptomatic with fewer 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[1]. Currently, even with national vaccination programs in some endemic countries, there are still an estimated 68,000 JE cases annually in Asia, with an overall incidence for all age groups of approximately 1.8 cases per 100,000 population. The highest risk for infection is in rural, agricultural areas because the primary breeding site for the main vector is rice fields[2] [[1]Vaughn DW, Hoke CH. Epidemiol Rev 1992; [2]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, activities, and accommodations. A JE vaccine was first licensed in the US in 1992. In the 25 years from 1992 through 2017, only 12 JE cases were identified among US travelers or expatriates. Travelers with longer trips or increased rural and outdoor exposures are at higher risk of acquiring JE virus infection. Among the 12 US traveler cases, 8 had traveled for a month or longer, 3 had traveled for less than a month but spent at least one night in a rural area, and 1 traveled for less than one month but there was no information on their itinerary or activities [Hills et al. CDC Yellow Book 2018].

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JE-VC manufactured by Valneva, Ixiaro®, is the only JE vaccine currently licensed and available in the US. The vaccine was licensed for adults 17 years of age and older in 2009, and the licensure was subsequently extended to children ages 2 months through 16 years older in 2013. The primary series is 2 doses administered 28 days apart, and the vaccine costs approximately $600 for the 2-dose primary series. There are no efficacy data for Ixiaro®. Because of the availability of several effective JE vaccines in Asia, randomized, controlled efficacy trials to evaluate a new JE vaccine would have been logistically difficult and potentially unethical. However, there is an established immunologic correlate of protection which is a JE virus 50% plaque reduction neutralization test ($PRNT_{50}$) titer of ≥10. The vaccine was licensed based on a non-inferior neutralizing antibody response compared with a licensed mouse brain-derived JE vaccine [Hombach J. *Vaccine* 2005; Markoff L. Vaccine 2000].

Following licensure of JE-VC for adults in 2009, ACIP approved recommendations for use of JE vaccine in US travelers. In 2013, following licensure of JE-VC for children, a GRADE analysis was performed and JE vaccine recommendations were reviewed but no changes were made [CDC. *MMWR* Rec Rep 2010; CDC. *MMWR* Morb Mortal Wkly Rep 2013].

The current review of the JE vaccine recommendations is a routine review in consideration of new safety, immunogenicity, and traveler risk data. In addition, an updated *MMWR Recommendation and Reports* document will be published that will combine information from the previous 2010 *MMWR* document and Policy Notes published since that time, and will incorporate new indications and dosing schedules.

In terms of public health importance, the first domain of the ErR Framework, JE virus is the leading vaccine-preventable cause of encephalitis in Asia and parts of the Western Pacific. In the highest risk areas in Asia prior to vaccination programs, incidence rates as high as about 20/100,000 children per year were reported. Thus, JE is clearly of public health importance in that region. However, based on numbers of cases, JE cannot be considered a substantial public health problem for US travelers. Based on 12 reported JE cases over a 25-year period and 4 to 5 million US citizen trips to Asia annually during this period, the estimated risk is less than 1 case per million trips to Asia. There also is no risk of subsequent local transmission in the US from an infected traveler, because of low level viremia when humans are infected with JE virus. While JE cannot be considered a public health problem for US travelers in general, it is an important individual concern for some travelers. For some persons, like those taking up long-term residence in rural areas of Asia, risk might approach a similar level to populations of endemic areas. Additionally, when disease occurs, only supportive treatment is available and the outcome is often severe, with a high rate of death and disability following clinical disease. Regarding the public health component of the EtR Framework, the WG concluded that firstly, JE is clearly a public health problem in endemic countries. Secondly, for US travelers, the question of public health importance is really not directly applicable as it is an individual traveler concern. The JE vaccine is typically paid for out of pocket, so the question is less relevant than for many other vaccines. Finally, for a judgement within the EtR framework, the WG decided the public health importance “varies” related to the individual person’s risk based on their itinerary and activities. For some travelers, risk of a potentially severe disease is sufficiently high that vaccination should be recommended.

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The next EtR domain regards benefits and harms. The WG presented the GRADE analysis to ACIP in June 2018, so Dr. Hills briefly summarized the benefits and harms based on that analysis. Data to assess seroprotection were from 4 RCTs and 8 observational studies. Seroprotection rates after the 2-dose primary series in all studies in individuals up to 64 years of age were at least 95% at 1 month and 83% or higher at 5 to 6 months. When data from the RCTs were combined and weighted using a random effects model, seroprotection rates after JE-VC compared to seroprotection rates in recipients of a JE vaccine previously licensed in the US, or JE vaccines licensed in other countries, were non-inferior at 1 month and significantly higher at 5 to 6 months. Therefore, the WG concluded that the vaccine benefits are "large." In randomized trials, there were no significant differences compared to placebo or other vaccines for SAEs or AEs of special interest (e.g., fever, rash, neurologic, hypersensitivity, or medically attended events). There were no safety signals in post-marketing surveillance and no patterns in the timing or types of adverse events. Therefore, the WG concluded that the vaccine risks are "small." The level of evidence for the GRADE analysis benefits and risks was Type 1, or high certainty, for vaccine effectiveness using seroprotection as the endpoint and type 2, or moderate certainty, for safety. When considering whether the benefits outweigh the risks, the WG noted that JE-VC has high seroprotection rates, JE is a rare disease among travelers but has potentially serious outcomes, and that JE-VC has no important safety concerns but rare SAEs can occur. The WG felt the benefits outweigh the risks for some travelers. Healthcare providers should discuss a traveler's risk based on their itinerary and activities, and vaccine should be targeted to travelers at increased risk.

The target population's perception of value was the next domain considered by the WG. The questions considered were: 1) Does the target population feel that desirable effects are large relative to undesirable effects?; and 2) Is there important uncertainty or variability in how much people value the main outcomes? To address these questions, a population survey was conducted using the Porter Novelli survey mechanism. The survey population included randomly recruited participants representative of the non-institutionalized US population. Overall, there were 6427 respondents. Participants were presented a scenario on travelling overseas and provided estimates of disease risk and outcomes for a disease such as JE, as well as vaccine safety, risk of side effects, and cost. They were queried regarding the likelihood of receiving the vaccine and factors important in their decision. The results showed that in regard the to the likelihood of receiving the vaccine, 32% said they were "very or somewhat likely" to receive the vaccine, 43% said they were "very or somewhat" unlikely to receive the vaccine, and 25% were "unsure." For those who were "very or somewhat likely" to receive the vaccine, the most influential factors were disease risk and risk of severe disease outcomes. For those who responded they were "very or somewhat unlikely" to receive the vaccine, influential factors were vaccine cost and also disease risk. The WG concluded there was variability in the population's perception of the potential benefits and harms of vaccination for a rare but potentially severe disease. Some of the population clearly value the availability of a vaccine to prevent a potentially serious disease, but others are less likely to place value on an expensive vaccine which while safe, has the possibility of rare serious side effects. With "disease risk" being considered a reason by some to receive the vaccine and by others not to receive the vaccine, there is clearly substantial variability in how people perceive and tolerate risk.

Acceptability to key stakeholders was the next domain addressed by the WG, which they considered in the context of acceptability of the proposed JE vaccine recommendations. Travel medicine practitioners were considered an important stakeholder. Mechanisms to survey US travel medicine practitioners were investigated, but none could be identified within the timeframe available. However, four members of the JE ACIP WG are practicing travel medicine practitioners and members of the International Society of Travel Medicine (ISTM) and they

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played an active role in discussions about the recommendations. The WG reviewed opinions about JE vaccine recommendations expressed in publications and in letters submitted to ACIP by US health care providers, and had two practitioners with dissenting opinions on the recommendations presented to the WG [[Caldwell. Curr Infect Dis Rep 2018; Connor. Trop Dis, Trav Med Vacc 2017; Burchard. J Trav Med 2009; Teitelbaum. J Trav Med 2009; Shlim. Clin Infect Dis 2002]. Overall, the WG concluded that there is stakeholder consensus that there is a low risk of JE for most travelers, there is a need to inform travelers about disease risks and prevention measures, and vaccination should be targeted to travelers at higher risk. The WG felt that the recommendations would probably be acceptable to most stakeholders as they are based on individual clinical decision-making with consideration of several important factors including:

- ❑ Risks related to the specific travel itinerary
- ❑ Likelihood of further travel to JE-endemic countries
- ❑ High morbidity and mortality of JE when it occurs
- ❑ The possibility, but low probability, of SAEs
- ❑ The traveler's personal perception and tolerance of risk

Resource use was the next domain considered by the WG. The EtR question the WG addressed was, "Is the intervention a reasonable and efficient allocation of resources?" Again, the WG considered this question in the context of the proposed JE vaccine recommendations that would target higher risk travelers. A comparative analysis of strategies was presented to ACIP in June 2018 by CDC's Health Economics and Modeling Unit (HEMU) with the objective being to provide perspective on numbers needed to vaccinate (NNV) and cost per case averted for travelers with different itineraries and disease risk, and the cost implications of possibly expanding the current JE vaccine recommendations to a broader group of travelers. There were 3 groups in this analysis. Risk Group l included travelers who planned to spend a month or longer in JE endemic areas and approximates the group for whom JE vaccine is recommended. Risk Group 2 included travelers who would spend less than a month in JE endemic areas with at least 20% of their time doing outdoor activities in rural areas, and this group approximates travelers for whom JE vaccination should be considered after evaluating their itinerary and weighing the benefits, risks, and costs. Risk Group 3 included the remainder of shorter-term and lower-risk U.S. travelers to Asia for whom JE vaccination is not recommended.

In terms of the estimated proportion and number of travelers to Asia per year in each of the risk groups, Risk Group 1 represented about 20% of all travelers, or about 0.9 million travelers per year. Risk Group 2 represented about 25% of travelers, or about 1.2 million travelers per year. Risk Group 3 represented the remaining 55% of travelers, or about 2.7 million travelers per year. The first key finding from the analysis was the NNV to vaccinate to prevent a case. In terms of the base case (reported incidence), to prevent one case of JE among US travelers, the number of travelers who would need to be vaccinated was 0.7 million in Risk Group 1, the highest risk group; 1.6 million in Risk Group 2; and 9.8 million in Risk Group 3. Because baseline incidence is based on reported JE cases, to address any uncertainty about the sensitivity of surveillance, the WG also did a sensitivity analysis using an incidence 100 times higher. With incidence 100 times higher, the NNV to prevent a case were 7,000; 16,000; and 98,000 in the three risk groups, respectively.

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With baseline assumptions, the cost from a societal perspective to prevent one case in the highest risk category is about $0.6 billion. Comparatively, for those in Risk Group 2 the cost per case averted is $1.3 billion, and for those in Risk Group 3, it is $7.9 billion. With incidence increased 100 times higher in the sensitivity analysis, the cost per case averted in each of the three risk groups is $5 million, $12 million, and $78 million, respectively. If JE vaccination recommendations were expanded from Risk Group1 to recommend vaccination routinely for all travelers in Risk Groups 1 and 2, it would cost society an additional $1.6 billion to prevent one additional case of JE. Similarly, expanding JE vaccination recommendations from Risk Groups 1 and 2 to all travelers would cost society an additional $14.6 billion to prevent an additional JE case.

There were two general resource considerations the WG noted when considering this domain of the EtR Framework. First, compared to vaccines used universally in the population, there are a relatively small number of travelers to Asia with an itinerary that puts them at increased risk for JE. Second, travel vaccines are usually paid for by the traveler themselves, and are not covered under the VFC program or by most private insurers. Overall, the WG conclusions were that JE vaccination is probably not an efficient use of societal resources as it is an expensive vaccine for a low risk disease. However, the question of resource use is less applicable to a travel vaccine as it is typically paid for by individuals who are deciding on purchase of a vaccine to prevent a potentially severe disease. The comparative analysis supported the proposed tiered JE vaccine recommendations as it indicated a large increased cost to society to prevent a case of JE when Risk Groups 1 and 2 were included compared with Risk Group 1 alone, supporting a more cautious approach or consideration of vaccination for those in Risk Group 2. In addition, there was a very large increased cost to society if Risk Group 3 was included, which does not support a broad recommendation for JE vaccination for all travelers. Finally, vaccine recommendations targeted to higher risk groups are probably a reasonable allocation of resources as the financial implications related to vaccine purchase will be borne by travelers most at risk of a severe disease.

The next domain was feasibility. The WG again considered this in the context of implementation of proposed risk based recommendations. Administration of vaccine would be feasible during a pre-travel consultation. With risk-based recommendations, barriers to implementation might include lack of understanding by health care practitioners of factors that might increase the risk for JE. However, specific information is provided in a table accompanying the recommendations and other resources such as the CDC Yellow Book are readily available to practitioners. Therefore, the WG considered that risk-based recommendations are probably feasible to implement. Next, the WG considered the balance of consequences. Considered in the context of recommendations targeting higher risk travelers, the WG felt that the desirable consequences would probably outweigh the undesirable consequences in most settings.

Regarding the specific JE vaccine recommendations proposed by the WG, based on the vaccine data and additional factors considered within the EtR Framework, the WG felt there was sufficient information to move forward with updated recommendations and that vaccination should be recommended for individuals based on individual clinical decision-making. The WG also considered that only minor updates were needed to the existing recommendations for use of JE vaccine in US travelers. ACIP members were provided with a copy of the recommendations in their folders, which laid out the recommendations in the way they would appear in a formatted document and included information that would appear in an additional box. During the meeting, Dr Hills presented the key information from the JE vaccine recommendations on five slides. The proposed JE vaccine recommendations are as follows:

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"JE is a very low risk disease for most travelers to JE-endemic countries. Some travelers will be at increased risk of JE virus infection based on their planned itinerary. Factors that increase the risk of JE virus exposure include 1) longer duration of travel, 2) travel during the JE virus transmission season, 3) spending time in rural areas, 4) participating in extensive outdoor activities, and 5) staying in accommodations without air conditioning, screens, or bed nets (**Box 1**)

Healthcare providers should assess a traveler's risk for mosquito exposure and JE virus infection based on their planned itinerary, and discuss ways to reduce their risk. All travelers to JE-endemic countries should be advised of the importance of taking precautions to avoid mosquito bites to reduce the risk for JE and other vector-borne diseases. These precautions include using insect repellent, permethrin-impregnated clothing, and bed nets, and staying in accommodations with screened or air-conditioned rooms.

For some people who might be at increased risk for JE based on travel duration, season, location, activities, and accommodations, JE vaccine can further reduce the risk for infection. The decision whether to vaccinate should be individualized and weigh the 1) risks related to the specific travel itinerary, 2) likelihood of further travel to JE-endemic countries, 3) high morbidity and mortality of JE when it occurs, 4) availability of an effective vaccine, 5) possibility, but low probability, of serious adverse events following vaccination, and 6) traveler's personal perception and tolerance of risk.

- ❑ JE vaccine is recommended for persons moving to a JE-endemic country to take up residence, longer-term (for example., 1 month or longer) travelers to JE-endemic areas, and recurrent travelers to JE-endemic areas.

- ❑ JE vaccine also should be considered for shorter-term (for example, <1 month) travelers with an increased risk of JE based on planned travel duration, season, location, activities, and accommodations. Vaccination also should be considered for travelers to endemic areas who are uncertain of specific duration of travel, destinations, or activities.

- ❑ JE vaccine is not recommended for travelers with very low risk itineraries, such as urban travel only for a short duration or travel outside of a well-defined JE virus transmission season.

The minor changes from the current JE vaccine recommendations are that there is additional information on factors that increase JE risk to assist providers with decision-making. Longer-term travel is no longer defined as a specific cut-off of 1 month or longer. The consideration of vaccination for travelers to an area with an ongoing JE outbreak has been removed. There are small wording changes to address questions that have been raised, including changing "expatriates" to "persons moving to a JE-endemic country to take up residence."

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JE-VC Accelerated Schedule for Adults Aged 18-65 Years

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Dr. Hills presented the data supporting, and proposed wording of, the recommendation for an accelerated schedule for JE-VC for adults aged 18 through 65 years. Although these data were presented to ACIP previously, the WG wanted to briefly review and summarize the data as they would like ACIP members to vote on this issue in February 2019. In terms of the timeline of relevant events in regard to this topic, the FDA approved JE-VC for use as a 2-dose primary series administered in the standard schedule at 0 and 28 days in March 2009. In October 2015, the manufacturer presented data to ACIP for an alternate accelerated primary series at 0 and 7 days in adults, and ACIP noted that the data looked promising. In December 2017, the manufacturer submitted the Biologics License Application (BLA) amendment to the FDA. In October 2018, the FDA approved the accelerated primary series.

The data supporting the accelerated schedule came from one randomized trial among adults aged 18 through 65 years. The study was conducted at seven study sites in Europe. The study had four arms, including JE-VC with rabies vaccine in an accelerated or standard schedule, and JE-VC and rabies vaccines administered alone in standard schedules. There was no arm that included JE-VC administered alone in an accelerated schedule, so Dr. Hills presented the comparative data for JE-VC administered with rabies vaccine in an accelerated or a standard schedule [Jelinek T. J Travel Med 2015].

In terms of the seroprotection rates and geometric mean titers (GMTs) at 28 days after the second JE-VC dose of the primary series, seroprotection rates were 99% for the accelerated schedule and 100% for the standard schedule. GMTs were significantly higher for the accelerated schedule compared with the standard schedule, with GMTs of 690 and 299 in the 2 groups, respectively[1]. At approximately 1 year, seroprotection rates were 94% for the accelerated schedule group and 86% for the standard schedule group. GMTs were again significantly higher for the accelerated schedule group compared with the standard schedule group, with GMTs of 117 and 39 for the 2 groups, respectively[2]. Regarding solicited AEs within 7 days after co-administered JE-VC and rabies vaccine for the accelerated and standard schedule groups, there were no significant differences in the percentage of subjects with the systemic AEs (e.g., fever ≥38^{0}C, headache, myalgia, arthralgia) or local AEs (pain, erythema, induration)[3] [[1]Jelinek T. J Travel Med 2015; [2]Cramer JP. J Travel Med 2016; [3]https://clinicaltrials.gov].

The proposed wording for a new recommendation for an accelerated schedule in adults 18 through 65 years of age would be as follows:

> "In adults aged 18–65 years, JE-VC can be administered in an alternate primary schedule of two JE-VC doses administered 7 days apart."

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JE-VC Pediatric Booster and Booster Dose Recommendations

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Dr. Hills noted that the JE-VC booster dose data also have been presented to ACIP previously, but the WG wanted to briefly review and summarize the data given the anticipated ACIP vote in February 2019. In September 2010, the FDA approved a JE-VC booster dose for adults aged 17 years and older. In February 2016, the manufacturer presented data to ACIP for a booster dose in children aged 14 months and older. In June 2017, the manufacturer submitted to the FDA a BLA amendment for a pediatric booster dose. In April 2018, the FDA approved the pediatric booster dose.

The current ACIP recommendation for a JE-VC booster dose is for adults aged 17 years and older. The wording of the booster dose recommendation is, “If the primary series of JE-VC was administered more than 1 year previously, a booster dose may be given before potential JE virus exposure” [CDC. MMWR Morb Mortal Wkly Rep 2011]. The topics for consideration during this session were to lower the recommended age for a booster dose to include children aged 14 months and older, and to strengthen the current permissive booster dose recommendation.

The data supporting a booster dose in children comes from one open label randomized trial conducted among children aged 2 months through 17 years. The study was conducted in the Philippines, which is a JE-endemic country. A total of 300 children were randomized to receive or not receive a booster dose of JE-VC. For the 150 randomized to receive the booster dose, it was administered at 11 months after the second dose of the 2-dose primary JE-VC series. Data from the children in this group were analyzed by age group based on the vaccine dosage given, which is 0.25mLs for children aged 2 years and younger, and 0.5mLs for older children. Dr. Hills firstly presented data for the 81 children aged 14 months through 2 years who received a 0.25mL booster dose. In terms of seroprotection rates and GMTs at 11 months after a 2-dose primary series (pre-booster), and 1 month after a booster dose, seroprotection rates were 98% prior to the booster and 100% after the booster. GMTs showed a substantial increase, with a GMT of 67 prior to the booster and 2911 after the booster. Among the 67 children aged 3 through 17 years for whom the JE-VC dose is 0.5mL, seroprotection rates were 90% prior to the booster and 100% at 1 month after the booster. Again, GMTs were significantly higher after the booster dose, with a GMT of 40 prior to the booster dose and 1366 after the booster [Kadlecek V. Pediatr Infect Dis J. 2018].

Based on data collected at 2 years after a booster for those children who received a booster dose and comparative data from the same time point for those who did not receive a booster dose, seroprotection rates at 2 years after the booster were 100% both for younger children who received the 0.25mL booster dose and for the older children who received the 0.5mL dose. Among children who did not receive a booster dose, the seroprotection rate was 90%. The GMTs were 4- to 7-fold higher in the children who received a booster dose compared with those who did not.

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Safety data were collected for 2 years after the booster dose. Solicited AEs were reported less frequently following the booster dose than following the primary series. The most common solicited AE following the booster dose was fever, which occurred in 8% of children [FDA. Ixiaro package insert. October 2018].

The WG concluded that the current booster dose recommendation for adults should be modified to include children aged 14 months and older. Based on the lower standard dose of JE-VC for younger children, children aged 14 months through 2 years should receive a single 0.25 mL booster dose, and children aged 3 years and older should receive a single 0.5 mL booster dose.

Data supporting the current adult booster dose recommendation came from three clinical trials that provided data on persistence of a protective neutralizing antibody response at 12-15 months after a primary 2-dose series of JE-VC in adults. These studies were conducted in Austria, Germany, Northern Ireland, and Romania. In terms of the seroprotection rates at 12-15 months after the 2-dose primary series of JE-VC, rates were quite variable in the 3 studies, ranging from 58% to 83%. GMTs ranged from 18 to 41 [Schuller E. Vaccine 2008; Dubischar-Kastner K. Vaccine 2010; Eder S. Vaccine 2011].

As mentioned, these studies were conducted in Europe where tick-borne encephalitis (TBE) vaccine is available in some of the countries. TBE virus is a flavivirus related to JE virus, and there was concern that there might have been a boosting effect of TBE vaccine which could explain some of the variability in study results. As a result, the manufacturer conducted a post-hoc analysis that stratified subjects by TBE vaccination status. These data were presented to ACIP in February 2016. The study groups included subjects who had not received TBE vaccine and subjects who had received TBE vaccine prior to or after JE vaccination. The seroprotection rates at 1 year, 3 years, and 5 years the primary JE-VC series were lower for those who had not received TBE vaccine compared with those who had received TBE vaccine [Dubischar K. ACIP presentation. February 2016].

The WG concluded that after a 2-dose primary series, long-term JE seroprotection rates are lower in those not administered TBE vaccine compared with those administered TBE vaccine. TBE vaccine is not available in the US and other flavivirus vaccines such as yellow fever (YF) vaccine are not routinely administered with JE-VC. Therefore, among US travelers, duration of protection following a booster dose of JE-VC is likely to be most similar to the subjects not administered TBE vaccine who had lower seroprotection rates through 5 years. Based on these data, the WG recommended that the permissive booster dose recommendation should be strengthened.

Summarizing all of the booster dose data presented during this session, the proposed new recommendation for JE-VC booster doses is as follows, with the relevant changes underlined:

- <u>For adults and children aged 14 months and older</u>.
- If the primary series of JE-VC was administered more than 1 year previously, a booster dose <u>should be given</u> before potential JE virus exposure.
- Children aged 14 months–2 years should receive a single 0.25 mL booster dose.
- Adults and children aged 3 years and older should receive a single 0.5 mL booster dose.

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In terms of next step to complete the JE Vaccine WG activities, the WG requested that ACIP members vote in February 2019 on the three topics presented during this session. As a reminder, these are minor updates to JE vaccine recommendations for US travelers, an alternate accelerated vaccination schedule, and minor modifications to strengthen the wording for the booster dose recommendation and lower the recommended age to include children. The WG plans to provide a draft updated *MMWR Recommendations and Reports* to ACIP prior to the February 2019 meeting.

Discussion Points

Dr. Romero expressed appreciation for the extremely clear presentations. Regarding the change from the current JE vaccine recommendations stating, "Longer-term travel no longer specifically defined as a cut-off of ≥1 month," he asked whether this would now be left up to physician discretion.

Dr. Hills indicated that they are still giving the example of ≥1 month as an example of longer-term travel. This is based on US traveler data. Of the 12 US cases of JE, 67% had traveled 30 days or more. The reasons they removed the very specific wording is because people were literally taking that at face value. The work group wanted to get the message across that it is longer-term travel, but not to be so definitive about the 1 month cut off.

Dr. Walter added that the WG did not want people to be so focused that they neglected some of the other risk factors.

Dr. Bernstein inquired as to the reason for stating that the booster "should be given" in the proposed new recommendations.

Dr. Hills replied that the analysis that assessed the TBE data and showed lower seroprotection rates in those who had not received TBE vaccine were not available when the initial recommendation was made that stated, "a booster dose may be given." The WG wanted to strengthen that recommendation in recognition of the additional data available since that time. If there is an ongoing risk of JE exposure, the WG would recommend a booster dose.

Dr. Moore inquired as to whether by "endemic areas" the intent of the WG was to mean country or rural areas where there is ongoing transmission. The elements to factor into the decision to vaccinate are well-itemized, but then the very first statement is to do it for travel of a month or longer. But then the last statement says it is not recommended if the travel is outside of a well-defined JE virus transmission season, which makes sense. The simplified recommendation could be somewhat confusing in terms of the WG's intent if travel is over 30 days but is outside of a transmission season. Given the high cost, personal payment, and very low risk, it is very important for the traveler understanding what the risks really are before they invest $600 out-of-pocket. She just wanted to ensure that those advising them have the best possible guidance.

Dr. Hills responded that they intended it to mean areas. They did not want to say countries because there are non-endemic areas within countries. There is still information in the Yellow Book on areas within countries that are considered to be JE endemic. In terms of the WG's intent with regard to travel for more than a month but outside of a transmission season, she pointed out that often those who are traveling more than a month will often span transmission seasons. This is an individual clinical decision, so she would say to consider and discuss various anticipated activities in that scenario. It is important to keep in mind that there is year-

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round transmission in some endemic areas, while in others there is a defined transmission season.

Dr. Fischer (SME) added that the assumption was made that longer-term and/or recurrent travelers would span the transmission season or, even if their primary travel will be to an urban area, they may spend time in rural areas. Therefore, the vaccine is still recommended for the longer-term or recurrent travelers given the assumption that they will be at risk at some point during their travel.

Dr. Hunter inquired as to how health inequities related to socioeconomic factors might be an issue with this, in that the conclusion that the benefits are large, individuals are paying $600. The societal benefits are not necessarily huge because this is a small number of people. The people who are probably going to be at higher risk are those who are going back to visit their relatives in a rural area who have very little money. They will be at higher risk medically, but will be less able to pay. It was not clear how to address this issue, but there are going to be inequities and there should at least be a comment about that.

Dr. Walter indicated that the WG did discuss this. He raised this point because he used to work in a travel clinic and would have families with 3 children come in who would be facing quite a high expense. Other WG members have raised that issue as well.

Dr. Hills added that the WG did have a very active discussion about that. That comment is included in the “Additional Information” section in the EtR Framework, but is not something that can be addressed in vaccine recommendations.

Dr. Kimberlin (AAP Redbook) observed that the Philippines study was open-label enrolling children from 2 months of age to 17 years of age, but no data were presented from 2 months to 14 months. The target of the recommendation was not entirely clear to him. Is this a travel medicine recommendation, or is it for the practicing pediatrician, for instance?

Dr. Hills indicated that the primary series started at 2 months of age and those data have been presented to ACIP previously. Those who received the vaccine at 2 months of age would be getting the booster dose at 14 months of age, which is why the data for the booster dose were from 14 months through 17 years of age. The vaccine is licensed and approved for children 2 months of age and older. In terms of the focus for the recommendations, the WG tried to base them as closely as possible on data. The first part of the recommendations focus on persons taking up residence in endemic countries, and 67% of US traveler cases have occurred in the 20% of all travelers who actually travel for a longer period. There is clear evidence that this is the highest risk group.

Dr. Fischer added that the recommendations are primarily targeted to travel health providers, some of whom will be travel medicine physicians and some who will work in other types of settings that provide recommendations in the broader context to travelers. Unlike YF vaccine, JE vaccine can be administered in other places and there may be some general pediatricians who administer the vaccine. This vaccine is typically being administered in the context of a pre-travel visit.

Dr. Walter said that as a general pediatrician, they do not stock JE vaccine in their clinic. They would refer a patient to a travel clinic for a consult. While this really is meant for travel medicine clinicians, it can be guidance for the general medical community as well.

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Dr. Hahn (CSTE) thought duration of travel was somewhat confusing, because people had already been put into the “less than a month” category. Someone traveling for a week versus 3 weeks might be considered differently.

Dr. Hills replied that the intent was for providers to consider risk factors and advise on JE vaccination for a 3-day traveler versus a 3-week traveler. The box in the recommendations provides information under all of the various headings, one of which is duration, to try to better explain what is meant.

Dr. Peter McIntyre (NCIRS) said he was glad the question of visiting friends and relatives came up. In the Australian context, there is fairly good information that those visiting friends and relatives typically do not consult travel medicine providers or uncommonly do. They typically rely on PCPs, often of their own ethnic group. The economic barrier is also relevant in the sense that there is a Chinese-manufactured live attenuated vaccine that is in the national immunization program of many countries in South Asia and East Asia, which has WHO prequalification and an extensive safety record, has been shown to be effective, and is a single dose product. He said it is also likely to be a lot less than $600. This certainly comes up in the context of advice in Australia. People know this if they are going back to their country of origin that this vaccine is on the national program and they can get it for nothing. For visiting friends and relatives, this may be a relevant consideration, but he was not sure what the politics would be of referring to it in a document.

Dr. Hills replied that the WG is aware of the SA 14-14-2 vaccine and the chimeric vaccine that are available overseas. That is a relevant point and the travel medicine practitioners on the WG often raised the issue about the availability of other cheaper vaccines overseas. Some of the issue are that this means that if the traveler arrives in country, they need to seek out a vaccination provider, and it takes about 2 weeks for sufficient immunity to develop for a protective immune response. It is certainly worth consideration and it is mentioned in the *MMWR* report, but for the US traveler it is not licensed/available and is not a solution if they wanted to have protection before departing overseas. “Visiting friends and relatives” travelers are an important group, but often may not access healthcare at all.

Dr. Patricia Whitley-Williams (NMA) pointed out that there may be US travelers who receive vaccine for the first time and then travel to a country to stay for 1 to 2 years, but then do not return in that timeframe. Mention should be made about lack of knowledge regarding interchangeability with other vaccines that might be available.

Dr. Hills indicated that the *MMWR* document notes that there are other vaccines available overseas, but they have not been licensed or reviewed in the US. There is no specific mention about interchangeability, but that is a good point.

Dr. Cohn acknowledged that this has been a very long but very impressive road, and that they look forward to bringing this to a conclusion in February 2019.

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Anthrax Vaccine

Introduction

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

Dr. Stephens reminded everyone that the Anthrax Vaccine WG was reconvened in March 2017 to discuss new data published since the last review in 2010. Anthrax vaccine is unique compared to the vaccines usually reviewed by ACIP. The US government stockpiles anthrax vaccine and antitoxin for PEP should there be a wide-area release of *Bacillus anthracis (B. anthracis)*. The WG considered the body of evidence since last review in 2010 for policy changes to optimize the use of anthrax vaccine for PEP following a wide-spread release of *Bacillus anthracis* spores. The WG also is reviewing the body of evidence for use of anthrax antitoxin for PEP when no effective antimicrobials are available. The topics of focus for this session included an informational session on a new anthrax vaccine (AV7909) for PEP, and an informational session on anthrax antitoxin for PEP.

AV7909L: NuThrax®

Paul-André de Lame, MD
Vice President, Clinical Development
Emergent BioSolutions

Jeffry Shearer MS, PMP
Director, In Vivo Testing
Emergent BioSolutions

In terms of clinical development, Dr. de Lame indicated that AV7909 is an anthrax vaccine adsorbed (AVA) drug substance with CPG 7909 adjuvant. AV7909 is being developed for PEP of disease resulting from suspected or confirmed *B. anthracis exposure*, when combined with the recommended course of antimicrobial therapy. AV7909 is to be administrated intramuscularly (IM) in a 0.5 mL dose, with 2 doses to be given 2 weeks apart. In terms of the timeline, there is a plan to submit an application for an Emergency Use Authorization (EUA) in December 2018 and an expectation to have the BLA files in 2022. Non-clinical data work has been ongoing, and there are two clinical studies. Lots are being manufactured for delivery after EUA approval.

In terms of current experience with the vaccine, 3 trials have been conducted between 2005 and 2015 for a total of 244 exposed subjects. Overall, those trials have shown that AV7909 as compared to BioThrax®, which is the same product without the adjuvant, is comparatively safe and has a better and faster immune response. The peak of AV7909 occurs just before Day 28 compared to the peak of BioThrax®, which occurs two weeks later and is lower. Looking at those studies together, the profile of AV7909 suggests that there is a faster, stronger response and they are similarly efficacious. After Day 42, the two are essentially identical. They also are very comparable in terms of the safety profile, if not identical.

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Dr. Shearer described the non-clinical studies conducted to support the immunogenicity endpoints for the upcoming AV7909 Phase 3 clinical trial. The goals of the non-clinical efficacy studies were to determine the circulating neutralizing toxin levels in terms of toxin-neutralizing antibody (TNA) expressed as 50% neutralizing factor (NF_{50}) associated with a 70% probability of survival following inhalational exposure to a lethal level of anthrax spores. The proposed Phase 3 clinical study immunogenicity endpoints are supported by a combination of BioThrax® and AV7909 efficacy studies. Because BioThrax® has been licensed for the PEP indication and because of the similarity of the products, it was considered prudent to determine whether AV7909 given on the proposed schedule is non-inferior to BioThrax® given on the licensed PEP schedule. The BioThrax® vaccine was evaluated in well-established rabbit and NHP models. A total of 6 clinical efficacy studies of the AV7909 were conducted. Of these, 3 were in Guinea pigs (GP) and 3 were in NHP. The reason GP were used for the AV7909 was because of the reduced response in the rabbits to the CPG 7909 adjuvant. In the BioThrax® studies, animals were vaccinated on Days 0 & 28 and challenged on Day 70. Two vaccination schedules were evaluated for AV7909, an accelerated schedule on Days 0 & 14 and the Days 0 & 28 schedule. For both studies, the animals were vaccinated with various dilutions of vaccine to produce a stratified immune response prior to challenge. Separate groups of animals were challenged in the AV7909 studies, with one group challenged on Day 28 and another on Day 70. For any deaths that occurred following vaccination and challenge, were confirmed to be deaths due to anthrax based on bacteremia and/or histopathology.

The data from the rabbit licensure enabling study showed that a TNA value of 0.56 was associated with protection of the rabbits in that study. In the BioThrax® NHP study, the TNA threshold value of protection was determined to be 0.29. This is the value that will be used to support the proposed AV7909 Phase 3 non-inferiority primary endpoint. In terms of the TNA NF_{50} threshold values associated with 70% protection in the NHP vaccinated with AV7909 according to the Day 0 & 14 day schedule, the 0.15 TNA threshold of protection will be used to support the AV7909 Phase 3 secondary immunogenicity endpoint for protection. A meta-analysis was performed in which all vaccination and challenge survival and TNA data were combined for all of the animals vaccinated with BioThrax® or AV7909. The conclusion from this meta-analysis was that because of the similarity in protection among the two vaccines, the 0.29 value from the BioThrax® study represented a conservative bridging endpoint for the Phase 3 clinical trial. All of these data have been submitted to the FDA, and BioSolutions just received feedback from them indicating that no additional non-clinical efficacy studies will be required to support the Phase 3 endpoints.

Dr. Shearer summarized that the TNA NF_{50} values derived from non-clinical studies supporting the BioThrax® licensure for the PEP indication will be used for the co-primary endpoints for AV7909 Phase 3 clinical trial, and the 0.151 NF_{50} threshold from NHP vaccinated with AV7909 according to the Day 0 & 14 accelerated schedule will be used for the secondary endpoint in the Phase 3 trial.

Dr. de Lame described the Phase 3, randomized, double-blind, parallel-group trial to evaluate the lot consistency, immunogenicity, and safety of AV7909 for PEP of anthrax in healthy adults. The primary objective is to show that three pre-production quality (PPQ) lots of AV7909 achieve a TNA $NF_{50} \geq 0.56$ on Day 64 and are non-inferior to BioThrax® vaccine at Day 64. A total of 3850 subjects will be involved in approximately 40 or more sites. There are 5 groups, one for each of the lots of AV7909 (N=1100 each) and one control for BioThrax® (N=550).

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In terms of lot consistency, both of the following co-primary endpoints have to be met for the study to conclude positively for the product:

- ❑ Equivalent immunogenicity across three consecutive AV7909 lots as demonstrated by the 95% CI intervals for the ratios of geometric mean TNA NF_{50} at Day 64 for each of the three lot-to-lot comparisons to be within 0.5 and 2.0
- ❑ Protective level of immunogenicity in all three consecutive AV7909 lots as demonstrated by the lower-bound of the two-sided 95% CI to be ≥ 40% for the proportions of AV7909 subjects in each of the three lots achieving a TNA NF_{50} ≥ 0.56 at Day 64

Immunogenicity also will be checked at Day 64, with the following endpoints:

- ❑ Lower bound of the two-sided 95% CI is ≥ 40% for the proportion of AV7909 participants in Groups 1-3 (three lots pooled) achieving a TNA NF_{50} ≥ 0.56 on Day 64
- ❑ At Day 64, *non-inferiority* of AV7909 to BioThrax® at Day 64 as determined by the one-sided lower 95% CI of the difference in the proportion of AV7909 participants (three lots pooled) with a TNA NF_{50} ≥ 0.29 and the proportion of BioThrax® vaccine participants with a TNA NF_{50} ≥ 0.29 being greater than -15%

The additional immunogenicity endpoint is:

- ❑ Lower bound of the two-sided 95% CI will be ≥ 67% for the proportion of AV7909 participants in Groups 1-3 (three lots pooled) achieving a TNA NF_{50} ≥ 0.15 on Day 29. *(Note: The primary lot consistency and immunogenicity endpoints must all be met for testing to proceed to the secondary endpoint.)*

The safety endpoints are as usual for this type of trials

- ❑ Primary: Incidences of SAEs from the time of the first vaccination on Day 1 through the 12-month safety follow-up telephone call following the last vaccination
- ❑ Incidences of AEs from the time of the first vaccination on Day 1 through Day 64
- ❑ Incidences of clinical laboratory abnormalities
- ❑ Incidences of autoimmune-associated AESIs from the time of the first vaccination on Day 1 through the 12-month safety follow up telephone call following the last vaccination
- ❑ Incidences of solicited systemic reactions and solicited injection site reactions by severity following each vaccination as reported in participant e-diaries

Dr. de Lame indicated that the second trial is a Phase 2 drug-vaccine interaction study to examine whether co-administering AV7909 with ciprofloxacin or doxycycline affects antibiotic pharmacokinetics (PK) or AV7909 immunogenicity in healthy adults. This study consists of 210 subjects assigned to the following groups:

Group 1: AV7909 + ciprofloxacin with ciprofloxacin PK (N=40)
Group 2: AV7909 + ciprofloxacin without ciprofloxacin PK (N=30)
Group 3: AV7909 + doxycycline with doxycycline PK (N=40)
Group 4: AV7909 + doxycycline without doxycycline PK (N=30)
Group 5: AV7909 only (N=70)

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The primary endpoints include the following:

- ❑ Area under the curve from 0 to 12 hours ($AUC_{0\text{-}12h}$) and maximum concentration (C_{max}) for ciprofloxacin on Days 8 and 35
- ❑ Area under the curve from 0 to 12 hours ($AUC_{0\text{-}12h}$) and maximum concentration (C_{max}) for doxycycline on Days 8 and 38

The secondary safety endpoints are:

- ❑ Incidence of AEs from the first dose of any IP through the Final Study Visit (Day 45 ± 1)
- ❑ Incidence of serious AEs (SAEs) from the first dose of any IP until the 12-month follow-up (Day 388 ± 14)
- ❑ Incidence of solicited systemic and injection site reactions reported in participant e-diaries following each vaccination
- ❑ Incidence of adverse events of special interest (AESIs) from the first dose of any IP until the 12-month follow up (Day 388 ± 14)
- ❑ Incidence of clinical laboratory abnormalities

The secondary PK and immunogenicity endpoints are:

- ❑ $AUC_{0\text{-}12h}$ and C_{max} for ciprofloxacin on Days 4 and 31 and for doxycycline on Days 2 and 32
- ❑ Geometric mean TNA 50% neutralizing factor (NF_{50}) values 2 weeks after the second vaccination (Day 37 ± 1)

Discussion Points

Dr. Stephens requested clarity about whether the CPG adjuvant is novel and what the rationale was for selection of that particular adjuvant.

Dr. de Lame replied that he thought the CPG adjuvant was selected because it is known and safe.

Dr. Messonnier recognized that this vaccine is meant to be a contingency plan in the setting of an anthrax attack. Understanding all of the constraints about that and the ethical considerations around use of the vaccine in a population that is not at risk, she expected that there were no plans to conduct studies among children as they are not at risk of anthrax unless there is an event. However, in the setting of a large-scale event ACIP will be faced with the need to make recommendations for use of an anthrax vaccine in children. With that in mind, she requested information about what is known regarding the safety of CPG in children.

Dr. de Lame responded that this is not the objective of the program at this point. They would like to know how it works and how it fares in adults before exposing children. That said, it is a valuable point and real concern should there be massive exposure for this type of attack.

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Anthrax Antitoxin for PEP

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

Dr. Bower began with a brief overview of anthrax pathogenesis and how anthrax antitoxins work to prevent disease. *B. anthracis* produces protective antigen that binds to anthrax toxin receptors on the cell's surface and forms a heptamer. *B. anthracis* also produces two toxins that are essential for the development of anthrax disease. These two protein exotoxins, lethal factor and edema factor, bind to the protective antigen heptamer complex and are taken into the cell where lethal factor and edema factor are released into the cytoplasm. Once released in the cytoplasm, lethal factor and edema factor inhibit bacterial clearance by phagocytes and help bacilli to escape from macrophages, thus allowing overwhelming bacteremia to occur. Anthrax antitoxin binds to PA, which blocks movement of toxins into the cells. This stops the ability of the toxins to exert their effects within the cells. However, it is important to note that antitoxin has no effect on toxins that have already been taken into the cell.

There currently are three anthrax antitoxins licensed for treatment of inhalation anthrax. Raxibacumab was the first one approved in 2012. It is a monoclonal antibody. Anthrax Immune Globulin Intravenous (AIGIV) was approved in 2015. It is a purified human IgG polyclonal antibody collected from individuals immunized with AVA. Obiltoxaximab was most recently approved in 2016 and, like raxibacumab, is a monoclonal antibody. They all work by binding the protective antigen produced by *B. anthracis.* All three anthrax antitoxins have an indication for the treatment of inhalation anthrax in adult and pediatric patients in combination with appropriate antimicrobials. The monoclonal antitoxins, raxibacumab and obiltoxaximab, also have an indication for PEP following exposure to aerosolized *B. anthracis* when alternative therapies are not available or are not appropriate. AIGIV does not have an indication for PEP use. This presentation focused mainly on the monoclonal antibodies for PEP. Of note, these antitoxins were all approved for their listed indications under the Animal Rule. This means that their effectiveness for anthrax treatment and PEP is based solely on efficacy studies conducted in inhalation anthrax animal models.

In terms of the data presented to the WG on antitoxin use for anthrax PEP, to show the effect of administration of raxibacumab for PEP, rabbits were exposed to a spore challenge of 100 LD_{50} and administered raxibacumab at 40 mg/kg at 0, 12, 24, and 36 hours after exposure. Of the rabbits, 100% survived when raxibacumab was given at the time of exposure or at 12 hours post-exposure. If administration was delayed to 24 or 36 hours postexposure, survival dropped to 50% and 42%, respectively. To show the effect of administration of obiltoxaximab for PEP, a similar study was conducted. NHP were exposed to a 200 LD_{50} of *B. anthracis* spores and administered obiltoxaximab at 16 mg/kg at 18, 24, or 36 hours post-exposure. Of the NHP, 100% survived when obiltoxaximab was given at 18 hours post-exposure, 83% at 24 hours post-exposure, and 50% at 36 hours post-exposure.

To test the impact of raxibacumab administration on the development of a protective immune response, 21 surviving NHP that had received a *B. anthracis* spore challenge of 100 LD_{50} in a dose-ranging efficacy study were used for a re-challenge study. These animals were re-challenged with 100 LD50s of *B. anthracis* spores 11 months after the dose-ranging study. Of the immunized animals, 100% survived compared to 0% of controls. A similar study was conducted with obiltoxaximab to determine if it interfered with development of a protective immune response. In phase 1 of the study, rabbits were challenged with 200 LD_{50} of aerosolized

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B. anthracis spores and treated with either obiltoxaximab, levofloxacin, or a combination of the two. In phase 2, the 13 surviving animals were re-challenged 9 months later with another 200 LD_{50} dose. All survived compared to none of the controls. These two studies suggest that these antitoxins do not interfere with development of a protective immune response.

The co-administration of AVA and AIGIV has been shown to reduce the development of a protective immune response to AVA significantly in a rabbit model. There was concern that co-administration of the monoclonal anthrax antitoxins could also blunt the immune response to AVA. To determine if raxibacumab had an effect on the immunogenicity of AVA when co-administered, a study was conducted in human volunteers. One group received AVA at days 1, 15, and 29 while another group received the same AVA vaccine schedule started immediately after administration of a single intravenous 40 mg/kg dose of raxibacumab. This study demonstrated that when a single dose of raxibacumab was co-administered with the first of three doses of AVA, the immune response in humans at day 29 was non-inferior to that for AVA given on its normal schedule. The study also showed that the percentage achieving a 4-fold or greater increase in toxin neutralizing activity titer from baseline at Week 26 after the first AVA dose was not different between the two groups. The FDA did not request this information as part of the approval process for obiltoxaximab, so there are no data on the effect of obiltoxaximab and AVA co-administration.

To summarize the Anthrax WG's discussions on anthrax antitoxin for PEP, the anthrax monoclonal antitoxins, obiltoxaximab and raxibacumab, have an indication for use as PEP for inhalation anthrax when alternative therapies are not available or are not appropriate. Situations when alternative therapies are not available or are not appropriate include settings in which the organism is resistant to all available PEP antimicrobials or supplies of antimicrobials to which the organism is susceptible are not available. The data show that anthrax antitoxin administered 12-18 hours after exposure to aerosolized *B. anthracis* spores can prevent 90% to 100% of disease in both rabbit and NHP models. However, survival rates are both concentration- and time-dependent.

Protection drops significantly with increasing time to intervention after exposure. In the studies the WG reviewed, after 36 hours, the survival rates in rabbits administered the maximum dose of raxibacumab dropped from 100% at 12 hours to 42% at 36 hours. Likewise, the survival rate in NHP administered the maximum disease of obiltoxaximab dropped from 100% at 18 hours to 50% at 36 hours. In animals that survived *B. anthracis* spore challenge, there was no late emergence of anthrax from residual spores and surviving animals were resistant to re-challenge up to 11 months later. This suggests that anthrax antitoxins can provide protection until, and do not interfere with, the development of a protective immune response. However, the animals in these studies all received high-dose spore inoculums. Whether antitoxin use in persons exposed to smaller dose spore inoculums would interfere with the development of an acquired protective immune response is unknown.

Data support raxibacumab co-administration with AVA as part of a PEP regimen. When a single dose of raxibacumab was co-administered with the first dose of AVA, the immune response in humans was non-inferior to that for AVA alone. However, no data on immune response are available for co-administered AVA on a dose-sparing vaccine schedule in conjunction with raxibacumab. In addition, no data on immune response are available for co-administered AVA in conjunction with obiltoxaximab. Since obiltoxaximab is a monoclonal antibody that is similar to raxibacumab, it is not unreasonable to believe that it also would not interfere with the immune response to AVA. However, at this time, there are no data to determine if obiltoxaximab would interfere with development of a protective immune response if co-administered with AVA. In

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contrast to the data for co-administered raxibacumab and AVA, the co-administration of AVA and AIGIV, which is a polyclonal antibody, has been shown to reduce the development of a protective immune response significantly in a rabbit model.

These are the statements the WG would like to include in the Policy Statement regarding the use of anthrax antitoxin for PEP:

- ❑ In situations where no alternatives for PEP are available after exposure to aerosolized *B. anthracis* spores, obiltoxaximab or raxibacumab may be considered to help prevent inhalation anthrax. The predicted effectiveness of both these antitoxins are based solely on efficacy studies conducted in animal models of inhalation anthrax.

- ❑ Data indicate that AVA can be co-administered with raxibacumab for PEP without impacting immunogenicity. Similar data are not currently available for obiltoxaximab. It is thus unknown if obiltoxaximab would impact the immunogenicity of AVA when co-administered.

- ❑ AIGIV does not have an indication for PEP use. In contrast to the data for co-administered raxibacumab and AVA, the co-administration of AVA and AIGIV has been shown to reduce the development of protective immune response to AVA significantly in a rabbit model.

Dr. Bower indicated that if the EUA is approved, the WG may be bringing this back to the ACIP in February 2019 on using the vaccine in an emergency.

Discussion Points

Ms. Stinchfield (NAPNAP) said she was reflecting on the practical application of this having just gone through PEP for measles in Minnesota last year, giving MMR within 72 hours and intravenous immunoglobulin (IVIG) in 6 days. The clock is always ticking in these situations, so 36 hours is really short to identify, get everything in order, and administer. One of the practical applications would be to drill this given the importance of having everything in order such as protocols, communications, sites for administration, who would administer and how are they licensed to do it, et cetera. It could be daunting.

Dr. O'Leary (PIDS) inquired as to how these would be administered, as this could add to the difficulty of administration.

Dr. Bower indicated that they are administered intravenously (IV). There is no intramuscular (IM) option. There are a lot of classes of antimicrobials that can be used for prophylaxis for anthrax. This is in the setting of a highly multi-drug resistant organism (MDRO). The chances of this happening though slight does have an indication, and there is a potential that it could need to be used with an MDRO.

Dr. Hunter noted that as an ACIP voting member, he had not ever voted on anything other than a vaccine. He wondered whether there were any other considerations for antitoxins, antimicrobials, et cetera and whether ACIP ever has to vote on non-vaccine recommendations.

Dr. Cohn requested that Dr. Bower clarify what the plan is for incorporating this guidance into recommendations. ACIP can vote on these types of products in the setting of a vaccine-preventable disease.

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Dr. Bower said that the majority of the focus in the *MMWR* will be on vaccines, but they want to include this as an option for PEP so that everything is discussed in one document. Given that this is guidance, they were not asking for a vote. It was nice to have input from the WG on the discussion as well.

Dr. Messonnier added that it is clear that this is the first step of what is needed in order to even think about implementing these vaccines and antitoxins, and that she did not want anyone to think that CDC was missing their concerns about the operational complexity. This conversation is just starting, these are FDA licensed products, and this would need to be worked out operationally with state and local health departments which would be in the setting of having to implement this type of guidance just like other clinical guidance.

Dr. Stephens noted that a significant reason for considering the antitoxins was in relationship to AVA administration. The polyclonal suppresses AVA response; whereas, at one monoclonal does not and there is uncertainty about the other monoclonal. In the context of AVA administration, knowledge of these antitoxins is important.

Understanding the greater use of these monoclonal and polyclonal antibodies, Dr. Romero asked whether consideration would need to be given to use of live-attenuated vaccines in children after receipt of polyclonal antibody.

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 the HepB and SHINGRIX vaccines supplies.

Merck is not currently distributing its adult HepB vaccine or dialysis formulation and will not be distributing vaccine through the end of 2019. Together, GlaxoSmithKline (GSK) and Dynavax have sufficient supplies of adult HepB vaccine to address the anticipated gap in Merck's adult HepB vaccine supply during this period. However, preference for a specific presentation (i.e., vial versus syringe) may not be met uniformly during this time.

Merck's supplies of pediatric HepB vaccines have been constrained since mid-2017 and Merck will continue to direct its limited supply to the public sector. Merck expects to have a limited supply of monovalent HepB vaccine through mid-second quarter 2019. GSK is able to continue to cover the supply gap through mid-second quarter 2019, with a combination of monovalent and combination vaccine. However, preference for a specific presentation (i.e., vial versus syringe) may not be met uniformly during this time. The expected monovalent supply remains sufficient to cover the birth dose for all children, as well as to provide some second and third doses.

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Due to high levels of demand for GSK's SHINGRIX® vaccine, GSK has implemented order limits and providers have experienced shipping delays. Order limits and shipping delays are expected to continue throughout 2018. GSK has increased the number of doses available for the US market in 2018 based on this, with further increases planned for 2019.

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

Discussion Points

Dr. Hunter requested confirmation about whether the adult HepA vaccine shortage is over.

Dr. Santoli replied that while it is true that the tightness of the constrained supply experienced last year is behind them, they are still controlling the ordering of HepA vaccine to ensure the ability to support routine vaccination and respond to outbreaks. Therefore, they are doing some watchful waiting and more controlling. That said, they are able to meet demand and need for the vaccine at this time.

Dr. Messonnier requested that Dr. Santoli comment on availability of influenza vaccine.

Dr. Santoli indicated that CDC tracks national influenza vaccination. As of the last report on October 19, 2018, approximately 125 to 130 million doses had been distributed. That is more than distributed at that time of year compared to any of the most recent seasons. That does not necessarily mean that everybody has the vaccine they want, where they want it, when they want it because vaccine continues to shift throughout the seasons. While she understands that is very frustrating, CDC has no concerns about the overall national supply of influenza vaccine for this season.

Day 1 Public Comment

Amy Pisani, MS
Executive Director
Every Child By Two

I'm Amy Pisani with Every Child by Two (ECBT). In November, we'll be known as Vaccinate Your Family. I am really here on, I'd say, the whole vaccine community and especially the National Meningitis Association (NMA). We wanted to remember a lovely, lovely woman who passed away last month named Lynn Bozof. We are also wearing a butterfly pin today to remember NMA and especially Lynn, so if anyone would like to have one of those pins, please come and see me. The folks at NMA are actually at a retreat today talking about their future, and they have a wonderful President that is going to continue with them, so I know they will be staying strong. Lynn was a constant here at ACIP. She often brought parents that had lost their children to meningitis to talk to us, and she often brought survivors. Lynn's son Evan was a junior in college when he contracted meningococcal meningitis, and that was in 1998. He died 26 days later after suffering amputations of all of his limbs. In 2002, Lynn founded NMA along with 4 other mothers who had also not heard of meningococcal vaccination. She and her husband, Alan, and these many families wanted us to know what it was, and I didn't even know

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back then. I started myself in 1998 with ECBT. I'd like to say that because of people like Lynn and Frankie Milley, we know what the word "meningococcal" is and we can say meningitis, and I think parents around the country know that word because of them. Now, because of NMA, there is awareness of the ACWY vaccine. We now have a vaccine recommendation for all pre-teens and teens at for others at risk. Many states now require the vaccine for all adolescents, and the rates are increasing steadily. Also, we have a wonderful vaccine now for meningococcal B. Just a little anecdote, I never got to tell Lynn how this played out, but I went to my pediatrician with my son who was 16 and they gave him ACWY. I said, "When is he getting the B vaccine?" They said to me, "Let's see what college he gets into and we'll decide then if he needs it." I said, "No, I don't think so." They said, "Well, then you're going to have to go and get the vaccine at the pharmacists, bring it back to us, and we will give him the vaccine." So, I went to Lynn and said, "What should I do?" She gave me everything I needed to do to educate them, and I'm proud to say that they are now giving vaccine to all kids in the practice, and that's because of Lynn. Paul wanted to say a little bit more.

Paul Offit, MD
Chief, Division of Infectious Diseases
Director, Vaccine Education Center
Children's Hospital of Philadelphia
Maurice R. Hilleman Professor of Vaccinology/Professor of Pediatrics, University of Pennsylvania School of Medicine
Voting Board Member, Every Child By Two

The best way for me to remember Lynn is to read a few sentences from something her surviving son, Ryan, wrote and posted to a number of us. Ryan wrote, "I can never put into words the impact a mother can have on a son. My mother was such a sweet, warm, innocent person who always made me feel loved. I've always been amazed at how she turned the inconceivable tragedy of losing a son and my only sibling to bacterial meningitis and became an endless advocate for meningitis prevention. She started the National Meningitis Association with several other parents who lost children or their children who were disabled by meningitis. She took it upon herself to be an ambassador for meningitis prevention and awareness. This became her passion in life to prevent other families from having to suffer this dreaded disease. Part of my peace during this difficult time is knowing that she is no longer suffering and she will be reunited with my brother, her other son Evan. My mom and I used to always say to each other, "I love you to infinity." She will always be in my heart and loved infinitely. Ryan Bozof."

Susan Olson-Corgan
Board of Directors
Informed Choice Washington

Hi. My name is Susan Corgan. I'm on the Board of Directors for Informed Choice Washington in Seattle. I have a speech written here, but after sitting here today listening to all of you and watching these presentations, I would just like to ask a couple of questions if that's okay. Is that okay? One is you heard a bunch of people talk that are in the vaccine risk aware community. I'm just curious, when you're listening to us speak, are you listening? Are you hearing our stories? Do you understand that we watched our children go through vaccine injury, and children like mine whose pediatrician is the one that called it because it happened in the doctor's office? Do you understand that this happening to even a small subset of individuals that it's still happening? To me, it's my only child. That's my whole world. Are you guys listening? [Dr. Cohn clarified that ACIP does not respond during the public comment period, but that Ms. Corgan could continue]. I guess I'll just end with this then. My son has a verifiable vaccine injury. It is

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real. It is possible. It's been proven. I do not wish this on anybody. I wish for all children—I'm just like you guys. I want all kids to be healthy, and safe, and protected in any way that we can. I would just hope that we would all work together and make the effort to start looking at some of the genetic testing for susceptibility. My son has mitochondrial disorder and methylation disorders. We've been told on numerous occasions now that that is a main part of what lent to his vaccine reaction. I would just ask that you guys would consider that evidence and read the book "How to End the Autism Epidemic" if you have not done that by J.B. Handley. There are three depositions in there that I think would be of interest to you. Thank you.

Tia Severino
Concerned Parent

Hello. My name is Tia Severino. I am what some might call an "anti-vaxer." That term is not representative of who I am. If I had been truly anti-vaccine, I would not have taken my daughter to get all of her vaccines. I would not have vaccinated my son. When I was here in June, I introduced you to him and I told you that he only had 4 single dose vaccines. I firmly believe that those vaccines injured him and causes his autism. My daughter, now 28, was recently diagnosed with Asperger's. I take issue with the theory that the rise in autism is due to better diagnosis. Children who have autism are frequently not diagnosed for a variety of reasons, not the least of which being the stigma attached to that label. There were not 1 in 40 autistic males when I was growing up in school. They did not exist. It is not better diagnosis. Truthfully, autism is a label we give to brain injury with gut involvement. A good friend of mine, James Lyons-Weiler, wrote this book "The Environmental and Genetic Causes of Autism." In this book, he presents the findings of over 1000 studies. The idea that autism is a genetic disorder which has always been with us deserves a closer look. It turns out that many of the genes associated with autism have to do with detoxification. Ultimately, genetics can only account for less than half of the incidence. No single gene is responsible for more than 1% of autism risk. The rest is clearly environmental. This book, very good. I recommend everyone on this panel to read it. There is no such thing as a genetic epidemic. For these genes associated with autism to result in autism, there has to be an environmental toxin exposure. These genetically predisposed individuals cannot excrete the toxins. Certain toxins are cumulative. They build up over time and they further the damage the brain, gut, and other organs. There are known toxins in vaccines. I don't think there's a single person in this room that can dispute that there are known, known toxins in vaccines. Now we're not saying—we acknowledge that vaccines are not the only source of toxins. But, they are without question the greatest and most widespread exposure. When this fact is taken into consideration, autism is environmental even when genetics are involved. What steps are you, the Advisory Committee on Immunization Practices at the CDC doing to ensure that genetic screening is done to find these vulnerable individuals. The answer as far as I can tell is none. Nothing seems to be happening regarding pre-screening children prior to vaccine. Maybe that would interfere with vaccine uptake.

ACIP is part of CDC. CDC is part of HHS. HHS is tasked by Congress, according to the 1986 National Childhood Vaccine Injury Act (NCVIA) to do the following: 1) Perform Safety Studies: Perform vaccine safety testing to ensure that vaccines are as safe as possible; 2) Promote vaccine uptake nationwide to ensure that the population is protected; and 3) Submit bi-annual reports to House Incident Committees detailing actions taken to ensure vaccine safety. A recent lawsuit against HHS revealed that these required reports have never been submitted, which begs the question: Where are the vaccine safety studies? Were they done? If they were done, why have 30 years passed with no one single report to Congress as required by law? Over the past 3 decades, HHS through CDC and this panel's recommendations, has aggressively promoted—you have succeeded at aggressively promoting widespread uptake of vaccines. In

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1983, the CDC's Childhood Vaccine Schedule included 11 injections of 4 vaccines. As of 2017, the CDC's Childhood Vaccine Schedule includes 56 injections of 30 different vaccines. That is a 5-fold increase without any safety testing on the cumulative effects or the effects of administering multiple vaccines at once, which is routine. Routine. I am not an anti-vaxer. I am an advocate, and I am part of a growing population that is informed and aware of the truth of the vaccine program. Every time a child or adult is injured by a vaccine, a potential activist is born. If this committee continues in the way that it has using manipulated, insufficient, and sometimes fraudulent science to justify adding more and more vaccines to the schedule with zero regard for how these vaccines may injure, disable, or kill, you will continue to see our numbers grow. I sincerely hope that you and your peers in pharmaceutical, medical, and scientific fields can start to see us for what we really are: intelligent, informed, fearless, capable of doing our own research. Our numbers include scientists, doctors, nurses, and ordinary folks that had to figure out what happened when a vaccine took our perfectly healthy baby and made him sick, disabled, or dead. There's also those among us who are not injured or affected. Some are raising unvaccinated children, and they're concern about the trend toward vaccine mandates and what that means for their families. The label "anti-vaxer" tries to lump us together in one group, and it has the effect of discrediting us as unreasonable, anti-science, and pro-disease. The reality is we have legitimate questions and concerns that are being ignored or dismissed. It is time for the CDC and HHS to do the right thing and find ways to reduce harm. Ensure that vaccines are made safe—something I don't think is possible, by the way. Stop enabling the only industry that enjoys not only immunity from liability when their products harm, but also are the beneficiary of this panel's recommendations. I'm sorry. I am emotional. But, you have to understand that I'm dealing with something every single day that you all want to deny exists. You all want to pretend like it's anything but the vaccines. I really appreciate you giving us the opportunity to come here and speak. Thank you very much.

Teresa Burke
Concerned Parent
Michigan for Vaccine Choice

Good evening. My name is Teresa Burke. I'm from Michigan. I am deaf, so I may mispronounce some words. Bear with me. I have to say that I find it very disturbing that we as society accept the following as the new normal childhood illnesses: cancer, asthma, allergies, attention-deficit/hyperactivity disorder (ADHD), eczema, childhood bi-polar, sudden infant death syndrome (SIDS), juvenile diabetes, autoimmune disorders, seizures, autism, autism spectrum disorder (ASD), speech delays, learning disabilities, head banging, non-verbal children, children past the age of 5 still in diapers. We accept these issues simply because these childhood illnesses or neurological disorders are not contagious. A child with HIV can go to school. A child with hepatitis B can go to school. But, a child that does not have a hepatitis B vaccine cannot go to school. That is unacceptable. I also find it very disturbing that we are led to believe that vaccines are safe with no possible side-effects and that one-shot-fits-all. In 2006, both of my daughters were nearly destroyed by the HPV vaccine. Actually, they were destroyed. Years of sickness with no answers from the doctors, because doctors are trained to ignore adverse reactions. I have been studying vaccine ingredients since 2010, and I have yet to find safety studies to prove that multiple vaccines given at one time are safe. According to the CDC recommended vaccine schedule, a 2-month old will receive 7 vaccines, then again at 4 months, another 7 vaccines. At 6 months, the child will receive 8 or 9 vaccines depending on if they get the flu shot. There are no studies to prove these multiple vaccines are safe for these small children, and the children cannot speak to us to tell us their adverse reactions. We all hear that everyone wants to prevent illness and deadly diseases. We want health. But, 8 out of 10 of our United States of America children have some type of learning disability, neurological disorders,

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or a serious health condition. The United States of American has the highest rate of vaccinations. We have the highest rate of unhealthy children, and the highest rate of autism. 7,213,599 children are currently on psychiatric medication. 125,361 of those children are under the age of 1 year old. Such medication is not even prescribed by a psychiatrist. It is prescribed by a pediatrician. You can find these numbers of CCHR International Mental Health Watchdog Website. It's unknown how our Amish community survives without all of these vaccinations. As you continue to add to the already heavy schedule, I ask that you please provide our doctors with the safety studies to prove that all of these vaccines given at one time are safe. Thank you.

LeeAnn Johnson
Autism Mother

Hello. My name is LeeAnn Johnson. I have two severely autistic little boys. They are 6 and 7. I would have loved to be here this morning, but last night I was up almost all night. I got about 3 hours of sleep because my 7-year old was having myoclonic seizures all night, so one of us was with him, and my other one was having GI spasms, which is associated with autism. So, tonight when y'all lay down, please think of me and my children. If you pray, pray for us, because this is the result of vaccine injury for my family. It is constant. We get maybe 2 to 3 hours a night a week. I constantly have family members there, therapists, friends coming in every day. It's a revolving door to help us take care of our two children. It is very sad and it is very, very unfair. So, we spread out our vaccines and I went against my gut because I talked to my doctor who swore up and down that nothing would happen to my boys. We went in on June 27, 2016 with my oldest. He was happy. We did the Modified Checklist for Autism in Toddlers™ (M-CHAT™). Perfectly advanced child. I agreed to do the DTaP because I was spreading them out. The nurse argue with me. She left the room and sent another person in. They ended up giving him Pentacel®, which we did not know until a couple of weeks later. Pentacel® is a 5-in-1 combo that he didn't need until he was 4 years old. So, that's a whole other issue in itself. So, the next day, little did we known at the time, we thought it was kind of cute and he was being silly, but he was already tiptoeing, flapping his hands, he didn't speak, and he didn't speak again for another 8 months, and all we got out of that was a "da." We assume that was for "da." He was uncontrollably laughing and he quit sleeping all together. So, I went back to the doctor and I said, "You said this couldn't happen." He said, "Oh, I don't do autism." Considering that he said that, I'm going to assume that he never reported it to VAERS. So, my youngest baby got one vaccine, the same one that hurt my child overnight—the oldest overnight. So, now we deal with severe autism, speech and language delay, sleep disorder, hypotonia, myoclonic seizures, and we now know that they have MTHFR mutation gene, which affects methylation and detoxification, as well as mitochondrial disorder. So, when I had told my pediatrician that I had the MTHFR gene, I had just learned about it, and again, I should have walked out the door because he said, "I don't really know what that means, and I don't think it affects your child." He might should have read up on that, because we could have made some better decisions for my two children. If we had a newborn screening for mitochondrial disorder or MTHFR, or at the very least we had pediatricians that would listen to parents when they present such important information, we would know which children are the ones that are susceptible to these adverse reactions and even death. My healthy children would have been spared, and they would have been living a happy, healthy, normal life. They wouldn't be at home all of the time. They would have friends. They would ride their bikes. They would talk.

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So, I've been a part of the Vaccine Court, which is a "kangaroo court" of sorts if you want to call it that. I had to withdraw because our Special Masters, stating similarities to past cases, felt that it was not needed to go before court. What he failed to realize is that our case is almost exactly like Hannah Poling's case who did win in vaccine court, and also deals with mito, but they didn't know until afterwards as well. He also didn't read any of the 25 affidavits that I have from my family and friends who witnessed my kids changing before their eyes. I'm not an anti-vaxer. I'm an x-vaxer. I reluctantly went along with the doctors and the CDC schedule, and it changed our lives for the worst. Our life is hard, and it's miserable, and I would not wish it upon the worst person in the world. While I'm here to share my story, I'm not here to fight for my boys, as they'll never be vaxed again. I'm here to speak for others who are afraid to share their stories, and demand better informed consent than a bright colored paper so parents can make the best decision for each of their own kids in such cases where they don't listen to the parents. As a citizen of the United States, I would like to see a true vaccine safety study on every vaccine, not one, as well as a vax versus non-vax study. We have the data. We deserve the truth and all the evidence whether profitable or not for pharmaceutical companies or patent holders. Furthermore, my last statement is that I am very perplexed by the revolving door between the CDC employees and pharmaceutical companies. I believe anyone who is voting, recommending, paid to work on vaccine safety, or are working on the schedule should not be able to be paid by pharmaceutical companies who make vaccines, nor should anyone who holds a patent. I believe this is a major conflict of interest. Why wouldn't someone go ahead and vote for what their product could be used to make money on? The Gardasil® slogan is, "I want to be one less." I would give anything for both of my kids to be one less vaccine-injured child.

Jaclyn Gallion
Board Member
Informed Choice Washington

Jaclyn Gallion. I am with Informed Choice Washington. ACIP must immediately end the reckless and dangerous recommendation that vaccine-exempt students be quarantined from school during outbreaks of infections on the recommended vaccine schedule. The primary reasons are the risks of provoking a self-harm attempt or completed suicide in the total absence of evidence that school quarantine is an effective intervention. You hear, and the CDC lists suicide as the second leading cause of death in youth aged 10 to 24, only behind accidents. None of the scheduled vaccine infections have been anywhere near the top 10 since before World War II (WWII). It is an objective fact that some students will and have responded to disciplinary suspensions and expulsions with attempted and completed suicide efforts. This has forced top to bottom reform of how disciplinary suspensions and expulsions are imposed. There is no functional difference between a disciplinary suspension and expulsion and a vaccine quarantine, except the disciplinary-attendance probations are implemented much more rationally and humanely. The disciplined student and their mental status is typically known to the excluding authority. During vaccine school quarantines, large groups of unknown students are thrown out with no pre-screening, no monitoring during quarantines, and no reintroduction support. Zero. These students are humiliated, discriminated, and segregated. Their privacy is violated. Where are the studies that show that school quarantines and mis-labeled school exclusions are safe? There are none. This is a reckless, evidence-free practice. There are no studies that show a school quarantine can interrupt an outbreak. In contrast, there is evidence of outbreaks in 100% vaccinated populations between vaccines that do not prevent transmission, primary and secondary vaccine failure, antigen escape, and numerous other factors. School quarantines are incapable of interrupting infectious spreading. The uselessness and danger of school quarantines was terrifyingly brought to focus during the 2016-2017 Marshallese mumps outbreak. School quarantines were used on exempt students from public

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health who knew all infections were centered in the fully vaccinated Marshallese. The Marshallese were allowed at school because they were vaccinated, even though it didn't work. They should have been quarantined. Leaving the Marshallese in school guaranteed a long-term continuing outbreak. In Spokane, some high school students were quarantined for more than 3 months. This jeopardized their GPAs, their sports, their theatre, music, art, and other participations, their college admission qualifications and scholarships, and more. Many parents observed mental decline in their children, and one quarantined student died by suicide. This unneeded and unsupported practice needs to stop today. These children are just as valuable. Thank you.

Erin Marie Olszewski
Nurses for Vaccine Safety Alliance

My name is Erin Olszewski. I am a Registered Nurse (RN) in two states. I came here from Florida and am very happy to have the opportunity to speak to you. I'm also an Army Special Operations Veteran. I did a year and a half in Iraq, so I understand what it means to serve our country. I feel like that should be your job and your number one priority as well. So, I hope you can listen to this and just really think about everything that's really going on with our children. I'm here today not only for myself, but also for all the other parents that cannot be here because they are taking care of their vaccine-injured children, because there are a lot. There are a lot of them, and we are waking up to this, and it is a very emotional thing for many people to go through. I was a pro-vaccine nurse, and I immunized my patients until our son who, at 12 months, went from smiling, bubbly face, talking and he completely regressed. The MMR vaccine at 12 months took away our son's bubbly, happy character. This is when I started researching and I started looking into everything that was really, really happening behind the scenes. The health care department I work for and I went in to help people, I realized that I was doing the opposite. We are not helping people. You are not helping people. I know that maybe you may not agree with this, but we are real people and this is really, really happening. Our sweet boy regressed after the MMR vaccine that was given to him at 12 months of age. He stopped, he stopped eating, he stopped all eye contact, he stopped hugs, he stopped kisses, and our life turned upside down. We had speech therapists. He underwent several tests, and he is just one. He's mine, but all of these moms and all of these parents are suffering because you are refusing to really look deep down into your hearts and understand that this is not safe and there needs to be more done about our safety in the United States. As a nurse, I thought I could trust my healthcare department. I just can't. I can't bring myself to really comprehend that the business that I went into thinking that I'm going to be helping people—we are doing the opposite. Everyone in this room needs to just consider this, and they need to look at it and really, really understand that we are real people, and we're going to be back, and there's going to be more of us, and more of us, and more of us, and we are not going to stop until change happens. So, I want to just leave you with this. I didn't risk my life fighting overseas for our country so you can just throw it right back in my face. So, I will be back, and I'll see you in February. Between now and then, I hope that each of you reaches deep down into your hearts and you really think about what you are doing to our children. Thank you.

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Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Messonnier began with a brief update on acute flaccid myelitis (AFM), reporting that CDC has identified seasonal clusters of AFM in 2014, 2016, and 2018. CDC; state, local, and territorial public health partners; and clinicians across the country are working diligently to find a cause for this mysterious illness. CDC is actively investigating AFM cases and monitoring disease activity, looking for risk factors and possible causes for the condition, collecting extensive information on each reported case, and collecting a variety of laboratory specimens. In addition, the agency is consulting with nationally recognized experts from academia and other sectors of government to inform the understanding of AFM. While CDC is investigating all possible causes, the bottom line is that what is causing this infection remains unknown. They have looked for all of the normal causes and have not found anything. She emphasized that AFM is not polio. People in the news are calling AFM a polio-like illness. AFM presents suddenly with weakness in the arms and legs in a couple of hours. It is devastating in a number of children, although some do recover. Of the cases, 90% are in those less than 18 years of age and the median age is 4 years. CDC knows this is not polio because the laboratory diagnostics of polio would tell them, and they are not finding this. The agency is actively investigating every possible cause, and will update ACIP when there is further information. She referred everyone to CDC's public AFM website where updated numbers of confirmed cases and patients under investigation are reported on Monday afternoons.

The annual results of immunization coverage data were reported recently in the *MMWR* from the National Immunization Survey-Child (NIS-Child) coverage data and the kindergarten vaccination coverage data. These data indicate that most US parents are protecting their children from vaccine-preventable diseases by making sure they are getting recommended vaccines. However, there is an increase among children younger than 2 years of age who are receiving no vaccines. That means that approximately 100,000 children under 2 years of age have not received any vaccines to protect them against potentially serious vaccine-preventable diseases. Personal choice may play some role, but CDC's data suggest that many of these parents do want to vaccinate their children, but may not be able to get vaccines for them. They may face hurdles such as not having a healthcare professional nearby, not having time to get their children to a doctor, and thinking that they cannot afford vaccines. There is a vaccine safety net, but these children are falling through that. Dr. Messonnier is very concerned about this, and CDC will be looking at this more closely.

With regard to influenza vaccine supply, there is an app called "Vaccine Finder" that is free online. This app will allow users to search for locations that offer immunizations. This can be used to track potential shortages of vaccines, which providers and parents can use.

In terms of departures, Dr. Amanda Cohn acknowledged two individuals for whom this represents the last ACIP meeting. The first was Dr. Kathy Neuzil, who has served as the liaison for Infectious Disease Society of America (IDSA) and has been involved with ACIP for at least 16 years and has constantly been an amazing force. Her comments have frequently shifted the direction of the discussion and helped to focus on key issues. Dr. Neuzil is departing to serve as a new member of the WHO's Strategic Advisory Group of Experts on Immunization (SAGE). The world will now benefit from her enormous expertise, and Dr. Cohn expressed hope that this

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would not be her actual last ACIP meeting, but that it would be merely a break. The second person Dr. Cohn acknowledged was Dr. Rafael Harpaz, who was retiring from CDC that day. Dr. Harpaz is known as the herpes zoster force of CDC. He arrived at CDC in 1992 as an Epidemic Intelligence Service (EIS) Officer and is an adult infectious disease specialist. Prior to his embarking on the journey of zoster, he worked on international and domestic control of hepatitis, programmatic aspects of vaccine delivery, measles, bioterror surveillance, smallpox vaccination, varicella, mumps, and pretty much every vaccine-preventable disease. Since 2004, he has served as the lead for the Herpes Zoster WG for ACIP. Over the last couple of years, he has shifted those responsibilities to Dr. Dooling, who will do an incredible job as he moves on. Dr. Harpaz has been a major mentor to Dr. Cohn personally, CDC staff, and ACIP members in terms of bringing together an incredible amount of science, thought, focus on vaccine policy questions and how to balance all of the aspects of decision-making, and helping CDC focus on how to make those decisions with ACIP. She presented Dr. Harpaz with a copy of his first *MMWR* signed by all of the ACIP members.

Dr. Harpaz expressed his gratitude and said that his feelings were very mixed. It has been wonderful working on VZV and zoster over many years. This family of viruses has evolved over the eons in species as diverse as oysters to humans, causing asymptomatic infections at one extreme and driving people to suicide at the other due to pain. Zoster is a clinical entity that affects over a million people, mostly at the vulnerable stages of their lives. As everyone has heard him say on many occasions, the cause of the increases in zoster over the years is not really known, and it is not understood why one-third of people get zoster and the other two-thirds do not. This disease has a huge burden and also is a fascinating disease, which satisfies his ravenous curiosity. On a more general note regarding ACIP, Dr. Harpaz said that it had been a real privilege to be able to work on vaccine policy for many years and to make vaccine policy as beneficial as is possible can be, both domestically and internationally. It has been a privilege and honor to work with the ACIP members and those who proceeded them on this big endeavor.

Department of Defense (DoD)

Dr. Deussing expressed the DoD's appreciation for CDC's continued inclusion of the DoD in this meeting and ACIP's WGs. With respect to the Yellow Fever (YF) vaccine supply, DoD continues its due diligence managing YF vaccine requests during the current manufacturer shortages. There are no changes from the June 2018 report. The DoD continues to judiciously administer its current supplies to its beneficiary population. On an administrative note, on October 1st, the Defense Health Agency (DHA) officially assumed administrative and management responsibilities for several hospitals and clinics as part of the first of the phased implementation reform plan of the Military Health System (MHS). Congress mandated these changes to create a more integrated, efficient, and effective system of readiness and healthcare that best supports patients and the DoD. As part of its outreach portfolio, the DHA Immunization Healthcare Branch (DHA-IHB) has completed the 9th Edition of the Immunization Toolkit (ITK), a practical hardcopy resource for vaccine administrators in the DoD who lack reliable internet access, which is frequently the case with units that are forward deployed and in austere environments.

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Food and Drug Administration (FDA)

Dr. Fink began by saying that it was an honor to be in attendance representing FDA for the first time, and that he looks forward to working with ACIP and trying to follow in Wellington Sun's formidable footsteps. He reported that 3 approvals have occurred since the last ACIP meeting in June 2018. The first is the approval of a shortened primary series regimen for IXIARO® JE-VC for individuals 18 through 65 years of age. The second approval was to extend the approve use of GARDASIL®9 to individuals 27 through 45 years of age. The third is the recent approval for the extension for the use of AFLURIA® trivalent and quadrivalent inactivated seasonal vaccines to include children 6 through 59 months of age.

Health Resources and Services Administration (HRSA)

Dr. Nair provided an update on the Vaccine Injury Compensation Program (VICP). HRSA is continuing to see an increase in the number of claims. In FY 2018, there were 1238 claims filed with the program. In FY 2018, the VICP awarded $226 million to petitioners. This includes attorney fees for costs, including fees for cases that were compensated, dismissed, and interim. The VICP website provides detailed data about the program and compensation. In April 2018, HRSA issued a Notice of Proposed Rulemaking (NPRM) proposing to add the category of "Vaccines Recommended for Pregnant Women" to the Vaccine Injury Table to bring them in compliance with the statute in the 21st Century Cures Act. A public hearing was held in September 2018 to provide the public an opportunity to comment on this Notice of Proposed Rulemaking. This period has ended and HRSA anticipates issuing the Final Ruling soon.

Indian Health Service (IHS)

Dr. Weiser reported that IHS has been focusing more on childhood immunization coverage, and is making efforts to increase childhood immunization rates. The IHS Immunization Program has been collaborating with the Great Lakes Inter-Tribal Epidemiology Center (GLITEC) and the Bemidji Area Office (BAO) on the Bemidji Area Child Immunization Project. They held an in-person meeting in Minneapolis in August with Immunization Coordinators from IHS, Tribal, and one urban facility in Chicago along with staff from GLITEC, BAO, and the state departments of health from Minnesota, Wisconsin, and Michigan. The purpose of the meeting was to discuss strategies for increasing childhood immunization rates and build capacity for providing education, training, and resources. Additional projects to further improve childhood immunization rates in other IHS areas also are being discussed. This is IHS's second year with a mandatory influenza vaccination policy for healthcare workers (HCW), which seems to be very strong. An increasing number of IHS sites are also adopting drive-up immunization clinics in their facilities, which has been very popular. One of the barriers to that seems to be the CMS reimbursement for activities outside of the 4 walls of the facility. However, most sites are willing to forego reimbursement if necessary to protect their communities.

National Institutes of Health (NIH)

Dr. Beigel indicated that NIH has implemented a few additional studies of vaccines of important pathogens, including H5 with novel adjuvant studies, universal influenza vaccines, Phase I for respiratory syncytial virus (RSV), and live attenuated Zika virus vaccine. In terms of program updates, there is a Funding Opportunity Announcement (FOA) for the Vaccine and Treatment Evaluation Units (VTEUs) and Leadership Group (LG). This turns over every 7 years and is a very large program with multiple sites that conduct important early development work. There also is a Broad Agency Announcement (BAA) for the Collaborative Influenza Vaccine Innovation

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Centers (CIVICs), which focus on early development work for influenza vaccines. There also is a program announcement for Research to Advance Vaccine Safety, which is a program that has been ongoing since 2009. Since 2009, this program has allocated 24 awards. This is a large program with a goal to improve research in vaccine safety.

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

Dr. Beckham said she was happy to be attending her first ACIP meeting as the new NVPO / NVAC representative. She thanked ACIP for the upcoming discussion on human papillomavirus (HPV) and GARDASIL®9 to expand the indication for that vaccine. In terms of following up on the last NVAC report titled, "Strengthening the Effectiveness of National, State, and Local Efforts to Improve HPV Vaccination Coverage in the United States: Recommendations of the National Vaccine Advisory Committee." NVPO is working with its partners and within the Office of the Assistant Secretary for Health (OASH) to implement and formalize a strategy that will address the recommendations from that report. As a first step, they have established an HHS WG to identify HPV efforts across HHS and leverage those ongoing opportunities. In addition, they are developing an implementation plan that will include a 3-pronged approach to address the recommendations in the report, which includes: 1) enhancing communications, awareness, and engagement with providers and patients on the benefits of the vaccine for cancer prevention; 2) working with integrated delivery networks and healthcare systems to implement evidence-based practices that have demonstrated the ability to increase uptake of the vaccine; and 3) addressing and understanding the challenges and opportunities for HPV vaccination in rural communities.

With regard to adult immunizations, NVPO and its partners developed prenatal and adult immunization status measures in July 2018 for inclusion in the Healthcare Effectiveness Data and Information Set (HEDIS) in 2019. The measures are expected to be utilized by health insurers in evaluating health service delivery, and ultimately improve uptake of prenatal and adult immunizations through value-based care. The Adult Immunization Status (AIS) measure has been submitted as a Medicare candidate measure for inclusion in the Merit-Based Incentive Payment System (MIPS) and the Medicare Shared Savings Program (MSSP). This measure is currently in the Pre-Rulemaking Process. If selected, it will be published on the Measures Under Consideration (MUC) List in December 2018 to be utilized in the Quality Reporting Programs (QRP).

Dr. Beckham indicated that she also is the Acting Director for the Office of HIV/AIDS and Infectious Disease Policy (OHAIDP) and as such, that falls under her as well. She expressed appreciation for the expertise and leadership of ACIP in promoting the expanded HepA and HepB vaccination and updating the indications for HepA vaccine to include the homeless. OHAIDP coordinates the implementation of the "National Viral Hepatitis Action Plan," as well as the federal WG of more than 20 agencies and offices spanning 4 departments. This year, they will begin updating that strategy and hope to have it completed by 2020. They are developing a plan and timeline for engaging federal partners and the broader stakeholder communities in the effort to update that strategy.

The NVAC convened in September 2018, during which its topics focused on vaccine innovation and HPV vaccination. The presentations and webcast from that meeting are available on the NVPO website at the NVAC meeting page. The next public meeting will be February 5, 2019 via webcast.

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Veteran's Administration (VA)

No report at this time.

Human Papillomavirus (HPV) Vaccines

Introduction

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

Dr. Szilagyi reminded everyone that the manufacturer filed a Supplemental Biologics License Application (sBLA) in April 2018 to expand the age indication for 9-valent human papillomavirus (HPV) vaccine (9vHPV) through age 45 years. FDA accepted the application in June 2018, gave this a priority review, and approved it on October 6, 2018. There was an HPV session during the June 2018 ACIP meeting that included an introduction and background with an overview, a history of the application for licensure in the expanded age group, HPV epidemiology and the burden of disease, and the clinical trial data included in the sBLA.

Since that time, the HPV Vaccine WG has been extremely busy reviewing a number of topics, including HPV epidemiology related to mid-adults, values and acceptability, post-licensure effectiveness data, impact modeling and economic analyses, GRADE, and recommendation options for consideration. In terms of the modeling and health economic analyses, three models are being used to provide evidence for this policy consideration. All are going through CDC/ACIP economic review. Modeling adult HPV vaccination is very challenging, and there are differences in results across the models. The ACIP WG has only recently been able to review preliminary data.

Dr. Szilagyi indicated that this session would include a brief vaccine safety update to address a question about the relationship between HPV vaccine and primary ovarian insufficiency (POI). In addition, there would be presentations on the expanded HPV vaccine age indication including: 1) background information on the regulatory basis for licensure, US vaccination coverage and impact, HPV epidemiology and post-licensure effectiveness, and global HPV vaccination; 2) GRADE; 3) the impact and health economic analyses; and 4) policy considerations. While there would not be a vote during this session, there possibly will be one during the February 2019 ACIP meeting.

Vaccine Safety Update: No Association with POI

Julianne Gee, MPH
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Ms. Gee indicated that the purpose of this presentation was to update the committee on a recent publication on and adolescent vaccination. Their study was published in *Pediatrics* in August 2018. She noted that during her presentation, she would provide background on POI, describe the methods the investigators employed, and present study results and conclusions [Naleway et al. *Pediatrics*. 2018;142(3). pii: e20180943].

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POI is sometimes referred to as premature menopause or premature ovarian failure (POF). POI is characterized by the following before the age of 40 years: dysfunction or depletion of ovarian follicles, menopausal symptoms (e.g., amenorrhea, hot flashes), or reduced fertility. Under the age of 20, POI is uncommon with an estimated prevalence is 1 case/10,000 females. Chromosomal abnormalities including Turner syndrome, Fragile X syndrome, and gonadotoxic cancer treatment are known etiologies. Most POI is idiopathic, but may be associated with underlying autoimmune or infectious diseases such as mumps.

Findings from over 12 years of post-licensure HPV vaccine safety studies are robust and reassuring. However, concerns surrounding fertility following HPV vaccine have developed after a few small case series studies were published, as well as reports of POI following HPV vaccination in the national media and circulating in social media and other internet sites. As a result, Ms. Gee and her colleagues conducted a retrospective cohort study. The objectives of the study were to: 1) identify and describe characteristics of POI diagnosed in females 11 through 34 years of age; 2) describe the prevalence and age-specific incidence of POI; and 3) estimate the risk of idiopathic POI in females following quadrivalent HPV (4vHPV) vaccination and other adolescent vaccinations (e.g., Tdap, MenACWY, and IIV). The study population included females aged 11 through 34 years enrolled for at least 30 days at Kaiser Permanente Northwest (KPNW), a Vaccine Safety Datalink (VSD) site, between August 1, 2006 through December 31, 2014.

Cases were ascertained by first searching electronic healthcare record (EHR) databases for outpatient encounters of select International Classification of Diseases (ICD)-9 diagnoses, which included codes for premature menopause, POF, and ovarian dysfunction. The first diagnosis identified in this study period was considered to be the index diagnosis. The medical records were then reviewed of presumptive cases to collect data on diagnostic and other laboratory testing, symptom onset, and other POI risk factors. Presumptive cases were excluded if they were miscoded, considered ruled out diagnoses, or the medical record was unavailable. In addition, cases of POI were excluded with known causes including cancer diagnosis, surgical menopause, and genetic conditions. All remaining idiopathic presumptive POI cases were reviewed and then adjudicated by an obstetrician-gynecologist to confirm case status.

The case definition used for this study was from the American College of Obstetrics and Gynecology (ACOG) guidelines for the diagnosis of POI. This definition includes the following criteria: 1) menstrual irregularity for at least 3 consecutive months; and 2) elevated follicle stimulating hormone (FSH) in the post-menopausal range and low estradiol levels on two separate occasions. Many of the presumptive cases could not be classified using the ACOG definition because the diagnostic tests were not consistently ordered by the treating providers. Therefore, the clinical adjudicator was instructed to classify presumptive cases as Probable, Possible, and Not POI with the criteria shown below:

- ❑ Probable POI: There is strong evidence to support a diagnosis of POI and/or most or all of the case definition is met.
- ❑ Possible POI: There is some evidence to support a diagnosis of POI, but the case definition is not met.
- ❑ Not POI: The case clearly does not meet the case definition.

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As part of the medical record review, symptom onset date was recorded when it was noted in the medical record or the onset date was estimated on the basis of other information documented in the medical record. Among the probable and possible POI cases, descriptive analyses were conducted and prevalence and rates were calculated for age-specific incidence rates of idiopathic POI. To estimate risk, time-dependent Cox proportional hazard modeling was utilized to estimate hazard ratios and 95% confidence intervals (CIs) with the adolescent vaccines of interest.

During the study period, nearly 200,000 female KPNW members 11 through 34 years of age were identified. Among these members, the following adolescent vaccines were received:

- ❑ 58,871 received 4vHPV (at least one dose)
- ❑ 119,078 received Tdap
- ❑ 46,231 received MenACWY
- ❑ 84,783 received IIV

A total of 120 members were identified with an outpatient coded diagnosis of premature menopause, ovarian failure, or ovarian dysfunction. Of those, 41 were excluded after initial review. After a second round of review, 26 cases were excluded with a known cause of POI (e.g., surgical menopause, chromosomal abnormality, or cancer diagnosis or treatment). The clinical adjudicator classified no POI among 7 cases, leaving 46 confirmed idiopathic POI cases of which 33 were considered probably and 13 were considered possible. Among the 46 cases, the majority were White non-Hispanic females, which is reflective of the population at KPNW; 20% met the ACOG case definition; 17% had a comorbid autoimmune diagnosis; 13% presented with primary amenorrhea; and 9% had a family history of POI. In more than half of the cases, symptom onset occurred in women ages 23 or older. More than half of the confirmed POI cases were patients who diagnosed at age 27 years or older. The median time from symptom onset to diagnosis was approximately 3 years. The prevalence of POI in the study period was 2.31/10,000 female patients. The incidence of diagnosed POI increased with age from a low of 0.87 cases/1 million person months in the 11-14 year age group, to peak of 12.85 cases/1 million person months in the 31-34 year age group.

Among the 46 confirmed cases, 18 had symptom onset prior to August 2006 and were excluded from the time-dependent Cox proportional hazard models. The vaccine exposure status of the remaining 28 confirmed cases are shown in the following table:

Vaccine Type**	Cases Vaccinated Prior to Symptom Onset
4vHPV	1
Tdap	6
MenACWY	3
IIV	11

*Some had more than one vaccine exposure
†15/28 no documentation of exposure to these vaccines in the medical record

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The 1 case vaccinated with 4vHPV vaccine prior to symptom onset was 16 years old at the time of diagnosis, and had received her third 4vHPV dose approximately 23 months prior to her symptom onset date. In this case, the symptom onset date was estimated as her first encounter for delayed menarche. The investigators think that POI onset was likely to have occurred prior to the estimated onset date. She also was negative for autoantibodies, had normal karyotype, and had no autoimmune diagnoses.

Among the 28 confirmed cases of POI, the following table shows the number of cases per vaccine type out of the number of unexposed for that specific vaccine type. Age-adjusted hazard ratios were calculated to estimate risk. None of the hazard ratios were statistically significant, all with confidence intervals for each vaccine overlapping 1:

Vaccine Type	Cases Vaccinated Prior to Symptom Onset	Unexposed Cases	Age-Adjusted HR (95% CI)
4vHPV	1	27	0.30 (0.07-1.36)
Tdap	6	22	0.88 (0.37-2.10)
MenACWY	3	25	0.94 (0.27-3.23)
IIV	11	17	1.42 (0.59-3.41)

Studying POI as a vaccine adverse event is challenging for many reasons. First, the time from symptom onset to diagnosis varies. In this study, the median time from symptom onset to POI diagnosis was 3 years. Because of the long time period to diagnosis, there is a possibility of underestimating true cases of POI. However, this was considered to be unlikely as the majority of this cohort were members in the health system for more than 24 months with an average follow-up time of 5 years. Furthermore, the diagnosis of POI is difficult. Many patients did not undergo all of the diagnostic testing required to meet the strict ACOG definition. For example, many of the study patients did not have two of the same hormonal tests performed on different occasions to meet the ACOG definition. Another challenge of this study was adequately capturing hormonal contraceptive use, which may mask POI symptoms and onset of POI and can underestimate true cases. It was not possible to adjust for contraceptive use in this study because these data are not routinely collected. However, based on previous studies showing no differences in hormonal contraceptive use among vaccinated and unvaccinated women, this is not believed to have impacted the study.

To the authors' knowledge, this is the first population-based study in which POI was evaluated as a possible vaccine adverse event. In this study of nearly 200,000 young women, no evidence was found of increased risk of POI following HPV vaccination or other routine adolescent exposures. They believe that this study should lessen the concerns surrounding the potential impacts on fertility from HPV vaccine or other adolescent vaccination.

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Background: Expanded Age Indication for 9vHPV Vaccine

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

In this presentation, Dr. Markowitz provided background for the expanded age indication for 9vHPV vaccine. This included data submitted in support of the application; data from the US program on vaccine coverage and impact, HPV epidemiology, and sexual behavior; post-licensure vaccine effectiveness (VE) evaluations by age at vaccination; and an update on global HPV vaccination.

In terms of HPV vaccine licensure and availability in the US prior to October 2018, three vaccines are licensed. Bivalent vaccine (2vHPV) is licensed for females aged 9 through 25 years, and 4vHPV and 9vHPV vaccines were licensed for use in females and males 9 through 26 years of age. Only 9vHPV vaccine has been available in the US since the end of 2016, while 2vHPV and 4vHPV vaccines continue to be available and used in other countries. At the beginning of October 2018, 9vHPV vaccine was licensed through age 45 years. Although 9vPHV was just recently licensed through this age group in the US, HPV vaccines have been licensed through age 45 years or older in other countries. However, no country has a public health HPV vaccination program targeting mid-adults, which Dr. Markowitz indicated would be how she would refer to this age group going forward.

As a reminder, the current recommendations for HPV vaccination in the US are as follows:

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

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

- Males aged 22 through 26 years may be vaccinated

During the last ACIP meeting, data submitted to FDA for the application to expand the age range was summarized. After approval, FDA published a Summary Basis for Regulatory Action. Approval was based on several studies, which Dr. Markowitz reviewed briefly. The first was the results of a randomized, double-blind, placebo-controlled trial of 4vHPV vaccine that included women 27 through 45 years of age.[1] The end of study results were published in 2011[2]. Second was an observational follow-up study of a subset of women in the base study showing no cases of anogenital warts and cervical intraepithelial neoplasia (CIN) through 10 years post-vaccination. The 10-year follow-up data were presented to ACIP in June 2018[2] [[1]Munoz et al. Lancet 2009; [2]Castellsague et al. Br J Cancer 2011; [3]Luna et al. PLoS One 2013 (6 year follow-up); Luxembourg (10-year follow-up presented at ACIP June 2018)].

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Approval also was based on several immunobridging analyses, including a cross-study immunogenicity analysis showing non-inferiority of the immune responses to 4vHPV vaccine in males aged 27 through 45 years compared to males aged 16 through 26 years. The antibody data in the older males were from an open label, single arm study of 150 men aged 27 through 45 years[1]. These were compared with the antibody data in males aged 16 through 26 years who were in the 4vHPV vaccine efficacy trial that was conducted to support the original licensure of 4vHPV vaccine in males[2,3] [[1]Giuliano et al. *Vaccine* 2015; [2]Giuliano et al. *N Engl J Med* 2011; [3]Palefsky et al. *N Engl J Med* 2011].

Approval also was based on extrapolation of effectiveness against the additional 5 HPV types in the 9vHPV vaccine based on a variety of data, and extrapolation of safety of 9vHPV vaccine in individuals 27 through 45 years of age based on safety experience with 4vHPV and the now robust safety experience with 9vHPV in individuals 9 through 26 years of age from the US.

Dr. Markowitz briefly reviewed the RCT in mid-adult women called FUTURE III (Females United to Unilaterally Reduce Endo/Ectocervical Disease Study) and a follow-up study that formed the major evidence in the application. This 4vHPV trial in women aged 24 through 45 years was a multi-national study that included over 3800 women of whom 85% were 27 through 45 years of age. The primary endpoint was a combined outcome of vaccine type 6-month persistent infection or vaccine-type related CIN1 or worse, and women were followed for 4 years. In the per-protocol analysis, which is limited women who received 3 doses and who were PCR-negative and seronegative to the relevant vaccine type at baseline and through month 7, efficacy against the combined endpoint was statistically significant at 88.7%. For the CIN2+ endpoint, efficacy was high but not statistically significant at 83.3%. There was only one case in the vaccine group and 6 in the control group. In the intention-to-treat (ITT) analysis, efficacy was lower for both endpoints. The ITT population includes even women who were HPV DNA or HPV antibody positive for the relevant type at the time of enrollment. In this population, efficacy for the combined endpoint was 47.2% and for CIN2+ was not statistically significant [Castellsague et al. Br J *Cancer* 2011].

After the base RCT was completed, placebo-recipients were offered vaccine. A total of 685 Colombian subjects who received 4vHPV in the base study consented to participate in a long-term follow-up for 10 years. Effectiveness was evaluated by incidence probability because there was no placebo group in this follow-up study. The primary effectiveness endpoint was vaccine-type-related CIN or condyloma, and the primary analysis was a per-protocol analysis. There were no vaccine-type CIN or condyloma during follow-up. However, there were a few cases of non-vaccine type outcomes during the follow-up period [Luna et al. PLoS One 2013; Luxembourg, ACIP June 2018].

Data considered for regulatory approval, as well as data from other studies, are included in GRADE to be presented next by Dr. Meites. Of note, there are no efficacy or immunogenicity data on 9vHPV vaccine in persons older than age 27 years. The manufacturer is conducting a study of immunogenicity and safety of 9vHPV vaccine in women 16 through 45 years of age. The primary objective of this study is to compare antibody titers and AEs at month 7 in women aged 16 through 26 years to women aged 27 through 45 years. Results are expected in the second quarter of 2019.

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Dr. Markowitz next reviewed data on vaccine coverage, the impact of HPV vaccination, HPV epidemiology, and sexual behavior in the US. Regarding estimated HPV vaccination coverage among adolescents aged 13 through 17 years, data were shown from the National Immunization Survey (NIS)-Teen from 2006–2017.The routine recommendation for females was made in 2006 and for males in 2011. Coverage among females has increased gradually for at least one dose, reaching 69% in 2017. Coverage among males began to increase after 2011 when the routine recommendation was made. In 2017, at least one dose coverage among males was 63%. The gap between females and males is narrowing very rapidly and was only 6 percentage points in 2017. In terms of 3-dose coverage through 2015 and up-to-date (UTD) coverage through 2016 and 2017, UTD is the new measure that has been used since the 2-dose recommendation for persons starting the series before age 15 years. In 2017, UTD for females was 53% and UTD for males was 44% in this age group. NIS-Teen does not collect data for older individuals and CDC does not have provider-verified data from other surveys in older age groups [Adapted from Walker et al. *MMWR* 2018].

The National Health and Nutrition Examination Survey (NHANES) is one of the national surveys that collects self-reported vaccination data in older age groups. Based on self-reported data from 2015-2016 among females 9 through 59 years of age, at least 1-dose coverage was highest among 14 through 19 year olds and 20 through 24 year olds at about 55%. Reported receipt of at least 1 dose was lower in the older age groups. For males, at least 1-dose coverage was highest in 12 through 13 and 14 through 19 year olds at about 40%. The differences in coverage by age between males and females is a reflection of the more recent recommendation in males and less time for vaccinated males to age into the older age groups. Dr. Markowitz noted that she was showing the date from NHANES to highlight coverage in the older age groups relevant for the discussion during this session. The US uses data from NIS-Teen to monitor coverage nationally in 13 through 17 year olds using provider-verified data. In a comparable age group of 13 through 17 year olds, the age group monitored by NIS-Teen, coverage in NHANES was lower by about 8 to 10 percentage points [Adapted from Lewis and Markowitz, *Vaccine* 2018].

In terms of the impact of the HPV vaccination program, data are available from NHANES where prevalence is being monitored through self-collected vaginal swabs. A decrease in vaccine-type prevalence in females was first detected just 4 years after introduction among 14 to 19 year olds when a 56% decrease was observed. By 8 years after introduction, larger decreases in vaccine-type prevalence was seen in 14 to 19 year olds of 71% and in 20 to 24 year olds of 61%. No statistically significant decrease was observed in older age groups from 2014. More data from this survey will be forthcoming [Markowitz et al. *JID 2013*; Oliver et al. *JID* 2017].

Data on anogenital warts from females from 2006-2014 from private insurance claims show that during this time period, there was a 61% decrease among 14 through 19 year olds and a 44% decrease in 20 to 24 year olds. A smaller decrease was observed in 25 to 29 year olds starting in 2009. Though not shown, there was a modest decrease in males aged 20 to 24 years starting in 2009 [Flagg et al. AJPH 2017].

It is more challenging to monitor cervical precancers. These lesions are detected by screening and diagnosed by histopathology. However, screening recommendations and histopathology terminology are changing in the US. Based on data from a 5-site population-based monitoring project that is collecting data on precancers and screening, rates of precancer lesions (cervical intraepithelial neoplasia grade 2 or worse, or adenocarcinoma in situ, CIN2+) among estimated screened women decreased between 2008-2015 among women aged 19-20 year olds and 21-24 years. Rates among screened women in older age groups, similar to findings from other

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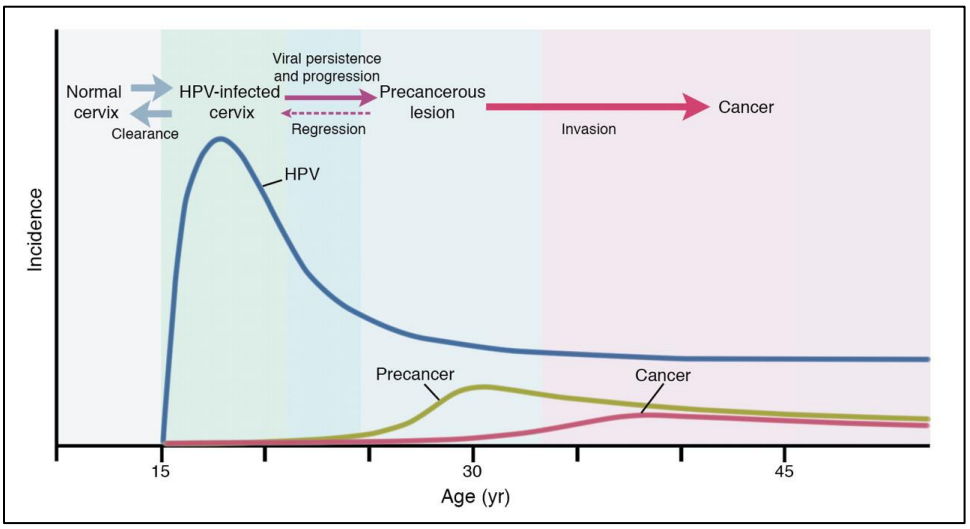
studies, have been increasing. These increases are felt to be due to longer screening intervals now recommended and/or increased sensitivity of new screening and diagnostic tests [Gargano et al. CID in press].

While declines are not expected to be observed yet in HPV-attributable cancers, there are good registries to be able to evaluate this. Data were combined using numbers from CDC registries and special studies of typing to be able to estimate the number of cancers attributable to HPV per year in the US using the most recent data from 2011-2015. CDC estimated that during this time, HPV caused about 33,700 cancers each year. Most (91%) HPV-attributable cancers in women were cervical cancers, while most (70%) in males were oropharynx. Of all HPV-attributable cancers, 93% are attributable to types that can be prevented by 9vHPV vaccine [https://www.cdc.gov/cancer/hpv/statistics and Saraiya et al. *J Natl Cancer Inst.* 2015].

This schematic of the natural history of HPV at cervical sites provides context for the considerations on the expanded age indication:



Incidence of infection peaks in the late teens and early 20s, pre-cancers in the early 30s, and cervical cancer in the late 30s and 40s. Because of this, vaccination in adolescence is important to prevent most infections and subsequent disease [Schiffman et al. NEJM 2005].

Due to the complex natural history of HPV and many unknowns, modeling has been crucial to provide guidance for vaccine policy. A well-documented natural history model based on US data was applied to address the question, “What proportion of cervical cancers are caused by HPV infections acquired by different ages?” This model estimated that among all cervical cancers in the US, 50% are due to an HPV infection acquired by age 21 years and 75% are due to an HPV infection acquired by age 31 years [Burger at al. CID 2017].

This strongly supports routine vaccination at a young age to prevent most infections, and also projects that some cancers are due to infections that occur at a later age. Less is known about the natural history of other HPV-attributable cancers, and similar modeling projections have not been made for non-cervical cancers. While vaccine trials found high efficacy in mid-adult women naïve to vaccine-type infection at the time of vaccination, the benefit and potential impact of HPV vaccination in this age group will be influenced by the likelihood of persons in this age group already having had an HPV vaccine-type infection, immunity after natural infection,

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risk of incident infection, risk of development of disease from that infection, and vaccine efficacy against reinfection after clearance of a vaccine type.

Based on national data of any HPV type prevalence by age group and sex, prevalence increases steeply in the late teens and early 20s with onset of sexual activity. The rise continues through age 20-24 years in females and 25-29 in males. By sex, patterns of prevalence differ. For females, prevalence is lower in age groups older than 20-24 years. Among males, prevalence was similar in age groups 25-29 years and older. It is important to note that when HPV is detected among adults, it indicates current infection. However, it is not possible to distinguish between new, persistent, or redetection of a previously acquired infection. For both males and females, prevalence in older age groups is more strongly associated with lifetime partners than with recent partners. Much of HPV detected in older age groups is thought to be prevalent and not incident infection. These are cross-sectional data and some of the differences by age group could be due to cohort effects [CDC, unpublished data; adapted from Lewis et al. JID 2018; NHANES, National Health and Nutrition Examination Survey].

In terms of whether there are estimates on susceptibility to 9vHPV vaccine type infection in mid-adults, for this question data were examined from NHANES for the period 2005-2006, which is pre-vaccine era data and the only years for which there are 9vHPV type serology in this national survey. It is important to remember that DNA and antibody are imperfect measures of current and past infection and both depend upon the sensitivity of the assays used. Importantly, not all persons develop antibody after HPV infection. Development of antibody after natural infection is higher in females than males and also is type-specific. In 2005-2006, DNA prevalence of at least one of the 9vHPV types was highest in 20-29 year old females at just over 20%. Seroprevalence was substantially higher than DNA prevalence in all age groups. Since most infections clear, DNA will under-estimate past infection. Among 20-29 year olds, about 45% had serologic evidence of exposure to at least one of the 9vHPV vaccine types. DNA prevalence and seroprevalence declined with increasing age. Declines in prevalence are thought to be due to clearance of infection and less exposure, and antibody declines due to titers falling below detectable levels. Again, these could also be due to cohort effects. With the combined measure of DNA or serology, over 50% of 20-29 year olds had evidence of infection or past exposure to at least one type. Since only 50% to 70% of females who have infection develop antibody, the proportion in this age group with either current or past infection is substantially higher and could be as high as 90%. However, no women had evidence of infection or past exposure to all 9 HPV types. Among males, there are no DNA from this time period in NHANES. Seroprevalence is much lower in males, and it is well-known from prospective studies that a smaller percent develop antibody after infection [Antibody measured by competitive Luminex immunoassay, Adapted from Liu et al. JID 2016 and Liu et al. STD 2016; Carter et al, JID 2000; Edelstein et al. JID 0211].

While HPV incidence is lower in mid-adult women than women in their teens and early 20s, new infections do occur. Some of these data were reviewed during the last ACIP meeting. Because it is difficult to distinguish new infection from redetection of a prior infection, studies have been designed to evaluate new incident infection by using sexual behavior to estimate recent exposure and past sexual exposure. In the Winer study, women were recruited from on-line daters, which is a relatively higher risk group. Among these women, 50% had a new partner during the study and incidence of new high-risk for oncogenic HPV detection was 29.5/100 person years. In the Rositch study in Baltimore, a which included a lower risk population, 10% of women had a new male partner and incidence was lower. In these two studies based on association between new HPV and risk behavior, it is estimated that for women with a new

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partner, most but not all detections are attributable to a newly acquired infection [Winer et al. JID 2016; Rositch et al. Cancer Res 2012].

Because a recent new partner is a risk for acquiring HPV, we examined the percent of females and males in the US with a new partner in the last year by age group. The percent of females with a new partner in 20-24 year olds was 31.9%, which decreased with increasing age. For males in the 20-24 year age group, 39.6% had a new partner in the last year. This also decreased with increasing age. Much of the change in sexual behavior with age is due to marital status. Looking at marital status by 5-year age groups for females, 17% of females 20-24 years of age were married. This increased to over 50% by 30-34 years and over 60% at 40-44 years. The percent widowed, separated, or divorced increased with increasing age. Data are slightly different for males, but show generally similar trends. Data on ≥1 new partner in past year, by sex, age group show differences by marital status. In 2013–2016, The percent of males and females with a new partner was markedly lower among those who were married or living with a partner and was lower with increasing age in those married or living with a partner and those other marital status categories [CDC, NHANES unpublished data, 2013-2016].

Understanding the potential benefit of vaccination in mid-adults is complex. HPV is common, and infection occurs soon after first sexual activity. There are challenges in studying HPV incidence, and HPV detection cannot distinguish between new, persistent, or redetection of infection. New HPV infections occur in adults and sex with a new partner remains a risk for infections. The percent of adults with a new sex partner in the past year decreases in older age groups. Contributing to the complexity of this issue is that not all individuals develop antibody after natural infection, and the percent developing antibody is lower in males than in females. There is uncertainty about immunity after clearance of infection. Importantly, no protective level of antibody has been identified.

Next, Dr. Markowitz discussed vaccine effectiveness studies. As background to this section as reviewed earlier, high efficacy was found in the clinical trials in mid-adult women in the per-protocol analyses, but lower efficacy was found in the ITT analyses that included women who were positive at the time of vaccination. The ITT population might be a better reflection of effectiveness that would be observed in a catch-up program in this age group. Effectiveness studies also can provide information on the real-world effectiveness of vaccine and vaccination programs. Studies in countries with catch-up vaccination have been able to evaluate effectiveness by age at vaccination.

Post-licensure effectiveness studies were reviewed that included analyses by age at vaccination. This was limited to evaluations of 3 doses of vaccine. Basic information was extracted on study design, age at outcome, age at vaccination, and buffer period. The buffer period is the time between vaccination and case counting, which is important as a short time between vaccination and case counting includes outcomes more likely to be due to infection that is prevalent at the time of vaccination. Studies with different buffer periods could produce different results. Shorter buffer periods can result in an underestimation of vaccine effectiveness in some age groups. Eleven studies were identified and reviewed of which 2 evaluated vaccine-type prevalence, 5 evaluated anogenital warts, and 4 evaluated cervical lesions .

Both of the studies of vaccine-type prevalence included women who were being screened for cervical cancer and were conducted in the US and Scotland. The Dunne study was conducted in the US where 4vHPV was used and the Kavanagh in Scotland where 2vHPVwas used; both evaluated prevalence among women in their 20s. In both studies, prevalence reduction was greater for vaccination of the younger age groups. The Dunne study looked at just two groups,

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<19 and ≥19 years. The Kavanagh study was a large national study that was able to evaluate data by individual year of age at vaccination. For those vaccinated at 12-13 years of age, the risk reduction was 0.11. For those 18 years of age and older, it was 0.71 [Dunne, J Infect Dis 2015; Kavanagh, Lancet 2017].

The 5 studies that examined the outcome of anogenital warts were conducted in the US, Sweden, Belgium, and Canada. Some of these studies used large population-based health registries. All studies were conducted in countries that introduced 4vHPV. The Leval study looked at multiple age groups from 10-13 to ≥27 years. The largest risk reduction was among those vaccinated at 10-13 years. There was no risk reduction in those vaccinated in the oldest age group. In the Zeybek and Willows studies, the relative risk was >1 among those vaccinated in the oldest age group. This was statistically significant in the Willows study. In that study, conducted in one province in Canada, the authors actually state that in the older age group high risk women were targeted for vaccination at the beginning of the program. In all of these studies, there were few data on risk factors and adjustment for differences in vaccinated and unvaccinated individuals was very limited [Leval, JNCI 2013; Herweijer, JAMA 2014; Dominiak-Felden, Plos One 2015; Zeybek, JLGTD 2018; Willows, Sex Trans Dis 2018].

Four studies evaluated the outcome of CIN2+ for Australia, Sweden, and the US. Similar to the other outcomes, the largest risk reductions were observed among those who received vaccine in the youngest age groups. In 3 of the 4 studies, the confidence intervals crossed 1 and no significant reductions were found for women in the oldest age category [Crowe, BMJ 2014; Brotherton, Papillomavirus Res 2015; Herweijer, Int J Cancer 2016; Silverberg, Lancet Child Adolesc Health 2015].

In summary, the 11 studies that were reviewed were conducted in 6 different countries. All found lower effectiveness with increasing age at vaccination, and 7 found no significant effectiveness in the oldest age group.

ITT analyses in the vaccine trials can help explain some of the findings in the post-licensure effectiveness studies. As in the post-licensure effectiveness studies, in the catch-up age group specifically, the ITT population included individuals who had vaccine-type infection at the time of vaccination. Based on data from one of the pivotal efficacy trials in women aged 16-26 years, no efficacy was observed in the first year after vaccination. Among those with an endpoint within the first year of follow-up, most cases in both the vaccine and control groups had evidence of infection or disease at the time of enrollment. During the second year of follow-up, incidence of disease associated with vaccine-type HPV in the placebo group continued to increase, while it plateaued in the vaccine group [Garland et al. New Eng J Med 2007]. This illustrates the importance of time between vaccination and case counting in the post-licensure effectiveness studies conducted in catch-up populations, referred to as the buffer period; a short buffer period could contribute to the higher risk of outcomes in the vaccinated compared to the unvaccinated populations in some of the studies.

In conclusion, estimated vaccine effectiveness was lower with increasing age at vaccination. This was as expected due to the higher HPV prevalence at the time of vaccination in older age groups. There were methodological challenges for evaluating vaccine effectiveness and biases due to differences in vaccinated and unvaccinated persons. Some findings could be the result of higher risk individuals being targeted for vaccination, which was reported in one of the studies. Finally, time between vaccination and case counting likely impacts the ability to observe VE in the oldest age groups. Because of this, effectiveness is likely underestimated, particularly in the

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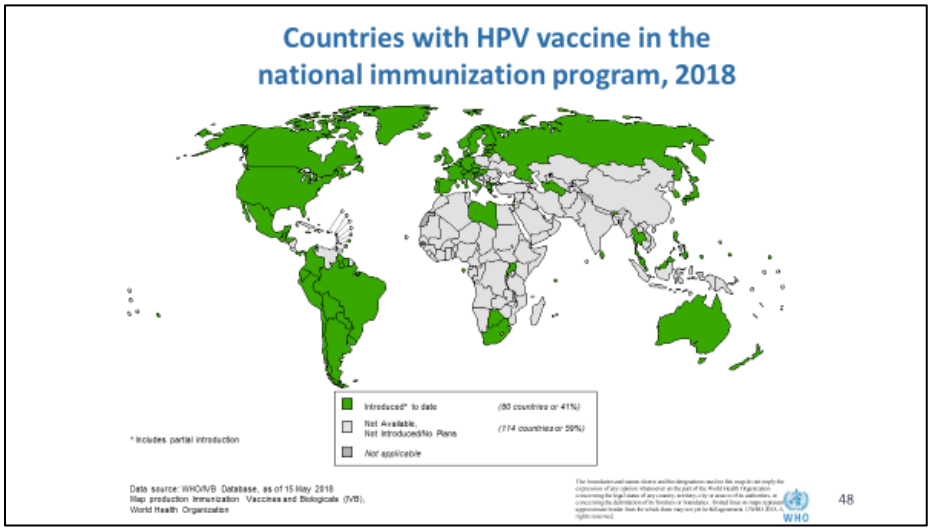
oldest age groups. Nevertheless, these data support the importance of vaccination in early adolescence.

Dr. Markowitz next briefly reviewed global HPV vaccine issues. This map shows countries with HPV vaccine in their national immunization programs as of 2018:



While tremendous progress has been made less than 12 years after the first vaccine licensure, less than half of World Health Organization (WHO) member states have introduced HPV vaccine into their national program. In terms of introductions by country category, middle income countries (MICs) and Global Alliance for Vaccines and Immunization (Gavi) countries lag far behind high income countries (HICs) and Pan American Health Organization (PAHO) procuring countries in introducing HPV vaccines. Countries that have introduced account for only 25% of the global target population. Only 13 of 73 Gavi countries have introduced HPV, but have >50% of HPV disease burden. MICs, of which only 39% have introduced, account for greater disease burden than HICs and PAHO combined [WHO/IVB Database, as of 15 May 2018. HPV Burden – WHO Position Paper 2017].

There are many reasons for the lag in vaccine introduction, but it is encouraging that there has been increasing interest in vaccine introduction in the past two years in many low income countries (LICs). Because of this increased interest in introduction and because of a 2017 WHO recommendation, the countries that introduce vaccine aim to do so initially with a multi-age cohort of 9-13 year olds in the first year of the program. The current HPV vaccine supply is insufficient to meet the demand and some countries have or will have to postpone introductions. These data are from a recent WHO report that displays current and forecasted demand and supply. The report projects that the imbalance of demand and supply is forecasted to grow and remain through 2023 due to an increased number of countries planning HPV vaccine introduction. From 2024 onward, supply is expected to support demand. While there is a global shortage of HPV vaccine at the current time, there is no current or expected future vaccine shortage in the US [http://www.who.int/immunization/programmes_systems/procurement/v3p/platform/module2/WHO_HPV_market_study_public_summary.pdf?ua=1].

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In summary, data submitted to FDA in support of the expanded age range through age 45 years included data from an RCT that found high efficacy in women naïve to vaccine types and lower efficacy in the ITT population. Data to inform the policy considerations show that HPV vaccine coverage is increasing in adolescents; the impact of the vaccination program has been observed among females in their teens and 20s; that most adults already have been exposed to a 9vHPV type, but not all 9vHPV types; that HPV incidence is lower at older ages, but new infections can occur in adults; and that a new sex partner is a risk factor for incident HPV infection. Post-licensure vaccine effectiveness evaluations show that effectiveness is lower with increasing age at vaccination. In terms of global HPV vaccination, less than 50% of countries have introduced HPV vaccination. A global vaccine shortage is limiting introductions in some countries, but there is no current HPV vaccine shortage in the US.

GRADE

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Dr. Meites presented the GRADE for HPV vaccination of mid-adults. The PICO question was, “Should catch-up vaccination with HPV vaccine be recommended for primary prevention of HPV infection and HPV-related disease in U.S. adults aged 27–45 years who were not vaccinated previously at the routinely recommended age?” The population of interest was adults 27–45 years of age, which are referred to as the “mid-adult” age range. The intervention was vaccination with a complete 3-dose series of HPV vaccine. Data were considered for all 3 licensed HPV vaccines, but only 9vHPV vaccine is available in the U.S. The comparison is no HPV vaccination. The outcomes of interest include important and critical HPV vaccine-related benefits and harms, which are listed in detail in the following table:

	Importance	Include in Evidence Profile
Benefits		
Persistent vaccine-type HPV infection	Important	Yes
Anogenital warts/condyloma/external genital lesions (EGL)	Important	Yes
Cervical or anal intraepithelial neoplasia (CIN or AIN) 1+	Important	Yes
Cervical or anal intraepithelial neoplasia (CIN or AIN) 2+	Critical	Yes
Combined endpoint: (Persistent infection, EGL, and/or CIN 1+)	Important	Yes
HPV-related cancer (Anal, Cervical, Oropharyngeal, Penile, Vaginal, and/or Vulvar)	Critical	No*
Immunogenicity (Seroconversion and GMTs to vaccine types)	Important	Yes
Harms		
Serious adverse events, any or vaccine-related	Important	Yes
Death, any or vaccine-related	Critical	Yes
*No HPV-related cancers were reported in per-protocol analyses from any of the studies reviewed; however, these outcomes are not necessarily expected in clinical trials of the current size or duration.		

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For evidence retrieval, a systematic review was conducted of HPV vaccine clinical trials in Medline, Embase, CINAHL, Cochrane Library, and clinicaltrials.gov published between 2006, when HPV vaccine was first licensed in the U.S., and October 18, 2018. The search specifically looked for clinical trials of HPV vaccination in 27 through 45 year-olds, with each search including terms to identify clinical trials using HPV vaccines and including mid-adults. Efforts were made to obtain unpublished or other relevant data from previous ACIP presentations, Cochrane reviews on immunobridging conducted for SAGE, data in the FDA label for 9vHPV vaccine updated October 5, 2018, and clarification of previously published data from the vaccine manufacturer. These searches identified 1,388 references. After reviewing titles and abstracts, 100 references were selected mentioning age 27 years and older for detailed review. Of these, 16 trials were selected for inclusion and 84 papers were excluded because 50 included duplicate data, 15 did not report data on the population of interest, 11 because they did not report data on an outcome of interest, and 8 because they did not report data on the intervention of interest. The evidence tables included 16 trials, the ACIP presentation from June 2018 on clinical data submitted to FDA supporting 9vHPV vaccine use in mid-adults, and personal communication from the vaccine manufacturer providing additional analyses of previously published data limited to the age group of interest here. Supplemental data for immunobridging included an additional 6 articles reporting immunogenicity and efficacy data from young adults and 2 ACIP presentations from February 2018 on 9vHPV vaccine safety.

For ACIP, evidence types are ranked as: 1 = High, 2 = Moderate, 3 = Low, or 4 = Very Low. Initial evidence types in GRADE are shown in the following table:

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 (Obs), or RCTs with notable limitations
4	Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

Since no studies have specifically examined use of 9vHPV vaccine in the mid-adult age range, the included studies involved either 4vHPV or 2vHPV vaccine plus supplemental immunobridging data. When multiple references are listed in the same row in the following tables, it means that they report data from different time points in the same study. For 4vHPV vaccine, there were 7 included trials, which are shown in the following table:

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CHARACTERISTICS OF INCLUDED STUDIES, 4vHPV

Author, year	Clinical trial number	Design	Participants (N=total enrolled)	Follow-up time	Main outcomes related to HPV vaccine types**
Muñoz, 2009 [1]* Castellsagué, 2011 [2]* Luxembourg, 2018 [4]	NCT00090220 (Future III)	RCT, 7 countries (through month 48), then Obs, Colombia (through month 120)	Women age 24–45 years (N=3819)	7 months; 48 months; 120 months	Immunogenicity Persistent HPV infection External genital lesions (warts) CIN 1+, CIN 2+ Combined endpoint Harms
Wei, 2018 [5]*	NCT00834106	RCT, China	Women age 20–45 years (N=3006, including 1166 women age 27–45 years)	78 months	Immunogenicity Persistent HPV infection External genital lesions (warts) CIN 1+, CIN 2+ Combined endpoint Harms
Einstein, 2009 [6] Einstein, 2014 [7]	NCT00423046	Obs, USA	Women age 18–45 years in the USA (N=1106)	60 months	Immunogenicity Harms
Huang, 2018 [8]	NCT01427777	Obs, China	Women age 9–45 years (N=468, including <250 age 27–45 years)	42 months	Immunogenicity
Giuliano, 2015 [9]	NCT01432574 (MAM)	Obs, USA and Brazil	Men 27–45 years (N=150)	7 months	Immunogenicity Harms
Money, 2016 [10]	None (CTN 236)	Obs, Canada	HIV+ women age 15–45 years (N=372, including 98 women age 24–45 years)	24 months	Immunogenicity
Wilkin, 2018 [11]	NCT01461096 (ACTG A5298)	RCT, USA and Brazil	HIV+ people age ≥27 years (N=575, including 472 men and 103 women)	12 months (trial halted; no per-protocol analysis)	Harms

* Age-restricted data obtained from Merck, 2018 [3]
** Per-protocol results for benefits; intention-to-treat results for harms

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Note that in the first row on the 4vHPV table, the Luxembourg reference is the ACIP presentation on the observational long-term follow-up study after the base RCT was complete. Of the included studies, 3 were randomized placebo-controlled trials and 4 were observational trials since they did not include a control group. These are large trials from multiple countries, each with hundreds to thousands of participants, and lasting from months to years. Most included women only, but 2 of the smaller trials focused on men. Note that throughout, a conservative approach was taken of grading the per-protocol results for benefits, since ITT results depend upon HPV prevalence and past exposure at the time of vaccination, which varies by population. ITT results were graded for harms.

For 2vHPV vaccines, there were 4 included trials shown in the following table:

CHARACTERISTICS OF INCLUDED STUDIES, 2vHPV

Author, year	Clinical trial number	Design	Participants (N=total enrolled)	Follow-up time	Main outcomes related to HPV vaccine types*
Skinner, 2014 [12] Wheeler, 2016 [13]	NCT00294047 (VIVIANE)	RCT, 12 countries	Women age ≥26 years (N=4407, including 3916 women age 26–45 years)	48 months; 84 months	Immunogenicity Persistent HPV infection CIN 1+ CIN 2+ Combined endpoint Harms
Schwarz, 2009 [14] Schwarz, 2011 [15] Schwarz, 2015 [16] Schwarz, 2017 [17]	NCT00196937; NCT00947115	Obs, Germany and Poland	Women age 15–55 years (N=667, including 226 women age 26–45 years)	1 month; 48 months; 72 months; 120 months	Immunogenicity Harms
Einstein, 2009 [6] Einstein, 2014 [7]	NCT00423046	Obs, USA	Women age 18–45 years (N=1106)	24 months; 60 months	Immunogenicity Harms
Zhu, 2014 [18]	NCT01277042	RCT, China	Women age 9–45 years (N=1962, including 1212 women age 26–45 years)	7 months	Immunogenicity Harms

* Per-protocol results for benefits; intention-to-treat results for harms

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Of these, 2 were randomized placebo-controlled trials and 2 were observational trials since they did not include a control group. Again, these were large trials from multiple countries, each with hundreds of thousands of participants, and lasting from months to years. All of the 2vHPV vaccine trials included women only.

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Supplemental data may not directly address the PICO question and is not included in the formal GRADE scoring, but it may be helpful for decision-making. Supplemental data included immunobridging data by age group and by vaccine. Of the analyses, across the top, 2 compared immunogenicity of 4vHPV vaccine among mid-adults versus young adults and showed non-inferior immunogenicity. The trial in males on the top row also included clinical efficacy outcomes. In the middle rows, 2 trials compared immunogenicity of 9vHPV vaccine versus 4vHPV vaccine and showed non-inferior immunogenicity. Across the bottom, 2 surveillance systems report post-licensure safety data for 9vHPV vaccine in the U.S. The supplemental studies included are shown in the following table:

CHARACTERISTICS OF INCLUDED STUDIES, SUPPLEMENTAL

Vaccine	Author, year	Clinical trial number	Design	Participants (N=total enrolled)	Follow-up time	Main outcomes related to HPV vaccine types*
4vHPV	Hillman, 2012 [19] Giuliano, 2011 [20] Palefsky, 2011 [21]	NCT00090285	RCT, 18 countries	Males age 16–26 years (N=4065)	7 months	Supplemental Immunogenicity (bridging of age groups: 4vHPV immunogenicity and clinical efficacy in young adult males)
	Luxembourg, 2018 [4]	NCT00092521 (Future I); NCT00092534 (Future II); NCT00090220 (Future III)	Post hoc analysis of data from RCTs	Females age 16–26 years	7 months	Supplemental Immunogenicity (bridging of age groups: 4vHPV immunogenicity in young adult females)
9vHPV	Joura, 2015 [22] Huh, 2017 [23]	NCT00543543	RCT, 18 countries	Females age 16–26 years (N=14215)	7 months; 42 months	Supplemental Immunogenicity (bridging of vaccines: 9vHPV in young adult females)
	Van Damme, 2016 [24]	NCT02114385	RCT, Belgium, Netherlands, and Germany	Males age 16–26 years (N=500)	7 months	Supplemental Immunogenicity (bridging of vaccines: 9vHPV in young adult males)
	Donahue, 2018 [25]	N/A	Obs, Vaccine Safety Datalink (VSD)	U.S. enrollees age 9–26 years	-	Supplemental Harms
	Arana, 2018 [26]	N/A	Obs, Vaccine Adverse Events Reporting System (VAERS)	Reports of potential adverse events following 9vHPV (N=8529 in the USA; n=73 age 27–45)	-	Supplemental Harms

* Per-protocol results for benefits; intention-to-treat results for harms

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In studies providing evidence regarding efficacy benefits, for HPV infection persisting at least 6 or 12 months, in 3 RCTs, HPV vaccines had an observed efficacy of 88.8% to 91.4%, and the confidence intervals were all positive. As a reminder, for benefits, only per-protocol results were included in GRADE ; ITT results would have had lower observed efficacy.

For anogenital warts, in 2 separate RCTs and an observational follow-up, HPV vaccine had an observed efficacy of 100%, with a very wide confidence interval that includes the null. The long-term follow-up study could not calculate efficacy because there was no placebo group left after everyone who completed the base study was offered vaccine. The second RCT could not calculate efficacy because no cases of anogenital warts were observed after 48 months in either the vaccine or placebo group.

For vaccine-type-related CIN of any grade, in 3 RCTs, HPV vaccines had an observed efficacy of 83.7% to 100%, and the confidence intervals were all positive. There was no placebo group in the long-term follow up study. For vaccine-type related CIN2+, in the same 3 RCTs, HPV vaccines had a similar observed efficacy of 79.8% to 100%, but with wider confidence intervals that included the null. Again, there was no placebo group in the long-term follow-up study.

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Looking at the combined endpoint of any of the HPV-related clinical outcomes (persistent infection, EGL, and/or CIN 1+), across 3 RCTs, HPV vaccines had an observed efficacy of 87.7% to 90.6% and the confidence intervals were all positive. The long-term follow-up study was observational and had no placebo group.

In studies providing evidence regarding immunogenicity benefits, “early” immunogenicity results are from month 7, which is 1-month post-completion of a 3-dose series of HPV vaccine. “Later” immunogenicity results are the latest available from each study. Geometric mean titers (GMTs) quantify the amount of antibody detected. For early immunogenicity of 4vHPV vaccine, across 5 studies, seroconversion ranged from 93.6% to 100%, and GMTs were high. For early immunogenicity of 2vHPV vaccine, across 4 studies, seroconversion ranged from 99% to 100%, and GMTs were also high. For later immunogenicity of 4vHPV vaccine, across 4 studies, seropositivity ranged from 85.3% to 97.3% for most vaccine types. Seropositivity was noticeably lower for HPV type 18, with a range of 37.6% to 69% at 3.5 to 5 years after completing the vaccination series. For later immunogenicity of 2vHPV vaccine, across 3 studies, seropositivity ranged 93.7% to 100% in 4 to 10 years after completing the vaccination series.

Before presenting the supplemental data for immunogenicity, Dr. Meites explained immunobridging studies. The minimum threshold level of HPV antibodies required for clinical protection has not been established and might vary depending on the assay. Data from clinical trials suggest that this minimum level of antibody needed for protection is below that which can be detected by current assays. Immunobridging studies are used to compare immunogenicity in a group of interest (e.g., age 27–45 years) with a comparison group in which efficacy has been demonstrated (e.g., age 16–26 years). Non-inferiority criteria are met when the lower bound of the 95% confidence interval for the ratio comparing the groups is not less than a preset value (e.g., 0.5). Immunobridging data contributed to the evidence base for 9vHPV vaccine licensure, including for the mid-adult age group.

In supplemental data for immunobridging across age groups, for 4vHPV vaccine, 2 large trials showed that immunogenicity among mid-adults was non-inferior to immunogenicity for young adults. Some GMTs may be lower in the mid-adult age group compared with young adults, but all meet non-inferiority criteria. Supplemental immunobridging data was also presented for males. Because there is no efficacy study in males for either 9vHPV or 4vHPV vaccine, the 4vHPV immunogenicity results from younger males can be used to extrapolate clinical efficacy using results from the 4vHPV efficacy trial in young adult men. In the initial clinical trial among young adult men, 4vHPV vaccine had an observed efficacy of 83.8% for ≥6-month persistent HPV infection, 89.4% for condyloma, 73.0% for AIN grade 1, and 74.9% for AIN grade 2 or 3 (Note these data were included in the original GRADE for 9vHPV vaccine, and first presented to ACIP in 2014). In supplemental immunobridging data across vaccines in the younger age group, comparison groups received vaccination with either 9vHPV vaccine or 4vHPV vaccine. In 3 large trials conducted among young adult females and males, immunogenicity of 9vHPV vaccine was non-inferior to immunogenicity for 4vHPV vaccine. For HPV type 16 and most other HPV types protected against by both the 4vHPV and 9vHPV vaccines, the confidence intervals for the GMT ratios include the null. For the 5 additional HPV types protected against by9vHPV vaccine only, no comparisons were possible and no immunobridging can be done.

Turning to evidence regarding harms for the PICO question, the accumulated evidence regarding safety of HPV vaccines is much broader than the data presented during this session, which was limited to trials in the mid-adult age range only. In 7 pre-licensure studies, 9vHPV vaccine was well-tolerated in over 15,000 study participants, with a similar AE profile as 4vHPV vaccine. Since 2014 in the U.S., over 29 million doses of 9vHPV vaccine have been distributed.

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For SAEs of any kind, the numbers were similar among the vaccine and placebo groups across 6 studies. For SAEs that were deemed possibly vaccine-related, numbers were smaller but again similar among the vaccine and placebo groups across 6 studies. For deaths due to any cause, across 7 studies, overall numbers were low but appeared to be slightly higher in the vaccine group than the placebo group. There was a range of causes of death, including road traffic accident, tuberculosis, homicide, and others occurring months to years after vaccination. It was noted that there was one death due to cervical cancer in the vaccine group in the Wheeler study, which was felt to be due to an HPV infection acquired before vaccination. As a reminder, ITT results for harms were purposefully assessed with the aim of identifying the most possible data. Furthermore, for vaccine-related deaths, the numbers dropped down to zero for all groups, across 8 studies.

Supplemental data included two previous ACIP presentations summarizing safety data on 9vHPV vaccine. In U.S. post-licensure safety data for over 29 million doses of 9vHPV vaccine, in VSD, for a list of pre-specified AEs, a signal was detected for syncope and injection site reactions. Initially detected signals were not confirmed for allergic reactions or appendicitis, since follow-up analyses showed no increased risk. No signal was detected for anaphylaxis, GBS, pancreatitis, seizures, stroke, venous thromboembolism, or chronic inflammatory demyelinating polyneuropathy. In VAERS, out of a total of 8529 reports of potential AEs following 9vHPV vaccination in the U.S., there were 73 involving mid-adults age 27 through 45 years. Of these, 3 were considered SAEs and none were deaths.

Regarding the GRADE evidence types for benefits of 9vHPV vaccine in mid-adults, the initial evidence level was 1, or high quality evidence, for each outcome based on data from RCTs. All were downgraded for indirectness since no studies reported data on use of 9vHPV vaccine in the mid-adult age range, and extrapolation from 9vHPV to 4vHPV vaccine was based on immunobridging data. Efficacy outcomes for which the 95% confidence interval crossed 1 were further downgraded for imprecision. For adults aged 27–45 years, GRADE scores were level 2 or moderate quality evidence that 9vHPV vaccine prevents ≥6 month- persistent HPV infection; level 3 or low quality evidence that 9vHPV vaccine prevents anogenital warts; level 2 or moderate quality evidence that 9vHPV vaccine prevents CIN of any grade; level 3 or low quality evidence that 9vHPV vaccine prevents CIN2+; level 2 or moderate quality evidence that 9vHPV vaccine prevents these HPV-related outcomes combined; and level 2 or moderate quality evidence that 9vHPV vaccine is immunogenic in the mid-adult age group.

The WG also wanted to be transparent about the differing amount of evidence for women versus men in the mid-adult age range, and so a second version of the benefits evidence table was completed for women and men separately. For women, this table is the same except for immunogenicity, since 1 less observational study was included. The evidence types did not change. However, for mid-adult men, the evidence types did change. One observational study of immunogenicity was conducted in men, with efficacy for other outcomes extrapolated based on immunobridging. The previous studies in women are still indirectly applicable to men, so the evidence type for each outcome was further downgraded for indirectness. All of the evidence types decreased by one additional level for men, for level 3 to 4 or low to very low quality of evidence.

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In terms of the evidence types for harms for mid-adults, all of the initial evidence levels were 1 for high quality evidence, and all were downgraded one level for indirectness, given the extrapolation required to bridge to 9vHPV vaccine. For female and male adults aged 27–45 years, GRADE scores were level 2 or moderate quality evidence that there were similar numbers of SAEs with 9vHPV vaccine versus placebo, few vaccine-related SAEs, and level 2 or moderate quality evidence that there were similar numbers of deaths after 9vHPV vaccine and placebo, and no vaccine-related deaths.

In summary, for benefits, comparing HPV vaccine for mid-adults aged 27–45 years versus no vaccination, 9vHPV vaccine is more efficacious against HPV-related outcomes than no vaccination, with level 2 or moderate quality evidence for women and level 3 or low quality evidence for men. In addition, 9vHPV vaccine is immunogenic with level 2 or moderate quality evidence. The overall evidence type for benefits is level 2. To summarize harms, comparing HPV vaccination for mid-adults aged 27–45 years versus no vaccination, there were similar harms among people receiving placebo versus 9vHPV vaccine for level 2 or moderate quality evidence. There were few vaccine-related SAEs and no vaccine-related deaths. The overall evidence type for harms is also level 2.

Impact and Economic Analyses

Harrell Chesson, PhD
Health Economist
Centers for Disease Control and Prevention

Dr. Chesson indicated that he would summarize 3 health economics models of 9vHPV vaccination among adults up to age 45 years in the US, noting that the ACIP review process is ongoing for all 3 models. Normally, the completion of the review is required before the information is presented. However, a waiver of the ACIP review policy was granted for this update to ACIP. He emphasized that the results should be considered preliminary.

In terms of what is known about HPV vaccine cost-effectiveness in the US, routine vaccination of 11- to 12-year-olds is likely cost-saving. When vaccination is expanded to older age groups as with the current recommendation, that expansion has a favorable cost-effectiveness profile as well. It also is known that HPV vaccination of adults becomes less cost-effective as the age of vaccination increases.

The new cost-effectiveness question that has to be answered now is: “What is the cost-effectiveness of “mid-adult” vaccination? Specifically, what is the cost-effectiveness of extending the upper recommended catch-up age of HPV vaccination up to 45 years for males and females?” To address this question, Dr. Chesson indicated that he would provide a summary of cost-effectiveness ratios for other vaccines in order to put the mid-adult cost-effectiveness ratios in perspective, give an overview of three US models of 9vHPV vaccination, review the results of the US HPV-ADVISE (Agent-based Dynamic model for Vaccination and Screening Evaluation) model, and compare the results across 3 models.

Dr. Chesson indicated that he compiled cost-effectiveness ratios from ACIP publications. The next 3 tables show the cost-effectiveness ratios for childhood vaccines, adolescent/adult vaccines, and HPV vaccination strategies. While many other childhood vaccines have been shown to be cost-saving, they were not included because they were not noted as such in the ACIP reports:

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Cost-effectiveness ratios for childhood vaccines

Published in ACIP policy notes and recommendations

Vaccine evaluated (vs. no vaccination unless noted)	Cost per QALY gained
MMR	<$0 (cost-saving)
Varicella, 1-dose	<$0 (cost-saving)
Varicella, 2-dose	<$0 (cost-saving)
Varicella, 2-dose vs. 1-dose	$115,000
Influenza (ages 6 through 23 months)	$15,000
Hepatitis A	$30,000

QALY: quality-adjusted life year.
MMR: Measles, mumps, and rubella.

Cost per QALY gained estimates were obtained from ACIP policy notes and recommendations on ACIP website. Ratios adjusted for inflation to 2017 US dollars and rounded to nearest multiple of $5,000. Base year for inflation adjustment was estimated if not provided in publication.

MMR estimate obtained from MMWR Vol. 47 No. RR-8, which notes a favorable benefit/cost ratio and suggests vaccination is cost-saving. Varicella estimates obtained from MMWR Vol. 56 / No. RR-4. Influenza estimates obtained from MMWR Vol. 58 / No. RR-8. Hepatitis A estimate obtained from MMWR Vol. 55/ No. RR-7. Hepatitis B cost per QALY estimates are provided in MMWR Vol. 67 / No. 1, but not included here because none of the estimates compared vaccination to no vaccination.

There is a large range for adolescent vaccines ranging from cost-saving for Tdap to $100,000 to $200,000 per/QALY gained for influenza, and meningococcal B with a cost per QALY gained of over $1 million. For adults, some vaccines are cost-saving such as influenza and zoster:

Cost-effectiveness ratios for adolescent/adult vaccines

Published in ACIP policy notes and recommendations
(Excludes HPV)

Vaccine evaluated (vs. no vaccination)	Cost per QALY gained
Adolescents	
Tdap	<$0 (cost-saving) to $25,000
Influenza (ages 12 through 17 years)	$150,000
Meningococcal (age 11 years, booster age 16 years)	$235,000
Meningococcal B (age 18 years)	$3.8 million
Meningococcal B (age 18 years)	$9.0 million
Adults	
Influenza (ages 65 years and older)	<$0 (cost-saving)
Zoster (ages 50 years and older)	$30,000

QALY: quality-adjusted life year. Tdap: tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine.
Cost per QALY gained estimates were obtained from ACIP policy notes and recommendations on ACIP website. Ratios adjusted for inflation to 2017 US dollars and rounded to nearest multiple of $5,000 (except Meningococcal B estimates which were rounded to the nearest $0.1 million). Base year for inflation adjustment was estimated if not provided in publication. Tdap estimate obtained from MMWR Vol. 55/No. RR-3. Influenza estimates obtained from MMWR Vol. 58 / No. RR-8. Meningococcal estimate obtained from MMWR Vol. 62 / No. 2. Meningococcal B estimates obtained from MMWR Vol. 64 / No. 41. Zoster estimate obtained from MMWR Vol. 67 / No. 3 and reflects $31,000 estimate for ages ≥ 50 years (CDC model), which is consistent with $30,000 estimate for age 60 years (academic group model, also reported in MMWR Vol. 67 / No. 3) for the recombinant zoster vaccine (see the MMWR for more details, including estimates from 2 other models).

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This table shows the HPV vaccination strategies that have been evaluated over time. Initially, it was estimated that vaccination of adolescent females would cost $5000 to $30,000/QALY. Recent studies comparing 9vHPV to 4vHPV vaccine found this to be cost-saving, and 2 doses were found to be cost-saving compared to 3 doses. While early on HPV vaccination was not said to be cost-saving, it now is said to be cost-saving due to the 2-dose schedule and 9vHPV vaccine among other issues:

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Cost-effectiveness ratios for HPV vaccination strategies

Published in ACIP policy notes and recommendations

Vaccine evaluated (vs. no vaccination unless noted)	Cost per QALY gained
Adolescent females (2vHPV or 4vHPV)	$5,000 to $30,000
Adolescent males (4vHPV), vs. female-only	$25,000 to $45,000 (favorable scenario) $85,000 to >$250,000 (unfavorable scenario)
MSM through age 26 years	<$50,000
9vHPV (vs. 4vHPV)	<$0 (cost-saving)
2-dose 9vHPV (vs. 3-dose 9vHPV)	<$0 (cost-saving)

QALY: quality-adjusted life year. 2vHPV: bivalent HPV vaccine. 4vHPV: quadrivalent HPV vaccine. 9vHPV: nonavalent HPV vaccine.

For adolescent males, in the "favorable scenario," female vaccination coverage is lower (e.g., 20%) and all potential health benefits are included in the analysis. In the "unfavorable scenario," female vaccination coverage is higher (e.g., 75%) and only the health outcomes for which the vaccine is indicated are included in the analysis.

Cost per QALY gained estimates were obtained from ACIP policy notes and recommendations on ACIP website. Ratios adjusted for inflation to 2017 US dollars and rounded to nearest multiple of $5,000. This table was previously published (in 2016 dollars) by Markowitz et al., 2018 Acad Pediatr. Because of rounding, the estimates in 2017 dollars are exactly the same as published by Markowitz et al.

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Moving on to an overview of the 3 models being used for 9vHPV vaccine, Dr. Chesson first shared a schematic of a model of HPV transmission and vaccination to illustrate how difficult it is to do these models. It is necessary to take into account HPV transmission, natural immunity, natural history of disease, cervical cancer screening, and a variety of outcomes attributable to HPV. This would be difficult enough if there was just one type, but there are all of the types in the vaccine and consideration must be given to the cost and quality of life impacts of these outcomes. Dr. Chesson then presented the following US models of 9vHPV:

- US HPV-ADVISE Model
  Brisson et al.
  Brisson, Boily, Laprise, Drolet, Bénard, Martin, Chesson, Markowitz: No conflicts

- Simplified Model
  Chesson et al.
  Chesson, Markowitz, Meites, Ekwueme, Saraiya: No conflicts

- Merck Model
  Daniels et al.
  Daniels, Prabhu, Pillsbury, Kothari, Elbasha
  Conflicts of interest statement: All authors are employees of Merck & Co, Inc.

All 3 of these models are dynamic. That means that they include transmission or "herd effects" of vaccination. All of the models include a wide range of health outcomes such as cervical pre-cancers and cancer; other HPV-associated cancers (e.g., anal, vaginal, vulvar, penile, oropharyngeal); genital warts; and recurrent respiratory papillomatosis (RRP), except for the HPV-ADVISE model, which does not include RRP. The Merck model and Simplified model include adult-onset and juvenile-onset RRP. All of the models apply recently updated, higher direct medical costs estimates for HPV-associated cancers and updated vaccine costs.

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The Simplified model has been used to examine a wide range of HPV vaccination strategies, and the results often have been similar to those of more complex HPV models. The model has been very useful, but is not always suitable or sufficient for all analyses due to key simplifications. Because of this, CDC has been collaborating with the HPV-ADVISE modelers from Université Laval in Canada to address the full range of ACIP needs. The HPV-ADVISE model was developed initially for Canada and was adapted to US data with funding from CDC. The US version of the HPV-ADVISE model has been used extensively as well by ACIP and other governmental health organizations. The Merck model has been used to examine a wide range of HPV vaccination strategies, and the results have been presented during all HPV-related ACIP meeting sessions regarding cost-effectiveness. All of the model equations have been published and like the other models, the Merck model has been used to inform other governmental and health organizations.

In terms of some of the selected model features, the HPV-ADVISE model is individual-based and keeps track of individual people in the model; whereas, the Simplified and Merck models are compartmental and keep track of groups of people. In the HPV-ADVISE and Merck models, people can be infected, recover, and be infected again. In the Simplified model, people who are infected cannot be infected again. The study approach used in the HPV-ADVISE and Merck models is similar to what is occurring now in which there is an HPV program in place for 10 to 12 years, and then the addition of a mid-adult vaccination program is examined. The Simplified model cannot change vaccine strategies mid-stream, so it just looks at 100 years of a vaccine program with mid-adult vaccination compared to 100 years of a vaccination program without mid-adult vaccination. Regarding natural immunity, the Simplified model does not include reinfection so it can be thought of as assuming 100% lifelong natural immunity after infection. The HPV-ADVISE and Merck models do allow for some degree of natural immunity. The HPV-ADVISE and Simplified models assume 95% efficacy against infection, and it is this protection against infection that leads to reduction in HPV-associated diseases. The Merck model is somewhat different in that it models specific efficacy against transient infection, persistent infection, and disease. In the HPV-ADVISE and Merck models, the vaccine is assumed to provide protection against reinfection. The HPV-ADVISE and Simplified models use NIS-Teen coverage estimates for the base case, while the Merck model uses NHANES. The probability of vaccination among mid-adults is different in the models. The HPV-ADVISE and Simplified models assume that roughly 2.6% of women and 1.9% of men are vaccinated each year; whereas, in the Merck model this is somewhat lower such that about 2.4% of eligible women and 1.0% of eligible men are vaccinated over the 100-year period.

Moving on to the results of the HPV-ADVISE model, the marginal impact of adding the adult vaccine on CIN2/3, cervical cancer, anogenital warts, and non-cervical HPV cancers is so low that the difference cannot be distinguished in the graph displayed. For example, with the current recommendation roughly 32 million cases of anogenital warts are averted over 100 years. Expanding the recommendation to include mid-adults would avert an additional 313,000 cases. If the recommendation is extended just to age 30 years, about 180 thousand additional cases would be averted. In terms of the NNV, with the current recommendation compared to no vaccination, there is 1 death averted for every 605 people vaccinated. However, if vaccination is expanded to include ages up to 45 years, approximately 10,500 additional people would have to be vaccinated per death averted. With regard to the incremental cost and health benefits, the bulk of the benefits come from the current recommendation. Adding the older age groups has a smaller marginal effect. The same trend holds for the incremental QALYs gained.

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In terms of the incremental cost-effectiveness ratios in the HPV-AVISE model, a vaccination program up to age 17 for both sexes would be considered cost-saving compared to no vaccination. If that is extended to the current recommendation of 26 years for females and 21 for males, the cost per QALY gained is about $33,000. If the table included a cost per QALY gained for both sexes ≤ age 26 compared to the current recommendation, it would be about $350,000 but instead is listed in the table as dominated. That is somewhat higher than the cost per QALY for vaccinating both sexes ≤30 years of age of $204,000. To explain, when a strategy is followed by a more effective strategy that has a lower cost per QALY, that strategy is referred to as "dominated" and it is removed from the comparison. There is a major jump when the cutoff age is moved from 35 to 40 from $310,000 to $1.6 million per QALY gained. The last strategy, ≤45 years versus ≤40 years, is dominated because no consistent population-level health benefits could be found for changing this cutoff. To summarize the HPV-ADVISE cost-effectiveness results, the current HPV vaccination program appears to offer good value for the cost, primarily because vaccination of adolescents appears to be cost-saving. Extending HPV vaccination above age 26 results in a substantially higher cost per QALY gained.

Moving on to the cost-effectiveness results across all of the models, the Simplified model has a higher cost per QALY gained for ages 30 and 35 ($306,000 and $499,000 respectively), but it does not increase as rapidly as the HPV-ADVISE model when moving from 35 to 40 ($499,000 to $639,000 respectively). The Merck model results show the same trend in that the cost per QALY gained increases with age at vaccination, though its cost per QALY gained estimates are notably lower at $53,000 through 30 years of age; $89,000 through age 35 versus 30 years; $145,000 through age 40 versus 35 years; and $252,000 through age 45 years versus 40 years. No single factor accounts for the different cost-effectiveness estimates across the model. A range of factors is being considered to try to explain this. Two of the important factors have been identified thus far, natural immunity assumptions and historic vaccination coverage assumptions. In terms of natural immunity assumptions, in general, the cost per QALY gained decreases as the degree of natural immunity decreases. All else equal, if a model has lower natural immunity, this will result in a lower cost per QALY. The Simplified model assumes 100% natural immunity, which could explain why its cost per QALY estimates are higher than the other two for some of the vaccination strategies. The HPV-ADVISE model assumptions may result in a higher effective degree of natural immunity than the Merck model. For the Merck and HPV-ADVISE base case results, vaccination through age 30 years compared to the current recommendation is $53,000 per QALY gained in the Merck model and $204,000 in the HPV-ADVISE model. In the lower natural immunity assumption scenarios, the cost per QALY in the Merck model is $146,000 but in the higher natural immunity it is closer to $230,000 per QALY gained. The same relative trend holds when looking at vaccination through age 40 years compared to the current recommendation.

Turning to the vaccination coverage assumptions, the preliminary results suggest that the HPV-ADVISE results and Simplified model results are not particularly sensitive to moderate changes in coverage. However, the cost per QALY gained by mid-adult vaccination increases with higher historic coverage assumptions in the Merck model. The Merck model looks at introducing mid-adult vaccination to an established HPV vaccination program, so if higher coverage is assumed during the first 10 to 12 years, then they have a higher cost per QALY of mid-adult vaccination. For example, in their base case using NHANES coverage assumptions, the Merck model's cost per QALY gained was $85,000. When they used NIS-Teen coverage assumption, it was $171,000.

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Regarding next steps, ACIP review of the models is ongoing as mentioned earlier. The modelers will continue working to document the main differences in model structures and assumptions to better understand the implications of these differences in the models. For example, the implied median age at which causal HPV infection is acquired for cervical cancer differs across the models. They also want to address feedback from the ACIP review and provide more details to the WG in subsequent presentations. Plans for the February 2019 ACIP meeting are to provide more details of the health economic models about the assumptions, limitations, sensitivity analyses, and so forth. In addition, responses will be provided to the ACIP health economics reviews and responses to ACIP feedback from the October 2018 meeting.

Discussion Points

Dr. Elbasha (Health Economist, Merck) said that the difference in the results of the three models was surprising to Merck, given that in previous reviews the models aligned when evaluating younger age groups. Therefore, it is very important to figure out the differences. Merck welcomes the next steps outlined in terms of understanding. The differences in the key assumptions that drive the result as outlined, natural immunity and vaccine coverage assumptions, are very relevant to this age group recommendation. The Simplified model makes the assumption that recovery from infection is not taken into account, which is fundamentally inconsistent with the natural history of HPV infection. In Merck's preliminary analysis, when that assumption was made, the results changed dramatically for vaccinating this age group. Regarding the median age of infection, the HPV-ADVISE model shows that most infections occur before age 18. If the median age of infection is around 18 years of age, by the time a person is 26 or 27 years of age, about 80% of infection occurs. Therefore, the benefit of vaccination of this age group as predicted by that model is going to be much lower. There is a lot of work ahead to try to align the assumptions and figure out all of the differences.

Dr. Maldonado (AAP) observed that all of the models included current recommendations and females and males of certain ages, which she presumed to include catch-up vaccination. One issue that comes up with pediatricians in practice is the gap between children who were vaccinated with 2vHPV and 4vHPV vaccines versus 9vHPV vaccine. Assuming that the vaccine for girls was licensed in 2006 and for males in 2010 and looking at a 9 to 12 year old age range for first vaccination with either 2vHPV or 4vHPV versus 9vHPV vaccine, for a 10-year period between 2006 and 2016 for girls and 2010 to 2016 for boys, there is a group of 10-year birth cohort for girls and 6-year birth cohort for boys who are now between 11 and 24 years of age in girls and 11 to 20 years of age for boys who have not received the 9vHPV vaccine. She wondered whether those catch-up vaccines were modeled into this, because this impacts a substantial number of children and AAP does get questions from pediatricians about what to do regarding those catch-up vaccines. In the past, they have heard that there is no recommendation to include them.

Dr. Chesson indicated that his understanding was that the HPV-ADVISE model did take those differences into account. One of the main issues is that they looked at the marginal impact of adult vaccination strategies, so they took the approach that whatever is happening with the young people would be the same in either strategy. That cancels out to some degree when the mid-adult vaccination strategy is compared to a scenario of no mid-adult vaccination strategy. They can provide a more detailed answer to that question in the future.

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Related to the FUTURES III study, Dr. Lee noticed that there was a difference in the efficacy between per-protocol and ITT. She asked whether the modeling vaccine coverage estimates assume per-protocol, so series completion, or if they allowed for people who perhaps started but did not complete the series and if there is variable effectiveness in the model.

Dr. Chesson replied that the models differ somewhat for that. The Merck model keeps track of doses, while the Simplified model assumed that people were vaccinated with the complete series.

Dr. Bernstein inquired as to why the Simplified model assumed that persons infected could not be infected again rather than making the same assumption as the other two models that persons who are infected can recover and be infected again.

Dr. Chesson responded that one of the simplifying assumptions of the Simplified model was to estimate the impact of vaccination based on the cumulative reduction and lifetime acquisition, and it does not model natural history from the time of infection to disease. This major simplification enables them to look at this in a different way than the other two vaccines. There are limitations and benefits to that approach.

Recommendation Options

Lauri Markowitz, MD
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To end this session, Dr. Markowitz briefly reviewed the WG's plans and policy considerations regarding the expanded age range for 9vHPV vaccine. As mentioned earlier, the policy question being addressed is, "Should the upper age for HPV vaccine catch-up vaccination be expanded beyond the current recommended ages?" Before discussing specific issues regarding this, Dr. Markowitz mentioned two points. In discussions with WG members, all members felt that they want to reinforce the importance of the routine schedule and the fact that HPV vaccine will have greatest impact when it is administered before onset of sexual activity and HPV exposure. The WG is still reviewing results from the health economic analyses, as well as other data related to this policy question.

As a reminder, the current recommendations for HPV vaccination in the US are as follows:

- Routine HPV vaccination at age 11 or 12 years
  - The vaccination series can be started beginning at age 9 years
- HPV vaccination is also recommended for the following persons if not adequately vaccinated previously
  - Females through age 26 years
  - Males through age 21 years
  - Certain populations through age 26 years*
- Males aged 22 through 26 years may be vaccinated

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

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In terms of the WG discussions, there would be no change for the routine age based on the expanded age indication. For routine catch-up, the WG discussed harmonization of the upper catch-up age for females and males. This has been discussed during several ACIP meetings, and there is general support for this. This harmonized age could be the current age of 26 years or a different age, depending on further considerations as mentioned earlier. While the WG is still reviewing the health economic modeling data, they did consider recommendations if the routine catch-up age is not expanded through age 45 years. For persons older than the determined catch-up age, whatever that is, almost all WG members felt that a recommendation for *Individual Decision-Making* could be considered, and that *Individual Decision-Making* would be through age 45 years.

The WG discussed the pros and cons of *Individual Decision-Making*, which used to be called *Category B* and before that a *Permissive Recommendation*. Many WG members are aware of the challenges of a recommendation for *Individual Decision-Making* for other vaccines. However, WG members felt that for this vaccine, which has a routine and a catch-up recommendation in some age groups, it could be recommended for *Individual Decision-Making* for individuals beyond the upper age for routine catch-up. Several liaison organization members are on the WG who supported this decision. The WG did discuss that if an *Individual Decision-Making* recommendation is made in some age groups, guidance would be needed. There would have to be discussion about what guidance to provide, how to communicate who might benefit, and how to communicate the lower effectiveness in this age group.

The next steps for the ACIP HPV Vaccines WG are to further review the health economic analyses, summarize values and acceptability in the expanded age group, review data for special populations, discuss policy options, complete the full EtR Framework, and prepare for a potential vote during the February 2019 ACIP meeting. With that in mind, the WG requested feedback from ACIP on the following:

- Catch-up vaccination age group
  - Harmonization of upper age for “routine” catch-up recommendation for males/females
  - Upper age: Could be the same age (26 years) or a different age, depending on impact and health economic analyses and other considerations

- Persons older than catch-up age through age 45 years
  - Potential recommendation for *Individual Decision-Making*

Discussion Points

Dr. Hunter said that for him personally it was pretty straightforward that harmonizing the upper age of catch-up at 26 would make it much easier, especially for primary care practitioners, to implement this recommendation. He also was generally in support personally of the *Individual Decision-Making* recommendation for the older group. If he understood the presentation earlier about vaccine supply, especially if the worldwide supply affects the US supply, if the US gives more vaccine to older individuals for the next 5 or 6 years, less vaccine would go to younger people. He wondered whether that had been calculated into any of the economic analyses.

Dr. Markowitz indicated that they have been told that there is no current or anticipated vaccine shortage for the US. She clarified that she showed the supply and demand situation internationally because some of the WG members were aware of and concerned about that. This has been discussed a lot in the international community.

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Dr. Hunter pointed out that they also were told that there would not be a shortage of the new shingles vaccine and that was not the case.

Dr. Yakubic (Merck Supply Chain Management) indicated that Merck remains extremely confident that it can meet the forecasted demand for the US market, given that the indication for the 27 to 45 year old age range has been planned for several years. They can also share and validate that there has been unprecedented increase in worldwide demand for HPV vaccines. Demand has doubled in the last year alone, which was driven by new and expanded vaccination programs around the world. Notably, the largest increase in demand was driven by policy changes for Gavi countries that will move from the demonstration programs to the multi-age cohorts. Increasing the global supply of HPV vaccine to meet this demand is a top priority for Merck. Plans are in place to triple Merck's supply over the next few years based against the 2017 baseline. For 2018, Merck was able to double its supply of GARDASIL® to Gavi countries compared to 2017 supply. Gavi country launches will remain a priority for Merck, and they anticipate that the volume for Gavi launches will represent the majority of the supply increases over the next few years. The biggest increase in 2019 from 2018 will be for Gavi countries, which will bring the supply to Gavi in 2019 in significant excess to the supply for the US. Merck's US supply against the global supply is less than 20%, which keeps them confident to be able to support the US demand.

Dr. Friedland (GSK) reminded everyone that over the last few years, GSK has reduced its manufacturing capacity for its 2vHPV in the US given the recommendations. However, around the world, it is important to provide an update on supply. GSK has been evaluating the potential to increase its capacity in the medium-term to supply the countries as outlined by Dr. Markowitz where there is an imbalance between supply and demand. They are looking to increase the capacity to meet the demand for the 2vHPV where it is recommended around the world so that they can continue to supply vaccine through the national vaccine immunization programs to meet the worldwide demand.

Dr. Fryhofer (AMA) said that as a practicing physician, this discussion had been so helpful and demonstrated the value of ACIP in going beyond FDA licensing and helping clinicians determine which of their patients will benefit from this life-saving cancer vaccine. As they also have been discussing, it also is a reality check on how US decisions can make an impact globally. This is a perfect example of how ACIP can help clinicians with value-based care and judicious use of resources. She congratulated Dr. Markowitz and her team for an excellent discussion, and she looks forward to February.

Dr. Foster (APhA) expressed appreciation for the excellent presentations. One thing to mention with regard to the potential recommendation for *Individual Decision-Making* that may have an impact is accessibility to pharmacies. Every state has a different law or rule on what pharmacists can do. A few states have regulations that indicate that unless a recommendation is a "Category A" or the recommendation to give as routine, pharmacists cannot administer the vaccine. Pharmacists will become an important partner in this type of program, because this is the age group that typically acquires a lot of their vaccines in a pharmacy.

Dr. Goldman (ACP) thanked the WG and ACIP for tackling this very important issue. Women's health is a very important initiative for ACP and they advocate for anything that can be done to promote that. He thinks increasing the catch-up age to 26 will be very helpful from the primary care perspective, and it would be interesting to see the economics for the *Individual Decision-Making* for those who are going to be changing their lifestyle at later years in life and how that

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might affect the decision-making. This could play into the recommendation in terms of how it affects quality of life and the cost.

As a family physician and clinician, Dr. Rockwell (AAFP) supported harmonization of the ages for males and females which would be extremely helpful, especially in the age of EHRs in which oftentimes much of the support staff are helping to immunize. Best practice alerts pop up in the EHRs and if a recommendation is not a "Category A," some staff are not up to date and may not realize that young men who may fall into other categories or who may wish to have HPV vaccination are eligible, so they are not getting it.

Dr. Lee thought it would be beneficial to understand what the financial coverage would be for an *Individual Decision-Making* recommendation, as well as what the potential disparities might be in terms of access, recognizing that there is a lot of evidence to suggest that this might be a reasonable choice.

Dr. Frey asked whether, should such a recommendation be made, there is a way to assess the impact on demand in general to determine whether there will be enough vaccine available to meet those demands in a timely manner.

General Recommendations

Paul Hunter MD
Chair, ACIP General Recommendations WG
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

Dr. Hunter indicated that as Chair of the ACIP General Recommendations WG, he would provide context for Dr. Kroger's presentation about the recent and upcoming changes in the *ACIP General Best Practice Guidelines for Immunization*. The WG meets monthly to achieve the goals and objectives identified by the following terms of reference, which are to:

- Revise the *ACIP General Best Practice Guidelines for Immunization* as needed (the last revision was in 2017), and some sections every two years
- Address issues related to general recommendations for vaccines and immunization programs
- Work on emergent issues that do not clearly belong to another specific pre-existing WG

In short, the WG is a gathering place for people who like making connections between disparate disciplines in order to come up with practical interventions that help clinicians and their patients.

Previously known as General Recommendations, the *General Best Practice Guidelines* provide expert opinion and, where available, evidence for issues in clinical practice that cut across multiple vaccines. As a consultant to public health nurses who administer thousands of vaccines each year, Dr. Hunter finds that the *General Best Practice Guidelines* are where he should have

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gone first to answer questions that are not answered by his standing orders. He encouraged everyone to go to these guidelines as well.

In the recent past, sections of these guidelines were presented for discussion over a series of ACIP meetings before the entire set of guidelines was voted upon by ACIP and published in the *MMWR*. The plan for this session was for Dr. Kroger to review recent errata and updates that have been added to the guidelines on the ACIP website. In addition, Dr. Kroger also planned to present for discussion the draft addition to the *General Best Practice Guidelines* about health care personnel who themselves have precautions or contraindication for certain vaccines, but may nonetheless administer those vaccines to patients. No votes were planned on the guidelines during this session.

Background and Posted Changes Since 2017

Andrew Kroger, MD MPH
Medical Officer
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

In terms of background, Dr. Kroger showed an image of the webpage. This still looks the same even though some of the websites upstream from this page look somewhat different. The *General Best Practice Guidelines for Immunization* is now an online document. It does not exist as an *MMWR* document anymore. All of the subject headers on the webpage now include links to html files for the following guideline topics:

- Introduction
- Methods
- Timing and spacing of immunobiologics
- Contraindications and precautions
- Preventing and managing adverse reactions
- Reporting adverse events after vaccination
- Vaccine administration
- Storage and handling of immunobiologics
- Altered immunocompetence
- Special situations
- Vaccination records
- Vaccination programs
- Vaccine information sources

This product is available for Continuing Education, which is renewed on a 2-year cycle. Clicking on the link will take the reader to all of the registration and continuing education information. Every word of the *General Best Practice Guidelines* exist not only as html, but also as a downloadable pdf file. There is a pdf file for each of the individual topics as well. The list of Errata/Updates is just above the block for Continuing Education. Clicking on this link will connect the reader to every update that has been made to this online document since April 2017, barring some punctuation and other typographical issues. The Errata/Updates entries are indexed by the date on which they were posted. For each entry, update, or errata, there is a page number, a link to the pdf for that particular section, a link to that section as an html version, a listing for the specific table, and a description of the change.

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Dr. Kroger reviewed some of the important changes to ensure that ACIP was aware of them, indexed by vaccine topic. These are either harmonizations of recommendations that already have been voted on and cleared through CDC, or interval issues already posted to CDC's Clinical Decision Support for Immunization (CDSi) web page.

For pertussis-containing vaccines, a clear statement was made about the minimum interval between Dose 3 and Dose 4 for DTaP, which varies depending upon whether looking ahead to scheduling the next dose (prospective) or counting a dose that has already been administered (retrospective). There is a statement that the 4-day grace period can be applied to both of these scenarios. The date on which this addition was made was October 23, 2017. This also is the way that CDSi is programmed. The other pertussis-containing vaccine change is that four precautions to DTaP were removed as they are no longer considered to be reasons to withhold the next dose of DTaP, given that they were considered to be related to use of whole cell DTP and not relevant to acellular pertussis vaccine. These changes were placed on the website between July and September 2018, but were published in the ACIP recommendations in February 2018:

- ❑ Fever ≥ 105° F within 48 hours following a dose of DTaP (09/20/18)
- ❑ Persistent, inconsolable crying lasting ≥ 3 hours within 48 hours following a dose of DTaP (07/18/18)
- ❑ Collapse or shock-like state with 48 hours following a dose of DTaP (07/18/18)
- ❑ Seizure within 72 hours following a dose of DTaP (07/18/18)

Minimum intervals for Serogroup B meningococcal vaccine were placed on Table 3-1 in the Timing and Spacing section. This is published on the CDSi webpage in the Business Language for Registries. This now also appears in the *General Best Practice Guidelines* as of September 20, 2018. Of note is that while minimum intervals are not used on a routine basis, these intervals are very important for providers to have in certain circumstance in which errors already have been made, such as mix and match of brands.

For Hepatitis A, Dr. Kroger made two changes. The dosages of IG were updated for prophylaxis. He also discussed with partners at FDA about the fact that even though the dose of IG has been adjusted, there is no need to adjust the interval to next subsequent MMR or varicella vaccines. A change also has been made in the Vaccine Administration section to specify that IG and HepA should be administered in different limbs. This is related essentially to the volume of the IG product and joins two other examples of this, TIG and tetanus-containing vaccines and HepB IG (HBIG) and HepB vaccines.

Some longstanding CDC published recommendations for varicella vaccine to the *General Best Practice Guidelines*. A family history of altered immunocompetence has been a published contraindication to varicella vaccine since 2007. It now appears in the General Best Practices table. This content also has been added for MMR vaccine, because it also is published in the MMR vaccine-specific recommendations, and there is a footnote explaining that the concern is with congenital immunodeficiencies and the intervention is to screen patients through histories of first-degree relatives or use of laboratory evidence of a congenital immunodeficiency. It is generally presumed that a congenital immunodeficiency will be detected prior to a decision to use varicella or MMR vaccine anyway. The other change is a precaution for the use of aspirin or aspirin-containing products. This is more of a recommendation than a vaccine precaution to avoid giving the medicine 6 weeks after the vaccine already has been given, which does not really meet the definition of a vaccine precaution. A precaution also has been added regarding

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avoiding receipt of specific anti-herpesvirus antiviral drugs 24 hours before vaccination and for 14 days after vaccination.

For zoster vaccine, a change was made in the Vaccine Administration section. With all of the other vaccines, there is a table in which vaccination injection volume is listed. However, unlike other vaccines for which administration of additional volume is allowed since vials are often overfilled, a specification was made that only 0.5 cc's should be withdrawn from a vial per the package insert even if the vial is overfilled for SHINGRIX® vaccine. As with varicella, the contraindication was added to LAIV that influenza antiviral medications within the previous 48 hours is a contraindication to administering LAIV. In this instance, it is not a feasibility issue or precaution. There is an alternate vaccine that can be used.

Vaccine Administration Discussion Topic

Andrew Kroger, MD MPH
Medical Officer
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Kroger presented some language for ACIP discussion, which the WG has discussed. This language will need to be cleared through CDC before it is placed on the online document. CDC often is asked about providers who are well-aware of the contraindications and precautions for vaccinations because they are screening their patients. However, HCP may have a labeled contraindication or precaution themselves which raises questions about whether they can still administer the vaccine.

There is no discussion of this in the *General Best Practice Guidelines*. However, there is a well-known vaccine-specific recommendation published for LAIV, which arose out of concerns expressed by pregnant HCP about administering LAIV. That recommendation states that LAIV can be administered by HCP who are pregnant or have any other contraindications. There is not thought to be much environmental spread, and there have been few cases of any type of transmission of LAIV from someone who was vaccinated to someone who was not vaccinated. That is a little different issue, but is similar to any risk to the HCP themselves administering the dose.

The General Recommendations WG debated whether this could be generalized to all vaccines, so they reviewed the literature related to HCP risk of AEs based on administration of vaccine and the intervention of withholding vaccine versus administering vaccine. The databases searched included: Embase. Cinhal, Scopus, PsycInfo, and Medline. This resulted in identification of 82 unique articles for which the abstracts were reviewed, with the exception of 2 or 3 that were not in English. Out of all of these abstracts, only the following 3 discussed this question specifically:

- ❑ Centers for Disease Control and Prevention. Recommendations for using smallpox vaccine in a prevention vaccination program: supplemental recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR 2003;52(No. RR-7):1-18.

- ❑ Leira HL, Baalsrud KJ. Fish vaccinology. In: Gudding R, Lillehaug A, Midtlyng PJ, Brown F, eds. Dev Biol Stand, Basel: Karger; 1997.

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- Windsor PA, Bush R, Links I, Eppelston J. Injury caused by self-inoculation with a vaccine of a Freund's complete adjuvant nature (Gudair™) used for control of ovine paratuberculosis. Australian Veterinary Journal April 2005;83(4):216-20.

The CDC article focused on vaccinators of vaccinia vaccine. While it is not the same microbe, it is the same general topic issue. The risk-benefit calculation was tipped toward not allowing vaccinators with contraindications to be allowed to administer the vaccine. That was based on inherent risk that the vaccinia virus posed to persons with underlying conditions and issues of transmissibility, which was known from patients who had received vaccine. The Leira article discusses the risk of vaccinating fish with an inactivated vaccine to prevent two types of vibrio, while the Windsor article discussed the risk of vaccinating sheep to prevent paratuberculosis. Both articles focused on needlesticks as the precipitating event that posed the risk to the provider. The risk in the Leira article was an allergic reaction to the vaccine, with 2 cases out of 50 needlesticks. The risk to the provider in the Windsor article was self-inoculation of the infectious agent. Based on this information, the WG crafted the following language for discussion with ACIP that would be placed in the Administration Section:

Health Care Provider Exposure to Vaccine Antigen

- Providers are sometimes concerned when they have the same contraindications or precautions as their patients from whom they withhold or defer vaccine. For administration of routinely recommended vaccines, there is no evidence of risk of exposure of vaccine antigen to the health care provider, so conditions in the provider labeled as contraindications and precautions to a vaccine antigen are not a reason to withdraw from this function of administering the vaccine antigen to someone else.

- Historic concerns about exposure to vaccine antigen are limited to non-parenteral vaccines in which some degree of environmental exposure is unavoidable (LAIV), situations in which adverse reactions from allergy or self-inoculation is likely due to reduced attenuation of vaccine virus (Smallpox), or the technical process of administration is complicated by vaccine recipients that struggle vigorously, leading to needle stick injury and reactions due to allergy or self-inoculation (veterinary vaccinology).

Dr. Kroger pointed out that instead of the parenthetical terms in red, the footnote for the citation will be included.

Discussion Points

Dr. Goldman (ACP) wondered whether there should be any language included about the obvious statement of using proper universal precautions and standard techniques to understand that if someone is using the proper best practices there is no chance of infection, reaction, or other issues.

Dr. Kroger indicated that this paragraph would be included in the section on Vaccine Administration that includes a discussion about risks of needlesticks to providers, which is followed by the second paragraph. Then there is discussion about the best practice techniques for vaccine administration with respect to routes, sites, needle lengths, et cetera.

With respect to the veterinary vaccinology, Dr. Moore inquired as to whether there would be a reference to link people with those types of concerns to an appropriate resource. Speaking as someone who vaccinates cats every year for her father's cattle farm, she has experienced those

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sorts of needlestick injuries and did not know quite what to do about that. People who have this kind of experience may looked to the ACIP recommendations for further information, so it would be beneficial to include referral information.

Dr. Kroger indicated that those citations will be included, and he will discuss this with CDC's injection safety folks who may have additional information about veterinary vaccinology.

Speaking as a state health official, Dr. Hahn (CSTE) indicated that they do receive these types of calls. In her 20 years there, she has never had a provider tell her that they got exposed to a vaccine while vaccinating a human. Veterinarians do call regularly, so that would be very helpful.

Ms. Stinchfield (NAPNAP) said that she receives questions about clinicians or moms who are on drugs such as REMICADE® who administer rotavirus vaccine. There is nothing written about that and it was not included in the proposed language.

Dr. Kroger indicated that the General Recommendations WG has begun a discussion about this. It would fall under Altered Immunocompetence, because the package insert for REMICADE® states an interval from birth to 6 months of age to avoid live vaccines. CDC guidance is that a specialist can be consulted, which is how that question is typically answered. The WG is trying to develop something specific for that topic, but that work was not fully pursued in time for this meeting. There also is the complicating issue of altered immunocompetence because ACIP and CDC are in the process of working with various partnerships to try to develop some type of harmonized guidance and aligning that guidance among the various partners' guidance. While it is not published, CDC always recommends consultation with an infectious disease specialist to weigh the risks and benefits.

Ms. Stinchfield (NAPNAP) indicated that this is how the calls come to her, so when she tries to give them articles or further information, there is nothing published. That would be very helpful. The REMICADE® package insert is about the individual getting REMICADE®, not the person administering it. It is clear someone on REMICADE® should not be given rotavirus vaccine. But the person may be someone who is giving rotavirus vaccine or who is taking care of a child who is shedding rotavirus for weeks. It would be helpful to include something about wearing gloves, hand washing, et cetera.

Dr. Whitley-Williams (NMA) added that there are populations in New Jersey that typically take their 1- or 2-week old babies back home to TB-endemic countries, who purposely take them to get BCG vaccine while they are there. The issue of disease-modifying drugs is an important one that should be considered by the WG, because it is devastating to do that when the mother has been on these medications.

Dr. Kimberlin (AAP Redbook) indicated that in the 2018 Edition of the Redbook, AAP added language specifically about that. However, a lot of it is extrapolation from what the anticipated risk is. The Canadians are doing some nice work in prospective assessments, and the AAP would welcome the opportunity to work with the WG's language to ensure that it harmonizes to the maximal extent possible.

Dr. Fink (FDA) indicated that some label contraindication or precautions for vaccines, particularly those related to allergic reactions, have to do not with the vaccine antigen but with excipients or non-active ingredients. Therefore, he wondered about specifically calling out the vaccine antigen in this recommendation.

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Dr. Kroger replied that the *General Best Practice Guidelines* has a section on Contraindications and Precautions in which every vaccine is listed in a table with contraindications and precautions. This is for the vaccine recipient and is unrelated to this issue. For all vaccines, if the recipient has a history of a severe allergic reaction (e.g., anaphylaxis) to a vaccine or to a vaccine component, that is a contraindication to the vaccine. That is believed to be general enough and is quite harmonized with FDA.

Dr. Cohn emphasized that the General Guidelines WG is attempting to address many situations, and invited anyone with specific additional feedback or comments to email them to her or Dr. Kroger.

Influenza

Introduction

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

Dr. Walter reminded everyone that during the June 2018 ACIP meeting there were presentations on 2017-2018 influenza VE; 2017-2018 influenza vaccine safety; the Systematic Observational Method for Narcolepsy and Influenza Immunization Assessment (SOMNIA) study, a multinational study of narcolepsy following adjuvanted monovalent pandemic H1N1 influenza vaccines; the results of a study from Seqirus™ of adjuvanted quadrivalent inactivated influenza vaccine in young children; and the 2018-2019 recommendations.

Since February 2018, the WG has engaged in calls twice a month during which members heard presentations on: 1) publication of the 2018-2019 ACIP influenza vaccine statement; 2) the Pregnancy Influenza Vaccine Effectiveness Network (PREVENT) study of effectiveness of influenza vaccine in preventing hospitalization among pregnant women; and 3) a study of Fluzone® Quadrivalent (IIV4, Sanofi Pasteur) at a 0.5mL dose for children aged 6 through 35 months.

There have been some changes in labeling information for influenza products. Afluria® (IIV3, Seqirus™) and Afluria® Quadrivalent (IIV4, Seqirus™) were previously licensed for ages 5 years and older. In October 2018, the age indication was expanded to ages 6 months and older. As a reminder, the dose volumes for that product are 0.25 mL for children 6 through 35 months of age and 0.5 mL for children 36 months (3 years) of age and older. There are now 5 IIV influenza vaccines licensed for children 6 through 35 months of age:

- Fluarix® Quadrivalent (IIV4, GSK): 0.5mL
- FluLaval® Quadrivalent (IIV4, GSK): 0.5 mL
- Fluzone® Quadrivalent (IIV4, Sanofi Pasteur): 0.25 mL
- Afluria® (IIV3, Seqirus): 0.25 mL
- Afluria® Quadrivalent (IIV4, Seqirus): 0.25 mL

Note that most of these products are quadrivalent, and the dose for persons aged 3 and older is 0.5mL for all IIVs.

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The agenda for this session included the following topics:

- ❑ Influenza VE in Preventing Influenza-Associated Hospitalizations during Pregnancy
- ❑ Fluzone® Quadrivalent 0.5-mL dose for children aged 6 through 35 Months

Influenza Vaccine Effectiveness in Preventing Influenza-Associated Hospitalizations during Pregnancy: A Multi-Country Retrospective Test Negative Design Study, 2010-2016

Mark G. Thompson, PhD
On Behalf of the PREVENT Network and
Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Thomson presented on the effectiveness of influenza vaccine in preventing influenza hospitalizations during pregnancy. Pregnant women are believed to be at increased risk of severe influenza disease, including influenza hospitalization. This was a prime driver behind WHO making pregnant women their priority group for influenza vaccination programs around the world. However, only 44% of WHO member states recommend influenza vaccination for pregnant women. Some of those include some trimester restrictions, influenza vaccination of pregnant women is contraindicated in many countries such as China, and even high-income countries underutilize influenza vaccine among pregnant women. The good news is that RCTs and observational studies provide growing evidence that the vaccine reduces by about half the risk of mild to moderately severe disease. The bad news, as WHO and others have pointed out, is that it is the reduction of risk of severe disease that is most valued by low and middle-income countries (LMICs), organizations like GAVI, and other decision-makers. This gap is going to be hard to address with RCTs and existing platforms for ethical and feasibility reasons.

A couple of years ago CDC decided to form PREVENT, a network of public health and healthcare systems with integrated medical, laboratory, and vaccination records. Over 2 dozen organizations were assembled in Western Australia; Alberta, Canada; Ontario, Canada; Israel; and the Western US. In Australia and Canada, public health organizations had the best integrated systems. In Israel and the US, the integrated care organizations had the best integrated systems with the Clalit Health Research Institute in Israel and Kaiser Permanente on the US West Coast. All of these sites contributed data for 3 to 6 seasons, for a total of 25 study seasons. All sites sought records going back to the 2010-2011 influenza season, and most were able to look through the 2015-2016 season.

This began with all of the organizations forming a retrospective cohort of pregnant women aged 18-50 years with records of live or still birth with gestations ≥20 weeks, with a focus on acute respiratory or febrile illness (ARFI) hospitalizations identified by ICD-9/ICD-10 discharge diagnosis codes of influenza, pneumonia, other acute respiratory codes, febrile only, sepsis-like, and other acute conditions associated with influenza. They had to rely on clinician ordered real-time reverse transcription polymerase chain reaction (rRT-PCR) testing for influenza within 3 days prior to admission through discharge, with a focus on any A or B influenza positive since subtyping was not done consistently on clinical specimens. In most of these organizations, there was an increase in PCR use in clinical practice following the pandemic. There were few rapid or other tests used in these settings, but those with these were excluded. A small number were excluded with missing influenza vaccination records or vaccination 0-14 days prior to admission.

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A test negative design (TND) was used, which is the currently established method for observational studies. In this design, the cases are rRT-PCR confirmed influenza positives and the controls are influenza negatives. This is believed to minimize bias due to access to vaccination and healthcare-seeking differences. Influenza vaccine effectiveness (IVE) equals 100% × (1 − odds ratio [ratio of odds of vaccination among influenza-positive cases to the odds of vaccination among influenza-negative controls]) using logistic regression. This study adjusted for site, season, season period (early, peak, vs. late), and the presence of high risk medical conditions (not pregnancy complications). These are the typical adjustments in this sort of model. They also were associated with both influenza positivity and vaccination status in the study sample. Other potential confounders (ARFI primary diagnosis, pneumonia or influenza diagnosis, pregnancy complication, ICU, or delivery during hospitalization) did not substantially change the adjusted VE by ≥5% and thus were not included.

With few exceptions, almost all sites were able to establish this cohort year-round. Among over 2 million pregnancies across all of this time, 84% of the pregnancies overlapped with influenza season. It is striking to see that the percentage of pregnancies affected by influenza in one way or another is that large. Over 587,000 hospitalizations occurred during influenza seasons. Of those, a subset of about 19,000 (3%) actually had an ARFI. For most hospitalizations, the ARFI diagnosis was not the primary reason the women were hospitalized. ARFI was the primary diagnosis in only 15% of those hospitalizations. About 19% of them were PCR-tested, with 64% being influenza positive. Not surprisingly, when ARFI was the primary driver of the hospitalization, there was lower testing of 3% of which 52% were influenza-positive. Among these hospitalizations, 67% were ARFI identified at delivery. A third were not delivery-associated. Perhaps not surprisingly, when ARFI was not associated with delivery, 14% were tested and 60% of those were positive. There was much less testing in the midst of a delivery of 2%, but when testing was done, 51% were influenza-positive. While there were differences in who was tested or not, many women were positive for influenza when they were tested.

The VE study focuses on the subgroup of the 19,450 ARFI hospitalizations in which clinical testing occurred, or 6%. Once some hospitalizations are collapsed that were relatively quick readmissions and treated as the same event (N=95), there were 1030 events. Of the 1030 ARFI hospitalizations with rRT-PCR testing, only 25 were repeated hospitalizations for the same woman. Dr. Thompson indicated that for the most part, he would talk about these as women even though the unit of analysis was hospitalizations. Most of the PCR-tested ARFI hospitalized were among women aged <35 years (79%) who were in their third trimester (65%) and had no high risk medical conditions (66%). Over 598 PCR influenza-positives were captured, of which 83% were positive for influenza A. A(H1N1)pdm was prominent in half of the seasons, while A(H3N2) was prominent in >70% seasons.

Looking at the 58% positivity (598/1030) among these hospitalizations, influenza positives were more likely to be in the third trimester, to have a pneumonia or influenza diagnosis, and to have ARFI as the primary diagnosis. Influenza positives were less likely to have had a high risk medical condition, have been diagnosed with a pregnancy complication, or to deliver during hospitalization. Across sites and seasons, about 16% (169/1030) were vaccinated. This varied across season and across sites from 8% to 21%. Not surprisingly, the US had the highest vaccine uptake at 50% compared to other sites at 8% to 14%. Influenza vaccination was higher among those who had a pre-pregnancy high-risk medical condition, delivered during hospitalization, or were diagnosed with a pregnancy complication. Influenza vaccination was lower among women who had a pneumonia or influenza diagnosis and for whom ARFI was the primary diagnosis.

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For all sites and all seasons, 13% were vaccinated among the influenza positives and 22% among the influenza negatives. IVE adjusted for site, season, season timing, and high risk medical conditions was 40% (95% CI = 12-59%). IVE varied across sites and seasons. The only significant IVE estimate by site was for the US (West) at 55% (95% CI = 7-78%). If the 2014 Southern Hemisphere and 2014-2015 Northern Hemisphere are removed for a poor vaccine match, IVE is 49% (95% CI = 22-67%). IVE is similar when stratified by season timing, high-risk medical conditions, and pneumonia/influenza diagnosis. IVE point estimates were higher if ARFI was the primary diagnosis.

In terms of the strengths of the study, best practices in observational VE assessments were applied. Highly sensitive and specific rRT-PCR influenza testing was utilized. Vaccination status was confirmed by medical records and registries. The TND design was used with standard adjustments. The takeaway is that the average field performance of IIV across multiple seasons and settings is similar to IVE estimates in recent meta-analyses looking at VE against influenza hospitalizations with working adults. There was a good mixture of A and B influenza viruses, and good and sub-optimal vaccine matches. There are limitations to potential generalizability of the results. Clinician-ordered testing of only 6% may favor more severe patients. High-income settings may not generalize to LMICs. The pooled estimate cannot disentangle sources of IVE variations, given the lack of influenza A subtype data and the variation in vaccine-virus match. Registries may miss some vaccinations, although this is unlikely to bias the results as long as it is not differential to cases vs. controls.

In summary, across sites and seasons (2010-2016), influenza vaccines had the potential to prevent 40% (95% CI = 12-59%) of influenza-associated hospitalizations during pregnancy. This is believed to be a conservative number looking forward at what would be expected of the vaccine in the next 10 years. It also is consistent with other studies that have been published, such as two prospective RCTs of VE in preventing symptomatic PCR-influenza illness during pregnancy and post-partum of 70% in a 2011–2014 RCT in Mali [Lancet ID, 2016] and 50% in a 2011–2012 RCT in South Africa [NEJM, 2014], and a study CDC conducted with Kaiser Permanente that showed 44% VE against symptomatic non-hospitalized PCR-influenza among pregnant women in a prospective TND study during 2010-11 and 2011–12 in the US [CID, 2014].

Across sites and seasons (2010-2016), influenza vaccines had the potential to prevent 40% (95% CI = 12-59%) of influenza-associated hospitalizations during pregnancy. This further strengthens the international rationale for maternal influenza vaccination programs. There is a substantial hidden burden of influenza virus infection among hospitalized pregnant women, with 84% of pregnancies overlapping with influenza season. In addition, half of rRT-PCR confirmed influenza was among those without clinical influenza or pneumonia diagnoses, and influenza infections may be frequent among women who deliver or suffer from pregnancy complications while ill with ARFI.

Discussion Points

Dr. Szilagyi inquired about whether there was any information about early deliveries or prior vaccination in previous seasons.

Dr. Thompson replied that they are looking at birth outcomes and will publish that information, but there is nothing super striking about it so far. They did not have prior vaccination data consistently across these sites. It would have been good to have those data for some seasons, because it modified the studies.

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Dr. Neuzil (IDSA) agreed that these are the data needed. In the Madhi study, influenza in pregnant women was reduced by about 50%, but there also was an impact on pneumonia in infants. In terms of the totality, Dr. Thompson presented part of it, but there also is protection afforded to the infant against severe disease.

Safety and Immunogenicity of Fluzone® Quadrivalent Vaccine 0.5-mL Dose for Children 6 through 35 Months of Age

Monica Mercer, MD
Director Scientific and Medical Affairs
Sanofi Pasteur

Dr. Mercer shared results from Sanofi Pasteur's Study GRC88, the purpose of which was to characterize the safety and immunogenicity of the 0.5 mL dose of Fluzone® Quadrivalent vaccine in children aged 3 to 35 months of age compared to the 0.25 mL dose that already had been licensed in this age group. Children are at increased risk for influenza illness and influenza-related hospitalizations. For more than 30 years, influenza vaccine for children under the age of 3 has contained a half-dose of antigen or 7.5 micrograms of hemagglutinin (HA) per strain to reduce the risk of fever or febrile convulsions that were associated with earlier whole virus vaccines. With the introduction of the split virus influenza vaccines, which are less reactogenic, the need to use a reduced dose in this young age group has most likely been eliminated. Recent studies have shown that in children 6 through 35 months of age, full-dose (0.5 mL) influenza vaccine generally induces higher antibody responses compared to those induced by a half-dose (0.25 mL) without materially higher rates of systemic or injection-site reactions. Accordingly, full-dose influenza vaccine is now recommended for children 6 through 35 months of age by health authorities in Canada, the UK, and Finland and more recently in the US.

The aim of GRC88 was to evaluate the safety and immunogenicity of a 0.5-mL dose of Fluzone® Quadrivalent vaccine compared to a 0.25-mL dose in children 6 through 35 months of age. The primary objective of the study was to compare the rate of any fever (temperature ≥ 100.4°F) following a 0.5-mL dose to that following a 0.25-mL dose during the 7 days after vaccination. The secondary objective was to compare antibody responses induced by a 0.5-mL dose to those induced by a 0.25-mL dose, as assessed by GMT ratios and seroconversion rate differences.

The study was a Phase IV, randomized, observer-blinded, 2-arm, multi-center study conducted in the US. The targeted cohort was 2190 healthy children 6 through 35 months old. An automated system was utilized to randomize subjects 1:1 to receive Fluzone® Quadrivalent vaccine administered in either a half-dose designated as Group 1 or a full-dose designated as Group 2. Enrollment was stratified by age to achieve equal proportions of subjects in each age subgroup, so half of the cohort were 6 through 23 months of age and the other half were 24 through 35 months of age. There also was a subset of 1600 subjects who were randomly selected to participate in the immunogenicity assessment. The investigators, study site personnel, sponsor's research team, and subjects were blinded to the group assignment. The exception were the unblinded study staff who administered the vaccines, and they were not involved in data capture.

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In terms of safety data and sera collections, subjects who were receiving 1 dose of vaccine were consented during Visit 1. If they were randomized into the immunogenicity subset, their blood was drawn and they were vaccinated with their designated dose of vaccine and were observed for 20 minutes for any immediate reactions. The parents or guardians were then given a diary card so that the children could then be evaluated for the next 7 days for solicited reactions. Along with the diary card, they received a digital thermometer and a ruler so that they could record daily temperatures and measure any local reactions. They also could record in the diary card any medications that were given for AEs, any healthcare provider contacts, or any hospitalizations. The parents or guardians were contacted on Day 8 to remind them to make sure that the diary cards were filled in. At the 28-day visit, Visit 2, they would return the diary card. During that time, any unsolicited AEs were captured. SAEs were captured for the duration of the trial. Subjects who received 2 doses of vaccine followed a similar format, but made 3 visits. Their third visit was 28 days following the second visit, at which time the second blood sample was drawn.

The study was conducted between September 2016 through March 2017. Due to lower than expected recruitment, 1950 participants were enrolled in the study instead of the planned 2190. However, the study remained sufficiently powered for both the primary and secondary objectives. The participants were randomly assigned in nearly equal proportions for the half- or full-dose. There were 6 participants randomized into the half-dose group and 3 into the full-dose group who were randomized but did not receive vaccine. That left a total of 1941 subjects in the safety analysis set. About three-quarters of those subjects were randomized to the immunogenicity subset. There were 715 participants in the half-dose group and 745 were in the full-dose group for the immunogenicity subset.

The study was completed by 90% of the participants. The most common reasons for participant discontinuation was voluntary withdrawal not due to an AE or non-compliance with the protocol. No participants discontinued the study for an AE or a SAE that was related to vaccination. At enrollment, there were nearly equal proportions of males and females within the full- and half-dose groups. The mean age of the participants was the same between the half- and full-dose groups. Subject distribution by race and ethnic origin are similar between the two vaccine groups.

The most important outcome of the study, that being associated with the primary objective to compare the rate of any fever following the 0.5 mL dose to the 0.25 dose. The fever rate was 11% for the half-dose and 12% for the full-dose. In order to demonstrate non-inferiority between the two vaccine groups, the upper limit of the 2-sided 95% confidence interval of the difference in fever rates between the two groups had to be <5%. The difference in rates of fever for the full-dose minus the half-dose of vaccine was 0.84% with the upper limit of the confidence interval being 3.8, meeting the pre-specific criterion for non-inferiority.

In terms of safety parameters, the solicited injection site reactions were captured. These consisted of injection site tenderness, erythema or redness, and swelling. Tenderness was the most frequent injection site reaction in both the half- and full-dose groups. Proportions of participants reporting solicited injection site reactions were similar between the full- and half-dose. In most participants, solicited reactions were Grade 1 or Grade 2 in intensity and resolved within 3 days. The rates of Grade 3 reactions were generally similar for the full- and half-dose groups. The most common Grade 3 solicited injection site reaction also was tenderness. In addition to fever, the other reactions consisted of irritability, abnormal crying, drowsiness, appetite loss, and vomiting. Rates of these reactions were again similar between both groups. Similar to what was observed for solicited injection site reactions, most systemic reactions also

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were of Grade 1 or 2 intensity and resolved within approximately 3 days. The most common Grade 3 solicited reactions were irritability and abnormal crying. A Grade 3 fever was reported for 0.6% of participants who received a half-dose and 1.2% for those who received the full-dose of vaccine.

Regarding immediate unsolicited AEs or those that occurred within the first 20 minutes after vaccination, there were 2 in the half-dose group and none in the full-dose group. Overall, the unsolicited AEs trended slightly higher in Group 1 subjects than in Group 2. Almost even numbers in both groups experienced at least one unsolicited adverse reaction (AR) after vaccination. For that, the most commonly reported ARs for Group 1 were diarrhea, cough, and rhinorrhea. In Group 2 the most commonly reported ARs were cough and rhinorrhea. No subjects discontinued the study due to an unsolicited AR. Two subjects in Group 1 discontinued due to other AEs and 1 subject in Group 1 discontinued due to an SAE of pneumonia. There were no subject discontinuations in Group 2, and none of the discontinuations were associated with or related to vaccination. A total of 5 subjects in each group reported an SAE throughout the study. One of these was considered to be related to the study vaccine, which was a case of chronic urticaria. This also was considered an AE of special interest (AESI). No deaths were reported in the study.

Moving on to the immunogenicity assessment, all 4 strains for the 0.5 mL dose included higher GMTs compared to the 0.25 mL dose. Non-inferiority with respect to GMTs was considered to be demonstrated if the lower limit of the 2-side 95% confidence interval of the GMT ratio was greater than 0.667 for each of the 4 virus strains. This was met for all 4 strains. Comparing seroconversion rates induced by the full-dose compared to the half-dose, the full-dose induced responses that were slightly higher than those induced by the half-dose. Non-inferiority with respect to conversation rates was considered to be demonstrated if the lower bound of the 95% confidence interval of the seroconversion rate difference was greater than -10%. The non-inferiority criteria with respect to seroconversion rates was met for all 4 strains.

In conclusion, Study GRC88 confirmed that a full-dose (0.5-mL) of Fluzone® Quadrivalent vaccine has a safety profile that is similar to that of a half-dose (0.25 mL) and may be more immunogenic. These clinical trial results are consistent with findings from other studies that have assessed safety and immunogenicity for a full- versus a half-dose. Sanofi Pasteur has submitted a sBLA to the FDA to permit use of a 0.5-mL dose of Fluzone® Quadrivalent vaccine in children 6 months of age and older. The action date for that application is in the first quarter of 2019.

Important safety information for Fluzone® Quadrivalent vaccine is as follows:

- ❑ Fluzone® Quadrivalent vaccine should not be administered to anyone who has had a severe allergic reaction (e.g., anaphylaxis) to any vaccine component, including eggs, egg products, or thimerosal, or to a previous dose of any influenza vaccine.

- ❑ If Guillain-Barré Syndrome (GBS) has occurred within 6 weeks following previous influenza vaccination, the decision to give Fluzone® Quadrivalent vaccine should be based on careful consideration of the potential benefits and risks.

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- The most common local and systemic adverse reactions to Fluzone® Quadrivalent vaccine include pain at the injection site (all ages) and redness and swelling at the injection site (in children); muscle aches, fatigue, and headache (irritability, abnormal crying, drowsiness, appetite loss, vomiting, and fever in young children). Other adverse reactions may occur. Vaccination with Fluzone® Quadrivalent vaccine may not protect all individuals.

The indication for Fluzone® Quadrivalent vaccine follows:

- Fluzone® Quadrivalent vaccine is indicated for active immunization against disease caused by Influenza A subtype viruses and type B viruses contained in the vaccine. Fluzone Quadrivalent vaccine is approved for use in persons 6 months of age and older.

- Before administration please see full prescribing information for Fluzone® Quadrivalent vaccine.

Discussion Points

Dr. Atmar asked whether the non-white groups were broken down further into Black, African American, Asian, and Other Groups. In addition, he inquired as to whether superiority also was done for the immunogenicity analysis

Dr. Mercer replied that the way they performed the analysis was either white or non-white. They did not formally specifically test for superiority because it was a non-inferiority study. If they had to use the same criteria used for the high-dose study, which looked at the lower bound of the 2-sided confidence interval in which the GMT ratios had to be >1.5 for two of the strains, then they did not meet superiority for this study.

Dr. Walter asked whether fever was assessed for the first 2 days when most fever would be expected and, if so, whether it was different between the two groups.

Dr. Mercer indicated that they did see more fever in the first 3 days. They did see more reactions in the younger cohort who received the 0.5 mL dose.

Dr. Schaffner (NFID) reported that in collaboration with a number of professional societies and colleagues, NFID has issued a “Call to Action” reinforcing the importance of immunizing people with chronic medical conditions. Obviously, everyone is all in favor of immunizing everyone older than 6 months of age. However, these are the people who get the most severe complications. He brought several copies of the publication to share and referred everyone to the NFID website for the downloadable pdf version of the document, which is titled, “Call to Action The Dangers of Influenza and Benefits of Vaccination in Adults with Chronic Health Conditions.”

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Rabies

Sharon Frey, MD, FACP, FIDSA
Saint Louis University School of Medicine
Chair, ACIP Human Rabies Prevention WG

Dr. Frey introduced the newly formed Human Rabies Prevention WG, which convened its first meeting in October 16, 2018. The WG's purpose and goals are to provide a forum for discussion to update the 2008 and 2010 ACIP recommendations on human rabies prevention. Members will review existing and new data and will provide individual input on topics that may inform changes in recommendations.

Rabies is an acute and fatal encephalomyelitis, but it is preventable. Over 200,000 persons in the US are exposed to rabies suspect animals each year. Over 30,000 persons receive PEP per year. Rabies PEP is safe and efficacious, but the costs are high. The ACIP rabies recommendations were updated comprehensively in 2008, while the PEP schedule was updated in 2010. In the interim, there are new data and the WHO has updated its recommendations.

The WG's draft terms of reference are to:

- ❑ Review the epidemiology and burden of rabies exposures and PEP administration in the US
- ❑ Review evidence-based recommendations regarding use of rabies vaccine(s) and immunoglobulin products among various populations for topics including the PrEP schedule, route of vaccine administration, amount and location of rabies immune globulin, and timing of serologic monitoring
- ❑ Review efficacy, immunogenicity, safety, cost-effectiveness, route and location of vaccine administration, and vaccination schedules of rabies vaccine(s) for PrEP and PEP
- ❑ Review rabies exposure risk for the general population and by occupational and recreational groups (e.g., veterinarians, laboratorians, travelers)
- ❑ Evaluate the effectiveness and costs to adhere to current assessment guidelines and ACIP serological monitoring recommendations
- ❑ Review evidence generated for new recommendations of the WHO and identify where additional evidence generation may be necessary to inform recommendations
- ❑ Identify areas in need of further research for informing future vaccine and immune globulin recommendations

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The WG is beginning Phase III of its timeline, which involves WG meetings. In mid-2018. the scope of work was determined by CDC in Phase 1 and the systematic reviews began in Phase II. The WG hopes to begin presenting information to ACIP between June or October 2019 to 2020 (Phase IV), and finalize the updated recommendations and vote in 2020 or early 2021 (Phase V).

Meningococcal Vaccines

David S. Stephens, MD
Chair, Meningococcal Work Group
Advisory Committee on Immunization Practices

Dr. Stephens updated the activities of the Meningococcal Vaccines WG. The terms of reference have been updated to focus on the following specific policy questions:

- Meningococcal B (MenB) vaccine booster doses for persons aged ≥10 years at increased risk for meningococcal disease.
- MenB vaccination in children aged <10 years at increased risk for meningococcal disease upon licensure of MenB vaccines in this age group.

Activities of the WG are to:

- Review available safety, immunogenicity, persistence of antibody protection, and effectiveness data for MenB, MenACWY, and future pentavalent MenABCWY vaccines.
- Develop an updated meningococcal vaccines ACIP Recommendation and Report.
- Review the epidemiology of meningococcal disease and identify areas in need of further research to inform potential future vaccine recommendations.

The WG has been reviewing newly available data for MenB vaccines including antibody persistence and response to a booster dose and immunogenicity of MenB vaccines in children aged <10 years, as well as reviewing and grading the evidence for booster doses of MenB vaccines for persons at increased risk.

Upcoming activities include an ACIP presentation in February 2019 on the review of data and the GRADE evaluation for the MenB vaccine booster dose. During the June 2019 meeting, the WG will present a full session on a MenB booster dose in persons aged ≥10 years at increased risk for meningococcal disease. Publication of consolidated ACIP Recommendation and Report on Meningococcal Vaccines (MenACWY and MenB) is anticipated in mid-2019.

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Pertussis Vaccines

Introduction

Henry Bernstein, DO, MHCM, FAAP
Chair, Pertussis Vaccines WG

Dr. Bernstein introduced this session on behalf of the newly convened Pertussis Vaccines WG. This WG terms of reference are to consider the evidence for recommendations that would allow any tetanus and diphtheria toxoid-containing vaccine, Tdap or Td, to be used for the decennial Td booster in adults and also as tetanus prophylaxis as needed for wound management.

The issues being considered by this newly convened ACIP Pertussis Vaccines WG will first be to review the previous ACIP WG work that was discussed about repeated Tdap vaccinations in 2013 and 2014 and published in the *MMWR* in 2018. They also recognize that the Tdap products available are currently licensed for a single use. This new Pertussis Vaccines WG that is being convened is going to assess potential FDA label changes and additional programmatic changes.

Dr. Bernstein indicated that this session would focus on the following:

- Background:
  - Current ACIP recommendations
  - Previous ACIP consideration of Tdap revaccination
- Safety and Immunogenicity of ADACEL® (Sanofi Pasteur)
- Safety and Immunogenicity of BOOSTRIX® (GSK)
- Discussion

The questions to be addressed by ACIP are as follows:

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

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

Background: Repeat Tdap Vaccination

Fiona Havers, MD, MHS
ACIP Pertussis Vaccines Work Group Lead
Medical Officer, Division of Bacterial Disease
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Havers discussed pertussis epidemiology; the vaccines available for protection against diphtheria, tetanus, and pertussis in adults and adolescents, which include Tdap and Td; and current ACIP recommendations for these vaccines. In addition, she reviewed the discussions

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that the previous Pertussis Vaccines WG and ACIP had on repeat Tdap vaccinations and the rationale for revisiting this issue now.
In terms of the number of cases of pertussis reported from 1922 to 2017, there was a decline in cases after the introduction of diphtheria, tetanus, and whole-cell pertussis vaccines for children in the 1940s. Overall, there were far fewer cases reported after vaccines were introduced than in the pre-vaccine era. However, there has been an increase in reported cases in recent decades. Regarding the increase in pertussis cases in the last several decades, acellular pertussis vaccines were phased in during the 1990s to replace the whole-cell vaccines previously used in the childhood series. The adolescent and adult Tdap booster was introduced in 2005. The number of cases peaked in 2012 when over 48,000 cases were reported in the US, the largest number in over 55 years. A number of factors are likely driving the resurgence of pertussis seen in the past several decades, which is occurring despite high vaccination coverage in children and adolescents [2017 data are provisional and subject to change; CDC, National Notifiable Diseases Surveillance System and 1922-1949, passive reports to the Public Health Service].

To protect adolescents and adults against tetanus, diphtheria, and pertussis, there are two formulations of Tdap licensed for use in the US, ADACEL® and BOOSTRIX®. These two products contain either 3 or 4 pertussis antigens in different quantities, as well as diphtheria and tetanus toxoids. As noted earlier, these are currently licensed for a single use only. In addition, there are 2 licensed tetanus and diphtheria toxoid-containing vaccines (or Td) vaccines, TENIVAC® and a generic Td vaccine manufactured by MassBiologics.

ACIP currently recommends that all non-pregnant adolescents and adults aged 11 years and older receive a single dose of Tdap, preferably at age 11-12 years. To ensure continued protection against tetanus and diphtheria, booster doses of Td are recommended every 10 years. The single Tdap dose can replace a decennial Td booster dose, but the dose of Tdap, when indicated, should be administered regardless of the interval since the last tetanus or diphtheria toxoid-containing vaccine. Td also may be recommended for tetanus prophylaxis in the setting of wound management if a tetanus-toxoid containing vaccine has not been administered in the last 5 years. In order to prevent infant pertussis, pregnant woman are recommended to receive a dose of Tdap during every pregnancy, irrespective of the patient's prior history of receiving the vaccine and regardless of the interval since prior vaccination with Td or Tdap. Note that this is an off label recommendation.

Pertussis vaccination coverage in the US is variable by age group. There has been sustained high coverage with pertussis vaccinations among children. With Tdap in adolescents, there have been substantial increases in coverage following the 2005 recommendation, with the most recent survey showing nearly 90% coverage. Coverage for Tdap in adults is more difficult to measure, but in general, the adult Tdap vaccination program has not been as successful in achieving high coverage, and coverage is lower than for adolescents [CDC National Immunization Survey: DTaP among children aged 19 through 35 months, Tdap coverage among adolescents aged 13 through 17 years; National Health Information Survey: Tdap among adults aged 19 through 64 years].

In terms of the timeframe, there were discussions of repeat Tdap vaccination after it was licensed in 2005. In addition to the discussion of Tdap vaccination during every pregnancy in 2012, the ACIP Pertussis Vaccines WG previously considered repeat Tdap vaccination for the general population in 2013 and for healthcare workers and other at-risk populations in 2014. Many aspects of repeat vaccination were previously discussed by the WG and their conclusions were presented to ACIP. These aspects included the changing epidemiology of pertussis, Tdap

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VE and duration of protection, immunogenicity, safety of repeat Tdap vaccination, the potential impact on overall disease burden, and economic impact. Dr. Havers summarized the conclusions of the previous WG on these topics.

The previous WG concluded that the increase in pertussis cases seen in recent decades was likely multifactorial. Improved diagnosis and reporting, as well as possible changes in circulating strains of pertussis, likely contributed. However, there also was evidence that waning of protection from acellular vaccines contributed to the rise in pertussis cases. Changes in the age distribution of reported cases raised concerns about the durability of protection from the childhood series and Tdap for those primed with only acellular pertussis vaccines. For example, emergence of disease among adolescents aged 13-14 in 2012, many of whom did receive Tdap, emphasized the importance of better understanding the effectiveness and duration of Tdap protection, especially among children primed with acellular pertussis vaccines.

The WG also examined multiple VE studies conducted on Tdap, most of which were in adolescents. The WG concluded that in observational studies, Tdap vaccine effectiveness is generally high at approximately 75% within first year, but wanes substantially in 2 to 4 years. This VE data was consistent with changing pertussis epidemiology [Gustafsson et al. NEJM 1996; 334: 349-55; Rank C, et al. Pediatr Infect Dis J. 2009 Feb;28(2):152-3; Schmitt et al. JAMA 1996; 275: 37-41; Wei SC, et al. CID 2010; 51(3):315-321; Pichichero et al. JAMA 2005; 293: 3003-11; Ward JI et al. N Engl J Med. 2005 Oct 13;353(15):1555-63; Acosta A, et al. Pediatrics. 2015 Jun;135(6):981-9; Breakwell L, et al. Pediatrics. 2016 May;137(5)].

The WG also reviewed data on immunogenicity for initial Tdap vaccination and repeat Tdap doses. Immunogenicity studies demonstrated that for pertussis antibodies after an initial Tdap dose, there is a rapid decline during the first year with a gradual decline afterwards. After 10 years, the concentration of pertussis antibodies, while higher than pre-vaccination levels, had declined substantially and were close to pre-vaccination levels. Of note, for pertussis, it is known that antibody contributes to protection, but there are no well-established antibody levels which correlate absolutely with protection. However, the rapid decline in antibody levels was consistent with the epidemiologic and VE data that indicated rapid waning of immunity and a short duration of protection conferred by Tdap. Studies that examined a second Tdap dose that were reviewed by the previous ACIP WG indicate that the immune response is similar to the first dose in cohorts boosted after 5 or 10 years after a first Tdap dose compared with naïve groups receiving an initial Tdap. For tetanus and diphtheria, there was a robust antibody response that was comparable to Td vaccination. The WG reviewed safety of repeat vaccination in these same trials of repeat Tdap vaccination. They noted that the majority of local and systemic AEs were mild to moderate and self-limited, and were generally comparable to those after the first Tdap. Among the few SAEs reported, none were determined to be related to receipt of the second Tdap. Safety profiles were comparable at the 5- and 10-year intervals [Halperin SA, et al. *Vaccine*. 2011; Tomovici A, et al. *Vaccine*. 2012; Booy R., et al. *Vaccine*. 2010; Mertsola J, et al. *Clinical Infectious Diseases*, 2010. Knuf M et al. *Hum. Vacc*. 2010].

In addition, the previous WG concluded that while there was evidence of direct protection, it is unclear what impact Tdap has on herd immunity and preventing pertussis transmission. For people vaccinated with acellular pertussis vaccines, symptoms are not as severe and they are presumably less likely to transmit. However, given evidence from animal models and the lack of strong epidemiologic data indicating a herd effect, the WG concluded that Tdap had potentially limited impact on disease transmission and herd immunity. In addition, they reviewed data examining the economic impact of repeat Tdap vaccination on an adolescent cohort at ages 16 and 21, and concluded that repeat vaccination with Tdap would not be cost-effective under the

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assumptions in this model, and that the reduction in disease burden would likely be limited with a second Tdap [Warfel JM et al. 2014 Jan 14;111(2):787-92. Mcnamara LA et al. Clin Infect Dis. 2017 Sep 1;65(5):811-818. Kamiya H et al. Vaccine. 2016 Apr 4;34(15):1832-8].

In summary, after examining the available evidence, the WG in 2013 and 2014 concluded that the increased number of cases of pertussis seen in the last several decades was expected to continue, although there is likely to be annual variation. Also, while Tdap had a high initial VE, there was substantial waning of protection within 2 to 4 years. The ACIP WG also concluded that a second dose of Tdap was safe and immunogenic, but that any reduction of disease burden resulting from repeat doses of Tdap would likely be limited. Given that Tdap is more expensive than TD, the WG also concluded that certain strategies were unlikely to be cost-effective. Overall, the WG concluded that the data did not support the recommendation for a second dose of Tdap, particularly given that any recommendation for more than one dose of Tdap would have been an off label use.

In terms of why repeat Tdap vaccination is again being considered, one of the main reasons for the timing of convening the new WG is that there has been an application for an FDA label change to remove the “single use” language from one Tdap product. The FDA has accepted the application and the review is expected to be complete by January 2019. There are several other reasons for revisiting this issue. There have now been several more studies on the safety and immunogenicity of repeat vaccinations. It also has been observed that multiple doses of Tdap are increasingly common. One large retrospective review identified persons who had received Tdap and then later received a dose of another Td-containing vaccine, either Td or Tdap. It found that the vast majority of those patients had received a second dose of Tdap and only 11% had received Td. This fits with anecdotal evidence that many EDs, clinics, and hospitals are no longer stocking Td and only have Tdap available. Allowing Tdap to be used for the decennial Td booster or wound prophylaxis potentially would be easier for providers [Jackson, M. et al. *Pharmacoepidemiol Drug Saf*. 2018;1–5].

Dr. Havers reviewed the questions for ACIP that Dr. Bernstein posed at the beginning and indicated that after the next two presentations, the WG wanted to hear from ACIP whether there are other specific data that they would like to have presented or if there are specific options or other considerations the WG should address to help inform this discussion.

Safety and Immunogenicity in Adults of Revaccination with ADACEL® Vaccine 8-12 Years after a Previous Dose

David P. Greenberg, MD
Vice President, Scientific and Medical Affairs
Chief Medical Officer, Sanofi Pasteur US

Dr. Greenberg provided an update on repeat vaccination with ADACEL® from Sanofi Pasteur’s recently completed study. In terms of the rationale for conducting this study, as previously noted, antibody concentrations to pertussis antigens wane during the years following Tdap vaccination. Similarly, protection against pertussis wanes over time resulting in an increased risk of infection. Revaccination potentially will boost protection against tetanus, diphtheria, and pertussis. However, ADACEL® vaccine is currently indicated for only a single dose[1]. Under various scenarios, Tdap may be more appropriate even when the history of a prior vaccination is unclear. Examples include persons who need tetanus prophylaxis for wound management, persons who are exposed to a pertussis outbreak, or persons who are caring for young infants [[1]Adacel vaccine [Product Monograph]. Sanofi Pasteur Inc].

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By way of background, in Canada[1] and many other countries, the ADACEL® label includes re-vaccination with at 5- to 10-year intervals to boost immunity to tetanus, diphtheria, and pertussis. In the US[2], ADACEL® vaccine is only approved as a single dose in persons 10 through 64 years of age [[1]Adacel vaccine [Product Monograph]. Sanofi Pasteur Limited. [2]Adacel vaccine [Prescribing Information]. Sanofi Pasteur Inc.].

For the Sanofi Pasteur revaccination study, 2 cohorts of individuals were recruited. In the US, individuals were enrolled who received ADACEL® vaccine in the pivotal pre-licensure Phase III clinical trial Td506 conducted in 2001-2002. In Canada, individuals were enrolled in specific provinces (Newfoundland and Nova Scotia) where ADACEL® vaccine was administered routinely to adolescents in school-based programs beginning in 2000. The primary goals of Study Td537 were to: 1) characterize the safety and immunogenicity of ADACEL® vaccine when administered approximately 8 to 12 years following the first dose; and 2) generate data to support revision of the US licensed indication to include repeat vaccination.

This was an observer-blinded, randomized, multi-center study to describe safety and immunogenicity of repeat administration of ADACEL® vaccine. The US cohort received their first dose of ADACEL® vaccine 8 to 12 years previously in study Td506 and they were 21 through 64 years of age at enrollment in study Td537. The Canadian cohort consisted of individuals who also received their first dose 8 to 12 years previously and were 18 through 24 years of age at the time of enrollment in Td537. The participants were randomized in a 3:1 ratio to receive either ADACEL® or TENIVAC® (Td) vaccine with nearly 1000 subjects planned for the first group and about 300 for the Td group. The ADACEL® and Td vaccines used in this study have the same quantities of diphtheria and tetanus toxoids (5Lf) and ADACEL® vaccine additionally contains 2.5 mcg of pertussis toxoid (PT), 5 mcg of filamentous hemagglutinin (FHA), 3 mcg of pertactin (PRN), and 5 mcg of fimbriae (FIM) types 2 and 3.

The primary objectives were to: 1) compare seroprotection rates (≥ 0.1 IU/mL) to tetanus and diphtheria toxoids induced by ADACEL® vaccine to those induced by Td vaccine; 2) compare booster response rates to tetanus and diphtheria toxoids induced by ADACEL® vaccine to those induced by Td vaccine; 3) compare anti-pertussis geometric mean antibody concentrations (GMCs) induced by ADACEL® vaccine to those induced by DAPTACEL® vaccine in historical trials; and 4) compare booster response rates to pertussis antigens following revaccination with ADACEL® vaccine to those induced in historical controls. The secondary objective was to evaluate anti-pertussis GMCs by age strata (18 to < 49 years and 49 to < 65 years) following revaccination with ADACEL® vaccine.

Blood samples were collected before vaccination on Day 1 and again 28 days after vaccination. Participants were observed for immediate reactions occurring the first 20 minutes after vaccination. Solicited AEs were pre-specified on diary cards, which were completed for 7 days after vaccination. Unsolicited AEs included any other health issue occurring within 28 days post-vaccination. SAEs, primarily hospitalizations, were monitored for 6 months post-vaccination. Approximately two-thirds of the participants were female, the median was about 29 years, approximately 95% of the participants were white, nearly all were not Hispanic or Latino, and all of the demographic data were similar in the two groups.

In terms of the study results, pain was the most commonly reported solicited injection-site reaction. Few participants reported swelling or erythema. Each of these reactions occurred at similar rates between the ADACEL® and Td vaccine groups. Most of the reactions were Grade 1 or 2 in intensity. Among the solicited reactions, myalgia, headache, and malaise were reported

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at modest frequencies. Fever was reported infrequently. As with the injection-site reactions, each of these systemic reactions occurred at similar rates between the ADACEL® and Td vaccine groups. Most reactions were Grade 1 and 2 in intensity. No immediate reactions were reported. Unsolicited AEs were reported at similar rates in each of the 2 vaccine groups. A total of 9 SAEs were reported, 8 in the ADACEL® group and 1 in the Td vaccine group. These occurred 25 to 149 days post-vaccination, and all were considered unrelated to vaccination. There were no deaths in this study.

Regarding the primary immunogenicity results, seroprotection rates were greater than 99% to both tetanus and diphtheria toxoids in both vaccine groups. ADACEL® vaccine met the non-inferiority criteria for this endpoint for both antigens. The booster response rates to tetanus were 74.5% in the ADACEL® group and 81.6% in the Td vaccine group. The difference for this endpoint for the two vaccines was -7.12% and the lower bound of the 95% confidence interval was (-12.0; -1.7), which did not meet the non-inferiority criterion requiring that the lower bound be >-10%. The response rate to diphtheria was similar in the two vaccine groups, and ADACEL® vaccine met the non-inferiority criterion for diphtheria. In terms of anti-pertussis GMCs, ADACEL® vaccine induced GMCs to each pertussis antigen that were similar to or 2 to 5 times greater than the GMCs induced by 3 to 4 doses of DAPTACEL® vaccine in historical studies. Therefore, ADACEL® vaccine met the non-inferiority criterion for GMC responses to each pertussis antigen. ADACEL® vaccine booster response rates to PT and FHA were similar to the expected rates in this age group. However, , ADACEL® vaccine-induced response rates to FIM and PRN were lower than the expected rates, with the lower bounds of the confidence intervals not meeting the pre-specified criteria. Therefore, ADACEL® vaccine met the non-inferiority criterion for PT and FHA but not for PRN and FIM.

In summary, ADACEL®-induced tetanus and diphtheria seroprotection rates were non-inferior to Td vaccine. The ADACEL®-induced booster response rate to diphtheria was non-inferior to Td. For tetanus, non-inferiority of ADACEL® vaccine was not achieved compared to Td vaccine. However, it should be noted that 100% of ADACEL® vaccine recipients achieved seroprotective antibody concentrations to tetanus. ADACEL® vaccine induced a robust anti-tetanus GMC of about 10.1 IU/mL, representing about an 8.6-fold increase pre- to post-vaccination. Therefore, the lack of meeting the non-inferiority criterion for the booster response rate should not impact clinical protection against tetanus.

ADACEL® vaccine induced GMCs that were non-inferior compared with those induced by DAPTACEL® vaccine in historical studies. ADACEL® vaccine induced non-inferior booster response rates to PT and FHA compared to the expected rates. ADACEL® vaccine-induced response rates to PRN and FIM did not meet non-inferiority criteria. However, pre-vaccination FIM and PRN antibody concentrations were 5- to 10-fold higher than those in the historical comparison in study Td506 and, therefore, it is clearly more difficult to induce a 4-fold rise in antibody. In addition, ADACEL® vaccine met the PRN and FIM non-inferiority criteria for post-vaccination GMCs. The GMCs were 2.9- and 2.2-fold higher in the ADACEL® vaccine group compared to the historical DAPTACEL® data. ADACEL® vaccine induced 6.4- and 5.2-fold rises post- to pre-vaccination ratios in PRN and FIM antibodies, respectively. Therefore, the missed non-inferiority results should not impact clinical protection against pertussis.

Regarding safety, there were no immediate unsolicited AEs or ARs reported in this study. For both vaccine groups, the most frequently reported solicited injection-site reactions were pain, swelling, and erythema. The most frequently reported solicited systemic reactions were myalgia, headache, and malaise. The majority of solicited injection-site and systemic reactions were Grade 1 or 2 in intensity. All SAEs were considered unrelated to vaccination.

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A few final thoughts regarding the results of this study, these results indicate that ADACEL® vaccine should be safe and effective when administered 8 to 12 years following prior ADACEL® vaccination[1]. Data from other studies not reviewed during this session suggest the safety of even shorter revaccination intervals. Sanofi Pasteur is seeking approval from the FDA for repeat administration of ADACEL® vaccine. HCPs often ask if Tdap is acceptable in caring for patients who do not remember and for which there is no documentation of a prior dose of Tdap received under various scenarios such as wound management, individuals exposed to a pertussis outbreak, and people who directly care for or live with young infants. If the FDA approves repeat vaccination of ADACEL® vaccine, Sanofi Pasteur hopes that efficiencies can be gained by not having to stock both ADACEL® and Td vaccines [[1]Halperin et al, J Pediatric Infect Dis Soc. 2018].

Discussion Points

Dr. Atmar asked about the seroprotection rates for tetanus pre-vaccination in the two groups and whether there were differences in the GMCs between the groups at baseline.

Dr. Greenberg replied that pre-vaccination seroprotection rates for tetanus at 0.1 IU/mL were 100% in both groups. At ≥1 IU/mL, they were in the 92% to 93% ranges and were similar between the two groups. The GMCs also were similar between the two groups pre-vaccination.

Given that the response to the booster is a similar reduction as the first dose, Dr. Ezeanolue asked what shows that the second dose will result in more effect. It is important to know whether the booster offers any advantage.

Dr. Greenberg indicated that the response to the second dose increases from 5- to 10-fold the antibody to tetanus, diphtheria, and pertussis antigens. At this time, there are no data regarding persistence after the second dose. That is an area of interest. If it does decline at a similar rate, one would expect similar protection and waning in immunity and protection. The primary point for him is that with the single dose indication and the current recommendations, what faces HCP and what Sanofi Pasteur receives as feedback is that they have patients for whom they do not know if/when vaccine was received and they feel somewhat cornered because they would like to administer the Tdap they have in their refrigerator. With the single dose indication and no suggestion that another dose can be given and would be safe, they do not know what to do. Just the knowledge that it would be safe would reassure many HCP.

Dr. Messonnier requested clarification regarding whether any studies either are being undertaken or are to assess antibody levels against pertussis specifically and if those will be available for ACIP to consider.

Dr. Greenberg replied that they appreciate the ACIP comments and will take that back to determine whether the subjects can be brought back for repeat vaccination. Among the many people who received the first dose of ADACEL® vaccine, it was extremely difficult to find them 10 years later. However, they will look for opportunities to bring them back.

Dr. Hunter requested clarity about whether tetanus levels of antibody responses are lower with Tdap than with Td, and whether they have any data and/or a model to project whether 10 years later there will still be enough tetanus antibody so that the interval of revaccination would not have to be shortened.

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Dr. Greenberg replied that while it is true that the booster response rate was different in the two groups, the GMC was clearly many-fold higher than the pre-vaccination levels. Pre-vaccination of the second dose, seroprotective levels of protective antibody were at 100%. While the boost measured by a 4-fold rise in the Tdap vaccine group was a little lower, the GMCs were as high in the Tdap as the Td group. He would expect that at or nearly 10 years later, there would be 100% persistence.

BOOSTRIX® Revaccination Studies at 9-10 Years: Studies 009 & 012

Leonard Silverstein, MD
US Clinical & Medical Affairs
GlaxoSmithKline

Dr. Silverstein presented information on GSK's two BOOSTRIX® revaccination studies 009 and 012. These studies were comprised of participants who previously received either ADACEL® or BOOSTRIX® 9 or 10 years previously who were revaccinated with BOOSTRIX®. These studies were done to show that BOOSTRIX® could be used for the decennial immunization dose of Td and also to help inform policy. During this presentation, Dr. Silverstein described the diphtheria and tetanus seroprotection rates, pertussis antigen GMCs, the booster response endpoints, and safety data.

BOOSTRIX® Study 009 was a continuation of BOOSTRIX® Study 007, which was conducted in 19 through 64 year olds. Both studies were conducted in the US. BOOSTRIX® study 007 was the study that was the basis or indication for BOOSTRIX® in 19 through 64 year olds. In BOOSTRIX® Study 007, subjects were randomized to receive either BOOSTRIX® or ADACEL®. Persistence was assessed at Years 1, 3, and 5 and then subjects were brought back in Year 9 for persistence and revaccination with BOOSTRIX®. The ADACEL® subjects received BOOSTRIX®, the BOOSTRIX® subjects received BOOSTRIX®, and a control group was added who had not previously received either BOOSTRIX® or ADACEL®.

For BOOSTRIX® 009, the co-primary objectives were as follows:

- Demonstrate Diphtheria (D) and Tetanus (T) seroprotection rates after a second dose of Tdap, non-inferior to seroprotection rate after first Tdap dose.
  - One month after vaccination, lower limit (LL) of 97.5% confidence interval (CI) for difference between groups (second dose of Tdap [BOOSTRIX®/ ADACEL® Groups] minus first dose of Tdap [Control Group]) is ≥ -10%

- Demonstrate PT, FHA, and PRN GMCs after a second Tdap dose, non-inferior to infant immune response in the German household contact efficacy study.
  - One month after vaccination, LL of 97.5% CIs for pertussis antigen GMC ratios (BOOSTRIX®/ ADACEL® Groups divided by Infanrix® Group in German Household Efficacy Study) are ≥ 0.67

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- Demonstrate D, T, PT, FHA and PRN Booster responses after second Tdap dose, non-inferior to immune response, after first Tdap dose.
  - One month after vaccination, LL of 97.5% CIs for difference between Groups (second dose of Tdap [BOOSTRIX® Group] minus first dose of Tdap [Control Group]) is ≥ -10%.

- Evaluate persistence of D and T antibodies at 1, 3, 5, and 9 years post initial vaccination.

The secondary objectives for BOOSTRIX® 009 were to:

- Evaluate percentage of subjects with PT, FHA and PRN GMCs ≥ the assay cut-off, at 1, 3, 5, and 9 years post initial Tdap vaccination
- Evaluate D, T, PT, FHA and PRN GMCs at 1, 3, 5 and 9 years after initial vaccination with BOOSTRIX® and ADACEL®
- Assess percentage of subjects with PT, FHA, and PRN GMCs ≥assay cut-offs, one month after re-vaccination
- Assess immunogenicity of BOOSTRIX® in terms of D, T, PT, FHA and PRN GMCs, one month after vaccination
- Explore the potential difference of D, T, PT, FHA and PRN GMCs between a second Tdap dose and a first Tdap dose
- Explore the potential difference in alternate booster responses for D, T, PT, FHA and PRN
- Safety of second and first Tdap doses - solicited local and general symptoms, unsolicited symptoms and SAEs

To define the study populations, Tdap-B defines the group who received BOOSTRIX® initially at Year 0 and then BOOSTRIX® again at Year 9. Tdap-A for ADACEL® denotes the subjects who received ADACEL® at Year 0 and then received BOOSTRIX® at Year 9. The Control Group had not previously received either BOOSTRIX® or ADACEL®. The first endpoint was achieved. Diphtheria and tetanus seroprotection rates for revaccination with BOOSTRIX® were non-inferior to vaccination with a first dose of BOOSTRIX®. For Tdap-B and Tdap-A, over 99% of subjects achieved seroprotection and the non-inferiority criteria were achieved. PT, FHA, and PRN re-vaccination GMCs were non-inferior to Infanrix® GMCs in the infant household efficacy study.

There is no immunogenicity level for pertussis antigens that correlates with protection. Efficacy of acellular vaccines can be assessed by comparing post-vaccination antibody levels in this study to those observed in a population where both efficacy and antibody levels are known, and where the same pertussis antigens were used to vaccine. This is a regulatory accepted method of inferring pertussis protection. In this study, the PT, FHA, and PRN immunogenicity were compared to the immunogenicity achieved by infants who received 3 doses of Infanrix® in the German Household Efficacy Study. Infanrix® contains the same antigens as BOOSTRIX®. The subjects in this study achieved at least a 1.5-fold higher GMC level for pertussis antigens than the infants did in the German Household Efficacy Study, and non-inferiority criteria were achieved.

Before showing the booster response endpoints, Dr. Silverstein spent a moment reviewing the criteria. For diphtheria and tetanus, if the pre-vaccination level was <0.1 IU/mL, there had to be at least a ≥0.4 IU/mL increase. If the pre-vaccination titer was ≥0.1 IU/mL, there had to be a ≥4-fold increase. Depending upon what the pre-vaccination level was for the pertussis antigens, there had to be either a ≥2-fold or ≥4-fold increase in GMCs. In terms of the booster response rates, non-inferiority criteria were met for the Tdap-B Group and for FHA in the Tdap-A Group.

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The results for the Tdap-B and Tdap-A Groups were similar, Dr. Silverstein shared only the Tdap-B results in the interest of time. For the Tdap-B Group, the seroprotection rates for diphtheria and tetanus were over 99%. The increase in GMCs from pre- to post-vaccination was at least a 4.7-fold rise for diphtheria and tetanus. The pertussis antigens had at least a 5.9-fold from pre- to post-vaccination. In terms of safety, the solicited local and general AEs for the Tdap-B and the Tdap-A Groups were higher than the group that received its first dose of BOOSTRIX®. However, the Grade 3 AEs were very low, similar between groups, and ranged between 0 and 1.6%.

BOOSTRIX® Study 012 was a continuation of BOOSTRIX® Study 001, which was conducted in 10 to 18 year olds. This was a study in which 3 lots of BOOSTRIX® were compared to Td. Both 001 and 012 were conducted in the US. Study 001 was the basis for licensure for BOOSTRIX® in this age range that was received in 2005. The subjects in 001 were brought back in 10 years. Those who received BOOSTRIX® in the first study received BOOSTRIX® in 012 (Tdap Group). Those who received Td received their first dose of BOOSTRIX® in 012 (Td Group). The plan was to enroll 500 subjects, but they were able to get only 165 subjects to return. However, a sensitivity analysis of persistence was done and there was no apparent bias based on the dropout.

The co-primary endpoints for BOOSTRIX® Study 012 were to:

- Demonstrate D and T seroprotection rates after a second BOOSTRIX® dose non-inferior to a first BOOSTRIX® dose
  - One month after vaccination, lower limit (LL) of 95% confidence interval (CI) for difference between groups (second dose of Tdap minus first dose of Tdap [Td-Control Group]) is ≥ -10%

- Demonstrate PT, FHA and PRN GMCs one month post revaccination, non-inferior to the infant GMCs in German household contact efficacy study
  - One month after vaccination, LL of 95% CIs for pertussis antigen GMC ratios (BOOSTRIX® Group divided by Infanrix® Group German Household Efficacy Study) are ≥ 0.67

BOOSTRIX® Study 012 secondary endpoints were to:

- Assess persistence of D, T, PT, FHA, and PRN antibodies, 10 years after previous booster dose of BOOSTRIX®
- Assess immunogenicity of BOOSTRIX® in terms of PT, FHA and PRN GMCs> assay cutoffs, one month after vaccination.
- Explore potential difference in D, T, PT, FHA and PRN Booster response between second and first BOOSTRIX® dose
- Explore potential difference in D, T, PT, FHA and PRN GMCs between second and first BOOSTRIX® dose
- Safety of second and first BOOSTRIX® dose- solicited local and general symptoms, unsolicited symptoms and SAEs

Diphtheria and tetanus seroprotection rates for re-vaccination with BOOSTRIX® were non-inferior to vaccination with a first dose of BOOSTRIX®. Seroprotection rates were 100% and the non-inferiority criteria were met. PT, FHA, and PRN re-vaccination GMC were non-inferior to the GMCs in the infant household study similarly to what was observed in BOOSTRIX® 009. The

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GMCs were at least 2-fold or greater higher than the GMCs in the infant household study. With respect to booster response rates, non-inferiority criteria were not met. However, there was 100% seroprotection at the level of ≥0.1 and the GMC fold-rise from pre- to post-booster was at least 3-fold or higher for diphtheria and tetanus. The GMC fold-rise for the pertussis antigens was at least a 6.5-fold rise from pre- to post-vaccine. Regarding safety, the percent of subjects with solicited local and general AEs was higher for the group who received 2 doses of BOOSTRIX® compared to the group who received its first dose of BOOSTRIX®. The incidence of Grade 3 symptoms were extremely low and were similar between the groups.

In summary, BOOSTRIX® Study 009 and Study 012 were re-vaccination studies in which subjects previously vaccinated with either BOOSTRIX® or ADACEL® were re-vaccinated at either 9 or 10 years with ADACEL®. Both studies met primary endpoints of diphtheria and tetanus seroprotection rates and pertussis antigen GMC ratios. As noted earlier, that is an accepted method of inferring pertussis seroprotection. Booster endpoints were missed. Over 99% of subjects had diphtheria and tetanus protection rates ≥0.1 IU/mL. However, looking at a seroprotection rate for diphtheria and tetanus 10-fold higher of ≥1.0 IU/mL, over 91% of subjects achieved the higher seroprotection rate in both studies. For pertussis antigen GMCs, there was at least a 5.9-fold increase from pre- to post re-vaccination. Local and general safety symptoms were generally higher after Dose 2 than Dose 1, and Grade 3 symptoms were similar after Dose 1 and Dose 2. In conclusion, BOOSTRIX® is immunogenic and well-tolerated when administered to adults 19 through 73 years of age 9 to 10 years after previous vaccination.

Discussion Points

Dr. Messonnier asked what studies GSK has planned and whether they can provide data to ACIP regarding the duration of immunogenicity of the pertussis components after the second booster dose.

Dr. Silverstein indicated that they would have to take this back to GSK for discussion.

Ms. Hayes (ACNM) said that she was very excited that both Sanofi Pasteur and GSK have new data, and wondered whether they planned to submit data on safety and pregnancy when they submit those data to the FDA. In addition, she wondered whether there was any intent to create a pertussis-only vaccine in the future.

Dr. Silverstein replied that they are considering this for the future. GSK intends to submit an sBLA for inclusion of the re-vaccination data in the label, and is evaluating the need for a new pertussis vaccine in light of the observed epidemiologic dynamics of pertussis. The different options that could lead to improvement of the current pertussis vaccine are under evaluation.

Dr. Greenberg replied that for the pregnancy indication or language, they are working with FDA on updating the label along with the submission for re-vaccination based on the newer FDA guidance on pregnancy. A pertussis-only vaccine is under consideration. Sanofi Pasteur will report back to ACIP on the determination about that.

Dr. Lee inquired as to why there was an increase in the GMCs in the control group, and whether the increase in the controls was related to background exposure.

Dr. Silverstein responded that in terms of the two groups' baseline GMCs are not comparable. There was a multi-fold difference between where the group who already had received a dose of BOOSTRIX® or ADACEL® was compared to the control group. When looking at the booster

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response, they were not comparing equal groups. The group who received one dose of BOOSTRIX® had a higher starting point than the group who never received a dose of BOOSTRIX® or any Tdap. Immunologically, it is harder to achieve the multi-fold booster response criteria set for these clinical studies. The increase in controls probably is related to background exposure and the cases of pertussis they cannot prevent.

Dr. Friedland (GSK) added that the control group is receiving Tdap for the very first time, so they are having a response to Tdap.

In conclusion of this session, ACIP members identified the following topics of interest on which they would like to hear presentations during future meetings:

- Pregnancy and pertussis-only vaccines
- Replacement of Td with Tdap every 10 years in terms of what the purchase cost would be in the private sector, and some economic analyses of the impact of the change
- Vaccines in the pipeline or on the horizon
- Strains and strain variability, which continue to be an issue
- Responses to multiple repeat doses of Tdap in terms of whether there is any diminishing return that would not be expected after just a single booster dose
- Whether allowing repeat Tdap has the potential to increase Tdap uptake in general in adults for the first dose and, if so, projection of the effect on epidemiology
- Tolerance to the antigens and whether that significantly affects any of the three antigens in the vaccine, and how often it is anticipated this vaccine will be given in one's lifetime
- Whether there are any disparities in terms of epidemiology and vaccine coverage, and understanding the populations who are included in any of the trials that are conducted
- Tdap considerations for travelers
- State coverage of Tdap in adults in terms of Medicaid expansion and effects on pregnant women on Medicaid

Day 2 Public Comment

Destiny Maynard
Concerned Parent

Hello everyone. My name is Destiny Maynard. This is our son, Christopher Bunch born December 5, 2003. I'm here to help spread awareness to plead to the people who call the shots. Christopher was not your average child. He was special—not just to us, but to anyone who was ever fortunate enough to meet him. He was such a leader and so compassionate to life. He was an honor roll student with a GPA of 3.9. He also loved playing baseball and football. Christopher, along with his best friends and girlfriend were beginning a new journey in their lives—high school. They all had such high expectations for this year: first dance, meeting new people, and as Christopher would say, better lunches. But, all that changes for Christopher on August 14, 2018. His friends attended high school games that he should have been at and playing in, but wasn't. His girlfriend attended her first high school homecoming dance without Christopher all because on June 29, 2018 I trusted my son's doctor's persistent advice about the HPV vaccination. "This is a preventative" he told me "and I will be giving it to my children." God, do I wish I knew then what I know now. By July 20th, Christopher was complaining of headaches; by July 31st, a sore throat and headaches; and by August 6th, Christopher was very

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ill and vomiting at football practice. On July 8th, we went to the local ER where we were transferred to the Iowa City Children's Hospital on August 9th. On August 10th, from a regular room to the Pediatric Intensive Care Unit (PICU) because Christopher's condition was rapidly deteriorating. On August 11th, the most terrifying thing that I have ever witnessed in my entire life—Christopher stopped breathing on his own. On August 12th, the swelling in Christopher's brain was so severe, the only action they had to potentially save my son's life was to perform a craniotomy on the right side of his skull. Unfortunately for Christopher and our family, the damage was so severe, that he was pronounced brain dead. On August 14th, his father and I had to make the decision no parent should ever have to make—to unhook our baby that we had raised from life support. We will never get to kiss our boy again or hear his voice tell us how much he loves us. He will never graduate from high school. He will never get married. He will never have children. That has all been taken from us. You voted on October 25, 2011 to offer the Gardasil® shot to boys. How does it feel knowing that your vote killed my son? I also have a letter that Christopher's neurologist wrote to us, "In many cases of acute demyelinating encephalomyelitis (ADEM), the patient received a vaccination shortly before the onset of the disease, thus strongly suggesting that this immune-mediated disease is triggered by vaccinations in at least some cases. Furthermore, the human papillomavirus vaccine has been specifically implicated in several published reports. Christopher received a vaccination against HPV one month before the onset of ADEM. Therefore, strong consideration must be given to the notation that the HPV vaccination triggered the ADEM in this case." Thank you.

Elijah Mendoza Bunch
Concerned Parent

My name is Elijah Bunch. As you've just seen, I was up here with my son's mother. It's affected us terribly. There was so much I wanted to say, but his mother and I kind of compiled stuff together in a short period of time. I wanted to ask you guys seeing that this is being broadcast live and I'm not as smart as a lot of people here, but I want to get some words out for my son, if I could invite someone to come up here to help me speak just for a minute or so, would that be okay? [Dr. Cohn indicated that it would]. Thank you for giving us a minute and hearing our story.

Brandy Vaughn
Founder
Council for Vaccine Safety

We were told that we might run out of time today, and I wanted to some of the science that they have just spoken about. As she mentioned, and as the neurologist mentioned in his comments in his letter, there are multiple dozens of studies linking Gardasil® particularly but the HPV vaccine in general to ADEM and multiple paralysis autoimmune-mediated diseases. I have 50 studies right here, and I tried to get them in hands of the working group, but I was not told that that was a possibility. This is just a selection of over hundreds of studies, case reports, but also epidemiological studies and meta-analyses showing that there are serious health issues following the HPV vaccination—not just in the US, but all over. In fact, there are 60,000 adverse reaction reports to VAERS regarding the HPV vaccine in the 12 years it's been on the market. There have been 432 deaths, not even including Christopher Bunche's because it's not included in the numbers yet. If this was a pharmaceutical drug, would it still be on the market? I would love an answer to that question. I know you guys don't answer public comments. Christopher Bunch should never have been sacrificed as a test subject on a vaccine that hasn't been tested properly and has shown so many adverse events. In 2010, the HHS decided that Harvard Medical School should do a report on whether VAERS was being used. According to that Harvard Medical School study, fewer than 1% of vaccine reactions are ever reported. So, this is

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Harvard Medical School. This is not us. This is not Christopher Bunch's parents, okay? We're giving you the information that pharmaceutical companies are not. You may not be able to stand up there and present it in a PowerPoint, which I would love to do one day, but this information needs to be looked at by every single member on the committee. If you use this estimate from the Harvard Medical School report that was funded by the HHS, that would mean thousands, thousands of children have died after this vaccine and millions, millions have been possibly injured. Yet, this vaccine is still on the market. The newest version, Gardasil® 9, has twice as much of the aluminum adjuvant, which is in most of these studies as the antigen that is triggering the autoimmune-mediated diseases. Twice as much aluminum and twice as much of the virus as well. So, I'm going to speak later on whether it even causes that, but thank you, Elijah, for giving me that time, because he wanted me to help him go over the science.

Hillary Simpson
Founder
CRAZY Mothers®
#crazymothers

Good afternoon. My name is Hillary Simpson. I am the founder of a non-profit called CRAZY Mothers®. We work at spreading vaccine injury and recovery awareness, because that is the crazy thing. If you catch your child's vaccine injury early enough, you can recover them. You can heal them without the use of a single pharmaceutical. But, enough about me, we're here to talk about you. Really, I just have a couple of quick questions. The first question is: Who? Who in here thinks it's okay to recommend 72 doses of vaccines for children without doing a single cumulative safety study? Who in here thinks that it's okay to refuse to do a vaccinated versus unvaccinated safety study so that we might truly be able to assess the advantages and disadvantages of vaccination? Who in here thinks that it's okay that 54% of our children are suffering from a chronic illness and 1 out of 36 of those children will be diagnosed with autism? My second question is: What? What are you as the committee working with the regulatory agencies tasked with protecting the public's health—what are you going to do about this about the vaccine-induced autism epidemic and the vaccine-induced autoimmune epidemic this country is currently experiencing? What are you going to do about the generation of children that we have lost? How? How are you going to continue to explain away those autism rates as they go from 1 out of 36 to 1 out of 25, to 1 out of 15, and eventually 1 out of 2, which will be by the year 2032 according to Dr. Stephanie Simmons if the numbers continue to increase at the rate they're current at? How are you going to persuade those mothers having children 15, 20 years down the road when the vaccine injury epidemic is so blatantly obvious it becomes impossible to ignore? Lastly, when? When are you going to start listening to the hundreds of thousands of parents screaming from the rooftops that vaccines injured or killed their children? When are you going to start actively working towards a resolution for this massive problem? When are you going to stop hiding behind the "We don't know why our children are so chronically ill? We don't know why we're experiencing an autism epidemic. We don't know why?" Because we do. Us crazy mothers know and we're healing our children. Biomedical treatments, holistic modalities, naturopathic medicine. We're healing our babies. If that—if that makes us crazy, so be it. Like I said, let us know when. Thank you.

Dr. Russel Myers, DC
National Health Federation

Hi. I'm Dr. Russel Myers of the National Health Federation (NHF). Ladies and gentlemen, we have a problem. Clearly, there has been a disconnect between trusted health officials and those people that you serve. You say that vaccines are safe and effective. We believe you. We

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receive them. Then when we get injured, we are ultimately ignored and told there is zero science in the claims. That needs to be addressed somewhat properly. It is unclear to me what scientific evidence you have been reading to make the claims that vaccines are safe considering that even the father of modern day vaccines who literally wrote the book on vaccines can't defend the medical procedure's safety under oath during his deposition earlier this year. But further than that, seeing the extreme lack of proper evidence presented in this room today and yesterday is quite terrifying. All these safety studies use the word "placebo" when in reality, it's an adjuvant-containing placebo or in some cases like the HPV ones over here, it was a straight shot of aluminum hydroxide. It is misleading to say the least. This speaks volumes of the lack of knowledge that is known in this area no matter how much one says that vaccines are safe. According to the Supreme Court, they are unavoidable unsafe by design defects. Your vaccine studies comparing those who get fewer vaccines to those who get more vaccines is obviously flawed and at worst, criminal considering the dire consequences. The epidemiologic studies have not held up to scientific scrutiny and at worst have been shown to be revised multiple times to get the desired results. You're not only losing faith with the people, but losing your reputation in the process, especially when CDC is testifying in Congress, blatantly unaware of any vaccine peer reviews showing how much damage they do cause. This looks like more of a political issue than a scientific one. The biological studies, the mechanism of action studies of vaccine adjuvants of ingredients such as aluminum hydroxide and human DNA are clear that not only do vaccine adjuvants cause damage, it's just a matter of how much. Many of these ingredients have even found to be neurotoxic at parts per billion (PPB) by themselves, but when added to a vaccine at 1200 micrograms, suddenly they become safe. There is a large gap as far as I see it of understanding with extrapolating evidence from the basic science to the clinical science realm. Now, I understand that we push vaccines under the umbrella of public health, but this is at the expense of taking lives and giving debilitating injuries like paralysis, encephalitis, myelitis, and death all without informed consent. CDC and doctors tell parents that the only real side effect of a vaccine is the redness and pain at the injection site whilst death and lowered consciousness are listed is not informed consent. You have not done a good enough job showing that these things are safe. The majority of those opposed to vaccines often believe in vaccines until their child or themselves were injured at the moment of injection and wish, at least, to be informed about the risks akin to surgery risks before they get the surgery and before they sacrifice to a medical community which then disregards and ridicules after performing. It concerns me from what I've seen from this panel and from what conversations I've had here with top vaccinologists. Most people here cannot comprehend any idea on how vaccines even cause damage. The science is clearly not settled and from what I've seen today, not even looked at properly. Let's do this right this time and not have another Verstraeten study where meetings are held in private to go over the problem that simply won't go away. Thank you very much.

Lara De La Vega
Representative, National Health Federation
The People United For Justice & Health Freedom

My name is Lara De la Vega. I am here also representing the National Health Federation. I don't have a vaccine-injured child. I don't have any children actually, and an environment like this scares me out of having children, because I don't want anything like this to transpire with my child that's happened to many of these families. But, I'm here to represent NHS and am 100% against vaccinations just so that you're aware. As of the beginning of October, the National Vaccine Injury Compensation Program (NVICP) has paid out about $3.9 billion dollars. I don't know how many of you are aware of that. I don't know what you all are aware of much, but that was created in the 1980s and this number continues to go up. The fact of the matter is, if safety

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reporting was done properly and truthfully, we would be paying out in the trillions, financially crippling our nation even more. I say that because it is merely 1% as Brandy Vaughn said that is reported of vaccine adverse events. I say "we" because it's common knowledge that amongst attendees like myself, pharmaceutical companies are liability-free, which is criminal. These vaccine injury payouts are complements of the taxpayers now and have been for quite some time. Now my comments on VAERS, the Vaccine Adverse Event Reporting System, I'm here representing the oldest health organization in the world, and we have very deep concerns about your scientific data related to vaccine safety and effectiveness. The mere fact that VAERS even exists indicates that you all have admittedly acknowledged that adverse events do occur, and we know that they exist because we've paid out in the billions like I pointed out. Since there is a risk for adverse events, my belief is that there must be choice as to whether or not we want to take that gamble. I say "gamble" because everybody's chemical make-up is completely different, and if you guys don't know that, none of us should be here. We should really be freaking out and going back to the drawing board, which we should be doing. With regard to VAERS, when this panel uses VAERS post-market adverse reaction surveillance, it sounds and seems very formal and matter of fact, but when VAERS is actually used by us, it's basically random free for all for those that are even aware of it. The masses are not aware of VAERS, and that is very dangerous. Since you're all taking all of these situations as matter of fact post-marketing surveillance, I don't understand that this is useable data, especially because only 1% are even reported, so to say that these assessments are way off is a gross understatement. But at this point, I want to urge you all, I'm imploring you if I can, to please place urgency on VARES for what it is meant to be, to receive proper data. I want to make it an absolute requirement for health officials to have a vaccine adverse event safety conversation with the recipients of vaccinations, as it is their right to be aware of what horrible things can come to them. Recipients of vaccinations must be informed on what to do and who to contact so that all of you can finally use close to factual data when making such important decisions for people of our country that are indoctrinated to trust you. You guys couldn't even determine yesterday what ultimately the definition of "homelessness" even was. What kind of data are we working with? I mean, you voted "yes" to vaccines. You're voting with data that's incomplete. It's not a fair assessment. We have no business being here right now. As far as I'm concerned, not only is the science not settled, it hasn't even been conducted. I feel like I traveled across the country from California only to watch a biased panel go through motions, and we're at the CDC. I'm not a singular individual speaking out against vaccination. This happens to be a movement now and one that is growing rapidly and exponentially, and not because we love or even like each other, but because you're creating more of us every single time you vote in favor of implementing more questionable vaccinations. Thank you.

Laura Ciminelli
Concerned Citizen
Health Freedom Georgia

I'll try to talk fast. I don't come here with any degree. I come here as the pubic. I live locally. You are our one and all. I'm going to start with a quote by William Wilberforce and he stated, "You may choose to look the other way but you can never say again that you did not know." I just retired from a local hospital here. No one believes in the flu shots. My colleagues and I didn't because the efficacy, and I won't give you data, you created the data, 10% one year, 18% the next, 40% at best. The FluMist® you gave to our children from 2 to 8 years for almost 4 years never worked. 3%, oh well. You know, I worked in a hospital where my colleagues, doctors and nurses and medical assistants and patient care and lab, we didn't believe in the flu shot. We were probably at 40%, and then came your mandates, and then came your recommendations. So, you know what? For 4 years before I retired I put a mask on 12 hour

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shifts. It wasn't easy to breath. That's how much I didn't believe in your efficacy. My colleagues didn't believe in it either, but some of them couldn't wear that mask for 12 hours so in the beginning they said, "I'm just getting the shot. I can't wear the mask." But in truth, the public's truth, my observation, which is the first step in scientific theory, they didn't believe in your shot. This year, I retired. I'm grateful for that because my soul was sick at what I saw go on. That flu shot was crazy. At first it was 10%. How can you do data? Which 10 got the shot out of 100? Then it was 30%. Then you get up here today and make new implications on our children and combine 4. Really? You govern globally and in this country. I'm glad I'm retired now, because now I can talk to you, because you know what? While I worked, I couldn't because if I did, conflict of interest. I would have lost my job. That's the truth. A lot of my colleagues did lose their jobs. I was in one of the few hospitals in this city that allowed us to mask. I can name 5 hospitals that don't. Goodbye. Pink slip. No flu shot. How did I survive 20 years and never get flu in that environment, ER, high volume? Was I not on the front lines with every flu case of 300 people a day? Every flu case it was me. I never had the flu. You know why? I knew how to wash my hands. I knew how to take Vitamin D. I knew how to take elderberry syrup. I don't approve of your flu shot. Now you have pharmacists giving it. You bribe us with cards at Target and you tell us, "This is free and it's everywhere. Get it. Get it. Get it." There are scare tactics and you should be ashamed. I do want my colleagues, other moms, to know what the CDC doesn't do for us. Robert F. Kennedy, Jr. fights for us. He does. He goes to court for us, for our kids who suffered. I'm looking around. Some of you are my age, and if I'm mistaken, I apologize. But, I'm in a generation where I got 7 shots and 26 years later, my daughter got 10. Her son got probably 60. My new grandson is expected to get 72, and I just watched you add more. I'm appalled. Robert F. Kennedy, Jr., you know what he says? His family started Special Olympics. There were no autistic kids. He says that, "Where are the 40-year olds wearing diapers with helmets on at the mall? If you misdiagnosed them, if you missed them, where are they? Where are the special ed classes with people of my generation? There weren't any because they didn't exist." That's what he says, you know, and it's the truth. But you know what's going to happen? I have a 10-year-old grandson and I don't care what you say that autism and vaccines don't exist, it does, because I watched a perfectly health, beautiful 2-year-old get those shots and become a severe autistic child. And guess what. He will be 40 walking around the mall with a diaper on and a helmet. Thank you for the studies that you don't do.

Brandy Vaughn
Founder
Council for Vaccine Safety

Hi. So, a little bit earlier, I gave you the statistics on the VAERS results for Gardasil®. I'm going to talk a little bit more about it and about the science about what's going on here. It's clear that this vaccine, Gardasil®, is harming more children at epidemic proportions. So, what are the benefits? Why would you add it to the adult schedule? I mean, the science is slowly showing—does HPV even cause cancer? There was a great study out of the University of California, Berkeley by a well-known professor, Peter Duesberg, that showed cervical carcinomas are not caused by the HPV virus. It is a passenger virus. A latent virus. We all have latent viruses in our bodies. Because it's in a carcinoma does not mean it caused it. So, quoting him, he says, "Since there is no scientific evidence that it will do anything else but occasionally cause warts, which will be eliminated by the immune system, there is no need for vaccination against this virus." His basis for this perspective was an in-depth study that he did in 2013 will colleagues from the University of California, Berkeley that was published in *Molecular Cytogenetics* under the title, "Individual karyotypes at the origins of cervical carcinomas." He is one of the leading experts on carcinomas in the world. The study states, "There is no direct functional evidence that cervical carcinomas depend on the latent papilloma viral sequences." Not only does evidence show that

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HPV is not the real cause of cervical cancer, newly released cervical cancer data out of countries that implemented the HPV vaccination more heavily than the US, so the United Kingdom (UK), Norway, and Sweden, are also showing increases rates of cervical cancer in the population that was vaccinated, up to 90% in the UK. This is not happening in the older populations. I have the numbers and I have the research here. So, in Norway, before the HPV vaccination, cervical cancer rates had fallen sharply. But, since widespread vaccination campaign in 2009, cervical cancer rates have increased and nearly doubled, doubled, between 2004 and 2015. Doubled. The rate continues to trend upwards. We're looking at a vaccine that is actually causing an increase in cervical cancer rates. So, what happened in the UK? The youngest group age reported for cervical cancer rates that's tracked by the government, 20 to 24, the change before and after the HPV vaccination campaign, which covered 90% of girls, began—it's shocking. This should cause every single one of you to rethink this push to have girls and boys like poor Christopher vaccinated for HPV. So, between 2002 and 2009 in the UK, the last year before the vaccination campaign started, cervical cancer incidence decreased 40% in girls age 20 to 24. It decreased 40% before the vaccination campaign—in the 6 years directly before the campaign. In 2009, the year the vaccination school campaign achieved an 80% coverage rate for girls 12 to 18, the incidence decreased—it slows and then stagnates. So, it was going down and then it stagnates. By the year 2011, cervical cancer begins to increase in girls age 20 to 24 only—not in older populations. So, these are the girls that got the vaccine. This trend is so pronounced, between 2012 and 2015, cervical cancer rates increased 45% in the population that received the vaccine—increased 45%. Older women did not show an increase. So, how did it happen? I'll be brief. This 2012 study by Dr. Lee published in the *Journal of Inorganic Biochemistry* shows the mechanism of action—the HPV gene binding it to the aluminum adjuvant in the HPV. So, it is taking aluminum to the reproductive area, because HPV is a reproductive virus, and it is possibly the mechanism of action that is creating the increase in cervical cancer risk. So, when you vote to add this to the adult schedule, you are voting to increase cervical cancer in this country for a vaccine that is causing widespread side effects and has never been proven to reduce cervical cancer rates—not even proven to reduce one case. Please, vote "no" to add it to the schedule and please, do the studies and pull this off the market. Thank you.

Unidentified
Engineer with Master's in Engineering
Concerned Citizen

Hi. I'm here as a member of the public. I'm also an Engineer with my Master's in Engineering. I've been here over the past two days just observing the studies and looking at the work that you're doing, and I've seen a lot of competent scientists and a lot of wonderful physicians who are doing great work. But, I did have a couple of concerns that I wanted to raise. The first concern is that the studies I've seen are very linear in nature. The subjects are given the vaccine and then immediately measured to see how much their immunity increases. My concern with this is that you're assuming that these vaccines don't have consequences later on down the road. I would really like to see you direct more money toward studies that look at the long-term consequences of these vaccines. My second concern is prioritization. As I sat here, I've seen that you looked at Japanese Encephalitis that affects people that go to the Philippines for over a month, while in our country we have children whose autoimmunity is being damaged by the day. I hope that you will re-prioritize. Thank you very much.

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Tiendra Severino
Concerned Parent

I said a lot yesterday, so I'm going to make this very brief. I have two lists to read to you. I want to start with a quote by Dr. William Thompson who is still employed here at the CDC. I'm sure you all know who he is. Dr. Thompson said, "Here's the deal. The CDC is paralyzed, the whole system is paralyzed, and the whole branch is paralyzed, and it's becoming more paralyzed. There is less and less being done and the place is coming to a grinding halt." He was referring to autism. Autism seems to be paralyzing the CDC. He should know. I just want to read you a quick list here. These are the theories of autism causation:

- ❑ Refrigerator moms (that was a good one)
- ❑ Genetics
- ❑ Better diagnosis
- ❑ Toxins (but not from vaccines)
- ❑ Advanced paternal age (this one's good)
- ❑ Wireless exposure
- ❑ Rubella in pregnancy
- ❑ Biological encephalitis
- ❑ Untreated PKU
- ❑ Pesticides
- ❑ Herbicides
- ❑ Heavy metals (but not the ones in vaccines)
- ❑ Viruses (again, not the ones in vaccines)
- ❑ Bacteria (not the ones from the vaccines)
- ❑ Low oxygen at birth
- ❑ Chemicals (just not the ones in the vaccines)
- ❑ Prematurity at birth (but hey, go ahead and vaccinate your premature baby with the same schedule as if they were born full-term; that's a good one)
- ❑ Neonatal exposure to environmental toxins (but, not the ones in the vaccines that you give to pregnant women)
- ❑ Phthalates exposure during pregnancy
- ❑ Living in cities
- ❑ Higher income parents
- ❑ Basically, anything but the vaccines

I am here representing a lot of families who could not be here as you know. You met yesterday my friend Pricilla and her husband Will who lost their daughter Willow after her 4-month vaccines. I have a list of deaths from vaccines, because yesterday we heard from Paul Offit and his friend about the lovely lady who started the meningitis B vaccine campaign. It kind of makes me think they're copying the anti-vaxers, but never mind that. Nobody likes to see a child die from a disease or anything. I wouldn't wish meningitis on anybody. I certainly wouldn't wish a death from meningitis on anybody. But, because this baby died, all kids have to have the meningitis B vaccine. That's interesting, so let's talk about it:

- ❑ Daniel Ramirez went for his kindergarten shots and died
- ❑ Ryan LeBree had a DTP vaccine and died
- ❑ Rose Hoss had the HPV vaccine and died
- ❑ Nicolas Catone had a DTaP in his infant vaccines and died
- ❑ Marshall Thomas had the flu shot and died
- ❑ Zara Schill went for her 16-month vaccines—dead

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- Holly Stola had the MMR—dead
- Kyle Dalemary at 3 months, dead from his routine infant vaccines
- Kelly Michelle Hall at 2 months, DTP, dead
- Colin Barrett had HPV vaccine because the doctor told him he would be protecting his future wife, athlete, paralyzed on a respirator, committed suicide because he couldn't go on that way
- Eric Prine had the DTP vaccine; he suffered over 100 seizures before he died at 22; his father spends countless hours online trying to spread the story of his son's death
- Mason Bundy who when he was 4 months old, his mother was told by a doctor "If you don't get this vaccine, you are signing his death certificate." Less than a week later, they were signing his death certificate. He would have turned 8 on Monday.

If I had given my son the full barrage of the CDC recommended schedule, because I told you he's had 4 single doses spaced out vaccines, if I had given him all of the vaccines the way that they are routinely administered to infants, he would be on this list. He certainly wouldn't be sitting here today. If he was alive, he would be so severe, that there is no way that I could be sitting here listening to you and talking to you. Please, any death of any child is tragic. But, you cannot ignore these deaths anymore. They are just as important as a baby who dies from whooping cough, meningitis, or any other vaccine-preventable disease. Thank you very much.

Unidentified
Concerned Citizen

I'd like to point out that the committee needs a timer. I've been to thousands of hearings and committee meetings, and there is usually a timer. So, are you going to end this, or are we going to be allowed to finish our public comments? Someone came up to mic, this is a lady who just jumped up there. May I also suggest cameras, because we have Dr. Paul Offit on camera shooting himself in the head while a mother of a very sick child was giving public comment who he was mocking, and that is not okay.

Susan Olson-Corgan
Board of Directors
Informed Choice Washington

Yesterday, I wasn't able to read my comment because of just being a little overwhelmed. Mine is about 13 sentences. FDA recently approved Gardasil® 9 for men and women 27 to 45, so the age range recommended for this vaccine now spans 9 to 45. FDA's decision to expand to older adults is concerning, given that FDA originally refused to approve Gardasil® for this age because there was insufficient evidence of the vaccine's effectiveness. In older women, FDA also noted increased risk of non-vaccine type related CIN2 or greater, but Merck erased this disease enhancement risk in the long-term follow-up by vaccinating the controls and then comparing those originally vaccinated versus later vaccinated women. Please see Page 8 of the recent FDA approval document showing how Merck and the FDA compared only vaccinated against vaccinated to mask any risk. Additionally, in another Gardasil® trial of 16 to 26 year olds, the FDA recognized that the vaccine actually increased the risk of women developing vaccine type-related CIN2/3 or worse by 44.6% if a woman had been previously exposed to vaccine-related HPV types and currently had an infection with vaccine-related types. Based on these disease enhancement signals, we are extremely concerned that this new recommendation for older adults is more likely to have HPV exposure, will increase a woman's risk for cervical disease and perhaps even cancer from both vaccine and non-vaccine HPV types. While this data should have supported doctors screening for HPV infection before vaccinating to reduce

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risk, the American College of Obstetricians and Gynecologists (ACOG) instead actively discourages pre-screening. Moreover, FDA approved Gardasil® 9 for men age 27 to 45 based on inferred efficacy for women and an incredibly small study in men, which is insufficient to recommend a blanket approval for all men in this age range in the United States. An immediate investigation is warranted, as we do not believe that the FDA examined this issue with close enough scrutiny. Thank you.

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Certification

Upon reviewing the foregoing version of the October 24-25, ACIP meeting minutes, Dr. Amanda Cohn, Acting 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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ACIP Membership Roster

Department of Health and Human Services
Centers for Disease Control and Prevention
Advisory Committee on Immunization Practices
November 2018 – June 30, 2019

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

EXECUTIVE SECRETARY
COHN, Amanda, MD
Senior Advisor for Vaccines
National Center for Immunization and Respiratory Diseases
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MEMBERS
ATMAR, Robert L., MD
John S. Dunn Clinical Research Professor in Infectious Diseases
Departments of Medicine and Molecular Virology & Microbiology
Baylor College of Medicine
Chief, Infectious Diseases Service
Ben Taub General Hospital, Harris Health System
Houston, TX
Term: 7/1/2016 – 6/30/2020

AULT, Kevin A., MD, FACOG, FIDSA
Professor and Division Director
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Term: 10/26/2018 – 6/30/2022

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EZEANOLUE, Echezona, MD, MPH
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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
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Term: 11/27/2017-06/30/2021

GRAVENSTEIN, Stefan, MD, MPH
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Brown University
Associate Director, Center of Innovation for Long-Term Care Services and Supports
Providence Veterans Administration Hospital
Providence, RI
Term: 10/26/18 - 6/30/2022

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

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

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

MOORE, Kelly, MD, MPH,
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Vanderbilt University School of Medicine
Nashville, TN
Term: 07/01/2015-06/30/2019

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Professor of Medicine, Division of Infectious Diseases
Chair, Department of Medicine
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Term: 07/01/2015-06/30/2019

SZILAGYI, Peter, MD, MPH
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Executive Vice-Chair and Vice-Chair for Research
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Public Comments / Letters Submitted

Peter Duesberg's quote referenced by Brandy Vaughn, Founder of the Council for Vaccine Safety:

"In sum, our data indicate that newly formed carcinoma-specific karyotypes generate and maintain carcinomas, independent of latent viral sequences or mutations of tumor suppressor genes. Based on our findings, it is expected that a vaccine against human papillomavirus will have no effect on the occurrence of cervical carcinomas."

https://molecularcytogenetics.biomedcentral.com/articles/10.1186/1755-8166-6-44#Sec16

Sacrificial Virgins Documentary: How The HPV Vaccine Destroys Teens
10:05
https://youtu.be/KAzcMHaBvLs

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County of San Diego

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WILMA J. WOOTEN, M.D., M.P.H.
PUBLIC HEALTH OFFICER

DATE: October 14, 2018

TO: Advisory Committee on Immunization Practices

FROM: Wilma J. Wooten, M.D., M.P.H., San Diego County Health Officer

SUBJECT: Support to Add Homelessness as an Indication for Hepatitis A Vaccination

Please find attached a statement in strong support of adding homelessness as a recommended indication for hepatitis A vaccination in the United States.

I am not able to present this statement in person, but appreciate the opportunity to have this added to the public record of your meeting on October 24-25, 2018.

Please let me know if you have any questions about this statement. I may be reached at wilma.wooten@sdcounty.ca.gov or 619-542-4181.

Respectfully,

Wilma J. Wooten, M.D.

WILMA J. WOOTEN, M.D., M.P.H.

Attachment

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Statement by Wilma J. Wooten, M.D., M.P.H., San Diego County Public Health Officer and Director, Public Health Services, County of San Diego Health and Human Services Agency, in Support of Adding Homelessness as a Recommended Indication for Hepatitis A Vaccination in the United States.

On behalf of the County of San Diego, I strongly support the addition of homelessness to the currently recommended routine indications for hepatitis A vaccination. A hepatitis A outbreak primarily affecting persons experiencing homelessness and individuals using illicit drugs has being occurring in San Diego County since November 2016. To date, 592 outbreak cases have been reported, including 407 (68%) hospitalizations and 20 (3.4%) deaths. Investigations of these cases revealed that 201 cases (34%) were homeless and used illicit drugs, 91 (15%) were homeless only, 79 (13%) were illicit drug users only, 167 (28%) were neither homeless nor illicit drug users, and 54 (9%) had unknown status for homelessness and drug use.

In May 2018, we conducted a test negative case-control study of cases reported to our department with possible hepatitis A. We found that those with PCR-confirmed hepatitis A were 3.1 times[1] more likely to report homelessness than those with similar hepatitis-like symptoms who tested negative. Analyzing those with PCR-confirmed hepatitis A, we found that people who are homeless were 3.8 times more likely to be hospitalized,[2] and 3.9 times more likely to die,[3] adjusting for age, illicit drug use, and coinfection with hepatitis B or hepatitis C.

Our analysis has limitations, including possibly incomplete medical records and the fact that homeless persons may be preferentially hospitalized for reasons beyond those measured. However, we feel the San Diego outbreak provides strong evidence that homeless individuals are an independent risk group, as they are at higher risk for contracting hepatitis A and having worse outcomes than those who are not homeless. The mechanisms by which homelessness may influence infection or severity may be multi-faceted, but it is biologically plausible that there is increased risk due the unsanitary conditions encountered by most homeless individuals, especially those that are unsheltered.

When the outbreak was identified in March 2017, I made a local recommendation to immunize persons experiencing homelessness with hepatitis A vaccine, in addition to emphasizing to the local medical community to vaccinate individuals with established ACIP indications. We worked closely with our local medical providers and found that persons experiencing homeless can be successfully targeted for vaccination. These efforts included: conducting mass vaccination events; providing vaccines through clinics and emergency departments that serve this vulnerable population; offering vaccine at homeless shelters, jails, and mental health facilities; and utilizing teams of public health nurses and homeless outreach workers to give shots in the field.

Of the reported outbreak cases in San Diego, none had completed a hepatitis A vaccine series, although 55% had established ACIP indications for vaccination (primarily illicit drug use or chronic liver disease). These are major missed opportunities for prevention. Among those who were homeless, 27% did **not** have an established ACIP indication for hepatitis A vaccination. We feel that extending the current national recommendations to include persons experiencing homelessness will more comprehensively protect those at risk for hepatitis A in the United States. A national recommendation to vaccinate homeless persons will also highlight for medical providers a vulnerable population in need of enhanced prevention efforts. Although our outbreak is nearly over, we will continue to protect homeless individuals in San Diego by providing and encouraging hepatitis A vaccination.

Submitted on October 14, 2018 by Wilma J. Wooten, M.D., M.P.H. Contact information: phone, 619-542-4181; email, wilma.wooten@sdcounty.ca.gov; mailing address, 3851 Rosecrans Street (Mail stop P-577), San Diego, CA 92110-3134

[1] Adjusted odds ratio (aOR) 95% confidence interval (CI) 1.4–7.4.
[2] aOR 95% CI 2.2-6.6.
[3] aOR 95% CI 1.1–17.

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