

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

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



**Summary Report
February 26-27, 2014
Atlanta, Georgia**

Table of Contents		Page
Agenda		4-5
Acronyms		6-8
Wednesday: February 26, 2014		
Welcome and Introductions		9-13
Influenza <ul style="list-style-type: none"> ♦ Brief Announcement: Novel Influenza Vaccine Work Group ♦ Introduction ♦ Influenza Activity Update ♦ Interim Estimates of 2013-14 Seasonal Influenza Vaccine Effectiveness ♦ Effectiveness of LAIV vs. IIV for Healthy Children (GRADE) ♦ Interim Influenza Vaccine Safety Update: LAIV and IIV in Persons <18 Years of Age ♦ LAIV vs. IIV comparative safety studies in children ♦ Safety of LAIV vs. IIV for healthy children (GRADE) ♦ LAIV update ♦ Proposed recommendations 		13-44
Meningococcal Vaccine <ul style="list-style-type: none"> ♦ Introduction ♦ Meningococcal Disease among Men who Have Sex with Men (MSM) ♦ Meningococcal Disease and Vaccine Response in HIV-Infected Persons ♦ Use of Serogroup B Meningococcal Vaccine During Outbreaks on College Campuses ♦ 		44-57
Pneumococcal Vaccines <ul style="list-style-type: none"> ♦ Introduction ♦ Update on PCV13 Effectiveness and Herd Effects in the U.S. ♦ Reduced Dose Schedules of PCV13 for Children: GRADE of Evidence ♦ PCV13 reduced dose schedules for children: considerations and WG conclusions 		58-83
Yellow Fever Vaccine <ul style="list-style-type: none"> ♦ Introduction ♦ Background: Yellow Fever Disease, Yellow Fever Vaccine, and Recent Vaccine Developments 		84-91
Vaccine Supply		91
Public Comments Day 1		92

Thursday: February 27, 2014	
Agency Updates <ul style="list-style-type: none"> ♦ CDC ♦ Center for Medicare and Medicaid Services (CMS) ♦ Department of Defense (DoD) ♦ Department of Veteran's Affairs (DVA) ♦ Food and Drug Administration (FDA) ♦ Health Resources and Services Administration (HRSA) ♦ Indian Health Services (I HS) ♦ National Institutes of Health (NIH) ♦ National Vaccine Advisory Committee (NVAC) ♦ National Vaccine Program Office (NVPO) 	92-95
General Recommendations <ul style="list-style-type: none"> ♦ Vaccine Storage and Handling 	96-101
Safety of Tetanus, Diphtheria, and Acellular Pertussis (Tdap) Vaccine <ul style="list-style-type: none"> ♦ Introduction ♦ Safety of Tdap vaccine during pregnancy: enhanced surveillance in VAERS ♦ Tdap during pregnancy: safety and coverage data from the VSD 	101-113
Human Papillomavirus (HPV) Vaccines <ul style="list-style-type: none"> ♦ Introduction ♦ HPV Type Attribution in Cervical Precancers ♦ HPV-Associated Cancers and Type Attribution ♦ 9-Valent HPV Vaccine Clinical Trial Data ♦ Summary and Next Steps ♦ Updated ACIP Statement-Bivalent and Quadrivalent Vaccines 	113-134
Smallpox Vaccine <ul style="list-style-type: none"> ♦ Introduction ♦ Use of ACAM2000 smallpox vaccine in laboratory personnel 	134-140
Public Comments Day 2	140
Certification	141
Membership Roster	142-149

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)
Centers for Disease Control and Prevention
1600 Clifton Road, NE, Tom Harkin Global Communications Center (Building 19), Atlanta, Georgia
February 26-27, 2014

	<u>AGENDA ITEM</u>	<u>PURPOSE</u>	<u>PRESIDER/PRESENTER(s)</u>
Wednesday, February 26th			
8:00	Welcome & Introductions		Dr Jonathan Temte (Chair, ACIP) Dr Larry Pickering (Executive Secretary, ACIP, CDC)
8:30	Influenza		
	<ul style="list-style-type: none"> Brief announcement: novel influenza vaccine work group Introduction Influenza activity update Interim estimates of 2013-14 seasonal influenza vaccine effectiveness Effectiveness of LAIV vs. IIV for health children (GRADE) Interim influenza vaccine safety update: LAIV and IIV in persons <18 years of age LAIV vs. IIV comparative safety studies in children Safety of LAIV vs. IIV for healthy children (GRADE) LAIV update Proposed recommendations 	Information Discussion	Dr Douglas Campos-Outcalt (ACIP) Dr Ruth Karron (ACIP, WG Chair) Dr Lyn Finelli (CDC/NCIRD) Dr Brendan Flannery (CDC/NCIRD)
		Vote	Dr Lisa Grohskopf (CDC/NCIRD) Dr Maria Cano (CDC/NCEZID)
			Dr Emmanuel (Chip) Walter (Duke University Medical Center) Dr Lisa Grohskopf (CDC/NCIRD) Dr Kathleen Coelingh (MedImmune) Dr Lisa Grohskopf (CDC/NCIRD)
10:45	<i>Break</i>		
11:15	Meningococcal Vaccines		
	<ul style="list-style-type: none"> Introduction Meningococcal disease among men who have sex with men (MSM) Meningococcal disease and vaccine response in HIV-infected persons Use of serogroup B meningococcal vaccine during outbreaks on college campuses 	Information Discussion	Dr Lorry Rubin (ACIP, WG Chair) Ms Jessica MacNeil (CDC/NCIRD)
			Ms Jessica MacNeil (CDC/NCIRD)
			Dr Manisha Patel (CDC/NCIRD)
12:30	<i>Lunch</i>		
13:45	Pneumococcal Conjugate Vaccine (PCV)		
	<ul style="list-style-type: none"> Introduction Update on PCV13 effectiveness and herd effects in the U.S. Reduced dose schedules of PCV13 for children: GRADE of evidence PCV13 reduced dose schedules for children: considerations and WG conclusions 	Information Discussion	Dr Nancy Bennett (ACIP, WG Chair) Dr Matt Moore (CDC/NCIRD) Ms Sara Tomczyk (CDC/NCIRD)
			Dr Tamara Pilishvili (CDC/NCIRD)
15:45	<i>Break</i>		
16:15	Yellow Fever Vaccine		
	<ul style="list-style-type: none"> Introduction Background: yellow fever disease, yellow fever vaccine, and recent vaccine developments 	Information Discussion	Dr Joseph Bocchini (ACIP, WG Chair) Dr J. Erin Staples (CDC/NCEZID)
	Adult Immunization		
17:00	<ul style="list-style-type: none"> Introduction Update on adult immunization coverage Update on CDC's adult immunization communication activities 	Information Discussion	Dr Tamara Coyne Beasley (ACIP, WG Chair) Dr Walter Williams (CDC/NCIRD) Dr Kristine Sheedy (CDC/NCIRD)
17:30	Vaccine Supply	Information	Dr Jeanne Santoli (CDC/NCIRD)
17:45	Public Comment		
18:00	Adjourn		

	<u>AGENDA ITEM</u>	<u>PURPOSE</u>	<u>PRESIDER/PRESENTER(s)</u>
Thursday, February 27th			
8:00	Agency Updates CDC, CMS, DoD, DVA FDA, HRSA, IHS, NVPO, NIH		
8:15	General Recommendations <ul style="list-style-type: none"> Vaccine storage and handling 	Information Discussion	Dr Jeff Duchin (ACIP, WG Chair) Dr Andrew Kroger (CDC/NCIRD)
9:00	Safety of Tetanus, Diphtheria, and Acellular Pertussis (Tdap) Vaccine <ul style="list-style-type: none"> Introduction Safety of Tdap vaccine during pregnancy: enhanced surveillance in VAERS Tdap during pregnancy: safety and coverage data from the VSD 	Information Discussion	Dr Arthur Reingold (ACIP, WG Chair) Dr Pedro Moro (CDC/NCEZID) Dr Elyse O Kharbanda (HealthPartners Institute for Education and Research)
09:45	<i>Break</i>		
10:15	Human Papillomavirus (HPV) Vaccine <ul style="list-style-type: none"> Introduction HPV type attribution in cervical precancers HPV-associated cancers and type attribution 9-valent HPV vaccine clinical trial data Summary and next steps Updated ACIP statement-bivalent and quadrivalent vaccines	Information Discussion Vote	Dr Joseph Bocchini (ACIP, WG Chair) Dr Susan Hariri (CDC/NCHHSTP) Dr Mona Saraiya (CDC/NCCDPHP) Dr Alain Luxembourg (Merck) Dr Lauri Markowitz (CDC/NCHHSTP)
12:15	Smallpox Vaccine <ul style="list-style-type: none"> Introduction Use of ACAM2000 smallpox vaccine in laboratory personnel 	Information Discussion	Dr Lee Harrison (ACIP, WG Chair) Dr Brett Petersen (CDC/NCEZID)
13:00	Public Comment		
3:15	Adjourn		

Acronyms

CDC	Centers for Disease Control & Prevention
CMS	Centers for Medicare and Medicaid Services
DOD	Department of Defense
DVA	Department of Veterans Affairs
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRSA	Health Resources and Services Administration
IHS	Indian Health Service
IIV	Inactivated Influenza Vaccine
LAIV	Live-Attenuated Influenza Vaccine
NCHHSTP	National Center for HIV, Hepatitis, STD and TB Prevention [of CDC/CCID]
NCIRD	CDC National Center for Immunization & Respiratory Diseases [of CDC/CCID]
NCZVED	National Center for Zoonotic, Vector-Borne, and Enteric Diseases [of CDC/CCID]
NIH	National Institutes of Health
NVPO	National Vaccine Program Office
SMART	Strategic Multi-Attribute Ranking Tool for vaccines
VAERS	Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Datalink
WG	Work Group

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core Surveillance
ACA	Affordable Care Act
ACCV	Advisory Commission on Childhood Vaccines
ACIP	Advisory Committee on Immunization Practices
ACNM	American College of Nurse Midwives
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
ADEM	Acute Disseminated Encephalomyelitis
AE	Adverse Events
AFP	American Family Physicians
AHIP	America's Health Insurance Plans
AI/AN	American Indians/Alaska Natives
AIM	Association of Immunization Managers
AMA	American Medical Association
ANA	American Nurses Association
AOM	Acute Otitis Media
APhA	American Pharmacists Association
APHA	American Public Health Association
ARI	Acute Respiratory Infection
ASTHO	Association of State and Territorial Health Officials
BARDA	Biomedical Advanced Research and Development Authority
BLA	Biologics License Application
BMBL	Biosafety in Microbiological and Biomedical Laboratories
CDC	Centers for Disease Control and Prevention
CIN	Cervical Intraepithelial Neoplasia
CISA	Clinical Immunization Safety Assessment
CMS	Centers for Medicare and Medicaid Services
CNS	Central Nervous System
COI	Conflict of Interest
COID	Committee on Infectious Disease
CSTE	Council of State and Territorial Epidemiologists
CVD	Cardiovascular Disease
DECIDE	Developing and Evaluating Communication Strategies to Support Informed Decisions and Practices Based on Evidence
DHS	Department of Homeland Security
DoD	Department of Defense
DOH-UK	Department of Health—United Kingdom
DSMB	Data Safety Monitoring Board
DTaP	Diphtheria, Tetanus, and Acellular Pertussis
DVA	Department of Veterans Affairs
EHR	Electronic Health Record
EIP	Emerging Infections Program
EMA	European Medicines Agency
EMR	Electronic Medical Record
ET	Eastern Time
FDA	Food and Drug Administration
GAVI	Global Alliance for Vaccines and Immunisation
GBS	Guillain–Barré Syndrome
GERMS-SA	Group from Enteric Respiratory and Meningeal disease Surveillance in South Africa

GMC	Geometric Mean Concentration
GMTs	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
GVAP	Global Vaccine Action Plan
HAART	Highly Active Antiretroviral Therapy
HCP	Healthcare Personnel
HHS	(Department of) Health and Human Services
HP2020	Healthy People 2020
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
IAC	Immunization Action Coalition
IARC	International Agency for Research on Cancer
IC	Immunocompromising Conditions
ICD	International Classification of Diseases
IDSA	Infectious Disease Society of America
IgG	Immunoglobulin G
IHR	International Health Regulations
IHS	Indian Health Service
IIS	Immunization Information System
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
ILINet	Influenza-Like Illness Surveillance Network
IND	Investigational New Drug
IOM	Institute of Medicine
IPD	Invasive Pneumococcal Disease
IRB	Institutional Review Board
ISD	Immunization Services Division
ISO	Immunization Safety Office
JE	Japanese Encephalitis
LAIV	Live Attenuated Influenza Vaccine
LMP	Last Menstrual Period
LNI	Log ₁₀ Neutralization Index
LRTI	Lower Respiratory Tract Infection
MAARI	Medically Attended Acute Respiratory Illness
MAW	Medically-Attended Wheezing
MCV4	Meningococcal Conjugate Vaccine
MedDRA	Medical Dictionary for Regulatory Activities
MMWR	<i>Morbidity and Mortality Weekly Report</i>
MSM	Men Who Have Sex With Men
NACCHO	National Association of County and City Health Officials
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
NFID	National Foundation for Infectious Diseases
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIS	National Immunization Survey
NMA	National Medical Association
NNV	Number Needed to Vaccinate
NP	Nasopharyngeal
NPPA	National Prevention Partnership Awards

NREVSS	National Respiratory and Enteric Virus Surveillance System
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
NYC DOHMH	New York City Department of Health and Mental Hygiene
OM	Otitis Media
OR	Adds Ratio
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PFGE	Pulsed-Field Gel Electrophoresis
PICO	Population, Intervention, Comparison, and Outcome
PIDS	Pediatric Infectious Diseases Society
PKIDs	Parents of Kids with Infectious Diseases
PRAMS	Pregnancy Risk Assessment Monitoring System
PRNT	Plaque Reduction Neutralization Test
RAD	Reactive Airway Disease
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
rMenB	Recombinant MenB+OMV NZ
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAEs	Serious Adverse Events
SAGE	Strategic Advisory Group of Experts (WHO)
SES	Socioeconomic Status
SGA	Small for Gestational Age
SME	Subject Matter Expert
SNPs	Single Nucleotide Polymorphism
Td	Tetanus-Diphtheria
Tdap	Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed
UK	United Kingdom
UN	United Nations
UNC	University of North Carolina
US	United States
USP	United States Pharmacopeia
USPSTF	US Preventive Services Task Force
VA	Department of Veterans Affairs
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Effectiveness
VFC	Vaccines for Children
VICP	National Vaccine Injury Compensation Program
VLP	Virus-Like particles
VRBPAC	Vaccine and Related Biologic Products Advisory Committee
VSD	Vaccine Safety Datalink
VT	Vaccine-Type
WER	<i>Weekly Epidemiological Record</i>
WHA	World Health Assembly
WHO	World Health Organization
YF	Yellow Fever

Welcome and Introductions

Welcome

Dr. Larry Pickering Executive Secretary, ACIP / CDC

Following Dr. Temte's greeting and call to order, Dr. Pickering welcomed everyone to the February 2014 Advisory Committee on Immunization Practices (ACIP) meeting. He indicated that the proceedings of this meeting would be available to people not in attendance via the World Wide Web, and welcomed those who could not attend the meeting in person. He then recognized several others in the room who were to be present throughout the duration of the meeting to assist with various meeting functions: Felicia Betancourt, Natalie Greene, Reed Walton, Stephanie Thomas, and Chris Caraway.

Emphasizing that there would be a full agenda for both days of the meeting, Dr. Pickering noted that handouts of the presentations were distributed to the ACIP members and were made available for others on the tables outside of the auditorium. Slides presented during this meeting will be posted on the ACIP website approximately two weeks after the meeting concludes, the live webcast will be posted within four weeks following the meeting, and the meeting minutes will be available on the website within 90 days following this meeting. Meeting minutes are posted on the ACIP website generally within 90 days of the meeting. Members of the press interested in conducting interviews with ACIP members were instructed to contact Jamila Howard Jones or Jason McDonald for assistance in arranging interviews.

Dr. Pickering then recognized the following domestic and international visitors who were in attendance at this ACIP meeting:

- ❑ Two Vaccine Science Fellows from the American Academy of Family Physicians (AAFP). The AAFP Vaccine Science Fellowship program is intended to develop a cadre of physicians with knowledge and practical experience in various aspects of vaccines, vaccine policies, and implementation in practice. The Vaccine Science Fellows are:
 - Chris Lupoid, MD, of Lancaster General Health in Lancaster, Pennsylvania
 - Mary Pat Friedlander, MD, from the University of Pittsburgh Medical Center—St. Margaret's in Pittsburgh, Pennsylvania
- ❑ Belinda Schoof and Jennifer Frost from the central office of AAFP, with whom CDC has had long-term interactions.
- ❑ Three representatives from the Ministry of Health in Vietnam, and one from Vietnam's CDC.
- ❑ The head of the Department of Arbovirology and Emerging Viral Infections from the Uganda Virus Research Institute.
- ❑ Two epidemiologists from Morocco's Ministry of Health.

- ❑ Three division directors from the Ministry of Health in Kenya.
- ❑ Two visitors from China, representing the Chinese CDC.
- ❑ Though Ministry of Health representatives from member countries of the WHO Pan American Health Organization (PAHO) usually attend each ACIP meeting, a group was unable to attend this meeting. CDC will host the next PAHO delegation at the June 2014 ACIP meeting.

With regard to information for future international visitors to ACIP meetings, due to changes in Department of Homeland Security (DHS) Policy, additional forms will be required for each meeting at the time an international guest registers. It is critical that international visitors complete and submit these forms as soon as possible following registration. Felicia Betancourt, Committee Management Specialist, will be able to help with any questions and concerns about the process. The next ACIP meeting will take place at CDC on Wednesday and Thursday, June 25-26, 2014. Registration for all meeting attendees is required and was anticipated to be open on the ACIP website during the week following this meeting. The registration deadline is June 2, 2014 for non-US citizens and June 9, 2014 for US citizens.

Dr. Pickering offered the following notes regarding liaison representatives and *ex officio* members:

Liaison Representatives

- ❑ Welcome to Terry Dwelle, the new ACIP liaison representative from the Association of State and Territorial Health Officials (ASTHO). Dr. Dwelle is a former clinical Professor of Pediatrics at the University of North Dakota School of Medicine, and worked as a medical missionary in East Africa. He currently serves as North Dakota's State Public Health Officer and as chair of the Infectious Disease Policy Committee for ASTHO.
- ❑ Carol Hayes attending as the American Nursing Association (ANA) liaison, on behalf of Katie Brewer.
- ❑ Pat Whitley-Williams, liaison representative from the National Medical Association (NMA) was unable to attend.

Ex Officio Members

- ❑ Avril (Melissa) Houston representing Vito Caserta as the *ex officio* member from the Health Resources and Services Administration (HRSA) during this meeting.
- ❑ Mary Beth Hance, the *ex officio* Member from the Centers for Medicare and Medicaid Services (CMS), was unable to attend.

To avoid disruptions during the meeting, Dr. Pickering instructed those present to turn off all cell phones. He explained that topics presented during the ACIP meeting include open discussion with time reserved for public comment. During this meeting, a time for public comment was scheduled following the afternoon sessions during both meeting days. Time for public comments also may be provided prior to specific votes by ACIP to enable these comments to be considered before any votes. Those who planned to make public comments were instructed to

visit the registration desk in the rear of the auditorium to have Felicia Betancourt record their name and provide information about the process. Those who registered to make public comments were instructed to state their name, organization if applicable, and any conflicts of interest (COIs) prior to making their comments.

Dr. Pickering announced several initiatives that are underway in an attempt to improve and accelerate communication and information delivery, including the following:

- CDC is launching vaccine schedule apps for mobile devices, both for the child and adult immunization schedules.
- CDC is working on content syndication of the immunization schedules between ACIP and the professional societies that publish them each year.
- This is the 50-year anniversary of ACIP, which held its first meeting in May 1964, which everyone would hear more about during future meetings.
- Safety issues will continue to be presented at every ACIP meeting.
- Educational sessions are being conducted for ACIP members. On February 25, 2014, a health economics overview was held for ACIP members and CDC staff. A review session on GRADE (Grading of Recommendations Assessment, Development, and Evaluation) is planned for members during a future ACIP meeting.

With regard to disclosure, to summarize conflict of interest provisions applicable to ACIP, as noted in the ACIP Policies and Procedures manual, Dr. Pickering indicated that members of the ACIP agree to forego participation in certain activities related to vaccines during their tenure on the committee. For certain other interests that potentially enhance a member's expertise while serving on the committee, CDC has issued limited conflict of interest waivers. Members who conduct vaccine clinical trials or who serve on data safety monitoring boards (DSMBs) may present to the committee on matters related to those specific vaccines. However, they are prohibited from participating in committee votes on issues related to those specific vaccines. Regarding other vaccines of the affected company, a member may participate in a discussion with a proviso that he or she abstains on all votes related to the vaccines of that company.

Applications for ACIP membership are due no later than November 15, 2013 for the 4-year term beginning July 1, 2014. Detailed instructions for submission of names of potential candidates to serve as ACIP members may be found on the ACIP web site:

E-mail: acip@cdc.gov Web homepage: <http://www.cdc.gov/vaccines/acip/index.html>

Nominations: <http://www.cdc.gov/vaccines/acip/committee/req-nominate.html>

A current CV, at least one recommendation letter from a non-federal government employee, and complete contact information are required. These may be submit as e-mail attachments to Dr. Jean Clare Smith at jsmith2@cdc.gov

During every ACIP meeting, an update is provided with regard to the status of ACIP recommendations. ACIP has a policy that every three to five years each recommendation is reviewed, and then renewed, reaffirmed, or retired. Links to these recommendations and

schedules can be found on the ACIP website. A listing of recommendations that have been published since the October 2013 ACIP meeting follows:

ACIP Recommendations Published Since October 2013		
Title	Publication Date	MMWR Reference
▪ Use of Japanese Encephalitis Vaccine in Children: Recommendations of the Advisory Committee on Immunization Practices, 2013	11/15/2013	2013:62:898-900
▪ Advisory Committee on Immunization Practices Recommended Immunization Schedules for Persons Aged 0 Through 18 Years — United States, 2014	2/7/2014	2014:63:108-109
▪ Advisory Committee on Immunization Practices Recommended Immunization Schedule for Adults Aged 19 Years or Older — United States, 2014	2/7/2014	2014:63:110-112
▪ Prevention and Control of <i>Haemophilus influenzae</i> type b Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP)	2/28/2014	2014:63(in press)

<http://www.cdc.gov/vaccines/hcp/acip-recs/recs-by-date.html>

Dr. Pickering shared the following resource information pertaining to ACIP:

Vaccine Safety:

www.cdc.gov/vaccinesafety/

Immunization Schedules (2013):

<http://www.cdc.gov/vaccines/recs/schedules/default.htm>

Childhood Vaccine Scheduler (interactive):

<https://www.vacscheduler.org>

Adolescent vaccine scheduler (interactive):

<http://www.cdc.gov/vaccines/recs/Scheduler/AdolescentScheduler.htm>

Adult Vaccine Scheduler (interactive):

<http://www.cdc.gov/vaccines/recs/Scheduler/AdultScheduler.htm>

Vaccine Toolkit:

<http://www.cdc.gov/vaccines/hcp/patient-ed/conversations/index.html>

Immunization for Women (American College of Obstetricians and Gynecologists)

www.immunizationforwomen.org

Before officially beginning the meeting, Dr. Temte called the roll to determine whether any ACIP members had conflicts of interest. The following conflicts of interest were declared:

- Dr. Tamera Coyne-Beasley: Research support is allocated to the University of North Carolina (UNC) by Merck Pharmaceuticals for clinical trials.
- The remainder of the ACIP members declared no conflicts.

Dr. Temte mentioned a couple of items of interest. The first regarded the *Weekly Epidemiological Record (WER)* that was published earlier in the month, which noted that during the timeframe between 2000-2012, measles worldwide has decreased by about 78%. Over that 12-year span, an estimated 13.8 million lives were saved by measles initiatives. Dr. Temte said he mentioned this because earlier in February at his home institutions, a young man who was not vaccinated presented from Southeast Wisconsin with a rash illness. The patient was diagnosed empirically with a rickettsial illness. Five days later the measles serology came back from a commercial lab in Iowa instead of the Wisconsin State Laboratory of Hygiene six blocks away where the test could have done immediately. During this timeframe, 97 hospitalized patients, 105 visitors, and 362 hospital employees were exposed. This resulted in case-contact investigations in 18 of Wisconsin's 72 counties. Suffice it to say that only 4 people were found to be at risk by serologic testing, including 1 infant, and 1 with an unknown serology. At this point, everyone had emerged from quarantine without developing measles. However, this was a reminder of just how pervasive these situations are and when they occur, their incredible impact. Dr. Pickering pointed out that part of the evaluation would include the cost of the outbreak to the institution.

Regarding the 50th year of ACIP, Dr. Temte reported that the agenda from the May 25-26, 1964 ACIP meeting included introduction of the committee, purpose and function, definition of the responsibilities, simplification of the immunization schedule, and relationships to other organizations such as the Redbook Committee, the American Public Health Association (APHA), and the Armed Forces Epidemiological Board (AFEB). No mention was made of AAFP, which was not in existence at that time. He read the committee's responsibilities, which follow:

"The Advisory Committee on Immunization Practices was appointed by the Surgeon General in May 1964. The committee is charged with the responsibility of advising the Surgeon General regarding the most effective application of public health practice of specific preventive agents, which may be applied in communicable disease control."

The initial committee had 10 members, and the Chair was Dr. James Goddard who was described in the *New York Times Magazine* as the "wild-eyed crusader with a battle axe flailing boldly," which reminded Dr. Temte of Dr. Pickering. The first item on the agenda of note in terms of any immunization was influenza. With that prompt, Dr. Temte requested that Dr. Karron come forward to start the February 2014 meeting with a discussion of influenza.

Influenza

Novel Influenza Vaccines Work Group

Dr. Doug Campos-Outcalt Chair, Novel Influenza Vaccines Work Group

Dr. Campos-Outcalt gave a brief announcement regarding the formation of a new work group, which he was asked to chair, the Novel Influenza Vaccines Work Group (WG). The rationale for this work group is that there are now two Food and Drug Administration (FDA)-licensed H5N1 vaccines available in the US, only indicated for high-risk populations, not for general or commercial use. There was believed to be a need for recommendations for use of these

vaccines during a non-pandemic period. This new work group will review the evidence for the use of these two vaccines, and will make recommendations for their use only in high-risk populations. ACIP was seen as the most appropriate body to develop recommendations for these vaccines, and it was thought that the Seasonal Influenza Work Group's workload precluded this additional task.

The WG was formed and convened its first call. The plan subsequent to the February ACIP meeting was to meet every two weeks initially and then monthly as needed. The WG anticipates a vote during the October 2014 ACIP meeting. The future of this WG will be determined after completion of this initial task.

In conclusion, Dr. Campos-Outcalt said he felt privileged to be able to chair this group and that he looked forward to the work they would be doing over the next year.

Introduction

Ruth Karron, MD Chair, Influenza Work Group

Dr. Karron noted that the Influenza Work Group meets every other week and sometimes more often than that, and expressed her gratitude to those who take the time to help the work group with its deliberations. She particularly recognized Dr. Lisa Grohskopf who completed most of the GRADE analyses to be presented during this session, as well Sonja Olsen and Leslie Sokolow who contributed tremendously to those analyses.

The Influenza Work Group has spent a considerable amount of time discussing and reviewing the evidence for the relative efficacy and safety of live attenuated influenza vaccine (LAIV) and inactivated influenza vaccine (IIV) for children. The group has also reviewed the GRADE analyses, and had a safety surveillance update on the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD). MedImmune has discussed the issue of LAIV supply with the WG. The WG has also heard from the US Flu Vaccine Efficacy Network about an interim estimate of the 2013-2014 seasonal influenza vaccine effectiveness.

Dr. Karron pointed out that the deliberations and GRADEing for LAIV versus IIV in children were conducted independently, but because we live in a global community, she thought it would be useful for everyone to know something about preferential LAIV recommendations currently in existence. To her knowledge, LAIV is preferentially recommended in four countries at this point: United Kingdom (UK), Canada, Israel, and Germany. The preferential recommendations of these countries differ somewhat from country to country and are as follows:

- ❑ United Kingdom: “[LAIV]...is strongly recommended as the vaccine of choice for children aged two years up to 18 years in clinical risk groups...”
- ❑ Canada: “Based on effectiveness, efficacy and immunogenicity data, NACI recommends LAIV for use in healthy children and adolescents 2 through 17 years of age. Available data indicates that LAIV would be preferred over TIV in this population...”
- ❑ Israel: “The Live Attenuated [Influenza] Vaccine is preferable to the Inactivated [Influenza] Vaccine in children two through 17 years of age due to its superior efficacy in this group.”

- Germany:** “STIKO recommends that LAIV should be used preferentially for influenza vaccination of at-risk children aged 2 through 6 years.”

Interestingly and in addition, two US states have a preferential recommendation: Oregon and Washington State. These preferential recommendations follow:

- Oregon:** “The Oregon Immunization Program (OIP) preferentially recommends the use of Live Attenuated Influenza Vaccine (LAIV) in healthy children 2 through 5 years of age.”
- Washington State:** “Data suggest that LAIV is more effective than inactivated influenza vaccine (IIV) for children 2 through 7 years of age. If a provider has access to both LAIV and IIV, they should consider using LAIV for healthy children 2 through 7 years.”

This session included presentations on the following topics:

- Influenza Surveillance Update
- Interim Vaccine Effectiveness Estimate, US Flu VE, Network, 2013-14
- Relative Efficacy of LAIV vs. IIV for Children (GRADE)
- Interim Influenza Vaccine Safety Update
- LAIV vs. IIV—Comparative Safety Studies in Children
- Relative Safety of LAIV vs. IIV for children (GRADE)
- LAIV Supply Update
- Annual Influenza Recommendations

Influenza Activity Update

Lyn Finelli, DrPH, MS
Influenza Surveillance and Outbreak Response Team
Epidemiology and Prevention Branch
Influenza Division
National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention

Based on the virologic surveillance data from the US World Health Organization and National Respiratory and Enteric Virus Surveillance System (NREVSS) collaborating laboratories, Dr. Finelli reported that for 2013-2014, there was a predominance of Influenza A virus. Of the influenza viruses that were characterized, Influenza A accounted for more than 95% (2009 H1N1) depending on the week. At the peak, 31% of the viruses characterized were positive for influenza. As of February 15th, the percent positive of specimens declined to 14%.

In terms of antigenic characterization from October 1, 2013 through February 15, 2014, of the Influenza A (2009 H1N1) viruses, 99.9% (919/920) were characterized A/California/7/2009-like, the H1N1 component of the 2013-14 Northern Hemisphere vaccine. For H3N2, 100% (86/86) were characterized as A/Texas/50/2012-like, the H3N2 component of the 2013-2014 Northern Hemisphere vaccine. For the Yamagata lineage of Influenza B, 62% (31/50) characterized as B/Massachusetts/2/2012-like, an Influenza B component of the 2013-2014 Northern Hemisphere vaccine. For the Victoria lineage of Influenza B, 38% (19/50) were from the B/Brisbane/60/2008-like, an influenza B component of the 2013-14 Northern Hemisphere vaccine. Regarding antiviral resistance, of the H3N2 viruses, none have antiviral resistance. Of the influenza B strains, none were resistant to antiviral. Of the influenza A (H1N1) viruses,

3471 viruses have been tested. Of those, 26 (0.7%) were resistant to Oseltamivir and none were resistant to Zanamivir.

ILI syndromic surveillance data in the Influenza-Like Illness Surveillance Network (ILINet) come from providers, clinics, and health departments that report to CDC the number of total visits they see each week and the number that are positive for ILI. There is a significant amount of coverage by ILINet throughout the US, with approximately 2900 reporters in the system actively reporting this year. Based on these data, this has been a moderate influenza season, which peaked in Week 52 at 4.6% contrasted by last year at 6.1%. Last year was a particularly bad influenza season. In terms of geographic spread, as of February 15th, there was primarily local or regional influenza activity in most of the US, with some widespread activity sustaining in the West and Northeast. Notably, these areas had a somewhat later influenza season than other areas in the country.

Hospital surveillance data are reported from the Emerging Infections Program (EIP), which is comprised of data from 15 jurisdictions in the US that conduct population-based surveillance. Rates from the laboratory-confirmed influenza hospitalization FluSurvNet system from February 14, 2013 through October 1, 2014 represent the reporting season. During that timeframe, there was an overall population rate of 26.1/100,000 which is contrasted with last year during which there was a rate of 35/100,000. As noted earlier, last year was a more severe influenza season. The highest rates were in those over 65 years of age (55/100,000). The next highest rates were in those 50 through 64 years of age (41/100,000). The rates cascade down after that with children 0 through 4 years of age (38/100,000) followed by those 18 through 49 years of age (18/100,000), and children 5 through 17 years of age (7/100,000).

Regarding proportions of hospitalizations in different age groups for the last 5 years, 2013-2014 had the highest proportion of hospitalizations in those 50 through 64 years of age and 18 through 49 years of age. This compares to the pandemic year in the highest proportions of hospitalizations. It is not just that there were the highest proportions of hospitalizations in these age groups just because there were not a lot in elderly. In fact, these are the highest rates in these age groups since the pandemic.

With regard to mortality data, there have been 52 influenza-associated pediatric deaths so far for 2013-2014. This system tends to lag somewhat compared to influenza activity, so more deaths are expected to accrue this year. In terms of the 122 Cities surveillance system, as of the peak during Week 2, 8.7% of all deaths in the US were influenza- and pneumonia-related, which is contrasted with last year at 9.9%. Again, the middle aged age group was somewhat more highly impacted. Looking at all pneumonia and influenza deaths, this change is not observed because pneumonia deaths occurred primarily in the elderly. However, just looking at influenza deaths, the 25 through 64 year old age group experienced a higher number of deaths this year than in the past few years. This is similar to the pandemic year, which was also an H1N1 year with 555 deaths in this age group compared to 352 this year, 138 in the 2012-2013 season, 37 in the 2011-2012 season, and 190 in the 2010-2011 season. There tend to be more deaths in the elderly in an H3 year like last year with 556, and fewer in an H1 year like this year with 194.

In summary, influenza activity in the US during the 2013–2014 season began in November approximately 4 weeks earlier than usual, and occurred at moderate levels. Activity peaked in late December to early January, depending upon the area of the country. Influenza A (H1N1) viruses predominated. There are higher rates of influenza-associated hospitalization in 2013-2014 in persons 18 through 64 years of age than during the past several seasons. There were

higher numbers of influenza deaths in the 122 Cities Mortality Surveillance System in 2013-2014 in persons 25 through 64 years than during the past several seasons.

In terms of why young and middle-aged adults were at higher risk for severe outcomes this season, preliminary vaccination coverage estimates for this season and past seasons indicate this age group has substantially lower vaccination coverage than other younger people and older age groups. This age group may lack the cross protective immunity to the pandemic H1N1 seen in adults over 65 years of age, likely acquired from past infection with antigenically-related viruses. This age group had lower attack rates during the pandemic H1N1 pandemic and may have less cross protective immunity from that time as well. As adults reach middle age, they start to develop types of underlying conditions such as diabetes mellitus cardiovascular disease (CVD), and lung disease that increase the risk for complications from influenza and may be at higher risk for serious outcomes if infected.

Discussion Points

Dr. Temte inquired as to whether there are any systems that track or monitor deaths of pregnant women from influenza.

Dr. Finelli responded that there are currently no systems. There was a pregnancy-related system in 2009-2010 and 2010-2011, but that system is no longer in operation. The pregnancy group at CDC is very keen on reinitiating that system, but so far, the states have not been able to provide the resources associated with reinitiating that system.

Interim Estimates of 2013-2014 Season Influenza Vaccine Effectiveness

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

Dr. Flannery presented the mid-season estimates of the current seasonal vaccine effectiveness. These data are from the US Flu Vaccine Effectiveness (VE) Network through enrollment as of January 23, 2014. Current participation in the US includes 5 institutions: Group Health Cooperative in Seattle (PIs: Lisa Jackson, Mike Jackson); Marshfield Clinic Research Foundation in Wisconsin (PI: Ed Belongia); University of Michigan in the Detroit area (PIs: Arnold Monto, Suzanne Ohmit); University of Pittsburgh (Rick Zimmerman, Patricia Nowalk); and Baylor Scott and White Health in Temple, Texas (PI: Manju Gaglani).

Regarding the methods used for estimating vaccine effectiveness in the Flu VE Network, the participating sites enroll outpatients 6 months of age and older with acute respiratory tract illness with cough of less than 7 days in duration. The data presented during this session were for the dates of enrollment beginning December 2, 2013 through January 23, 2014. The sites begin enrollment when there is circulating influenza activity in the area. This is a prospective case-control design, referred to as a test-negative design, which is slightly different from the traditional case-control design. In this test-negative design, all outpatients who are enrolled are tested for influenza by real-time reverse transcription polymerase chain reaction (RT-PCR). Cases are comprised of outpatients with confirmed PCR-positive influenza, while controls are outpatients who test negative for influenza.

Vaccination status for this analysis is defined as receipt of at least one dose of any 2013-2014 seasonal influenza vaccine. While the records are used at all of the sites, receipt of vaccine is confirmed by medical records and registries at two sites. Self-reports were accepted from three sites, because the medical record searches are not complete. VE is estimated as in a traditional cases-control study, $1 - \text{adjusted odds ratio (OR)} \times 100\%$. The estimates presented during this session were adjusted for study site, age, sex, race/Hispanic ethnicity, self-reported health, and days from illness onset to enrollment.

This has been a predominantly H1N1 year, with the vast majority being 2009 H1N1 strain (N=742) identified among positive cases at the sites. This analysis included 2319 enrollees, of which 1535 (66%) were influenza RT-PCR negative and 784 (34%) were influenza RT-PCR positive. Among the 784, 742 were 2009 H1N1, 23 were A non-typed, 13 were H3N2, and 6 were Influenza B. There were not enough H3N2 or B strains to provide any information about vaccine effectiveness for this season against H3N2 or B.

In terms of enrollment by study week, more negatives were enrolled in every week during the period including Weeks 49 through 52 in 2013 and Weeks 1 through 4 in 2014. Positivity ranged from about 20% to 30% and declined slightly from the period of time the last group was enrolled that is included in this analysis.

Regarding the interim adjusted VE estimates for 1 or more doses of 2013-2014 seasonal influenza vaccine, approximately 50% of influenza negatives were vaccinated among the enrollees versus about 29% of influenza cases or positive outpatients. Overall VE for A and B was 61% with a confidence interval of 52% to 68%. For 2009 H1N1, the numbers were very similar with 50% vaccinated among the negatives, 28% vaccinated among the influenza positives, and a VE of 62% with a very similar confidence interval of 52% to 69%. H1N1-specific VE the percentage vaccinated among controls ranged from 79% among those 65 years of age and older to about 38% among 18 through 49 year olds. All of the influenza-positive age groups had a much lower percentage of vaccinated among the enrollees. VE estimates ranged from 67% with pretty tight confidence intervals (51% to 78%), to 56% in those 65 years of age and older with quite a wide confidence interval (7 to 79). Consistent VE is observed across all four age groups in contrast to what was seen last season with H3N2, with a wide confidence interval in those 65 years of age and older.

For comparisons with other estimates of the pandemic H1N1 virus, data were assessed from several studies in several settings over four influenza seasons. For 2013-2014, these included a comparison of mid-season estimates from the USFluVE Network with recently published studies from Canada and estimates from Spain. For 2011-2012, these included a comparison of estimates from the USFluVE Network with Canada. For the 2010-2011 season, USFluVE estimates were compared specifically to Marshfield and estimates from Europe. Notably, all of the systems in Europe, Canada, and Spain use the same test negative design for their estimates. Therefore, study design does not explain the relatively small differences here. A recently published study with Mark Thomas as the first author was conducted among US pregnant women for the 2010-2011 and 2011-2012 to assess H1N1 VE for those two periods. The take-home message is that the estimates seen for the mid-season is consistent with 2009 H1N1-specific estimates observed essentially for every season since the 2009 pandemic.

In conclusion, 2009 pandemic H1N1 virus predominated among influenza viruses identified from December 2, 2013 through January 23, 2014 in the US. It was also identified as the predominant virus in the USFluVE Network. The interim adjusted VE against 2009 pandemic H1N1 associated with medically attended acute respiratory infection (ARI) was 62% with a confidence interval from 53% to 69%. This estimate was similar for all age groups assessed, and was similar to VE estimates for 2009 pandemic H1N1 from previous seasons and in different settings. These estimates are consistent with laboratory data for the current season showing that the virus and vaccine virus remain a good match. The final analyses for the 2013-2014 season will investigate the effects of prior vaccination. Hopefully, estimates will also be provided for vaccine types, specifically for live attenuated influenza vaccine (LAIV) versus inactivate vaccine. The ability to estimate VE for H3N2 or B infections this season will depend upon the final sample size.

Discussion Points

Dr. Duchin inquired as to whether it was possible to tell whether vaccine effectiveness varies according to whether the site used confirmed versus self-reported vaccination status in general. He also wondered whether any analyses were planned of VE according duration between immunization and illness—the waning protection issue.

Dr. Flannery responded that an analysis will be performed at the end of the season to assess the effect of using confirmed versus self-reported vaccination status. Comparing the self-report and medical record data in this analysis from the sites that used both, additional people were detected as vaccinated using self-report information, so it is believed that the medical records are complete. The data are very similar when limited just to the medical records. Major differences are not anticipated in the final analyses. Regarding waning protection, Dr. Flannery noted that some of the data shown were from a group that uses sentinel hospital and outpatient settings in Europe specifically. They have shown intra-season waning in the second half of the season. For several seasons with H3N2 predominance, they have shown lower VE. CDC is still trying to address whether those are methodological issues or if there is true decrease in VE in the second half of the season. Their hypothesis is that people who are vaccinated early and have a long time before being infected may have lower levels of protection from vaccination. That would be a contrast to what has been observed with prior year vaccination offering some long-lasting protection. CDC is still assessing methodologies to evaluate that through the USFluVE Network, but is planning to do that with these datasets. There is a unique opportunity to look at a virus that essentially has not changed, and look at prior vaccination as well as the question of relation of immunity.

Dr. Reingold thought it would be interesting to know whether effectiveness varied by whether people are healthy or not.

Dr. Flannery replied that in the final analysis, co-morbid conditions were used that are defined based on identification of International Classification of Diseases (ICD)-9 codes, so there is verification of co-morbid conditions. This analysis was only adjusted for self-rated health status. That has been shown to be correlated with co-morbid conditions, but it is really not an analysis by co-morbid conditions. That will be done later. In terms of whether VE varied by whether co-morbid conditions were present, adjusting for this made no difference. A separate analysis has not been done for levels of self-rated health.

Regarding the wide confidence intervals for VE in individuals over 65 years of age for the H1N1 sub-type, Dr. Coyne-Beasley noted that there were very wide confidence intervals in the categories of Influenza A and B as well. She wondered whether that was solely related to the fact that there were fewer people in that age range who were influenza-positive, or if Dr. Flannery thought that other factors contributed to such a wide estimate.

Dr. Flannery said that essentially, the 65 years of age and older population is a more difficult group to enroll in outpatient settings. All five of the sites have made extra efforts to increase their enrollment of people 65 years of age and older. The number of people enrolled is the actual limitation, so the confidence intervals are wider because the numbers are lower. The percentage influenza-positive is similar in this group. Canada has a slightly younger population overall. Only about 5% of their population is 65 years of age and older for their enrollees. In the US study population it is about 15%, which reflects the additional efforts the sites have gone to in order to enroll patients 65 years of age and older. That does not explain the difference shown in Canada, but CDC believes the differences are less than the similarities. The estimates for H1N1 are pretty similar.

In response to a question regarding enrollees, Dr. Flannery responded that this is active surveillance. Subjects are recruited and consented to participate in the study, and they all present to a participating clinic with ARI and cough.

Dr. Jenkins inquired as to whether self-reports would be included in the analysis of the effect of prior vaccination. It seemed like for prior vaccination, reliability might decrease.

Dr. Flannery responded that self-report was not included for the analysis for vaccine type at the end of the season or for prior vaccination. Given that it is very difficult to tease out current and prior VE effects, and that this is such a "hot" area right now in influenza, that analysis is limited to verified vaccination.

Dr. Kimberlin (AAP) was struck by the one-third of tested samples that were PCR-positive for influenza. In virtually all of the prospectively performed treatment studies, the rate of detection using similar methodology in terms of fever, cough, and so forth has been two-thirds positive and one-third negative.

Dr. Flannery replied that for reasons of sensitivity and to try to get as many influenza-positive cases as possible, all five participating sites decided to use acute respiratory illness with cough as their case definition. If they limit it to ILI (people needing a definition of cough, additional respiratory symptoms, and fever for ILI) that would increase the proportion positive. Using an ILI definition as is done in Canada, the percentage of influenza positives actually increases compared to the outpatients who test negative. Fever especially increases the specificity of the case definition. That is a major difference with the USFluVE Network.

Dr. Gorman (NIH) asked whether the one-month discordance between the CDC dataset from early January and the peak of the influenza season that seemed to peak in December had any impact on the efficacy data.

Dr. Flannery did not think so, although there could be a question about timing and whether there is some change in VE during the season. Last season, with the very early onset of the influenza season, some of the sites had to scramble to begin enrolling patients in the beginning of the season. They also had a change at the end of the season to a predominance of B circulating at some sites. It was good for the VE estimates to have enough B to assess by B lineage for the

final VE that was presented here. There has not been enough antigenic change in the H1N1 virus to say that there is not an accurate representation of VE, because of the period of time. Final analyses do control for calendar time because there are those differences of cases and controls who are enrolled by sites depending upon their local influenza circulation and when they start. Dr. Flannery did not believe it meant in this particularly case that they missed the influenza season or were late in enrollment, because each site essentially begins once they see influenza. This is a more efficient approach.

Dr. Gorman (NIH) observed that two of the sites seemed to have electronic medical record (EMR) capabilities and the ability to search medical records. If the previous year influenza vaccinations were limited, he wondered whether that would be a possible way to assess that.

Dr. Flannery responded that all of the sites have EMRs. Most of them also receive data from state immunization registries, and may receive vaccination data from other sources. Extra effort is made at most sites. If someone says they were vaccinated and they have a provider, the study site may actually seek that information to try to document it. A large difference has not been observed with the mid-season estimates and the full-season estimates, which includes only verified vaccination. Some may not be possible to verify, and the previous year's estimates seem to be decreasing from the early, to the mid, to the end of season. But some of that pertains to co-morbid conditions and other variables for which adjustments can be made. He did not believe that they were missing things because of the way vaccination status is being used here.

Ms. Stinchfield (NAPNAP) said she appreciated the emphasis on the outpatient. She was thinking about how this is communicated, and how it often is translated to whether vaccines work and the percentages—people and a number. This is VE and ARI in an outpatient setting, which does not fit on a Tweet or headline. She thought it was important as they communicated this information, they must emphasize that these are patients in the outpatient setting who presented to clinics—not overall vaccine effectiveness against all influenza. She wondered about assessing effectiveness with inpatient hospitalizations and impact on deaths.

Dr. Flannery responded that CDC is interested in evaluating the impact of vaccination on hospitalizations, but these are difficult studies to conduct and CDC does not currently have a surveillance system that assesses inpatient VE. CDC is also interested in assessing VE against pediatric deaths specifically because of the pediatric mortality surveillance system. The question regards finding a good comparison group to be able to evaluate what would be expected for vaccination in that population. As noted in the MMWR the previous week, overall vaccination is much lower than would be expected in groups that have been hard hit this year. In the pediatric mortality surveillance, the percentage vaccinated is much lower than what would be expected. CDC is very interested in these two areas, especially with regard to the vaccine communication messages and how important vaccination is to prevent severe outcomes.

Ms. Pellegrini asked whether it was true every year that vaccination rates were lower among those 18 through 49 and 50 through 64 years of age.

Dr. Flannery clarified that regarding the message from the surveillance that those populations were hard hit, it would be nice to be able to have VE in inpatients in that age group to say that the vaccine is effective against inpatient disease. It is true that every year, those age groups have had low vaccination coverage. This year, that has been a focus of media or communication of messages about these being important groups to vaccinate because they have high severe illness and hospitalization rates.

Effectiveness of LAIV vs. IIV for Healthy Children (GRADE)

Dr. Lisa Grohskopf
Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Grohskopf noted that the next several presentations would be related to the use of LAIV and IIV among children, particularly among younger children. No change in the recommendations for these vaccines in children was proposed for this meeting. It is anticipated that there will be further discussion within the Influenza Work Group, and that this topic would be revisited in June 2014.

According to current CDC and ACIP recommendations, healthy children aged 2 through 17 years may receive either LAIV or inactivated influenza vaccine. Several studies indicate that LAIV may have advantages over IIV for children. This is somewhat in contrast for adults, for whom comparative studies have generally indicated either that the two vaccines are similarly efficacious or perhaps that the inactivated vaccines are somewhat better. Particularly for younger children, there are several lines of evidence indicating better vaccine efficacy for LAIV, better onset of immune response and duration of immunity, and better heterotypic protection against drifted strains [Belshe NEJM 2007; Ashkenazi PIDJ 2006; Bernstein PIDJ 2003; Belshe NEJM 1998].

Currently, the ACIP recommendations express no preference for LAIV versus IIV for children for whom either is indicated. However, recent recommendations (e.g., within the last two years) have been published over the last several years in several other countries and US states expressing some degree of preference for LAIV for children. The age specifications of this preference vary, with Canada, the UK, and Israel stating a preference for children aged 2 through 17 years and Germany, Oregon, and Washington State limiting the preference to younger children.

To frame some recent background, the ACIP Influenza WG selected the comparison of LAIV and IIV for children as the first policy question to be addressed using GRADE. A preliminary GRADE efficacy assessment was presented during the October 2012 ACIP meeting. At that time, the safety assessment was deferred, in large part because the trivalent formulation of LAIV (LAIV3) was anticipated to be replaced with a quadrivalent formulation (LAIV4) in 2013-2014, which has occurred, and no post-marketing safety data were yet available for LAIV 4. The objective of the series of presentations during this meeting was to describe GRADE assessments for the safety and efficacy of LAIV versus IIV for healthy children, in particular younger children.

The policy question posed was “should LAIV be recommended preferentially over IIV for healthy children.” Healthy children were specified for this initial assessment, because LAIV is currently recommended for children without medical conditions that confer a higher risk of severe illness from influenza. Data were assessed separately for younger versus older children, stratified into ages 2 through 8 years and 9 through 18 years. The rationale for the selected age categories and the break point at 8 years was that LAIV is not licensed for children under 2 years of age, so the lower limit was relatively simple to define. The upper limit was less straightforward. While superior efficacy of LAIV has been demonstrated in children, it has not in adults, and it is not clear at what age the better relative efficacy of LAIV begins to decline. Eight years is the

upper limit of the age range for consideration of whether a child needs 1 versus 2 doses of influenza vaccine, and was selected for simplicity of the recommendations.

Studies included contained data pertaining to healthy children primarily, although one study specifically was of children with asthma; data pertaining to vaccines licensed in the US or similar to US-licensed vaccines; and studies including both LAIV and IIV arms. Only literature in English was used. Excluded were data for adjuvanted, whole virus, and virosomal vaccines; data for LAIV produced using different seed strains from US products; studies in which all participants were outside of the indicated age range; and studies with outcomes defined by ICD-9 codes only.

The WG had several discussions about generating lists of relevant outcomes and assigning values to them. The outcomes of laboratory confirmed influenza (confirmed by culture or PCR) and influenza-associated mortality and hospitalization were considered critical. Medically attended acute respiratory illness (MAARI), influenza like illness (ILI), and influenza-associated otitis media (OM) were considered important. The literature review through PubMed identified 9 papers, including 5 randomized trials and 5 observational studies.

Of the 5 randomized trials, 2 were open label. These included Ashkenazi et al 2006, a study of 6 through 71 month olds with a history of recurrent respiratory tract infections; and Fleming et al 2006, a study of children aged 6 through 17 years with asthma. Belshe (2007) assessed children 6 through 59 months. Regarding the blinded studies, with the exception of Neuzil et al (2001), which included data from 5 influenza seasons, each study was conducted over a single season. Not surprisingly, not every study included every outcome. The most data were available for laboratory confirmed influenza, and there were no data for influenza-related mortality. Of note, Fleming (2006), Neuzil (2001), and Clover (1991) included both age groups of interest, and the results for the outcomes needed were not age-stratified, such that the data as reported spanned both age groups of interest. These data were examined separately as a 2 through 18 year old group, without stratification into the two age groups of interest. This analysis was not part of this presentation.

In terms of the characteristics of the observational papers and studies, Treanor et al (2002), Ohmit et al (2013), and Fry (2013) summarize three successive seasons for data from the US Flu VE network. Macintosh (2013) and Eick-Cost (2013) come from the Department of Defense (DoD). The observational studies reported only laboratory-confirmed influenza as an outcome, and contributed to the assessment of laboratory-confirmed influenza.

Because lab-confirmed influenza is an important outcome that figured heavily into this presentation, Dr. Grohskopf took some time to describe how this information was collected in the various studies—particularly, what the criteria were for collecting specimens for culture. The main thing to note is that collection of cultures in each case was prompted by symptoms of clinical illness in the participants. The specific criteria used, as reported in the papers, varied somewhat, with some criteria (such as that of Ashkenazi and Fleming) being more detailed than others. The take home message is essentially that in general, there was manifestation of an illness, although in Ashkenazi and Belshe cultures could also be obtained at the investigators' clinical discretion, even if the child did not quite meet the definition that was cited. The outcome with the most data was lab-confirmed influenza, with all 10 papers contributing. Seven papers contributed to the assessment of children ages 2 through 8 years. Five papers contributed to the assessment of children ages 9 through 18. No papers contributed data on mortality due to influenza. For hospitalizations, two papers contributed to assessment of children ages 2 through 8 and one contributed to assessment of children ages 2 through 18. For MARRI, two

papers contributed to assessment of children ages 2 through 8 and one contributed to assessment of children ages 2 through 18. For ILI, one paper contributed to assessment of children ages 2 through 8 and one contributed to assessment of children ages 2 through 18. For OM, two papers contributed to assessment of children ages 2 through 8 and two contributed to assessment of children ages 2 through 18.

Next, Dr. Grohskopf presented results for the younger age group, 2 through 8 years. Laboratory-confirmed influenza, which was considered a critical outcome, included two studies: Ashkenazi et al and Belshe et al. Both of these studies included children who are younger than 2 years of age, the indicated age for Flumist[®], but the majority were 24 months and older. Studies were not downgraded for risk of bias, inconsistency, indirectness, or imprecision. In pooled analysis, significant relative benefit of LAIV was noted, with a risk ratio of 0.46 for lab-confirmed influenza and a 95% confidence interval of (0.39 to 0.54). Overall evidence quality was therefore rated as high.

Data from the same two studies restricted to those aged 24 months and older were published by Ambrose et al in a subsequent meta-analysis [*Vaccine* 2012]. In this paper, lab-confirmed influenza was the only outcome discussed. Studies were not downgraded for risk of bias, inconsistency, indirectness, or imprecision. In pooled analysis, significant relative benefit of LAIV was noted, with a risk ratio of 0.47 and only a slight widening of the confidence interval, which would be anticipated due to having slightly less data. Overall evidence quality was assessed as Type 1 or High.

Regarding summary information for lab-confirmed influenza from observational studies, as noted earlier these various reports included children of different age groups. For this analyses, however, the authors were able and kind enough to provide the data stratified specifically to the work group's age categories of interest. There is some heterogeneity in the point estimates; however, there is also appreciable overlap of the confidence intervals, so there was no downgrade for inconsistency in that regard. The confidence interval was somewhat on the wide side, and on that basis the Results were downgraded for imprecision. This downgraded the overall quality of evidence for this outcome from 3 or Low (the initial rating for observational studies) down to Very Low.

The next outcome is hospitalization, which was also a "critical" outcome. Influenza-specific hospitalizations were desired rather than all-cause hospitalizations. Such data were not available; however, Ashkenazi reported hospitalizations for respiratory illness. This was more similar to ILI-related hospitalization than influenza-related hospitalization. Therefore, this study was downgraded for indirectness, since they were not influenza-related hospitalizations specifically. The study was also downgraded for imprecision, given the width of the confidence interval, which straddles 1. No significant difference was observed between the two vaccines. Overall evidence quality was Type 3, Low.

Medically-attended acute respiratory illness was also a "critical" outcome, for which Ashkenazi et al provided data. This study was downgraded for indirectness because the outcome is not influenza-specific. No significant difference was noted. Overall evidence quality was 2, or Moderate.

The influenza-like illness outcome was valued as "important." The results were downgraded for indirectness, as this outcome is not influenza-specific. No significant difference was noted between the two vaccines. Overall evidence quality was Moderate. The last outcome for this age group is otitis media, which was deemed "important." Both the Ashkenazi and Belshe

studies included this outcome. No serious concerns were identified for risk of bias, inconsistency, indirectness, or imprecision. Overall evidence quality was deemed high. The pooled risk ratio was 0.47, and was significant.

For the age group 9 through 18 years, laboratory-confirmed influenza was considered to be a “critical” outcome.” The 5 observational studies contributed data. These results were downgraded for imprecision, given the width of the confidence interval around the pooled estimate. This downgraded the overall quality of evidence for this outcome from 3 or Low (the initial rating for observational studies) to 4 or Very Low. The pooled odds ratio was not significant for a difference between LAIV and IIV.

In addition to the relative efficacy of LAIV versus IIV among young children, there are other important considerations as the WG moves forward and formulates a decision. Harmonization with the American Academy of Pediatrics (AAP) recommendations is an important consideration, and it is anticipated that there will be more discussion on that matter in the coming months. LAIV supply is also an important issue if there is going to be a preference. As mentioned earlier, the safety of the newer quadrivalent vaccines, for which no data are available among the cited studies, is an important consideration. Another important matter is the relative cost of the two vaccines. Direct comparisons are somewhat complicated by the fact that in contrast to LAIV, for which there is only one formulation, there are numerous presentations for IIV available (e.g., trivalent, quadrivalent, single and multidose vials, and syringes). Per the Vaccines For Children (VFC) private sector prices, for 2014-2015, the cost of LAIV4 is roughly similar to that of the most expensive quadrivalent inactivated vaccine.

To summarize the outcomes, for the critical outcome lab-confirmed influenza decreased risk with LAIV was noted, and overall evidence quality was 1 or High. Quality was 3 or Low for hospitalization, and 2 or Moderate for MAARI. No differences in these two outcomes were noted. For the important outcomes, no differences were observed between the two vaccines for otitis media and evidence quality was moderate. For otitis media, decreased risk was observed with LAIV and evidence quality was 1 or High. For 9 through 18 year olds for lab-confirmed influenza, there were no differences and overall quality of evidence was 4 or Very Low.

Discussion Points

Dr. Temte noted that GRADE was starting to feel routine.

Dr. Kempe asked whether the other four countries with a preferential LAIV recommendation for young children were assessing different data that are non-English, and what kind of criteria those countries were using in terms of precautions for children with asthma.

Dr. Grohskopf replied that the literature cited is not known for all countries, but based on what is known, the literature appears to be essentially the same overall. For Germany, for example, Falkenhorst et al published a GRADE analysis of this very recently, and the literature is largely the same. However, they did their analysis for older children slightly differently using a paper by Fleming. CDC is highly interested in children with chronic illnesses, particularly with asthma, because that group is at higher risk for influenza complications. Thus, it is important to have the best possible vaccine for them. There is some variability in Canada in that for controlled asthma, there would not be any prohibition to using LAIV and it would be preferred in that population. Not everything reads the same way that it does for the current US recommendations. More discussion is anticipated in the WG about that particular issue.

Dr. Warshawsky (NACI) added that Canada updated its preferential recommendation in their statement in November 2013, acknowledging that there is clear evidence for children 2 through 6 year olds. However, the evidence for children through 17 years of age is not quite as clear, so it is not clear when the cutoff would be. Canada used the Fleming article in its assessment of the older age group, which is the one RCT that goes up to that age group and is in asthmatics. Canada thought that it offered some evidence that there is some superior efficacy in that age group, although it is not clear when that cuts off and it is only one study. That was the reason Canada reviewed its recommendations to state that they are clear on the evidence up to 6 years of age, but that beyond that they were not clear on higher age groups or the cutoff. Canada's recommendations are for healthy children only, and recommended that the vaccine be used in chronic illness conditions. However, Canada does not have a preferential recommendation in chronic illness because there are no data to support that.

Dr. Decker (Sanofi Pasteur) acknowledged that the data overall suggested that there is an efficacy relationship benefit in younger children, that there are benefits from IIV in older people, and that it is not clear what the transition is. Presumably the difference is because of experience with the virus previously or experience with vaccine previously—something like that. In that regard, the fact that the newest study assessing efficacy was conducted over a decade ago and the oldest almost two decades ago, raised a question in his mind. It was not influenza that had changed, but the population. He believed that CDC showed that younger children were far more likely to be vaccine-experienced now than they were 10 or 20 years ago. In that regard, he knew that MedImmune was in the process of conducting a post-marketing commitment trial to generate current estimates of efficacy by year of age. In light of that, he wondered if the committee planned to wait to review those data, or go ahead on the basis of the 10 or 20 year old data.

Dr. Grohskopf responded that at this point, the WG was continuing to have discussions about a number of topics. It is true that the Belshe and Ashkenazi studies were conducted at a time when most children were vaccine-naïve simply because of the recommendations at that time. She anticipated that the WG would continue to have discussions regarding this issue.

Dr. Karron added that it certainly is true that fortunately many more children are currently immunized against influenza than when those studies were conducted. Currently, a relatively small proportion of children are receiving LAIV. Data that she saw most recently indicated about 7% to 10% of children in that age group. It is certainly known that with IIV, immunity wanes—even by the springtime. She wondered if they assessed children with an IIV immunization background, who are most likely to be the majority of children immunized, if that would make a difference. She thinks the best way over time to evaluate repeated LAIV immunizations will be through the type of data collected by the VE Network that actually stratify by immunization status.

Dr. Decker (Sanofi Pasteur) thinks the concern is that as one acquires immunity over repeated experience, and there is enough nasal antibody, LAIV does not have the chance to stimulate an immune response before getting squashed by what someone already has. That is the conjecture as to why there is an age transition, and after a while, IIV works better than LAIV.

Interim Influenza Vaccine Safety Update: LAIV and IIV in Persons <18 Years of Age

Maria Cano, MD, MPH
Immunization Safety Office
Centers for Disease Control and Prevention (CDC)

Dr. Cano gave an interim influenza vaccine safety update for LAIV and IIV influenza vaccines in persons less than 18 years of age in the US for the time period July 1, 2013 through December 31, 2013. Recently licensed influenza vaccines that became available during the current season are listed in the following table:

Vaccine	Abbreviation	Brand Name (Manufacturer)	Recommended Age Group
Quadrivalent live attenuated influenza vaccine	LAIV4	FluMist® Quadrivalent (MedImmune)	2 through 49 yrs
Quadrivalent inactivated influenza vaccine	IIV4	Fluarix® Quadrivalent (GlaxoSmithKline)	≥3 years
		Fluzone® Quadrivalent (Sanofi Pasteur)	≥6 months
		Flulaval® Quadrivalent (GlaxoSmithKline)	≥3 years
Cell culture-based trivalent inactivated influenza vaccine	cclIV3	Flucelvax® (Novartis)	≥18 years
Recombinant trivalent inactivated influenza vaccine	RIV3	FluBlok® (Protein Sciences)	18 through 49 years

There was a complete switch to quadrivalent LAIV influenza vaccine this season, so comparison between the trivalent and quadrivalent forms will be between seasons. For IIV, both trivalent and quadrivalent forms are available, and the comparison is done within the current season.

CDC reviewed US VAERS reports after LAIV or IIV, with report dates from July 1, 2013 through January 31, 2014 and vaccination dates from July 1, 2013 through December 31, 2013. LAIV4 this season is compared to last season's LAIV3. IIV4 versus IIV3 is a within season comparison. Adverse events that were reviewed and coded into the VAERS database using the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA terms of note are not mutually exclusive, and a report may have several different MedDRA terms. FDA conducted empirical Bayesian data mining to detect disproportional reporting in the VAERS database [Banks D, et al. Comparing data mining methods on the VAERS database. *Pharmacoepidemiology and drug safety* 2005;14:601-9].

As a reminder, VAERS is co-managed by CDC and FDA. The strengths of VAERS is that it includes national data; accepts reports from anyone; has rapid signal detection; captures rare adverse events; collects information about vaccine, characteristics of vaccinees, and adverse events; and data are available to the public. VAERS also has limitations, including reporting bias, inconsistent data quality and completeness, general inability to assess whether a vaccine caused an adverse event, lack of an unvaccinated comparison group, and lack of inclusion of pregnancy status.

A summary of reports to VAERS following LAIV among those aged 2 through 17 years, the recommended age group in children, are shown in the following table:

	LAIV4 2013-14* Total N = 276 N (%)	LAIV3 2012-13* Total N = 244 N (%)
Serious reports [†]	25 (9)	23 (9)
Male	128 (46)	115 (47)
Median age (yrs)	7	7
Median onset interval (days) [range]	1 [0-99]	0 [0.5-44]
LAIV given alone	163 (59)	127 (52)

A report is considered “serious” based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization or permanent disability. A limitation of this classification is that any reporter can classify an adverse event even if it does not appear to be a life-threatening condition, which is one of the criteria for a serious report. It is important to look at the percentage rather than the actual numbers when comparing the results. Of the reports 9% were classified as serious for both vaccines, 46% were males for LAIV4 versus 47% for LAIV3, and the rest of the findings for LAIV 4 and LAIV 3 are comparable.

In comparing adverse events that are of particular interest for LAIV, the grouping of terms were based on MedDRA codes. For anaphylaxis and seizures, the onset interval was 0 (day of vaccination) to 1 day after vaccination. Overall results for LAIV4 are comparable to those of LAIV 3. For the current season, approximately 12.5 million LAIV4 doses were distributed in 2013-2014, and approximately 13 million LAIV3 doses were distributed in 2012-2013 for all ages. There was no disproportional reporting in data mining for the pre-specified terms for the season of Guillain-Barré Syndrome (GBS), seizures, febrile seizures, or anaphylaxis for the 2013-2014 season as of January 31, 2014.

With respect to the top 12 MedDRA terms following LAIV given alone in children ages 2 through 17 years, pyrexia is the most common adverse event for both vaccines. Most of the top adverse events (e.g., cough, vomiting, urticaria, headache) following LAIV4 also appear for LAIV3 for last season. With regard to US reports to VAERS following IIV in those ages 6 months through 17 years, as a reminder this was an in-season comparison between IIV4 and IIV3. There were 121 total reports for IIV4 and 715 for IIV3. Of the reports, 10% were classified as serious for IIV4 versus 7% for IIV3. Gender, median age, median onset interval, and percent IIV given alone were similar for both vaccines. In terms of the adverse events noted for inactivated influenza vaccines, the results were comparable for IIV4 and IIV3. For this season, approximately 12.9 million IIV4 and about 122.6 million IIV3 doses were distributed for all ages. There was no disproportional reporting in data mining for GBS, seizures, febrile seizures, or anaphylaxis for the 2013-2014 season as of January 31, 2014. Regarding the top 12 MedDRA terms following IIV given alone in those ages 6 months through 17 years, injection site erythema was the most frequent adverse event for IIV4 and IIV3. As expected, the most frequent adverse

events were injection-type reactions such as injection site erythema, warmth, swelling, and pain for both vaccines.

Turning to Vaccine Safety Datalink (VSD) surveillance for the 2013-2014 influenza season, Rapid Cycle Analysis (RCA) was performed for the pre-specified outcomes of anaphylaxis, acute disseminated encephalitis, encephalitis, transverse myelitis, GBS, Bell's palsy, and seizures. With the exception of anaphylaxis, the outcomes were neurologic adverse conditions. Interim data for RCA analysis during the current season show that as of January 16, 2014, approximately 194,080 doses of LAIV4 Dose 1 and approximately 3 million doses of IIV3 Dose 1 had been administered. Thus far, there has been limited uptake of IIV4 (19,182 Dose 1 doses), the cell culture-based IIV3, and recombinant IIV3. There were no signals in RCA during the 2013-2014 influenza season for any of the pre-specified outcomes.

Dr. Cano briefly described one of the Clinical Immunization Safety Assessment (CISA) projects, a fever study in children ages 24 through 59 months after LAIV IIV using text messaging for US influenza vaccines. Columbia University and CDC are conducting an observational study of influenza vaccine safety during 2012-2013 and 2013-2014. The primary aim of this study is to assess rates of fever in 24 through 59 month old children receiving LAIV compared to children receiving IIV in the 0 to 10 days after vaccination. Regarding the design, children receive LAIV or IIV per usual care, with or without other childhood vaccines. Temperatures are monitored daily via text messaging. Preliminary data are expected by June 2014.

In summary, no new safety concerns were detected for LAIV4, IIV4, or IIV3 during the 2013-2014 influenza season in persons less than 18 years of age. VAERS and VSD surveillance data were both studied. A comparable safety profile was observed for LAIV4 versus LAIV3 and IIV4 versus IIV3 in persons less than 18 years of age. Influenza vaccine safety monitoring in VAERS, VSD, and CISA is continuing.

Discussion Points

Regarding the top MedDRA terms following LAIV administration, Dr. Karron noted that one of those was injection site erythema and requested that Dr. Cano comment on that in the context of LAIV.

Dr. Cano replied that LAIV is also given with other injectable vaccines, which was why there were local types of reactions.

Dr. Sawyer (PIDS) was surprised by the low uptake of IIV4 in the VSD study population, and wondered whether that was representative of the distribution across the country or if it was an artifact of the VSD sites and decisions by groups like Kaiser to not use that vaccine.

Dr. DeStefano (ISO) responded that he was not familiar with the national data in terms of uptake or coverage with LAIV.

Dr. Rubin asked whether it was possible to break out the VSD data in terms of seizures looking at the younger age group 2 through 8 years of age versus 2 through 49 years of age to determine whether there was any difference in seizures.

Dr. DeStefano (ISO) responded that it is possible to stratify the data in other age groups, but that had not yet been done. The strata shown are the ones used thus far.

For reference, Kim Bradley (GSK) reported that GSK distributed 10 million doses of quadrivalent vaccine during the last season.

Phil Hosbach (Sanofi Pasteur) indicated that Sanofi Pasteur distributed about 7.5 million doses of quadrivalent vaccine. Their estimates from publicly available data are that of all of the quadrivalent vaccines available, which would probably include LAIV4, 80% went into 6 month olds to 18 year olds. Therefore, it seemed as though the data were somewhat off for these groups.

LAIV vs. IIV Comparative Safety Studies in Children

Emmanuel (Chip) Walter, MD, MPH
Duke University Medical Center

Dr. Walter discussed the comparative safety studies in children for trivalent LAIV and IIV influenza vaccine. The Pediatric Influenza Vaccine Safety Evidence Review Group was charged with trying to assist the GRADE process by conducting an evidence review for influenza vaccine safety in children 2 through 8 years of age. This group consists of experts from CDC and CISA. CISA is a collaborative national network of vaccine safety experts from the CDC's Immunization Safety Office (ISO), seven medical research centers, and other partners, which is charged with providing a comprehensive vaccine safety public health service to the nation. CISA conducts research and reviews clinical cases and issues about vaccine safety.

The objective for the evidence review for influenza vaccine safety in children 2 through 8 years of age was to evaluate the evidence for the safety of trivalent live, attenuated influenza vaccine, compared with trivalent inactivated, influenza vaccine in children aged 2 through 8 years using the ACIP GRADE process. The safety outcomes selected and considered to be "Critical" included immediate hypersensitivity/anaphylaxis, febrile seizure, medically-attended wheezing (MAW), and GBS. The safety outcomes selected and determined to be "Important" included other neurologic outcomes and respiratory symptoms.

All of these safety outcomes were discussed intensively in the smaller WG, as well as in the larger CISA WG. Other neurologic outcomes and respiratory tract symptoms, which were GRADEd as "Important," were fairly non-specific. Thus, there were not included in the final safety analysis. Several outcomes were assessed (anaphylaxis, immediate hypersensitivity, febrile seizure, and GBS) that were not selected as final safety outcomes for this review, given that these events are fairly rare or uncommon and there is limited information for review in terms of comparative studies of LAIV versus IIV. The decision was made to keep MAW for review because it is common and clinically important. Fever was added as an outcome for these studies because it is common, it is medically important, it is somewhat comparable across the studies, and it is a potential proxy for febrile seizure risk. SAEs were also added as an outcome because they are considered to be important, they have been used in other safety reviews, and they include some of the rare and less common events.

In terms of the methods used for this evidence review, eight publications directly comparing LAIV to IIV3 were selected for review. These manuscripts were reviewed by members of the work group using grading sheets. The WG reviewed outcome definition, study design, season, ages of study population, sample size, and limitations or potential for biases. For the randomized trials, allocation concealment, blinding, loss to follow-up, failure to adhere to an intention to treat analysis, stopping early for benefit, and failure to report an outcome were assessed. For the observational studies, failure to apply and develop appropriate eligibility

criteria, flawed measures for exposures or outcome, and failure to control for confounding were evaluated. Each study was also reviewed for indirectness in terms of population; intervention; outcomes differing from those of interest; and whether vaccines were each compared with a placebo, but not one another. Assessments were reviewed by the Pediatric Influenza Vaccine Safety Evidence Review Group, CISA investigators, and the ACIP Influenza WG.

Amongst the trials, three were initially chosen but were then excluded for various reasons from the safety assessment. The Clover study was conducted in the years 1986-1987 in a population of children 3 through 19 years of age. It was a double-blind placebo controlled study of approximately 200 children comparing IIV and nasal saline placebo to saline placebo injection and bivalent LAIV. However, no safety outcomes were described in that study so it was eliminated from the safety assessment. The Neuzil study was conducted for the years 1985-1990 in healthy persons 1 through 65 years, and reported on subjects less than 16 years of age. This was a randomized controlled trial; however, in terms of the outcomes of interest in the manuscript, only fever was described. The study was also somewhat problematic in making comparisons in that Group 2 who received the LAIV only containing two Influenza A strains also received an inactivated monovalent B strain, so a head-to-head comparison could not be done. Thus, it was omitted from the analysis. The Holloran study was an open label non-randomized community-based intervention conducted over several years in children 5 through 18 years of age, with a fairly large number of subjects. However, the safety outcomes were not described in this study so it was eliminated from the assessment.

That left five evaluations for the safety assessment. The Ashkenazi and Fleming studies are fairly comparable studies conducted in the same year or same season. The Ashkenazi study was conducted in younger children who had recurrent respiratory tract infections; whereas, the Fleming study was conducted in children 6 through 17 years of age with asthma. They were both open-label randomized studies with about the same number of subjects (N=~2000 in each), and children and adolescents were randomized to get either IIV3 or LAIV. The Belshe paper described a study conducted in the years 2004-2005 that was conducted in children 6 through 59 months of age. This study included some children with wheezing or history of asthma. It did not exclude those children. It was a double-blind placebo-controlled study in which children received either IIV and LAIV placebo, or received IIV3 placebo and LAIV. About 8000 children were enrolled in that study. The Toback and Baxter studies were observational studies conducted over slightly different time periods. The Toback study was conducted in younger children 24 through 59 months of age; whereas, the Baxter study included children in a slightly older age range. These studies were conducted primarily through the Kaiser system, which included fairly large study populations. In terms of the outcomes of interest (fever, MAW, and SAEs), Ashkenazi, Fleming, and Belshe describe those as outcomes. The Toback and Baxter studies can be used to assess MAW and SAEs.

The WG began by assessing fever, thinking that would be a fairly simple outcome. However, fever was described somewhat differently in each study. Each of the articles described fever, and the measurements were different from study to study (axillary or rectal; oral; or axillary, oral, or rectal) depending upon the study. The measurement intervals differed from study to study from 10 to 15 days. Also, how fever was described in the methods differed somewhat from how fever was described in the results. From paper to paper, there were quite different descriptions of fever, making it somewhat more challenging. However, based on the outcomes, a direct comparison can be made in each of the studies children who received LAIV to children who received TIV. The Ashkenazi study measured temperature during an 11-day period. In terms of temperature over 37.5°C and 37.6°C, after Dose 1 and Dose 2 there were not significant differences between the LAIV and TIV groups. The Fleming paper assessed fever over a 15-

day period. They reported four different levels of fever. Recall that these were older children. They only received a single dose of vaccine. Again, there were no observed differences between children who received LAIV and children who received TIV or IIV. The Belshe paper did observe some differences in fever rates. Reported in the paper is Day 2 fever. However, this is broken out over a several day period in the Biologics License Application (BLA). The paper only reported Day 2 fever after the first dose. For fever over 37.8°C there was a significant difference in the rate of fever being 5.4% in the children who received LAIV versus 2% in children who received TIV. For higher fevers over 38.9°C, no difference was reported.

In grading the evidence, the WG assessed the four papers. In the Ashkenazi paper, the population differed somewhat from that of interest. Some of the children were younger, and these were children who had recurrent respiratory tract infections. The Fleming paper was downgraded somewhat because some of the children were older, and asthmatics were also included. In the Belshe paper, some of the children were younger and none of the children were in the 60 to 96 months age range in the population of interest, which is 2 through 8 years of age. In terms of grading the evidence for limitations and potential biases for RCTs, Ashkenazi and Fleming were downgraded because these were not blinded studies. In the Ashkenazi, Fleming, and Belshe studies, there was some loss to follow-up for which the evidence was downgraded.

Moving to the second outcome of interest, MAW, the definitions were somewhat different from study to study, making it somewhat difficult to compare among the studies. The Ashkenazi paper definition was “wheezing episodes observed by a medical practitioner.” The Fleming paper definition was “incidence of asthma exacerbation (acute wheezing illness associated with hospitalization, any unscheduled clinical visit, or any new prescription including rescue medication).” The Belshe paper definition was “presence of wheezing on a physical examination conducted by a health care provider, with a prescription for a daily bronchodilator; respiratory distress; or hypoxemia.” The Toback and Baxter definitions were similar, “asthma and wheezing – asthma/reactive airway disease (RAD) encompassed individual diagnosis of asthma, cough variant asthma, and exercise-induced asthma; the term wheezing/shortness of breath (SOB) included the diagnosis of wheezing and dyspnea/SOB.” The time intervals for each of these events for MAW differed somewhat from paper to paper as well. Ashkenazi admitted the first 10 days after the dosing in their observation period, which one might consider an important time interval to look for MAW after dosing. Fleming looked at the 42 days after each dose, as did Belshe, Toback, and Baxter.

The results for each of these studies were reported somewhat differently, which was confusing. The Ashkenazi and Fleming papers looked at the percent difference in wheezing between the LAIV and TIV groups, and basically they did not observe any difference in wheezing episodes between either of their groups after the first dose, and for the Ashkenazi paper after the second dose. Belshe reported adjusted rate differences in wheezing between the LAIV and TIV groups. There was some difference in the overall group, but when age-stratified, most of that difference was really in those children less than 24 months of age, with the difference being 1.18%. This held true for those who were previously unvaccinated, but not in those who had previously been vaccinated and not after a second dose. This becomes more problematic looking at the observational studies, which assessed hazard ratios, comparing rates of wheezing or MAW in children after receiving LAIV or IIV. The hazard ratios are 0.38% comparing LAIV to IIV, meaning a lower rate in the LAIV group to the IIV group. This was true for the Toback and Baxter comparisons. This really has to do mostly with the current recommendations for how LAIV and TIV are given, meaning that LAIV is not recommended for children who have underlying medical conditions such as asthma; whereas, IIV is recommended. Natural

wheezing episodes would be expected to occur at a higher rate in the IIV group. So, these data are confounded.

In terms of GRADEing the evidence, the population differs from that of interest for Ashkenazi, Fleming, Belshe, Toback, and Baxter. The evidence was downgraded for the Ashkenazi paper because MAW was not reported in the first 10 days after receipt of the vaccine dose. Regarding other limitations for the RCTs, Ashkenazi and Fleming were not blinded. And there was loss to follow-up in all three studies. For the observational studies, Toback and Baxter were downgraded for failure to control for confounding. For SAEs, the definitions differ somewhat and some of the papers were not well-described in terms of what constitutes an SAE. The Fleming and Belshe papers used fairly standard definitions. The time intervals for monitoring SAEs for most of the studies from the time of enrollment through the influenza surveillance period differed, except for the Toback and Baxter papers for which the time interval was 0 through 42 days post-vaccination. Relatedness in most of these studies was determined, with the categories ranging from possibly, probably, potentially. All studies were determined as per investigator in each of the studies.

The rates of SAEs were fairly comparable in the Ashkenazi paper between the LAIV group and the TIV group at 5.8% and 4.7%, respectively. A small number of SAEs were considered related to study product in that particular paper. In the Fleming paper, the rates for SAEs were comparable, with a few of these events in the LAIV group and TIV group being ascribed as related to the vaccine. There was one episode of pneumonia and asthma attack in the LAIV group on Day 2 that was considered vaccine-related. The Belshe paper reported similar rates of SAEs in both groups. They do note in the manuscript that most of the SAEs were hospitalizations. Interesting, hospitalizations usually constitute an adverse event in all studies, the rates were fairly similar in terms of the whole population at 3.1% and 2.9%. However, when age-stratified, for children 6 through 11 months of age, all-causes hospitalization was higher in that group at 6.1% (LAIV) versus 2.6% (TIV). Again, this is outside the age range of interest for this particular evidence review. There were no differences in the other age groups. In terms of vaccine-related SAEs, there were a fair number of respiratory tract events in the LAIV group (e.g., bronchiolitis, asthma exacerbation, wheezing, RAD). Likewise, there were several in the TIV group (e.g., pneumonia, wheezing, febrile convulsion, febrile convulsion and pneumonia, viral gastroenteritis).

In the Toback observational study, the rate of SAEs was slightly higher in the TIV group at 1.14 versus 0.91 per thousand person months. Again, one might ascribe that to the fact that the TIV group is generally a potentially sicker population with more medical compromise or underlying medical conditions. A few vaccine-related SAEs were described in the LAIV group (e.g., one child with RML infiltrate, fever, RSV and one child with intussusception and viral infection). In the Baster article, the rates for SAEs were not noted to be different between the two groups of interest. In the LAIV group there were two vaccine-related SAEs (e.g., one dystonic tongue posturing 3 days post-vaccination, and one Bell's Palsy 2 days post-vaccination).

In terms of GRADEing the evidence for SAEs, the population for all studies differed from that of interest. The limitations for the RCTs were the same as described for the other outcomes. The observational studies failed to control for confounding for SAEs. For the Toback paper, all of the SAEs were described as being diagnosed in the hospital setting, possibly excluding some children who may have had SAEs outside the hospital setting.

In conducting this review, there were several limitations. Few studies directly compare LAIV and IIV. Some studies did not assess outcomes of interest. The definitions for the outcomes of

interest are not standardized, which is a particularly problem for studies. Follow-up intervals varied across studies. The observational studies were somewhat confounded. The findings observed for fever and MAW pertained to only one study during a single season. It is difficult to judge any risk of SAEs from these trials. It is difficult to distinguish if a temporal association between influenza vaccine and an adverse event is coincidental or causal. This review was limited to trivalent influenza vaccines giving according to current indications, and does not include any data on the new quadrivalent products.

In summary, when given according to current indications, there is no evidence for an increased risk of SAEs or MAW after LAIV versus TIV in this age group. There is evidence for some transient increased risk of mild fever after LAIV versus TIV, but this was only noted during one influenza season.

Safety of LAIV versus IIV for Healthy Children (GRADE)

Dr. Lisa Grohskopf
Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Grohskopf expressed her hope that Dr. Walter's presentation set the stage to illustrate that the safety evaluation was somewhat complicated relative to efficacy. Dr. Walter laid out the characteristics of individual studies, while Dr. Grohskopf indicated that she would be discussing the pooling of data from those studies. She emphasized that this is not always easy to do because of the way that definitions and procedures vary across studies. An effort was made to pull out information that is clinically meaningful, but not overwhelmingly complicated.

As outlined in the last presentation, the GRADE assessment for safety of LAIV versus IIV focused on three outcomes (e.g., fever, MAW, and SAEs). The focus of this presentation was on younger children 2 through 8 years of age. For these analyses, observational studies were excluded, because of concerns that differences in the underlying health status of the two populations (e.g., over-representation of less healthy children in the inactivated vaccine groups) may affect the results and interpretation of safety outcomes. This analysis focused exclusively on the RCTs and children 2 through 8 years of age.

Several outcomes related to wheezing, which was valued as a "Critical" outcome. All of the data for these outcomes were provided by the Belshe et al 2007 study, given that it was possible to get a fairly consistent definition across several categories of children who participated in this study. It was also possible to obtain information limited to children 25 through 59 months of age, which the work group thought was important because there has been some concern about the younger children and the occurrence of wheezing in younger populations who are not recommended to received LAIV, but were also included in the Ashkenazi paper.

Children in the Belshe study received either 1 or 2 doses of influenza vaccine, depending upon whether they had previously been vaccinated. Those children who had received influenza vaccine previously received one dose, while those who were vaccine-naïve received 2 doses. The data are reported along the lines of after Dose 1 and after Dose 2, so it was possible to break this out in several ways just as it is in the paper. In terms of data following Dose 1 without regard to previous vaccinations, follow-up was 42 days post-vaccination. These data were restricted to those children aged 24 through 59 months, so they were all within the indicated age

population for LAIV. Considering all of the characteristics that fall under “Risk of Bias” and “Indirectness,” the WG decided that there was not a serious risk of bias or indirectness. They did, however, downgrade the data for imprecision due to the fairly wide confidence interval that straddles 1.0. Overall in this particular slice of the data, there was not a significant difference the risk of wheezing between the two vaccines. The evidence quality for this outcome was assessed as Type 2, or Moderate quality evidence.

Regarding wheeze after Dose1 restricted to children who were not previously vaccinated, there was no significant difference in risk. Results were downgraded for imprecision due to the width of the confidence interval. The point estimate of risk fell more on the side of favoring IIV. However, the confidence interval was fairly broad and straddled 1.0. The evidence quality was again Type 2, or Moderate. In terms of risk of wheeze over days 0 through 42 for children 24 through 59 months olds, again following Dose 1, there was no significant difference in risk for children with a history of previous vaccination. The point estimate falls more on the side favoring LAIV, which might be anticipated because the children were not vaccine-naïve. Still there was a broad confidence interval that straddled 1.0, so the results were again downgraded for imprecision due to the width of the confidence interval, and the evidence quality was again Type 2, or Moderate. With regard to the risk of wheeze over days 0 through 42 for children 24 through 59 months olds, this time following Dose 2, there was no significant difference in risk. The point estimate was actually fairly well over into the side favoring LAIV, although it did cross 1.0 just barely with an upper bound of 1.06. This would still be considered a non-significant difference between the two vaccines. Again, results were downgraded for imprecision due to the width of the confidence interval and the evidence quality was determined to be Type 2, or Moderate.

The outcome of “Fever” was valued as important. As noted in the last presentation by Dr. Walter, fever is complicated in that the definitions and data reported vary. This made pooling of data across studies difficult. Ideally, pooling data from multiple studies allows for larger numbers. However, it was somewhat tricky to determine the best way to do that in this particular circumstance because the definition of fever did vary across the studies and were reported out in different ways. For this analysis, data were pooled from Ashkenazi et al and Belshe et al. The temperature thresholds for fever used in the respective studies differed slightly, but were roughly comparable. For Ashkenazi, the information was reported for fever of 39.6°C, or roughly 101.5°F, and up. For Belshe, the information was reported for fever for 38.9°C, or about 102°F, and up. In this analysis, follow-up was day 0 through day 10, which is somewhat longer than what Dr. Walter reported when discussing some of the earlier fever outcomes such as the slightly increased risk of fever during one seasons for two days post-vaccination. Pooling these data, there was no significant difference in fever risk. The GRADE handbook recommends downgrading for imprecision when the lower bound crosses 0.75 and this goes to 0.73, so the WG made a call to downgrade for imprecision. The evidence quality was determined to be Type 2, or Moderate.

Focusing on SAEs deemed by the study investigators to be related to vaccination, a value was not assigned for this outcome because it is unclear how meaningful it is. There was not readily apparent consensus from the WG about how they would want to value it, but they did feel it was important to consider because some of the more rare and serious outcomes are so rare, it was not possible to get an accurate assessment for them. They were hoping to use this as some sort of proxy to see if they could find anything. However, they did not. The rates of related SAEs were rather low for both vaccines in both studies, leading to a wide confidence interval, for which there was downgrading for imprecision. Overall evidence quality was determined to be Type 2, or Moderate.

To summarize the safety outcomes, no difference was observed for medically attended wheezing, fever, or related SAE. Overall evidence quality was judged to be Type 2, or Moderate. There are several limitations to this assessment, including that as illustrated by Dr. Walter, definitions of the outcomes of interest were not standardized across the studies. Some differences made it fairly tricky to determine how data might be pooled in a way that was both meaningful and would allow for a better assessment and somewhat better power from better numbers. The available studies also were not adequately powered to detect differences in rare but serious outcomes, such as GBS or anaphylaxis. In addition, all of the studies related to trivalent vaccine because that was what was available when these studies were conducted.

Discussion Points

Referring to the first dose in naïve children where the confidence interval clearly crossed 1.0, but it looked like there was a trend, Dr. Karron recalled that in the WG also looked at a shorter interval than 0 to 42 days that was related more to the period of LAIV replication. She thought the FDA had perhaps given them those data, and she wondered how that looked relative to the 0 to 42 day period.

Dr. Grohskopf responded that while it was not included here because strictly speaking it did not meet the criteria for MAW, the Ashkenazi paper reported for days 0 through 11 that they did record wheezing as an outcome. However, it was as reported on diary cards from the parents so there was no practitioner verification that it occurred. The take home point from that was that there was no difference between the two. The WG was able to obtain some information from the FDA with regard to wheezing during earlier intervals for children 24 months and older, which basically following the first 10 days following vaccination showed no difference in the rates of wheezing. Those data came from the Belshe study, which Dr. Grohskopf said she would disseminate following the meeting.

LAIV Update

Kathleen Coelingh, PhD
Senior Director, Medical Affairs
MedImmune, Specialty Care Division of AstraZeneca

Dr. Coelingh first presented information about the relative efficacy of LAIV in vaccine-naïve children, children who have been vaccinated previously, or children who have experienced influenza. Four randomized placebo-controlled studies were conducted during the clinical development of LAIV. All four of those studies were two-season studies. This was absolute efficacy compared to placebo. During the first season of the Belshe study, absolute efficacy was 93%, and during the second season was 100% after revaccination. In the Vesikari study, absolute efficacy was 85% in the first season and 89% in the second season after revaccination. In the Bracco study absolute efficacy was 74% during the first season and the second season after revaccination. In the Tam, absolute efficacy was 73% in the first year and 84% during the second year after revaccination. These studies were performed in children who were not in the exact age group of interest of 2 through 8 years of age, but were generally younger. Also relevant is that in the large Belshe study, which was a head-to-head trial of LAIV versus TIV, children who had been previously vaccinated with IIV were assessed and that was compared to children not previously vaccinated with IIV. The efficacy was similar regardless of whether the children were previously vaccinated. If they were previously vaccinated, the efficacy was 51% fewer cases in the LAIV group compared to the IIV group. When they were

not previously vaccine, the efficacy was 57% fewer cases in the LAIV group compared to the IIV group.

In terms of the supply update, seasonal LAIV is approved in the US for eligible individuals 2 through 49 years of age. It contains $10^{6.5 \text{ to } 7.5}$ fluorescent focus units (FFU) of each vaccine strain per dose. The quadrivalent vaccine was introduced in the US starting in the 2013-2014 season. It contains no preservatives or adjuvants, it is stored refrigerated at 2°C to 8°C, and it is administered as a nasal spray. Over 75 million doses of LAIV have been distributed in the US since its licensure in 2003. In the early years following licensure, production was very modest but increased around 2008 when the product was licensed down to age 2, when it no longer had to be stored frozen in a freezer, and when ACIP recommended routine annual vaccination of all children. There was a large spike in 2009, which was a combination of the pandemic and seasonal vaccines. There was a gradual increase in production for the 2013-2014 season. MedImmune produced 22 million doses during that timeframe, of which about 13 million have been distributed in the US. The plan is to produce about 24 million doses in the upcoming 2014-2015 season, unless additional information justifies either increasing or decreasing that number.

LAIV has been increasingly administered to US children 2 through 17 years of age based on national insurance claims data, excluding the pandemic doses. Over the time period from 2007-2008 through 2011-2012, the use of multi-dose preservative-containing vials decreased from 69% in 2007-2007 to 35% in 2011-2012. In contrast, the use of the prefilled syringes of IIV increased from 19% to 25% during this same period. The use of LAIV increased from 12% to 40% during the same time frame. While the information for the current season is just beginning to come in, it appears that these trends are continuing and that LAIV use is about 44%.

Regarding MedImmune's capacity for responding to LAIV manufacturing compared to a potentially greater demand for LAIV in the US, the estimates assume a 50% overall vaccination rate among US children 2 through 17 years of age for any vaccine type. For the 2013 current season, there has been a demand for LAIV of 16 million doses—13 million in the US and 3 million ex-US. The manufacturing capacity is 30 million doses, so there is a large amount of unused manufacturing capacity. Looking forward to the 2014-2015 season, if there were a theoretical demand that 70% of all children eligible for LAIV would receive it, demand would still be adequately met by MedImmune's manufacturing capacity. With a prediction for 2014-2015 of excess manufacturing capacity, because manufacturing capacity will increase to 35 million doses then. Assuming that going forward in the US, if the goals of Healthy People 2020 are met with a 70% coverage rate, MedImmune will be able to manufacture a sufficient number of doses even with higher market shares due to plans to increase manufacturing capacity to 47 million doses for the 2016-2017 influenza season.

In summary, MedImmune's current and projected manufacturing capacity for LAIV is sufficient for eligible US children 2 through 17 years of age at current and higher future LAIV use, current and higher future vaccination coverage levels, and to meet both US and ex-US demand. Additional increases in demand could be met by further increases in manufacturing capacity.

Discussion Points

Dr. Karron requested further information about the relationship between capacity and supply in any given year, and how those potentially relate to future policy decisions. For example, there might be a situation in which there is a clear preferential recommendation for LAIV in a certain age group. There might be a situation for consideration of use of LAIV in various age groups.

Dr. Coelingh responded that it is difficult to predict what kind of demand would be triggered by a preference in the US. MedImmune chose to look at 70%. Historically when ACIP has made a recommendation for a new vaccine, it does not trigger an automatic movement toward following that recommendation. It always takes a few years for that to go into effect. While it is somewhat of a guess, MedImmune thought that modeling this over the next few years would provide some reassurance that capacity is adequate. MedImmune is using only half of its capacity for the current season, which will expand to 47 million doses for the 2016-2017 season, which would be adequate in their estimation to cover everybody who would be likely to want to get the vaccine.

Dr. Karron pointed out that influenza vaccine is the most perishable vaccine of all, and obviously a company has to weigh demand against capacity and might not produce all that could be produced if it could not be used. What she was driving at was not just in terms of absolute capacity to produce, but also regarded trying to understand more about the forecasting process depending on policy recommendations.

Dr. Coelingh replied that policy recommendations are taken into account, but people do not typically follow recommendations right away. She said that because she was not involved in forecasting, it was somewhat difficult for her to answer that question. Clearly, policy plays a major role in the demand for vaccines and will be even more so going forward with the changes in healthcare.

Dr. Sawyer inquired as to whether there was a coverage rate at which MedImmune would no longer be able to meet the demand, for example, a 70% coverage rate with 70% of those children receiving LAIV.

Dr. Coelingh responded that MedImmune did model that, but she did not include it for simplicity. If the coverage rate is increased to 70% and the market share is also 70%, capacity is adequate.

Ms. Stinchfield (NAPNAP) asked Dr. Coelingh to comment on the true eligible children. The work group talked a lot about those children for whom influenza vaccine is contraindicated, so she wondered what the true contraindications are versus the ACIP statement that talks about healthy children. Defining that clearly impacts who the vaccine is given to, as well as the supply and projected capacity. She thought it was important to highlight the difference between the true contraindications versus healthy 2 year olds and older.

Dr. Coelingh responded that the contraindications in the label, which is issued by the FDA, are for children who are on aspirin therapy or anyone who is allergic to a previous dose of vaccine. Dr. Karron added that in terms of the label and true contraindications, immune-compromised should be included. She wondered whether their colleagues from places where LAIV is being used in children with previous history of wheezing, NACI or the UK DOH, could comment on whether they have any type of registry or data collection to monitor adverse events that occur in this population. LAIV is used differently in some other countries.

Dr. Warshawsky (NACI) responded that Canada does have a vaccine adverse event registry as the US does, which is a passive system for reporting. She was not aware of a particular analysis conducted on LAIV, but she was also not aware of any safety signals. Nothing has been brought to their attention with regard to LAIV and wheezing.

Dr. Salisbury (UK DOH) replied that so far the UK has only been vaccinating 3- and 4-year olds this winter. There is 40% coverage in those two age groups. He also was unaware of any specific adverse events, because so far they have only been using the license-specified indications and contraindications. Anything that may come from use outside of the recommendations has not yet surfaced. The other difference is that the UK is only using one dose in all age groups from 2 years of age and older, on the basis that the incremental advantage of the second dose does not really seem to warrant its use.

Dr. Karron thought that the contraindication for the European product was children with severe wheezing or active wheezing at the time of immunization, which would be outside the label, but it would not exclude children with any history.

Dr. Salisbury (UK DOH) replied that it was closer to the Canadian situation.

With respect to the question regarding forecasting versus planning, Lance Minor (MedImmune Operations Strategy and Planning) reported that MedImmune does plan to produce additional bulk and finished goods material every season above and beyond the expected demand. There are also options mid-season to produce even further.

Proposed Recommendations

Dr. Lisa Grohskopf
Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Grohskopf noted that for the 2013-2014 influenza season, the ACIP Influenza Statement was published in an *MMWR* recommendations and reports document. For next season, 2014-2015, the plan is to return to the smaller policy note format. The current draft of this document was distributed to the ACIP members, and at present contains information on those topics anticipated to remain the same for next season. No changes to the recommendations or groups recommended for vaccination were proposed at this time. Any proposed changes to the recommendations, or new recommendations, will be discussed during the June 2014 meeting. No new influenza vaccine products have been licensed since the last guidance was published. Currently licensed vaccines were listed in the policy note in the draft table, and were essentially identical to those for the current season. This will be updated as any new package inserts come out, and with any new licensures as they occur. Any new licensures will be discussed during the next meeting. During this session, the WG proposed reiterating the core recommendation that annual influenza vaccination is recommended for all persons aged 6 months and older.

In terms of the vaccine strain selection for the 2014-2015 season, WHO recommends the same composition for the Northern Hemisphere 2014-2015 influenza vaccines as for 2013-2014, including the following:

- An A/California/7/2009 (H1N1)pdm09-like virus
- An A/Texas/50/2012 (H3N2)-like virus
- A B/Massachusetts/2/2012-like virus
- For quadrivalent vaccines, these viruses and a B/Brisbane/60/2008-like virus

The FDA's Vaccine and Related Biologic Products Advisory Committee (VRBPAC) will make a final decision regarding the US vaccine composition.

Discussion Points

In terms of proposed changes, Dr. Harrison wondered what information would be available in June that they did not have during this meeting.

Dr. Grohskopf responded that one issue with regard to any language related to LAIV and IIV, even if there were not to be a preference, the GRADE analysis has been done and a summary of that will be presented either in or linked to the policy note. Because the policy note is such a short format document, there will probably be a URL link in the document. Typically, the entire document is not put into the *MMWR*. Another issue regards harmonization with AAP, and AAP will not be meeting on this topic until April 2014.

Dr. Duchin clarified that the Influenza WG is strongly considering a preferential recommendation for LAIV, and it would be beneficial if ACIP members would actively think about that before the June 2014 meeting since they would not be voting on that during this meeting. Many WG members feel that this is long overdue, and a vaccine is available that even CDC has acknowledged on a public webpage as superior in young children. However, the step has not been made to make that recommendation which does influence a lot of healthcare providers.

Dr. Temte inquired as to whether the ACIP members would request that the Influenza WG proceed with language and such a recommendation for a preferential use of vaccine, keeping in mind the timing for clinicians and health systems to place orders. He asked Drs. Neuzil and Duchin, from Washington State where there is a preferential recommendation for LAIV in children, to provide further information on that.

Dr. Duchin responded that unfortunately, their recommendations do not carry the weight of a recommendation from ACIP, and it is not really clear that they have the penetration desired throughout the clinical community. He always takes the opportunity to remind their clinical colleagues that there are data that suggest that LAIV is better in younger children, and that CDC has more or less endorsed those data by posting that on the CDC website without making a formal recommendation. In the context of ordering vaccine, clinicians should keep in mind that there are already data available to suggest that that is a wise thing to do for younger children. There is not a specific cutoff yet, which would be useful. There has not been any issue with shortage. The supply has been adequate, and many physicians are aware but do wait for more clear guidance from ACIP before changing large system practices.

Dr. Harrison requested a sense of AAP's stand on this issue.

Dr. Brady (AAP) responded that AAP has not really discussed this, but will do so in April as mentioned. Therefore, he was unable to say whether there was consensus amongst the group. Some of this information will be presented for the first time during the April meeting.

Dr. Kempe thought that the data seemed strong and compelling in many ways. If, in fact, a preferential recommendation is made, it is going to put front and center the issue of wheezing. While well-defined asthma is fairly straightforward, many young children have wheezed or have wheezed in the last year but do not have a diagnosis of asthma. If ACIP makes a preferential recommendation, she would like to discuss further where the current precaution, not contraindication, came from and whether this can be pinned down better given data of whatever type from other countries, for example.

In terms of the yearly *MMWR* on influenza, Dr. Bennett asked whether Dr. Grohskopf was saying that if ACIP made a preferential recommendation in June, it would be too late.

Dr. Grohskopf replied that it would not. There have been votes in June in the past. It is too late in the sense that ordering has occurred by that point. On the other hand, because there is always so much going on with influenza, the argument can be made that ACIP has to consider issues as they come along and try to keep things moving. It would not be too late to go into the *MMWR*. Among the concerns that some people on the WG have expressed about having a preference, there is the fact that ordering has occurred already, so it would be difficult to implement for the 2014-2015 season. On the other hand, there is precedent for having a recommendation that stated, "Vaccinate this age group if feasible this season. Implement completely by the following season." That can be done.

Catia Ferreira (GSK Medical Affairs) wondered when there would be a review of the efficacy data for the quadrivalent vaccines and the recent study just published regarding the efficacy in the 3 through 8 year old population.

Dr. Grohskopf responded that as usual with influenza, there are many topics to be discussed. This will likely be discussed at a future date, though she did not yet know when that would be.

As a member of the WG, Dr. Loehr (AAFP) respectfully disagreed with Dr. Kempe and suggested that the focus should be mostly on whether a preferential recommendation could be agreed upon versus worrying about the details of wheezing at this time. He requested that ACIP give guidance to the WG regarding what they would need to feel comfortable voting on a preferential recommendation in June, which was what the work group was wrestling with currently. His understanding was that there has not been a preferential recommendation, so he wondered whether there were other issues ACIP would like for the WG to explore before bringing this back to them in June. Many of the work group members would like to have a vote on this, with some language for a preferential in recommendation, in June.

Dr. Rubin said he was compelled with the data as well. As discussed in a previous meeting, one of the hang-ups was that the quadrivalent LAIV was a new product. He would like to see the VSD honed down on the age group that might potentially be given a preferential recommendation to see if there are signals for seizures in particular, and of course quadrivalent inactivated vaccine as well if there are sufficient data.

Dr. Bocchini emphasized that harmonization with AAP is very important so that there is a single message. Therefore, he would like to see what the Committee on Infectious Disease (COID) reviews and to have their input so that ACIP and AAP could potentially move forward in a harmonized way.

Dr. Temte agreed that this would be a very reasonable approach.

Dr. Karron noted that the recommendations as sent to ACIP members had a red highlight for issues related to contraindications with respect to LAIV. She thought that was an issue that the WG was going to specifically consider, and that might arise again during the June meeting. As they voted, she wondered whether there would be a way to incorporate that because those are part of the annual recommendations, yet they may reconsider those.

Dr. Temte said that as part of the minutes, a strong suggestion could be made to the WG to consider those issues as opposed to putting this in the recommendation per se.

Dr. Karron asked for clarification as to whether, if she voted "yes," she would be voting to approve the current recommendations for limitations of use and how that would work.

Dr. Grohskopf replied that her understanding was that for the last several seasons, there has been a footnote in the table of available vaccines that concerns issues surrounding groups for which there is a precaution against LAIV use, for example those with chronic medical conditions and those with asthma. That footnote was red and was marked with a comment in the draft provided to ACIP members, indicating that there would be further discussion about that between this meeting and the next. Her further understanding was also that there would be an opportunity to make changes at any point if necessary and the committee votes on it. For example, there tend to be updates to the tables based on new package inserts and other information.

Dr. Temte noted that there is currently a package insert that states the contraindications and precautions. He expected that those would not be changed.

In terms of background, Dr. Sun (FDA) reminded everyone that there are only certain ways in which the FDA can revise a package insert. The most common way is when presented with data from the manufacturer concerning the specific topic for change. The second method is if specific safety concerns are raised that have come to be known, and that are of such seriousness this needs to be in the label. Those are the only true mechanisms to change labels. MedImmune would have to comment on whether they planned to submit further data or work with FDA to develop such data.

Dr. Karron clarified that currently, the label from the FDA has fairly narrow contraindications. The current ACIP recommendations as she read them lump together the contraindications and the precautions. The question the WG wants to work on regards whether those should be lumped together as one, or because precautions are different from contraindications, whether those should be considered separately. That would not require something from the FDA. That would require ACIP to review what is already in its recommendations.

Dr. Kempe said she personally had enough information to be in favor of making a recommendation in June, but she also thought it was important to get into this more specifically because it is going to put it front and center. She stressed that she did not mean to imply that this would hold up the decision.

Dr. Rubin requested clarification regarding what they were being asked to vote on during this meeting. Best he could tell, it would be only a reaffirmation of last year's statement with a change from 2013-2014 to 2014-2015.

Dr. Temte confirmed that this was correct.

Following up on Dr. Karron's comments, Dr. Sun (FDA) thought it would be beneficial to make a distinction between contraindications and warnings and precautions in the package insert. FDA has very specific definitions of those. According to the FDA a contraindication describes a situation in which the drug should not be used because the risks clearly outweigh any possible benefit, and there is substantial risk of the patient being harmed. These are supposed to be known hazards, not theoretical possibilities. Whereas warnings and precautions merely describe clinically significant information—information that would affect a decision on whether to prescribe that drug, any recommendations for patient monitoring that are critical for safe use of the drug, and any measures that can be taken to prevent or mitigate harm. That is very different from a contraindication in that the risk-benefit may be very different, and then it becomes a judgment call based on advisory committees or healthcare providers.

In response to the question regarding submission of data, Chris Ambrose (MedImmune Medical Affairs) indicated that MedImmune has an active submission with the FDA in which the data have been submitted from the Fleming study that has the safety data in children with asthma, as well as data from the Belshe and Ashkenazi studies with younger children with a history of wheezing or asthma. MedImmune is in conversations with the FDA about this, and looks forward to working with them to determine the resolution of that submission.

Ms. Stinchfield (NAPNAP) noted that with a preferential LAIV but use of existing language that precludes use in children with metabolic disorders, as a clinician she would have a hard time telling a diabetic that this is a better vaccine, but they cannot have it because they are not considered healthy. Wheezing aside, she thought they should be clear about the true contraindications and those precautions that would allow them to open it up for use more.

Dr. Fryhofer (ACP/AMA) pointed out that ordering must be done now, and she thought this would put clinicians in a strange position if they order now based on the current recommendations and then in June, the order does not align with what is recommended.

Dr. Duchin agreed with Ms. Stinchfield, and said he thought it would be a task for the work group to clarify the language and to address those concerns. Many feel that the language is not beneficial the way it is currently described in the statement. Regarding the issue of ordering, there is always a problem with ordering. Things never synchronize, so there are two good vaccines available for children. Clinicians already know that LAIV may be better in younger children, and they can take that into account when they order now, and they can anticipate that they may be seeing some more directive language from ACIP on this. However, it is not going to put them in a very poor position to have more or less LAIV versus IIV either way because both vaccines are good. There is always a transition period when new recommendations are made before everybody comes on board. People may not have the optimal mix that they would desire, but they certainly will have good vaccines they can use in all of their patients either way.

Dr. Temte noted that the biggest problem in his mind was that influenza vaccines are underutilized in general for children, especially school-aged children.

Vote: Reaffirmation of the 2013-2014 Statement for 2014-2015

Dr. Bocchini made a motion to accept the recommendations as proposed. Dr. Duchin seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Bennett, Bocchini, Campos-Outcalt, Coyne-Beasley, Duchin, Harriman, Harrison, Karron, Jenkins, Kempe, Pellegrini, Reingold, Rubin, Temte, and Vazquez
0 Opposed: N/A
0 Abstained: N/A

Meningococcal Vaccines

Introduction

Lorry Rubin, MD
Chair, Meningococcal Working Group
Advisory Committee on Immunization Practices

Dr. Rubin noted that the purpose of this session was informational in order to describe how both licensed and unlicensed meningococcal vaccines have been used in response to recent outbreaks in the US, and that no votes would be taken. The topics discussed during this session included meningococcal disease among men who have sex with men (MSM); meningococcal disease and vaccine response in HIV-infected persons; and use of serogroup B meningococcal vaccines during outbreaks on college campuses.

In terms of additional activities of the work group, the comprehensive meningococcal vaccines statement was published in March 2013. The updated Hib vaccines statement was scheduled to be published February 28, 2014. A Policy Note from a previous vote on the use of Menveo[®] in infants at increased risk for meningococcal disease was scheduled to be published in March 2014. The work group has been involved in early thinking about the approach to recommendations for routine use of meningococcal serogroup B vaccines.

An ad hoc meningococcal work group has been convened that is comprised of ACIP Meningococcal Work Group members, ACIP members, state public health officials, college health professionals, and CDC members. The objectives of this ad hoc work group are to review available data on the recent epidemiology of meningococcal disease and outbreaks; consider options for updating the current meningococcal disease outbreak guidelines; and develop guidance for use of meningococcal vaccines (both licensed and unlicensed) in an outbreak setting.

Meningococcal Disease Among Men Who Have Sex With Men (MSM)

Jessica MacNeil, MPH

National Center for Immunization and Respiratory Diseases

Centers for Disease Control and Prevention

With respect to meningococcal disease, Ms. MacNeil discussed outbreaks that have been reported in men who have sex with men (MSM). The first outbreak occurred in Toronto in 2001. Subsequent outbreaks have been reported in Chicago (2003) and New York City (2012). These outbreaks have all been caused by serogroup C sequence type 11 (ST-11), a common invasive strain of *Neisseria meningitidis* and a frequent cause of outbreak cases. Pulsed-field gel electrophoresis (PFGE) patterns have differed in each of the MSM outbreaks, which suggest that different strains have been responsible in each of those outbreaks.

The largest and most recent outbreak among MSM occurred in New York City and it spanned from August 2010 through February 2012. A total of 22 cases and 7 deaths were reported in this outbreak, the mean age of cases was 34 years, and 55% were HIV-infected. In October 2012, the New York City Department of Health and Mental Hygiene (NYC DOHMH) began recommending meningococcal vaccine for all HIV-infected MSM who met certain high-risk criteria. These recommendations were later expanded to include vaccination of all HIV-infected MSM and MSM regardless of HIV status who had regular close or intimate contact with men and met through an online website, digital application (“app”), or at a bar or party. Meningococcal vaccination of MSM in New York City began in October 2012. Uptake was relatively slow in the target population from October 2012 until March 2013. The final case in the outbreak occurred in mid-February 2013. Increased awareness and press related to the outbreak and vaccination campaign began after the expanded vaccination recommendations in March 2013, which increased uptake over the next several months. During the 5-month period between December 2012 and April 2013, 4 cases of serogroup C meningococcal disease and 2 deaths were also reported among MSM in Los Angeles County. The mean age of these cases was 31 years, and all were HIV-negative.

Little is known about the epidemiology of meningococcal disease among MSM, and most states do not routinely collect information on MSM status during their meningococcal case investigations. With the outbreak in New York City and the additional cases in Los Angeles County, CDC felt that there was a need to better understand the burden of disease and potential risk factors for meningococcal disease in the MSM population. A call for meningococcal cases among MSM was posted on Epi-X on May 14, 2013, which asked states to review all of their meningococcal case reports among males 16 years of age or older occurring between January 2012 through May 2013 to determine if MSM status was recorded. Questionnaires were completed for cases that occurred among MSM which collected demographic, risk factor, clinical, and laboratory information. Cases were classified as either MSM cases residing in New York City (MSM-NYC); MSM cases residing in Los Angeles County (MSM-LAC); MSM sporadic cases (all other MSM cases) (MSM-Sporadic); or Men, not known to be MSM (other men). The MSM population in each reported jurisdiction was estimated using 2012 Census data for males 18 through 64 years of age, and published estimates of the proportion of MSM in the US, which is 3.9%.

All contacted health departments responded to CDC’s request for information. Of these, 45 health departments reported 1 or more meningococcal disease cases in a male between 18 through 64 years of age from January 2012 through May 2013 for a total 235 cases. Of these, 33 reported from 10 health departments were identified as occurring among MSM. Of the 33

MSM cases. 17 resided in New York City, 4 resided in Los Angeles County, and an additional 12 cases identified as occurring among MSM were considered sporadic.

Serogroup C accounted for all of the New York City and Los Angeles County MSM cases, and the majority of MSM sporadic cases. Serogroups B, C, and Y each accounted for approximately 20% of cases occurring among other men, and serogroup W accounted for 7%. Serogroup information for 34% of the cases was unknown. Among the MSM cases, 5 cases (15.2%) has a record of travel within 2 weeks prior to disease onset, 11 (35%) cases reported current drug use, 7 of the 11 who reported current drug use were related to the New York City cluster, the prevalence of smoking among MSM cases and cases among other men was similar, meningococcal vaccination history for MSM cases was largely missing.

HIV prevalence was higher among sporadic MSM cases and MSM cases occurring in New York City when compared to cases occurring among other men. No MSM cases from Los Angeles County were HIV-positive. In terms of the estimated annualized rate of meningococcal disease among MSM and other men, for other men the estimated annualized rates were similar for men living in areas where sporadic cases only were reported and for those living in New York City and Los Angeles County. The estimated rate for MSM living in New York City was 11.7/100,000 and in Los Angeles County was 2.3/100,000. The estimated rate for MSM living in areas where only sporadic cases were reported were 0.24/100,000.

Several considerations regarding estimated rates for meningococcal disease among MSM should be noted. First, most health departments in the US do not systematically collect information on MSM status during case investigations. While this information is sometimes captured during case interviews, the number of meningococcal disease cases occurring among MSM may be underestimated. Additionally, MSM population estimates were not available for the majority of queried jurisdictions, and a single population proportion estimate was uniformly applied across all jurisdictions. Therefore, MSM population denominators may be over- or underestimated for certain geographic areas.

CDC has continued to request passive reporting of meningococcal cases occurring among MSM since May 2013. During that time, 10 additional cases have been reported from 7 states. Of these, 6 were serogroup C, 3 were serogroup B, and 1 was serogroup Y. None of these states has met the current outbreak definition of more than 3 cases of the same meningococcal serogroup occurring in less than a 3-month period that results in a primary attack rate of more than 10 cases/100,000 persons.

In conclusion, outbreaks of meningococcal disease do occur among MSM. A small increase in risk was identified among MSM living in areas where only sporadic cases were reported. However, the overall burden of disease is low. In addition, a high proportion of MSM-sporadic cases were also HIV-infected. The ACIP Meningococcal Work Group does not propose recommendations for vaccination of all MSM in the US at this time. ACIP recommendations for HIV-infected persons will be discussed in the following presentation. CDC supports state and local health department recommendations for vaccination during identified outbreaks, and continued study is needed to better understand transmission and risk factors in the MSM population.

Meningococcal Disease and Vaccine Response in HIV-Infected Persons

Jessica MacNeil, MPH

National Center for Immunization and Respiratory Diseases

Centers for Disease Control and Prevention

Regarding meningococcal disease in HIV-infected persons, Ms. MacNeil HIV pointed out that HIV is an established risk factor for several bacterial infections. However, the current incidence of meningococcal disease and HIV infection in the US has made evaluating the risk for meningococcal disease in HIV-infected persons challenging. HIV infection is not an indication for routine vaccination in the current ACIP recommendations; however, if a HIV-infected person is vaccinated the recommendation is that they should receive a 2-dose primary series.

Data on the relationship between HIV and meningococcal disease has historically been limited. An analysis of surveillance data from 1988 through 1993 from an 8-county Atlanta metropolitan area found that HIV-infected adults had a nearly 24-fold increased risk for meningococcal disease¹. More recently, a study from Group for Enteric, Respiratory and Meningeal disease Surveillance in South Africa (GERMS-SA)² reported that the incidence of meningococcal disease for HIV-infected persons was 11 times greater than that among HIV-uninfected persons, and HIV-infected cases had a higher case fatality ratio [¹Stephens DS, Hajjeh RA, Baughman WS, Harvey RC, Wenger JD, Farley MM. Sporadic meningococcal disease in adults: results of a 5-year population-based study. *Ann Intern Med.* 1995; 123:937-40; ²Cohen C, Singh E, Wu HM, Martin S, de Gouveia L, Klugman KP, et al; Group from Enteric Respiratory and Meningeal disease Surveillance in South Africa (GERMS-SA). Increased incidence of meningococcal disease in HIV-infected individuals associated with higher case-fatality ratios in South Africa. *AIDS.* 2010; 24:1351-60].

A chart review of HIV-infected meningococcal disease cases reported through the Active Bacterial Core surveillance system (ABCs) has recently been completed. Incidence calculations from this analysis were limited to cases that met the CDC-AIDS surveillance case definition because name-based HIV reporting was not available in all of the states during the study years. During 2000 through 2008, 32 HIV-infected meningococcal disease cases were reported in ABCs sites. Of these, 25% were caused by serogroup B, 39% by serogroup C, and 29% serogroup Y. In the four years since the review was completed, an additional 9 cases of meningococcal disease have been reported in HIV-infected persons in ABCs.

HIV-related clinical data were collected for meningococcal cases with HIV infection as part of the expanded chart review. In general, patients presented with a wide range of CD4 counts and several had a history of an AIDS defining condition or met the CDC AIDS surveillance case definition. The majority were also reported to currently be taking highly active antiretroviral therapy (HAART) at the time of meningococcal disease presentation. Of the 32 cases, 17 met the CDC AIDS surveillance case definition and were included in the incidence calculations. Meningococcal disease incidence among persons with AIDS was 3.48/100,000 compared to 0.28/100,000 among persons not meeting the CDC AIDS case definition, with a rate ratio of 12.6.

In New York City, meningococcal surveillance data was matched to death and HIV registries, and as part of the study and age-matched case-control analysis was also performed among HIV-infected persons, which included a subset of cases with CD4 count and viral load measurements near the time of meningococcal disease. In New York City during 2000 through 2011, 40 HIV infected meningococcal disease cases were reported. Of these, 33% were

caused by serogroup C, and 48% by serogroup Y [Miller L, Arakaki L, Ramautar A, Bodach S, Braustein S, et al. Elevated Risk for Invasive Meningococcal Disease Among Persons with HIV. *Ann Intern Med.* 2014; 160:30-38]. Incidence of meningococcal disease among persons infected with HIV was calculated for an incidence of 3.4/100,000 in HIV-infected persons, compared to 0.34/100,000 among HIV-uninfected persons for a risk ratio of 10. A higher case fatality ratio was observed among HIV-negative cases compared to HIV-positive cases. The risk of meningococcal disease decreased during the study period for both HIV-infected and HIV-uninfected persons in New York City. Meningococcal disease incidence among HIV-infected persons decreased from 4.7/100,000 in 2000 through 2002 to 1.9/100,000 in 2009 through 2011. An increased incidence was also observed for both HIV-infected women and men, although the risk ratio was slightly higher for male cases compared to female cases. In the case-control study among persons with HIV, patients with meningococcal disease were 5.3 times as likely as age-matched control patients to have a low CD4 count and 4.5 times as more likely to have a high viral load [Miller L, Arakaki L, Ramautar A, Bodach S, Braustein S, et al. Elevated Risk for Invasive Meningococcal Disease Among Persons with HIV. *Ann Intern Med.* 2014; 160:30-38].

To summarize the epidemiologic data, there is an increased incidence of meningococcal disease in HIV-infected persons. Among HIV-infected persons, a low CD4 count or high viral load increases risk. However, risk of disease is declining along with meningococcal disease incidence in the US. Data on the case-fatality ratio for HIV-infected meningococcal disease cases is mixed.

Regarding vaccine response in HIV-infected persons, rates of seroresponse to a single dose of MenACWY-D at Week 4 by serogroup were compared in HIV-infected and healthy adolescents. The data for HIV-infected adolescents were based on approximately 300 adolescents included in the study, and the proportion of HIV-infected adolescents with more than a 4-fold increase in rSBA titers at Week 4 was 52% for serogroup C and 63% for serogroup Y. For HIV-infected adolescents who received a single dose of MenACWY-D, the response was significantly lower for those with either a low CD4 count or a high viral load [Phase I/II, Open-Label Trial of Safety and Immunogenicity of Meningococcal (Groups A, C, Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine in Human Immunodeficiency Virus-Infected Adolescents. *Pediatric Infectious Disease Journal.* 29(5):391-396, May 2010].

In terms of the geometric mean titers (GMTs) for serogroup C, for those with low CD4 counts at study entry, despite a second dose of vaccine at 24 weeks, response remained low through 72 weeks. In subjects with higher CD4 counts at study entry who received one dose of MenACWY-D, after an initial response at 4 weeks, GMTs waned rapidly. In subjects with higher CD4 counts at study entry who received a second dose of MenACWY-D, response waned quickly after both Dose 1 and Dose 2. While the overall the response of GMTs to serogroup Y was higher than for serogroup C, the same pattern of rapidly waning titers was observed. In terms of the percent of subjects who still had antibody at Week 72, or approximately 1.5 years after 1 or 2 doses of MenACWY-D, the primary study endpoint was the percent of subjects with rSBA titers greater than 1:128. For serogroup C, titers waned to 21% to 35% and for serogroup Y, titers waned 63% to 71%. The proportion of subjects with rSBA titers greater than 1:8 were slightly higher for each group than subjects with rSBA titers 1:128 [Immunogenicity and Safety of 1 vs 2 Doses of Quadrivalent Meningococcal Conjugate Vaccine in Youth Infected with Human Immunodeficiency Virus. *The Journal of Pediatrics.* 161(4):676-681. October 2012].

In summary, seroresponse to MenACWY-D in HIV-infected adolescents is suppressed compared to healthy adolescents. A low CD4 count or high viral load suppresses the response even further. In addition, immune response to MenACWY-D wanes rapidly and although a boost response is seen to second dose, duration of protection is still an issue.

In conclusion, there was a modest increase in absolute risk of meningococcal disease among HIV-infected adults of about 2 to 4 cases/100,000 persons, but the risk is declining over time. As a comparison, the incidence of pneumococcal disease in adults with AIDS was 298 cases/100,000 in 2007 in the US¹. Overall, the number of preventable cases is low. Given current incidence of both meningococcal disease and HIV infection in the US, the total number of meningococcal disease cases in HIV-infected persons is likely low, and the duration of protection from vaccine is short in HIV-infected persons. The Meningococcal Work Group does not propose changes to the current ACIP recommendations for HIV-infected persons at this time [Cohen AL, Harrison LH, Farley MM, Reingold AL, Hadler J., et al. Prevention of invasive pneumococcal disease among HIV-infected adults in the era of childhood pneumococcal immunization. *AIDS* 2010, 24:2253-2262].

The rationale for the Meningococcal Work Group's support of no changes to the recommendations is that persons with HIV are at lower risk compared to other recommended groups (e.g., microbiologists, complement component deficiencies, et cetera); however, the risk is lifelong and there would be a need for multiple booster doses. In addition, it is not known if persons vaccinated when CD4 counts are high will be protected when CD4 counts decline. A cost-effectiveness analysis has not been done for the use of meningococcal vaccines in HIV-infected persons, but would likely not impact the work group's conclusions.

Discussion Points

Dr. Harrison inquired as to whether there were any data on immunogenicity in HIV-positives with MCV4-CRM.

Ms. MacNeil responded that she did not believe any data were available on that. There is nothing published.

Dr. Zahn (NACCHO) pointed out the importance of getting a sense in all communities of how many cases occur in the MSM community. Los Angeles County wrestled for a while with 4 cases in a community of 10 million. Los Angeles County concluded that there was nothing and they did not make recommendations compared to New York City, but they received a lot of noise from the community regarding whether they should do something. Local counties make recommendations about vaccinations. For example, meningococcal vaccination is considered to be a travel vaccine, so multiple counties in California made recommendations that MSM who were traveling to New York City should be vaccinated. The point is that from what he saw in the data in New York City, whatever was occurring there seemed to be subsiding. His thought was that we are a lot better at letting people know that there is an issue as opposed to letting them know that it is subsiding. Making that clear so that local counties and providers can make recommendations about whether any of this is necessary anymore would be worthwhile.

Ms. MacNeil indicated that these data would be published in the *MMWR* in a couple of weeks.

Dr. Duchin inquired as to whether the work group's deliberations identify any areas that would help or lead to changes in the approach to outbreaks among communities where there are high numbers of HIV-infected persons.

Ms. MacNeil replied that the work group had not discussed this issue specifically, but has been discussing outbreak guidelines in general for institutional and community settings.

Dr. Reingold asked whether there had been a study assessing risk factors predicting meningococcal disease in MSM in terms of their behaviors, such as use of bath houses. He was curious what New York City's recommendations were based on.

Ms. MacNeil responded that there have not been any formal studies. CDC did try to acquire some of that information through the Epi-X, but she did not believe they were aware of any specific behaviors for MSM that would present an increased risk.

Dr. Cohn (SME) added that New York City's specific recommendations were based on the epidemiology investigations they conducted. They found that numerous of these cases had recently used some of these apps and had been visiting these bars that they were trying to target.

Dr. Harrison pointed out that there is a lot of behavioral data in the non-MSM population to show that behavioral risk factors are very important (e.g., drinking, going to pubs and discos, kissing).

Dr. Temte asked whether the rates of vaccine uptake were known for these two populations for other vaccines that are commonly recommended (e.g., hepatitis B, recommended suite for HIV).

Dr. Schuchat said she did not believe there were great data. Years ago, there were some data on pneumococcal polysaccharide vaccine in HIV-infected individuals that was in the 50% range or so. However, she was not aware of the hepatitis data for instance. She thought some of the coverage surveys tended to group immunosuppressive groups together so that they do not identify those with HIV. However, CDC can check to determine whether there are data and if so, will make those available.

Dr. Reingold noted that historically in San Francisco, it has been difficult to get men to take all three doses. The follow-up after the first dose has been very strong and the coverage with three doses remains quite low.

Dr. Zucker (NYC DOHMH) indicated that from their perspective, and the persistent increased risk for invasive meningococcal disease in their MSM and HIV populations, they are currently struggling with what to do about recommendations going forward. In fact, NYC DOHMH is leaning toward the need for a routine recommendation for meningococcal vaccine in this group, and has had internal deliberations as well as with partners. A large population would there would have an indication for vaccine. The department was somewhat disappointed that there had not been a more formal review in GRADE, and deliberation by the full work group regarding whether there should be a recommendation. NYC DOHMH has also struggled with whether they should be out in front of ACIP on this recommendation. While they appreciated the results and conclusions, they requested that a more formal consideration and GRADE review of those recommendations.

Dr. Bennett asked whether the vaccination status of the cases was known, given that many of them may have been young enough to have received previous meningococcal vaccine.

Ms. MacNeil replied that the vaccination status of most of them were unknown.

Use of Serogroup B Meningococcal Vaccine During Outbreaks on College Campuses

**Manisha Patel, MD, MSc, Medical Officer
Meningitis and Vaccine Preventable Diseases Branch
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention**

Dr. Patel presented on the use of serogroup B meningococcal vaccine during outbreaks on university campuses. The incidence of meningococcal disease in the US has been steadily decreasing, and reached an all-time low in 2013 with a provisional count of 519 cases among all serogroups. Serogroups B, C, and Y cause the majority of disease, with each serogroup contributing to about a third of cases. Although outbreaks of meningococcal disease are typically caused by serogroup C, recently serogroup B outbreaks have been observed, particularly on college campuses. Meningococcal disease rates peak in less than 1 year olds and again in adolescents and young adults between the ages of 16 through 21 years. The peak in adolescents occurs similarly for all serogroups, and possibly reflects the frequency of exposure to people from whom one can acquire carriage. With the recommendation of conjugate MenACWY vaccines for adolescents in 2005, serogroup B now accounts for the highest incidence of disease in this age group. Over the past five years, five serogroup B outbreaks on college campuses have been reported to CDC. Universities 1 and 2 both had small clusters in which cases occurred within a relatively short time of each other. The epidemiology at University 3 differed in that the outbreak spanned over two academic years. With the availability of a meningococcal serogroup B (MenB) vaccine in 2013, there was now a potentially different approach to control the outbreaks at Princeton University and University of California—Santa Barbara (UCSB).

Eight cases of MenB were reported among Princeton University students or persons with links to Princeton University from March through November 2013. The attack rate was 134/100,000 among undergraduates, which was more than 1400 times higher than the background incidence rate for 17 through 22 year olds in the US. There have been no fatalities, but there were 2 cases with sequelae, including 1 with a neurocognitive deficit and 1 with partial hearing loss. Although laboratory testing demonstrated that all of the strains isolated from the cases were identical by sequence type, PFGE patterns, and molecular antigen typing, there was no direct epidemiologic link between cases. Cases were reported in all 4 class years among students living in dorms, and occurred 2 to 4 weeks apart during the academic year over an 8-month period.

With this evidence of sustained transmission in a large population at risk in which the majority of students reside on campus, Princeton University, the New Jersey Department of Health, and CDC decided to implement a vaccination campaign to prevent additional cases. Although there is no currently licensed MenB vaccine in the US, Pfizer has a MenB vaccine currently in development. Novartis, the manufacturer of Bexsero[®], a recombinant MenB+OMV NZ (rMenB), had its vaccine recently licensed in Europe, Australia, and Canada. Effectiveness was inferred based on immunogenicity of a 2-dose series, with an immune response seen after 1 dose. Safety data in almost 1600 adolescents showed that greater than 10% reported non-serious adverse events; however, no serious adverse events were reported. rMenB contains 4 antigenic components (fHBP, NHBA, *NadA*, *PorA*). The isolates from Princeton expressed 2 of the 4 antigens (fHBP and NHBA) in sufficient quantities to suggest protection with rMenB. Additional testing demonstrated that isolates from 4 of the cases was killed by pooled post-immunization sera.

Based on recent licensure of rMenB elsewhere, a good safety profile, and the concern for occurrence of additional cases upon commencement of the new academic year at Princeton University, CDC and FDA began to explore the use of rMenB in outbreak settings under an expanded access Investigational New Drug (IND) Protocol in August 2013. Expanded access INDs provide investigational products for serious or life-threatening conditions when there are no otherwise adequate approved alternatives. Expanded access INDs are not intended for product development or clinical trials. As part of the IND submission process, Novartis performed testing of isolates between September and November 2013 to determine vaccine antigen matching. CDC and the New Jersey Department of Health conducted an epidemiologic investigation at Princeton in October 2013 to identify the target population. The IND was officially submitted in November 2013, and included a safety monitoring plan, consents, vaccine information sheets, and data collection instruments. Approval by both FDA and CDC Institutional Review Boards (IRBs) shortly followed. Additionally, negotiations and contractual agreements between the various stakeholders were finalized in early December 2013.

The recommended population for vaccination included all undergraduate students, graduate students living in dorms, other persons with medical conditions putting them at increased risk for meningococcal disease, and spouses or parents living with undergraduates in dorms. The total number of people in the target population was 5772. To date, there have been 3 vaccination clinics. The first dose clinic was held over a 4-day period in December 2014, and the second dose clinic was held the week of February 17-20, 2014. Over 75 people from Princeton University, Maxim Healthcare, and CDC were onsite during these clinics. High coverage was seen for both doses, with 95% of the target population receiving the first dose and 88% of first-dose recipients receiving the second dose. An additional catch-up clinic is planned for March 2014.

Mandatory reporting of all SAEs is required to FDA and includes death, a life-threatening AE, hospitalizations, substantial disruption in the ability to conduct normal life functions, or a congenital anomaly or birth defects. To date, the rate of SAEs reported is 2.0/1,000 vaccinees following the first dose and 0.2 /1,000 vaccinees following the second dose. No SAEs have been determined to be causally related to rMenB. Additionally, there have been no concerning patterns among other types of AEs reported to date.

In November 2013, 4 cases of MenB with no direct epidemiologic links occurred among undergraduate students at UCSB. All 4 cases recovered, with complications in 1 case patient resulting in bilateral foot amputation. During the epidemiologic investigation, an additional case associated with UCSB was identified in March 2013. This suggested that there was sustained transmission of MenB occurring at the university and that vaccination would be an appropriate strategy to control the outbreak. The attack rate was 21.1/100,000 or 230-fold higher than the background incidence rate for 17 through 22 year olds in the US. Isolates from the 4 cases were ST-32 with identical antigens. There were two different PFGE patterns, which is thought to be due to horizontal gene transfer between the circulating strains, and thus still considered to be the same outbreak strain. Although this strain is different from the Princeton strain, additional testing of isolates from 3 of the cases demonstrated killing using pooled rMenB post-immunization sera.

Due to the concern that additional cases would occur, a CDC-sponsored expanded access IND was approved by FDA for use in the UCSB outbreak. The target population was similar to Princeton University and included all undergraduates, graduate students or faculty living in dormitories, and others with high-risk conditions for meningococcal disease. The estimated target population was approximately 20,000 people. The first dose campaign began February

24, 2014 and will continue through March 7, 2014. A second dose clinic is planned for April 2014. A safety surveillance plan is in place in collaboration with UCSB and CDC.

Although the primary objective for implementing a vaccination strategy is to prevent additional cases, there are a number of challenges associated with using an unlicensed vaccine to control outbreaks. The IND preparation process is unique for each setting, and must address the specific epidemiologic and laboratory findings for each outbreak. There are also specific safety monitoring requirements that must be followed when using an unlicensed product under an Expanded Access IND. There are also the logistics of vaccine procurement, and implementation requires participation from multiple stakeholders in order to conduct a campaign in a timely and effective manner. Despite these challenges, both Princeton University and UCSB demonstrated extraordinary efforts in rapidly standing up these campaigns.

Although an increase in MenB outbreaks in college campuses is not expected, CDC has recently formed a Meningococcal Outbreak Work Group comprised of ACIP Meningococcal WG members, ACIP members, state public health officials, college health professionals, representatives from university administration and the insurance industry, and CDC to address potential issues related to management of these outbreaks. The objectives are to review the available data on the recent epidemiology of meningococcal disease and outbreaks; consider options for updating the current meningococcal disease outbreak guidelines; and develop guidance for use of meningococcal vaccines (both licensed and unlicensed) in an outbreak setting.

In summary, vaccination now possible in response to MenB outbreaks. Implementation of an unlicensed vaccine requires coordinated efforts between the institution, state and local health departments, the manufacturer, FDA, and CDC. An ACIP outbreak workgroup is currently developing guidance for management of MenB outbreaks. This interim guidance will be presented during the June ACIP meeting.

Discussion Points

In each of these cases, Ms. Pellegrini wondered which entity was responsible for drawing up and submitting the IND to FDA.

Dr. Patel responded that for the CDC-sponsored IND, CDC is the principal investigator and each site has its own site investigators.

Dr. Zahn (NACCHO) pointed out that a lot hinged on the one UCSB case that occurred in March. He inquired as to how common this specific strain is. If it is a common type, one could argue that this was a random event that did not necessarily attach to everything else.

Dr. Patel responded that ST-32 is the second most common MenB strain seen in the US. The key is that the PFGE patterns were similar to the outbreak cases. The other issue is that it is not possible to predict what will happen, which is one of the greatest issues. In the setting of having a vaccine potentially available, all stakeholders were interested in pursuing that route.

Dr. Pickering said he believed in Canada, MenB was the major serogroup causing disease in all people, not only infants. He inquired as to whether there was any history of travel to Canada in the Princeton group, particularly in the early cases.

Dr. Patel replied that for Princeton, there was one traveler to Greece. None of the others traveled outside of the country. This is not known for UCSB.

Dr. Warshawsky (NACI) confirmed that serogroup B is Canada's most common serogroup largely because they control serogroup C, and is still a very rare disease in Canada. As mentioned, the Bexsero[®] vaccine was recently authorized for use in Canada and the NACI plans to issue recommendations in the next few weeks.

Dr. Harrison inquired as to how it was determined that the PFGE variability was due to horizontal gene transfer as opposed to single nucleotide polymorphism (SNPs) in the restriction site.

Dr. Patel indicated that there was a complicated discussion with the laboratories involved.

Dr. Cohn (SME) added that that was the hypothesis. Additional genetic analyses are underway to assess SNP variation and sequencing. The preliminary suggestion was that the isolate from March may be a progenitor for both of these two strains, but there is a lot more work to be done.

Dr. Clark (SME) added that the PFGE patterns were dramatically different in multiple bands, so this seemed like some large event rather than small ones, but that is just a hypothesis.

Dr. Plotkin (Vaccine Consultant) said he was surprised not to hear any carriage studies, and that it would be extremely interesting to know whether the MenB vaccine has any effect on carriage and, indeed, to know how widespread the organism was at Princeton or UCSB. Related to that, it would be interesting to know what the carriage rate is in group C in MSM related to the previous discussion. He pointed out that the advantage of the conjugate vaccine is to affect carriage, so that there might be some argument for using the conjugate vaccine in population with widespread carriage regardless of the rate of active disease in order to terminate an outbreak more quickly.

Dr. Temte noted that as someone who does a lot of nasal swabs for influenza, coupling a vaccine clinic with 97% attendance with a nasal swab would provide an incredibly rich set of data to assess issues such as carriage.

Dr. Duchin requested further information about the visitor to Princeton University, such as whether the individual was a non-student or there was anything remarkable that would explain why that person would become part of the outbreak.

Dr. Patel responded that this student was visiting the campus as part of an athletic recruitment. In April, the university has Princeton Preview where students spend a day or night with Princeton students. This was somewhat different in that this student engaged in social behaviors and activities similar to other college students in general, and then developed disease shortly after that.

Dr. Duchin inquired as to whether any consideration had been given to changing the surveillance form, or the recommendations, or working with the Council of State and Territorial Epidemiologists (CSTE) on the national surveillance for meningococcal disease to include HIV status and/or sexual preference.

Dr. Cohn (SME) replied that all of these are under consideration. Changes to national reporting forms are complicated and can take a long time to implement. Consideration is being given to recommendations for what data state and local health departments can collect on their own. How they report that may be challenging.

Dr. Harriman indicated that some state health departments have already made this decision. For example, California is now collecting this information routinely and trying to go back in time to get it for as many as they can. However, this is not something that always comes up or is discussed necessarily. Having that asked regularly might be an issue, but an effort is being made.

To expand on Dr. Duchin's question, Dr. Clark (SME) said he thought the prospective student was the exception in that this person was a resident in the dorm for just a couple of days. The risk is not zero to visitors, but it is quite low. One concern that was expressed was the risk of ongoing transmission when students return home, and whether the outbreak would spread. There is no indication that that occurred, as there were no secondary cases. Consideration has been given to carriage studies, and Dr. Dull could comment on what is known about the impact of this vaccine on carriage. CDC has discussed and is still thinking through carriage surveys after vaccination, but in this case, IRB approvals would have to be in place and the urgent goal was to stand up the vaccination program.

Peter Dull (Novartis) thanked CDC and the organizations that brought this effort to happen. He thought it was a great example of collaboration with FDA, manufacturers, recommending bodies, and various state health departments. However, he cautioned everyone that this is not a sustainable solution for outbreaks of MenB. Aside from the work with FDA approving the IND and setting up the campaigns, the manufacturers are not in surge capacity such that they can label and ship unlicensed vaccine to someplace in the US very quickly. These outbreaks occurred fast, and it is necessary to have a more sustained solution for this. Novartis is actively talking to FDA about how to get this vaccine licensed in the US as well. Novartis has conducted a large carriage study in the UK, with approximately 3000 subjects enrolled. They showed some data during a conference in the UK last fall that showed some effect on MenB carriage with the Bexsero[®] vaccine. In order to see a true impact on a herd effect, there would have to be broader implementation, but there is an early assessment of the impact on herd immunity with this vaccine.

Dr. Temte indicated that between the meningococcal and pneumococcal sessions, public comments would be presented.

Public Comment

Frankie Milley
Founder / National Director
Meningitis Angels

I just want to say thank you for all the work that this body did to make sure that these kids were protected, and you stopped this outbreak at these two universities. I also want to say that I think moving forward, and my opinion and \$5 will get a cup of coffee most places, okay, and I know my opinion compared to the people that sit here at this table every day and work hard to make sure that we're all protected, is nothing in comparison. But, I would really encourage this committee moving forward that we make sure that we don't pick and choose groups that should be vaccinated against other groups that should be vaccinated. I think moving forward, as we do

have new and better vaccines, more vaccines to cover meningococcal disease, especially in infants, we need to move forward with recommendations to protect infants all the way through that recommended ACIP group plus MSMs and anybody else who might be at risk. I also believe that we risk too many lives when we wait for an outbreak somewhere. You know, we've seen it in Oologah Elementary School. We've seen it recently in Princeton and California. We need to be proactive. Public health is the best thing—the best money—that we can spend in this country. I firmly believe that if we put our money into public health, vaccinations and public health, that our health care bills are going to go down and health care overall will go down—the cost. It's the best money we can spend. Again, thank you for allowing us to have a say in these committee hearings.

Robin, Keith, and Gregory Kephurt Parents of a Child Who Developed Pneumococcal Meningitis

Hello. My name is Robin and this is my husband Keith and my son Gregory. We also have a daughter Kayla, at home staying with friends.

I would like to start off reading a paper that Kayla wrote recently as an assignment for school. The assignment was about a formula, if you could create a formula what would it be? Here is her shortened version of her 3rd grade response with no help from us. She nailed many of what we are dealing with Gregory because of his illness with meningitis.

“I seek a formula that will make my big brother able to walk. Gregory was diagnosed with meningitis when he was a baby. Gregory is in a motorized wheelchair. Gregory needs braces on his arms and AFO's on his legs and feet. Gregory plays soccer for kids with disabilities. He is the only one in a gait trainer. Gregory and I have a cat named Oliver and a dog named Apollo. Greg is funny, fun, sweet and kind. Gregory would not have so many seizures. He would have seizures when he was sick. If Gregory could walk he could pet Apollo and Oliver like the rest of us. He could feed himself with no help. It would be so much easier for my dad to get him up and down the stairs. He can have fun with me in the sandbox. He would be able to give me a hug by himself. He could ride more rides at Disney. He can play more games with my friends and I instead of sitting with the parents. He could play tag and hide and seek. If it works, I hope for all of the boys and girls that have disabilities to be able to walk. I hope that Gregory can walk soon.”

There was a shortage of the vaccine. My son was unable to get his booster. He developed pneumococcal meningitis. As a result, Gregory suffered brain infarcts with traumatic brain injury. His ongoing diagnosis includes spastic quadriplegia, dystonia, seizure disorder, learning disability and speech delays. He is unable to care for himself, is not potty trained and wears diapers, cannot feed himself, cannot sit unsupported, or even walk. He will need therapy for the rest of his life. He will need one-on-one aide to help assist him with simple everyday task such as feeding, dressing, changing his diaper, transfer him from wheelchair to bed and other things, and as simple as hold a toy or whatever he wants to hold. He will need hip surgery in the near future.

Is it cost-effective for the booster? Let's look at the financial burden we had to pay due to Gregory's illness. His anti-seizure meds are \$800/month. His therapy bills are over \$1000 a month. His ongoing doctor appointments with all the specialists to manage his ongoing care and treatment. He requires braces and AFO's annually because he is still growing. His motorized wheelchair is \$20k. An accessible conversion van is additional \$25k. To date we have incurred close to 1/2 million dollars in medical expense. Gregory is on both of our

insurance through our employer. We maximize our out of pocket expense every year. All this could have been prevented had Gregory received his booster for a vaccine preventable disease. Think of how many lives we could save with the 1/2 million we spent on care of Gregory. One child is too many.

I am pleading with you not to change the dosing schedule as we may see more children like Gregory, or worse, more children die. Thank you.

Trish Parnell
Parents of Kids with Infectious Diseases (PKIDS)

Last summer, I read an article in *Pediatrics* that looked at the cost-effectiveness of using two, rather than three, primary doses of 13-valent pneumococcal conjugate vaccine. We talked about this at PKIDs, and, while we were surprised, we thought it was probably more of an intellectual exercise than a course of action that our public health leaders in the US would take. After all, our tradition in the US is to use all of the tools we have to protect our citizens and prevent infections. But, here we are, looking at this as a real option. If a primary dose is removed, we may have an opportunity to save money, \$400 to \$500 million, but it's not a risk-free deal. In order to save that money, we have to be willing to see harm come to a lot of people. This flies in the face of what we, as immunization advocates, say every day to the folks we meet, which is: "Get immunized!"

Use the safe and effective prevention tools that we have. It's easier to make this kind of decision and to talk about the numbers of folks who will be harmed if it's not personal. But, as goes ACIP, so goes the nation when it comes to prevention through immunization. We have to consider the personal side of this decision. We can't dehumanize our people, our loved ones, friends, and neighbors, by thinking of them only as numbers. If the third primary dose is removed, an average of 2.5 more people will die each year. Who are those people? One could be my niece, Millie, who's just learning to crawl. Another could be your grandson, who loves cheerios and bananas.

Forty-four more people will get invasive pneumococcal disease. My daughter could get meningitis, and your son could get a bloodstream infection. Fifteen hundred more people will be hospitalized for pneumonia. When my oldest was a toddler, she was hospitalized for pneumonia. It's a terrifying experience and one that I would not have anyone else go through, if possible. An additional 10,000 of our friends and neighbors and loved ones will have to be treated for pneumonia as outpatients. Twenty three hundred more ear tubes will have to be inserted into the tiny ears of children that we know. A staggering 261,000 more children will get earaches, fevers, and possibly ruptured eardrums. All of this happens if we decide to save money and remove a primary dose of PCV13. It's all about the numbers. We just have to decide which numbers are more important to us as a nation—the dollar amounts or our people?

Pneumococcal Conjugate Vaccine (PCV) Session

Introduction

Nancy M. Bennett, MD, MS
Pneumococcal Vaccines Working Group Chair
Advisory Committee on Immunization Practices

Dr. Bennett introduced the pneumococcal conjugate vaccine (PCV) session by outlining the Pneumococcal Vaccines Work Group's terms of reference, which are as follows:

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

The focus of this session was the routine infant immunization schedule for 13-valent pneumococcal conjugate vaccine (PCV13), and the emerging evidence supporting use of a 3-dose PCV13 schedule. A 3-dose PCV13 schedule is approved by the European Medicines Agency (EMA) and other licensing bodies. The World Health Organization (WHO) recognizes a 3-dose schedule as an acceptable alternative to a 4-dose schedule [Pneumococcal vaccines WHO position paper, *Wkly Epidemiol Rec*, 2012]. A 3-dose schedule is routine in many low-income countries. At least 21 high- and 13 upper-middle income countries have also introduced PCV13 or PCV10 with 3 doses or have switched from 4- to 3-dose schedule. It is important to recognize that the value of a 3-dose schedule is being observed throughout the world.

The evidence supporting the use of a 3-dose PCV schedule is emerging, the perceptions among parents that the vaccine schedule has become crowded and confusing, and safety concerns that too many simultaneous injections are being given have grown^{1,2}. This may lead an increasing number of parents to delay or refuse recommended vaccines³. Rare safety issues associated with co-administration of routine vaccines are emerging (e.g., febrile seizure with co-administration of PCV; diphtheria, tetanus, and pertussis (DTaP), and influenza vaccines) [¹Bardenheier *Arch Ped Adol Med* 2004, ²Gust *Pediatrics* 2008, ³Freed *Pediatrics* 2010].

Another issue that has driven the WG to consider this change is that PCV7 use has led to dramatic reductions in disease burden in the US, including invasive pneumococcal disease (IPD) and pneumonia in children and adults and reductions in otitis media in children. PCV7 serotypes have virtually been eliminated from all age-groups, which is a remarkable accomplishment, and the US now has a mature PCV program. Disease due to PCV13 serotypes is also rapidly declining. Evidence supporting the use of 3-dose PCV schedules is emerging. PCV7 use led to dramatic reductions in disease burden.

Dr. Bennett emphasized that this would be an information-only session, with no specific recommendations presented at this time. The session included review of the GRADE of evidence, discussion of ACIP's questions from October 2013, and discussion of considerations for including a 3-dose PCV13 schedule for infants. The following questions were posed to the

committee subsequent to the presentations: Is the evidence adequate to consider including a 3-dose PCV13 schedule for infants? If not, what additional data or information would be required?

Update on PCV13 Effectiveness and Herd Effects in the US

Matthew R. Moore, MD, MPH
Captain, USPHS
Medical Epidemiologist

Dr. Moore reminded everyone that CDC monitors IPD using active, population-based surveillance conducted in 10 areas around the United States (US) through the Active Bacterial Core surveillance (ABCs). ABCs is part of the Emerging Infections Program (EIP) at CDC. Rates of IPD over time have been evaluated. Subsequent to the introduction of PCV13, the focus has been primarily on the impact of that vaccine on 5 additional PCV13 types not affected by PCV7. There is a focus on those 5 additional serotypes because it is known that the 7-valent vaccine included an antigen against serotype 6B, but that antigen actually has activity or cross-protection against a serotype that is not included in the vaccine, 6A. 6A is also included in the 13-valent vaccine. PCV7 includes serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. If the 8 serotypes are removed that are affected by PCV7, the 5 additional serotypes remain.

Evaluation has also been done for emergence of serotype replacement. This occurs initially at the level of the nasopharynx when children are vaccinated with pneumococcal conjugate vaccines. These vaccines eliminate carriage of vaccine types and are replaced by non-vaccine types. With the PCV7 experience, what was observed over time was that some of those non-PCV7 types began to cause invasive disease. Monitoring began for a similar type of effect after PCV13 introduction. In addition to discussing these evaluation efforts, Dr. Moore presented an update on individual-level vaccine effectiveness (VE) evaluated among children 2 through 59 months of age using a case-control method.

Regarding annual trends in IPD from 2006 through 2013, a major reduction has occurred among children less than 5 years of age in disease caused by the additional serotypes included in the 13-valent vaccine, which is driving the reduction in the overall invasive disease. Because there has not been much uptake in 13-valent vaccine in adults, especially not in adults 18 through 49 years of age, it is believed that much of what is being observed in reductions in adults is related to use in children and the prevention of transmission of those vaccine types from children to adults. The picture is slightly different in adults 50 through 64 years of age, with a decline in the additional serotypes in PCV13 after vaccine introduction in 2010 and the suggestion of an increase in the non-vaccine types that are not included in the 13-valent vaccine. A similar pattern is observed among adults 65 years of age and older.

When a modeling approach is used to estimate percent changes in disease in each of these groups, the general pattern is that the largest reduction observed following the first year after vaccine introduction was in children under 5 years of age. Reductions were lower for unvaccinated populations and older age groups through the herd effect. In each successive year, the reductions were larger than in previous years. This shows that with each successive year of use of PCV13, reductions continue to be seen in the additional vaccine types affected by PCV13. This is all very good news. With respect to the non-PCV13 types, it was only in 2012-2013 and in the 50 through 64 year old age group that a small and statistically significant increase was observed in non-vaccine types in that particular age group. This is not present in any of the other age groups. When all of these data are combined (e.g., the residual effects on the 7-valent types, the new effects on the additional types in PCV13), even after accounting for

the small increase and the changes in all groups, IPD is still moving in the right direction. That is to say that in each of these age groups, there are primarily statistically significant reductions, especially in the latter years in the older age groups. If that is evidence of serotype replacement in the 50 through 64 year olds, it is not overshadowing the continued reductions being observed in those serotypes included in PCV13.

As of June 2013, approximately 30,000 cases of IPD have been prevented following PCV13 introduction, roughly a third among children under the age of 5, about a quarter among adults 65 years of age and older, and about a quarter in adults 50 through 64 years of age. Approximately 3,000 deaths from IPD have been prevented over the first three years of the program. Relatively smaller numbers of children actually die of IPD compared to adults. This is why, when the distribution of the deaths prevented is examined, most deaths are being prevented in adults who are not actually receiving the vaccine—again speaking to the herd protection of the vaccine.

Regarding the ongoing case-control study of PCV13 effectiveness, children 2 through 59 months old with IPD residing in 10 ABCs areas, New York City, Los Angeles County, and Utah have been enrolled. From May 2010 through September 2013, the program enrolled 760 cases. Of these, 224 (29%) had PCV13-type IPD and 209 (93%) were caused by serotypes 19A, 7F, and 3. Also enrolled were 3,519 controls (3 controls per case). Preliminary data show that receipt of 1 or more doses among controls increased from 38% in June through November 2010 to 96% in May through September 2013. Compared to data presented during previous ACIP meetings, there are now individual level estimates of serotype-specific effectiveness. Evaluation of the individual serotypes shows vaccine effectiveness of about 90% for serotype 19A, 100% for serotype 7F, and about 76% for serotype 3. All of these are statistically significant, so these data are encouraging.

In summary, reductions are being observed in IPD caused by the additional serotypes in PCV13 among all age groups, which is indicative of direct and indirect effects. There is early evidence of increases in non-PCV13 serotypes in adults 50 through 64 years of age, which is possibly suggestive of serotype replacement—an experience that was similar with PCV7. The increases in non-PCV types are not overshadowing the reductions in the PCV13 types. There is now preliminary evidence of serotype-specific effectiveness for the 3 most common PCV13 serotypes. Additional analyses are pending.

Discussion Points

Referring to Slide 8, Dr. Michael Decker (Sanofi Pasteur) submitted that the data suggested that there was an increase in the lower three age groups (e.g., the positive numbers in the right hand column). The sample size is simply not large enough to offer a confidence limit that does not cross null. The point estimates for all three of those is a positive number. Therefore, he cautioned against excluding the possibility that the point estimates are actually telling the truth. He noted that Dr. Moore said that only the one in red differed, which was not true.

Dr. Moore clarified that he said that only the one in red was statistically significant, but said that Dr. Decker's point was well-taken.

Dr. Vazquez inquired as to whether there was a trend in the non-vaccine type disease type toward a specific type of illness (e.g., pneumonia, bacteremia) or particular serotype.

Dr. Moore replied that an assessment had not yet been done to determine whether a particular syndrome was rising to the top. With respect to individual serotypes, what was being observed were very small and not statistically significant increases in any individual serotype. At least six or seven appear to be somewhat higher than they were before, but each of those increases is very small. The statistically significant change was observed in that particular group only when the serotypes were all added together.

Recalling the data presented earlier in the morning about last year's influenza season being more severe than usual, Dr. Gorman (NIH), wondered whether that would have impacted the numbers for this year.

Dr. Moore responded that it appears that in some of the ABCs areas, there was at least a temporal relationship between influenza activity and increases in some of the non-vaccine types. However, this was not consistent across all sites and in some of the sites there was no increase in non-vaccine types at all. That was not necessarily associated with an absence of influenza. There may be the beginning of a signal, but he would not call it a clear-cut message.

Reduced Dose Schedules of PCV13 for Children: GRADE of Evidence

**Sara Tomczyk
EIS Officer
Respiratory Diseases Branch
NCIRD, CDC**

Ms. Tomczyk presented the results of the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) process evaluating the evidence for 3-dose schedules of the 13-valent pneumococcal conjugate vaccine. The policy question posed was: Should a 3-dose schedule of PCV13 be recommended for generally healthy infants in the US? This presentation addressed the GRADE process and GRADE conclusions. The GRADE process begins with defining the population, intervention, comparison, and outcome (PICO).

The population of interest for this policy questions was comprise of children 2 through 15 months of age with no underlying chronic medical conditions present. The interventions and the comparisons were addressed in two different steps. In step one, all evidence was graded for each PCV schedule compared to no vaccine to assess the strength of the evidence supporting each individual schedule as if policy decisions were considered pre-PCV7. Thus, the intervention for step one included the currently used schedule of 4 doses of PCV13 given at 2, 4, 6, and 12 through 15 months (3+1) and two different 3-dose schedules with 3 doses given at 2, 4, and 6 months (3+0) or at 2, 4, and 12 through 15 months (2+1). The comparison was no PCV13 or a placebo. In step two of the GRADE process, only studies with direct comparisons of schedules available within each study were graded. This included the 3-dose schedules of 3+0 and 2+1, as compared to the currently used 4-dose schedules (3+1).

A modified Delphi process was used to rank the importance of possible outcomes. A survey was conducted of WG members and their colleagues, practitioners, and public health professionals. Pediatricians (14; 29%) and public health professionals (21; 44%) represented the majority of the 48 total respondents. The respondents were asked to rank a list of outcomes 1 through 9, and the rankings were used by the work group to select "critical" or "important" outcomes for which GRADE review of evidence would be conducted. Outcomes rated 7 to 9 were determined to be "critical" for decision-making according to GRADE guidelines in step one (e.g., mortality, IPD, bacteremic and non-bacteremic pneumonia, serious adverse events, and

indirect effects on IPD). Indirect effects ranked slightly below the critical outcomes threshold, but the WG determined that it was still critical. Pneumococcal meningitis and hospitalizations were also ranked as critical, but were incorporated primarily in the IPD outcome. Additional outcomes ranked but not included because of low ranking were office visits for pneumococcal disease, vaccine-type carriage, systemic adverse events, local reactions to the vaccine administration, and cost-effectiveness. In step two, any outcomes with studies providing direct comparisons between schedules were included as determined by the work group (e.g., immunogenicity or antibody response as surrogate for IPD, lower respiratory tract infection, and acute otitis media).

Ms. Tomszyk presented the GRADE framework for each step. For step one, she presented a summary of included studies and assessed the quality of evidence for each schedule and by outcomes. Randomized controlled trials (RCTs) were selected first for each schedule and outcome. When data from RCTs were not available for an outcome and schedule, observational studies were considered. The data combined for all outcomes were then used to determine the overall type of evidence for each schedule. Lastly, values and preferences of outcomes were considered according to the a priori rankings of outcomes and a judgement on recommendation category of each schedule was made. Step two was organized according to comparisons between the schedules 3+0 versus 3+1, 2+1 versus 3+1, and 2 versus 3 primary doses; and the identified outcomes including immunogenicity data as surrogates for IPD, lower respiratory tract infection, and acute otitis media. The final recommendation category was judged for each 3-dose schedule (3+0 and 2+1) as compared to a 4-dose schedule (3+1).

Starting with step one to present the GRADE of evidence for each schedule compared to no vaccine to assess the strength of evidence supporting each schedule, for the 3+1 schedule and IPD and pneumonia outcomes, 4 RCTs were included in the US, US Navajo community, Finland, and Brazil. These studies evaluated the efficacy of PCV7 and PCV10. Vaccine efficacy for IPD ranged from 83% to 100%. Vaccine efficacy for radiographic confirmed pneumonia ranged from -8% to 20.5%. A focus was placed on chest radiographic confirmed pneumonia for all of the pneumonia outcome data.

For estimates of baseline disease incidence among unvaccinated, pre-PCV7 incidence per 100,000 population was used of PCV13-type IPD or all-cause pneumonia among US children less than 2 years of age. The pooled vaccine efficacy estimates were applied for vaccine-type IPD and pneumonia based on the studies shown previously to the baseline incidence to estimate incidence among the vaccinated per 100,000 population. Using these data, the absolute risk difference per person and numbers needed to treat or vaccinate calculated. On a 3+1 schedule, PCV had a 94% vaccine efficacy for IPD and 11% vaccine efficacy for pneumonia, and the number needed to treat or vaccinate estimate showed that 613 people need to be vaccinated in order to prevent one case of IPD. Numbers needed to treat for pneumonia was not meaningful because the VE estimate was not statistically significant.

To evaluate the indirect effects of PCV introduction on IPD at the population level, data were used from a pooled analysis of 21 surveillance datasets among countries with different PCV7 schedules. In spite of the differences in surveillance methods and extent of catch-up, the effect estimates across all countries were between 0.20 and 0.80 or 80% to 20% reduction in vaccine-type IPD among adults despite a few estimates in Canada and the Netherlands that were not statistically significant. PCV use in children has led to large indirect effects on IPD among adults of all age groups in countries using PCV on 3+1 schedule.

In the GRADE process, the evidence type for 3+1 schedule data was determined by first assigning an initial evidence type as follows: Type 1 included mainly RCTs or overwhelming evidence from observational studies, type 2 included RCTs with important limitations or strong evidence from observational studies, type 3 included observational studies or RCTs with even more notable limitations, and type 4 included clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations. Next, the initial evidence type could be downgraded or upgraded according to pre-specified GRADE criteria, including: risk of bias, inconsistency, indirectness, imprecision, and other considerations such as strength of association, dose-response, opposing plausible residual confounding or bias. Evidence could be downgraded minus 1 or 2 when any GRADE criterion was serious or very serious. It could be upgraded plus 1 or 2 if the strength of association was large or very large and there was no apparent risk of bias.

Thus, for the 3+1 schedule, the type of evidence was assessed according to the GRADE criteria. Both for IPD and pneumonia, the WG started with 3 RCTs and there were no serious concerns for any criteria, so the type of evidence for both outcomes was determined to be 1. For indirect effects, the 3 surveillance studies were a part of a pooled analysis, so the initial type of evidence was 3 and it was upgraded by 1 due to strength of association and no apparent risk of bias for a final evidence type of 2. The key point here is that there is high quality evidence which shows that the 3+1 PCV schedule is effective against IPD and pneumonia and, in addition, has demonstrated large indirect effects.

For the 3+0 PCV schedules, for invasive pneumococcal disease and pneumonia, 3 RCTs were included. These were conducted in South Africa, the Gambia, and the Philippines. These studies evaluated efficacy of PCV9 and PCV11. Vaccine efficacy against IPD ranged from 77% to 83%, and for radiographic confirmed pneumonia ranged from 23% to 37%. As before, data from included studies were used to obtain pooled VE estimate for each outcome, which were then applied to the baseline (pre-PCV) incidence rates among US children less than 2 years of age for each outcome to calculate incidence among the vaccinated per 100,000 population. PCV had a 74% vaccine efficacy for IPD and 26% for pneumonia. The number needed to treat or vaccinate estimate showed that 779 people need to be vaccinated in order to prevent one case of IPD, and 370 people need to be vaccinated in order to prevent one case of pneumonia.

To evaluate the indirect effects of PCV introduction on IPD at the population level for 3+0, the same pooled analysis of 21 surveillance datasets was used. This included Australia, which has used the 3+0 schedule. The effect estimates ranged between 0.20 and 0.50 or 50% to 80% reduction in IPD rates. The key point here is that the use of PCV on a 3+0 schedule among children in Australia also resulted in large reductions in IPD among adults of all age groups.

The abstracted data were then used to determine the evidence type for the 3+0 schedule. For both IPD based on 2 RCTs and pneumonia based on 3 RCTs, there were no serious concerns for any criteria, so the type of evidence was determined to be 1. For indirect effects, based on surveillance data evaluation from one country using a 3+0 schedule, the initial type of evidence was 3, but it was upgraded by 1 due to strength of association and no apparent risk of bias for a final evidence type of 2. The key point to be made after the review of data supporting the 3+0 schedule is that there is high quality evidence which shows that PCV use on the 3+0 schedule leads to large benefits, is effective against IPD and pneumonia, and has demonstrated large indirect effects.

For the evidence review supporting 2+1 schedule, for the IPD outcome 1 RCT was included that was conducted in Finland evaluating efficacy of PCV10. In that study, vaccine efficacy for IPD was 92%. For pneumonia outcome assessment, 3 observational studies were included that were conducted in Quebec, Canada; Italy, and Poland. Studies in Canada and Poland evaluated impact of PCV7 introduction on chest x-ray confirmed pneumonia in children. The Quebec study demonstrated a 72% reduction in lobar pneumonia before and after introduction of PCV7 on 2+1 schedule. In Poland, there was a reduction in radiographic confirmed pneumonia 4 years after PCV7 introduction on 2+1 schedule, with 65% in 0 through 1 year olds and 23% in 2 through 4 year olds. The study in Italy was a large cohort study, which showed a 65% vaccine efficacy for radiographic confirmed pneumonia.

As presented for 3+1 and 3+0 schedule, vaccine efficacy estimates for each outcome were applied to the baseline (pre-PCV7) incidence of PCV13 type IPD and all-cause pneumonia among US children less than 2 years of age to calculate incidence among the vaccinated per 100,000 population. PCV had a 96% vaccine efficacy against IPD and 70% against pneumonia. The number needed to treat or vaccinate estimate showed that 600 people need to be vaccinated in order to prevent one case of IPD, and 139 people need to be vaccinated in order to prevent one case of pneumonia.

To evaluate the indirect effects of PCV introduction on IPD at the population level for the 2+1 schedule, the same pooled analysis of 21 surveillance datasets was used. The effect estimates across all countries were between 0.20 and 1.20 or 80% reduction to no change in cases; and the estimates in Switzerland, Denmark, and Scotland were not statistically significant. Although there was some variability, there was also good evidence that the use of PCV on a 2+1 schedule leads to large reductions in IPD among adults.

The abstracted 2+1 data were then used to determine the evidence type for 2+1 schedule. For IPD, the evidence relied on 1 RCT and there were no serious concerns for any criteria, so the type of evidence was 1. For pneumonia and indirect effects, observational studies were used but the type of evidence was upgraded by one due to the strength of association for a final evidence type of 2. The key point here is that there is high quality evidence which shows that PCV use on the 2+1 schedule is effective against IPD and pneumonia, and has strong indirect effects which have been observed in several countries using PCV on this schedule.

The take-away point for the mortality outcome was that mortality due to IPD is low in high-income countries, including the US. None of the studies were powered to detect the impact of any schedule on this outcome, so the WG was unable to assess the impact of PCV schedules on mortality.

The last outcome in step one was serious adverse events, which was assessed across all schedules and by dose number where possible. Three different types of evidence were used to grade this outcome. Evidence comparing PCV13 to no vaccine were not available. Thus, data comparing PCV13 to PCV7 as part of PCV13 licensure application and comparisons between PCV7 and the Meningococcal C vaccine from 1 RCT conducted in the US were used. Additionally, an observational study was included to assess the incidence and timing of febrile seizures associated with PCV13 alone and when co-administered with influenza vaccine.

Using the data from the Prevnar[®] licensure application, a comparison was made of incidence of overall serious adverse events between PCV13 and PCV7 groups. There were 3 deaths in the PCV13 group and 1 death in the PCV7 group. In the PCV13 group, the date of death included: one 3 days post-dose 1, one 14 days post-dose 2, and one 76 days post-dose 3. In the PCV7

group, the date of the one death 13 days post-dose 1. For overall serious adverse events, there were small differences between the two groups. Investigators believed that these serious adverse events were related to the vaccine. Regarding the incidence of deaths in the PCV7 group as compared to the control group, in the PCV7 group, there were 4 deaths or 0.2 cases/1000 children. In the control group, there were 8 deaths or 0.4 cases/1000 children or 8 deaths in the control group. Although investigators reported that these deaths were not related to the vaccine.

The WG also reviewed a published study using Vaccine Safety Datalink (VSD) Project data that evaluated the risk of febrile seizures in children following a co-administration of influenza vaccine and PCV13. Risk difference estimates varied by age due to the varying baseline risk for seizures in young children, with the highest estimates occurring at 16 months, around the time when PCV booster is administered. The risk differences peaked at 13.7 per 100,000 doses for PCV13 without co-administration of the influenza vaccine, and at 44.9 per 100,000 doses for both the influenza vaccine and PCV13. The lowest estimates occurred at 59 months. Overall, there are many unique vaccine combinations given, so it may be difficult to estimate the risk for each combination due to lack of statistical power. Additional analyses assessing different vaccine combinations and comparing risks within different age groups are ongoing and will be presented to this committee at a future date.

The evidence type was then determined for serious adverse events. Fourteen RCTs were included for an evidence type 1. However, due to indirect comparisons made where PCV13 was compared to PCV7 and PCV7 was compared to a control vaccine, the evidence type was downgraded by 1 for a final evidence type of 2. The key point here is that PCV appears to be safe across all schedules.

Next, the evidence types were combined per outcome for each schedule to assess overall evidence type by schedule. The lowest evidence quality from critical outcomes assessed for each schedule was used. Thus, each schedule was supported by type 2 or strong evidence. The WG next considered prevailing values and preferences. WG members determined that the values and preferences were high for IPD, pneumonia, and serious adverse events, but were of relatively lower value for indirect effects.

Lastly, the data were assembled to make a judgment of recommendation category for each schedule. WG members were asked to respond to the following 4 questions:

1. In response to the question: Is the evidence quality low? The work group determined that evidence quality supporting each schedule was high.
2. In response to the question: Are the net benefits low or is there uncertainty about the balance of benefits versus harms? The WG determined that there was no uncertainty about each schedule providing protection against critical outcomes.
3. In response to the question: Is there variability or uncertainty in what outcomes are important to prevent? The WG agreed on which outcomes are important to prevent.
4. In response to the question: If there is uncertainty about whether the net benefits are worth the costs? The intervention was determined to be cost-effective. Cost-effectiveness studies for PCV have been conducted and published, and for the sake of time these data were not presented again during this session.

These answers indicate that each schedule is supported by a category A recommendation, which is a recommendation for which the desirable effects clearly outweigh the undesirable effects. Overall, the GRADE process suggests that if policy decisions had to be made to recommend PCV on either schedule for the first time, the data would support the use of any of these schedules.

In terms of step two of the GRADE process focusing on the GRADE of only studies with direct schedule comparisons, most of the direct schedule comparisons were obtained from immunogenicity studies. Data were abstracted on IgG antibody concentrations and the proportion achieving a response with concentrations $\geq 0.35 \mu\text{g/mL}$ following the primary series of PCV or following a booster dose for each schedule. A threshold of $\geq 0.35 \mu\text{g/mL}$ is a reference point which was developed for antibody comparisons in infant vaccine trials to support an IPD indication. Comparisons between schedules were made using: 1) Risk ratios comparing % ≥ 0.35 between groups, and 2) Ratios of geometric mean concentrations (GMCs) in each group.

For step two, immunogenicity RCTs with direct schedule comparisons included were studies conducted in Israel, the United Kingdom (UK), one across Europe, in Fiji, in Iceland, and in Gambia. Four studies had comparisons between 2+1 or 3+0 versus 3+1, while two studies had comparison between 2 versus 3 primary series. PCV7, PCV9, and PCV10 were evaluated in these studies.

Regarding the comparison of immunogenicity data for 3+0 versus 3+1 showing proportions with antibody levels $>0.35 \mu\text{g/mL}$ for each group, and the risk ratio comparing the percentage above the threshold and GMC for 3+0 versus 3+1, antibody levels for 3+0 schedule were assessed post-primary, or at approximately 7 months, and for 3+1 were assessed post booster at approximately 13 months. Three serotypes (6B, 23F, and 1) had a significantly lower proportion above $0.35 \mu\text{g/mL}$ threshold in the 3+0 schedule group as compared to 3+1. For all serotypes, GMCs were significantly lower for 3+0 schedule. These results highlight a strong boosting effect observed when the last dose is given in the second year of life following a primary series. However, it is important to note that both groups had high proportions above the $0.35 \mu\text{g/mL}$ cut-off.

In the same comparisons for 2 versus 3 primary doses, the response in each group was measured approximately 1 month post-last dose. No serotypes showed differences by the percentage above the threshold, and two serotypes (6B and 23F) had a significantly lower GMC for 2 compared to 3 primary doses. However, again, both groups still had high proportions above the $0.35 \mu\text{g/mL}$ cut-off. In the comparison for 2+1 versus 3+1, only one serotype (6B) had a significantly lower proportion above 0.35 cut-off for 2+1 schedule, as compared to 3+1 and two serotypes (6B and 18C) that had a significantly lower GMC ratios. However, again, both groups still had high proportions above the threshold.

To summarize the key points for immunogenicity, the proportions $\geq 0.35 \mu\text{g/mL}$ are high for schedules with 3- and 2-dose primary series. Post-primary, the 3-dose schedule appears to be better than 2-dose schedule for some serotypes according to the GMC ratio data. In the second year of life (pre-booster and post-booster dose), there were small but significant differences for some serotypes according to the GMC ratio data. The differences appeared to be more pronounced after the primary series and when comparing GMC values or ratios rather than proportions $\geq 0.35 \mu\text{g/mL}$.

However, it is also important to draw attention to some caveats that need to be considered with respect to the immunogenicity data. Regarding a cut-off of 0.35 µg/mL, WHO determined a cut-off value that correlated with protection against IPD through various stages. First, the results of the US PCV7 trial showed that a 0.2 µg/mL cut-off post-dose 3 correlated with 97.3% vaccine efficacy against IPD. Later, data from two RCTs were added, one PCV7 trial among American Indians that showed a cut-off value of 1.0 µg/mL which correlated with 76.8% VE, and one PCV9 trial in South African infants which showed a cut-off value of 0.68 µg/mL which correlated with 90% VE. After adding data for these 3 trials, the aggregate cut-off value was raised to 0.35 µg/mL. What these data illustrate is that children at a higher risk for pneumococcal disease, such as those with HIV, may require higher antibody levels to achieve an equivalent protective efficacy. The key point here is that the cut-off for IPD of 0.35 µg/mL is likely higher than necessary US population of generally healthy infants.

Overall, the GMC cutoff of 0.35 µg/mL should be interpreted with caution. It was developed as an aggregate cutoff for all serotypes combined and its clinical significance is not established for individual serotypes, post-booster measurements of antibody levels, and for non-IPD endpoints. In addition, GMC ratios presented to compare the schedule should also be interpreted with caution because they do not take into account absolute values for antibody levels for groups compared. For example, the values of 2 versus 4 µg/mL and 0.35 versus 0.7 µg/mL have the same GMC ratios. The key point here is that differences may not always be meaningful and it is important to look at both the ≥ 0.35 µg/mL and absolute values.

Thus, for all immunogenicity comparisons, the type of evidence is 1 because the evaluation started with RCTs and no serious concerns were noted across the GRADE criteria. Two observational studies were also identified with direct schedule comparisons in the US using PCV7 on lower respiratory tract infection (LRTI), and on acute otitis media. Although it should be noted that acute otitis media was not ranked as one of the critical outcomes in step one.

The first observational study using a propensity-score-matched case-cohort design in the US evaluated the rate of hospitalizations and ambulatory visits for pneumonia in a 2002 birth cohort, comparing 2 versus 3 primary doses. The study found that there was a statistically significant rate difference of 7.8 cases per 1000 children or fewer pneumonia-related admissions in those who received 3 doses versus 2 doses. This difference disappeared after the booster dose was administered. The same study was repeated for 2003 birth cohort. Post-primary, 3+1 had greater incidence as compared to 2+1, but the absolute rate difference was not statistically significant. Post-booster, 3+1 had lower incidence as compared to 2+1 but again the absolute rate difference was not statistically significant. It is difficult to interpret these results, given that pre-booster, the 2-dose primary series had lower rates and post-booster, the 3-dose primary series had lower rates. As mentioned before, none of the differences are statistically significant. The authors of the paper concluded that there were no differences observed between schedules for this 2003 birth cohort. They hypothesized that by 2003, or 3 years after introduction of PCV7, herd effects had lessened the difference in risk between the two groups.

The second observational study compared the incidence of acute otitis media in children born in 2002 who received two or three doses in the primary PCV7 series using propensity score matched data from an insurance claims database. The study assessed acute otitis media rates after completion of the primary series and before the booster dose, and after the booster dose until four years of age. The results showed that pre-booster dose incidence rates were 0.38 per person for children receiving 2-doses primary series and 0.35 per person for children receiving 3-dose series, but these rates were not statistically different. Post-booster incidence rates were

also not statistically different between the groups. The key point here is that there were no differences between schedules with 2 versus 3 doses in the primary series pre- or post-booster.

The direct comparisons of clinical pneumonia-related hospitalizations and acute otitis media were observational studies, so the initial evidence type of both started as 3 and remained this type because no GRADE criteria were applied for downgrading or upgrading. The key point here is that there are limited studies with direct head-to-head comparisons and clinical endpoints, so the evidence quality for critical outcomes is low.

Using the evidence type tables presented by schedule and outcome, the overall evidence type was determined for each schedule. The lowest evidence quality from critical outcomes assessed for each schedule comparison was used. Thus, all schedules had a type 3 evidence. WG members determined that the values and preferences were high for pneumonia, but of relatively lower value for acute otitis media and immunogenicity. Immunogenicity data was ranked as relatively lower value because the clinical significance of these surrogate data is not established for non-IPD outcomes, post-booster dose, or individual serotypes.

Lastly, the assessment data were assembled to make a judgment of recommendation category for each schedule. The WG members were asked to respond to the following 4 questions:

1. In response to the question: Is the evidence quality low? The WG determined that the evidence quality supporting each 3-dose schedule compared to 4-dose schedule was low because limited head-to-head comparisons were available, and the available immunogenicity data were used as surrogates for IPD but not other critical outcomes.
2. In response to the question: Are the net benefits low or is there uncertainty about the balance of benefits versus harms? The WG determined that there was some uncertainty about the balance given the observed differences for some serotypes in antibody response and clinical relevance of these differences.
3. In response to the question: Is there variability or uncertainty in what outcomes are important to prevent? The work group reached a consensus on which outcomes are important to prevent.
4. In response to the question: If there is uncertainty about whether the net benefits are worth the costs? As mentioned earlier, the cost effectiveness analysis comparing the 2+1 schedule to 3+1 was presented last October to this committee. This study was published and based on the results, it was determined that when compared to a 2+1 schedule, the 3+1 schedule is less cost-effective.

To conclude the findings of GRADE review, in step one, there was strong evidence supporting each individual schedule as compared to no vaccine. In step two, there was more limited evidence with few studies showing direct schedule comparisons. Thus, the GRADE process supports an overall category B recommendation for each 3-dose PCV schedules: 2+1 and 3+0 as compared to the 4-dose schedule (3+1), meaning one for which the desirable consequences probably outweigh undesirable outcomes.

Discussion Points

Dr. Harrison inquired as to whether there were longer-term persistence data for all three schedules comparing the three. He said he was thinking of data from the UK with the meningococcal C conjugate vaccine where the accelerated 3+0 schedule had limited persistence of antibody and efficacy disappeared after one year.

Ms. Tomczyk replied that they did not find any of these data. The measurements shown were limited to what was available in the studies.

Regarding the UK study, Dr. Matt Moore (SME) pointed out that it was a completely different vaccine. That is a 2-, 3-, 4-month accelerated schedule versus what was presented by Ms. Tomczyk of a 2-, 4-, 12- or a 2, 4, 6-month schedule. That probably makes an important difference.

Regarding the importance of timing between vaccines, Dr. Vazquez said she understood that RCTs offer the best information because they are experimental. However, effectiveness tends to be lower than efficacy. In the trials Ms. Tomczyk showed, the intervals were adhered to in controlled studies. In thinking about the real-world, a change to the 2+1 schedule, someone might receive a 2-month dose, not receive another vaccine until they are 9 or 10 months of age, and then return potentially for a booster. If the initial short interval is important, it will remain unknown whether administration outside of the recommended interval work as well.

Ms. Tomczyk agreed that this was a good point, noting that interval was not addressed in the GRADE process in particular.

Referring to Slides 24, Dr. Gorman (NIH) asked whether, if the incidence of these diseases in the countries where the studies were conducted was higher, the number needed to treat might well have fallen.

Ms. Tomczyk responded that this was correct.

Regarding Slide 25, Dr. Gorman (NIH) inquired as to whether the rate ratio was the same as the US rate or if those rates were specific for those countries before and after the introduction of the vaccines.

Ms. Tomczyk replied that the rates were specific to those countries, because they were from a completely separate study of a pooled analysis of specific countries' surveillance data.

Regarding Slide 48, Dr. Doskey (AHIP) inquired as to whether the statistically significant increase in hospital admissions for lower tract infections during the primary series until pre-booster was expected to hold up now that there is some herd protection .

Referring to Slide 49, Dr. Matt Moore (SME) in the 2003 birth cohort, this has been interpreted by the authors of the study and others to mean that once the herd effect increases, those serotypes are less available to cause disease so the differences between the schedules are smaller.

Dr. Brady (AAP) said he thought the GRADE system worked well for GRADEing the evidence, but sometimes it does not help with the conclusions. In terms of invasive pneumococcal disease, with the 3+0 schedule, vaccine efficacy was only 74% and the 2+1 and 3+1 schedules were in the mid-90s. He did not think these could be said to be equivalent. A 3+1 schedule prevents pneumococcal disease, it is not equivalent for the other schedules. The 3+0 studies were conducted in Africa countries. The US has done a really nice job of eliminating the difference of disparity in pneumococcal disease in African American children. It would be unfortunately to find that higher levels of antibody are actually needed to protect African American children, and that disparity levels would return in that group with a 2+1 or 3+0. That issue needs to be addressed.

Dr. Moore (SME) pointed out that the trials in Africa were conducted with schedules of 6, 10, and 14 weeks so there are only 4 weeks in between. It is known with pneumococcal vaccine a better response is achieved if the doses are spread out to at least 2 months. Two months are better than one month. The balance that must be stricken is that the interval cannot be spread too far, because a single dose is not believed to offer enough protection. This is one possible difference between the African versus the Kaiser trials.

PCV13 Reduced Dose Schedules for Children: Considerations and WG Conclusions

Tamara Pilishvili, MPH
Respiratory Diseases Branch
National Center for Immunization & Respiratory Diseases

Dr. Pilishvili acknowledged that GRADE has a somewhat narrow focus that does take away from the conclusions. She pointed out that several factors must be considered when deciding whether a policy change is warranted, but first and foremost consideration must be given to whether the available evidence supports the change. During the October 2013 ACIP meeting, the results of the extensive evidence review by the work group were presented. This review included studies with two different 3-dose PCV infant schedules, 2+1 and 3+0. The work group reviewed RCTs evaluating the efficacy of these schedules, post-licensure effectiveness studies (case-control or indirect cohort analysis), and ecological studies evaluating the impact of PCV introduction on a population level. Key studies were highlighted and the conclusions were presented for each outcome, including invasive pneumococcal disease, pneumonia, acute otitis media (AOM), nasopharyngeal colonization, and immunogenicity studies; as well as indirect effects of 3-dose schedules. This included the outcomes that GRADE did not consider, because it is limited to the critical outcomes.

Following the suggestion received from the full ACIP committee to assess the quality of the evidence, the WG applied the GRADE framework to the review of evidence, which was presented by Ms. Tomczyk during this session. GRADE procedures narrowed the scope of the evidence review to only those outcomes which were deemed as critical based on ranking. Using each schedule (3+1, 2+1, 3+0) as compared to no vaccination, the GRADE conclusion was that there is strong quality of evidence (type 2) supporting each individual schedule when compared to no vaccine, and a category A recommendation. When comparing the schedules only to each other (2+1 versus 3+1 and 3+0 versus 3+1), the WG was limited to only those studies that made such comparisons and to three outcomes: immunogenicity (surrogate for IPD), pneumonia, and AOM. Because of the limited evidence with direct comparison, the evidence was of lower quality (type 3), and the consensus of the WG was that GRADE supports a category B recommendation. However, policy conclusions are not yet being made.

Some key issues were not covered by GRADE review. As noted, the outcomes were limited because of the ranking and only critical outcomes were included. For example, data on nasopharyngeal carriage were not included in the GRADE review. Observational studies for IPD also were not included. According to the GRADE guidelines, if sufficient data are available through RCTs, only RCTs are included. However, a vast amount of post-licensure data has been accruing over the years from countries that have used these various schedules. Those data were overlooked by GRADE. GRADE does not conclude anything other than the type of evidence and the category of the recommendation. Some of the conclusions are missing, so perhaps the main conclusions that largely remain unchanged by outcome as presented in October should be revisited.

During this session, Dr. Pilishvili presented a summary of PCV13 breakthrough cases and failures; programmatic considerations for policy change (e.g., NIS, PCV13 coverage data, parental acceptance of vaccines, and factors influencing refusals and delayed vaccination); work group conclusions so far, and next steps. She also revisited the evidence not accounted for by GRADE (e.g., observational studies for PCV impact on IPD, effects of reduced schedules on nasopharyngeal carriage).

The work group assessed three case-control studies and 3 studies using indirect cohort method evaluated effectiveness of various schedules of PCV7, including the following:

- Canada (Deceuninck 2010)
- USA (Whitney 2006)
- Spain (Barricarte 2007)
- USA (de Serres 2008)
- USA (Mahon 2006)
- Germany (Ruckinger 2010)

For the 2+0 schedule that some of the studies were able to evaluate, the effectiveness estimates ranged from 70% to 99%. Two studies evaluated the effectiveness of a 2+1 schedule, with the effectiveness estimates ranging from 98% to 100%. It is important to keep in mind that none of these studies were powered to make across study comparisons, especially when comparing two values that show high effectiveness. None of these studies were powered to detect a difference between 99% effectiveness and 100% effectiveness. Also important is to consider the difference in settings in countries and the methodologies. It can be concluded that all of these schedules are quite effective at reducing invasive disease.

In terms of surveillance studies conducted in 10 countries (11 populations) describing the impact of national PCV introduction on vaccine-type-IPD among young children by country/schedule and year post-vaccine introduction, the impact was measured as rate ratios for vaccine type (VT) IPD rates post-vaccine introduction compared to pre-vaccine baseline. In this analysis, an effort was made to control time since vaccination introduction and the country's vaccination schedule. The similarities in the magnitude of the impact observed between the schedules and between the countries are striking. Although surveillance methods varied and each study only reported the impact of one particular PCV dosing schedule, some general comparisons between schedules can be made across this group of reports. One similarity observed among nearly all studies was a large and significant impact of PCV introduction on VT-IPD over time in populations routinely using 2+1, 3+0, and 3+1 schedules as soon as 1- to 2-years post-vaccine introduction, with reductions ranging from 65% to almost 100%. In general, the reductions for all countries and schedules were greater with more years post-introduction.

Very relevant to the objective of this session was the example of PCV impact from the experience with PCV introduction in Canada. In Calgary, PCV7 was introduced as a 4-dose program in 2002 and PCV13 replaced PCV7 using a 3-dose, 2+1 program (2, 4, 12 months) for healthy children in 2010. High risk children receive 4 doses, and there was a brief catch-up PCV13 program for preschool children. Following the introduction of PCV7 on a 3+1 schedule, rates of PCV7 type IPD have dropped dramatically among children less than 2 years of age. The rates have also declined among older children and adults. In 2010, PCV13 replaced PCV7 on a 3-dose schedule, and the rates of PCV7 type disease continued to decline for all age groups. In 2013, rates of PCV7 type IPD were at less than 1 case per 100,000 for all age

groups. The rates of PCV13 type IPD increased post PCV7 introduction but then in 2010, PCV13 was introduced and 2+1 PCV13 directly and indirectly reduced vaccine-serotype IPD quickly and continued to decline through 2013 [Ricketson LJ et al. *ISPPD* 2014].

To summarize the findings for IPD, evidence from RCTs and observational studies suggests each schedule (3+1, 3+0 and 2+1) is highly effective at preventing IPD. None of the studies were designed to compare any of the 3-dose schedules to a 4-dose schedule head-to-head. It is also important to note that direct comparisons across studies are not meaningful, because they do not take into account differences in populations and methodology, and they are not powered to detect a difference between two highly effective schedules.

To summarize the findings for the pneumonia outcome, evidence from RCTs and observational studies shows that each schedule (3+1, 2+1, and 3+0) prevents pneumonia. One observational study showed that a 3-dose primary series is better than 2-dose primary series before the booster dose against pneumonia early in the US immunization program. There are no statistically significant differences observed post-booster or for later birth cohorts. The conclusion is that a schedule with 4 doses maybe more beneficial early post-introduction; however, later in vaccine introduction those differences may disappear.

Carriage data were not considered as part of the GRADE because nasopharyngeal (NP) carriage was not ranked as a critical outcome. However, NP carriage data are important to consider because NP colonization is necessary before infection can occur; reductions in vaccine-serotype colonization means that those serotypes are less available to cause disease; and these data provide direct evidence of reduced transmission expected with each schedule in addition to evidence observed through indirect (herd) impact on IPD. In October, the work group presented studies showing effects on nasopharyngeal carriage of different PCV schedules. Results of a carriage study evaluating the impact of PCV13 on carriage of PCV13 serotypes were also presented at that time.

To summarize the key points, all schedules (2+1, 3+0, and 3+1) reduce acquisition of colonization with vaccine serotypes compared with no PCV. A 3-dose primary is better than 2-dose primary before booster dose at 1 through 7 months following the series. There are no differences at 12 months of age before a booster dose, and no differences have been observed after a booster dose. Post-PCV13 introduction US carriage data suggest PCV7 types are very rare and PCV13 type carriage is decreasing.

To conclude the overall evidence review, 3-dose PCV schedules are effective against IPD, pneumonia, and otitis media. Immunogenicity and carriage studies show that a 3+1 schedule may be better than a 2+1 schedule before a booster dose. However, no differences have been observed post-booster for most serotypes. Strong direct and indirect (herd) effects have been observed in countries using 3-dose PCV schedules. It is important to interpret the results of the evidence review in the context of the US PCV13 program. Differences in antibody response between schedules may lead to differences in carriage and, potentially, in disease rates. Differences in antibody response between schedules may lead to differences in carriage and, potentially, in disease. Differences may not be meaningful in a setting of a strong national immunization program and already observed large direct and indirect benefits of PCV use. PCV7 serotypes are very rare in the US and are, therefore, less likely to cause disease. Rates of PCV13 type IPD are extremely low among children 6 through 11 months of age and continue to decline among all age groups. The population level impact of 3-dose PCV programs (both direct and indirect effects) are similar to the ones observed in the US.

The risk of invasive pneumococcal disease among children less than 2 years of age is low. Overall rates are 14.6/100,000 and PCV13 type rates are 2 cases/100,000. The rates of meningitis are 1.2 cases/100,000 and rates of PCV13-type meningitis 0.3 cases/per 100,000. The -+WG wanted to determine, given the window of time during which the differences in antibody responses following the primary series were observed, what the risk is of disease among children 6 through 11 months of age. More than 1/3 of PCV13 type cases in this age group occur before 2 months of age, and only one PCV13-type case was reported in 2012-2013 among children 6 through 11 months of age.

Vaccine failure and breakthrough infections reported to the ABCs surveillance system were reviewed in order to evaluate whether any particular incomplete PCV schedules were associated with breakthrough infections. From 275 cases of IPD who also received at least 1 PCV13 dose, 44 cases were caused by PCV13 serotypes and were classified as breakthrough cases. Of these, 5 received the full 4-dose PCV13 schedule and were true failures. The vaccination status was assessed of breakthrough cases by serotype and PCV13 schedule. Only 4 serotypes were associated with breakthrough infections. The majority of breakthrough cases (74%) were caused by type 19A, followed by type 3 (22%), and one case of 7F. Only one PCV7 serotype (19F) was associated with one breakthrough infection. The majority of breakthrough cases were vaccinated using schedules other than 3+1, 3+0, or 2+1 and the majority of those in the "other" category received only one PCV13 dose. All 4 meningitis cases followed 1 dose of PCV13. No deaths were associated with breakthrough infections, and only 7 cases had underlying conditions.

Though not discussed in detail during this session, Dr. Pilishvili highlighted the points discussed by the WG so far. An economic analysis was presented to the committee in October 2013 and was considered as part of the GRADE process, although the analysis did not consider that the vaccine price may be adjusted. Safety data were presented as part of the GRADE review. There is an additional analysis ongoing using VSD data to evaluate the risk of febrile seizures associated with co-administration of childhood vaccines. The results of this study will be presented to the committee at a future meeting. The WG also discussed programmatic considerations.

Programmatic considerations discussed so far by the WG include evaluating the performance of the vaccine program to deliver high coverage at each time point in the immunization schedule. They took into consideration adherence to the currently recommended schedule, as well as delay in the timing of each dose and the effects on completion of the recommended schedule. The potential for non-adherence to introduce disparities in coverage was also evaluated. National Immunization Survey (NIS) data were utilized to assess parental acceptance of the recommended vaccination schedule and factors contributing to delays and refusals.

Based on cumulative PCV uptake for children included in the 2012 NIS, 84% of children surveyed received their first dose on time (<3 months of age); 73% received their second dose on time, 63% received their third dose on time (or before 7 months of age), 63% received their booster as recommended between 12 through 15 months of age, and 84% of children received their primary series before 12 months of age (and therefore, would have still been eligible for a booster in their 2nd year of life).

With regard to how timeliness of doses in the primary series affects uptake for the rest of the recommended doses, among children starting the series on time, 86% and 74% received doses 2 and 3 on time, and 73% received a booster dose on time; and 94% completed the 3-dose primary series before age 12 and, therefore, were still eligible to receive a fourth booster dose. In contrast, among children who started the series on or after 3 months of age, less than 10% received doses 2 and 3 on time, only 29% received a fourth booster on time, and only 47% completed the 3-dose series before age 12 and were eligible to receive a fourth dose in the second year of life.

In terms of uptake for the third and fourth doses among children who received the second dose on time versus those who received their second dose late, a similar picture is observed. Among children, high proportions received their third and fourth doses on time; whereas, among children who were late in receiving dose 2, less than 10% received dose 3 on time and 36% received the fourth dose booster on time. Fifty-nine percent of those who delayed dose 2 versus 98% of those who did not delay dose 2 completed the 3-dose primary series before 12 months of age and, therefore, were eligible for a fourth dose in the second year of life.

PCV13 coverage among children receiving currently only 3 doses was also assessed to understand which 3-dose schedules they received. According to 2012 NIS data, around 10% of children received a total of 3 doses. Also assessed was the timing of administration for the third dose. For example, 22.5% of children who received a total of 3 doses received a third dose at age 6 months and, therefore, were vaccinated on a 3+0 schedule. Similarly, 43% of children who received a total of 3 doses received their third and last dose at 13 months or after and, therefore, were vaccinated on a 2+1 schedule. Given that only a small percentage of children overall received a total of 3 doses, these data cannot provide input on what the preferred 3-dose schedule would look like. However, the data show that children are receiving 3-dose schedules and the third dose may be given anywhere between 6 months of age to 13 months or later.

Coverage was also evaluated by schedule and poverty status. The data in the 2nd and 3rd column are coverage estimates (%vaccinated and 95%CI) for children receiving at least 3 doses before age 12 months by poverty status. The next 2 columns are estimates for children receiving at least 2 doses before 12 months of age and 1 dose in the 2nd year of life, and the last 2 columns, estimates for children vaccinated with 3+1. For each schedule evaluated, the coverage decreases with increasing poverty level. Overall and within each poverty level strata, the coverage is lowest for 3+1, and highest for the schedule with at least 2 primary doses and a booster. There are actually no statistically significant differences between schedules 1 and 2 within any of the poverty strata. However, the overall difference between schedules 1 and 2 (84.4 versus 85.9) is significantly different.

To summarize PCV13 coverage in the US, the vast majority of children receive PCV doses in the primary series on time. A majority of children complete the PCV primary series by 11 months of age and, therefore, are still eligible for a fourth (booster) dose in the second year of life. Among children for whom either dose 1 or dose 2 is delayed, a smaller proportion is eligible for and/or complete a 4-dose schedule. A small proportion receives a total of 3 doses. It is difficult to identify which 3-dose schedule would be preferred if ACIP were to make that recommendation. The coverage decreases with increasing poverty level for all schedules. Within each poverty strata, coverage is lowest for 3+1 schedule.

Next, published studies were reviewed that evaluated parental acceptance of vaccinations and factors influencing vaccine refusal and delay. As part of 2009 NIS survey, parents of children 24 through 35 months old were interviewed to evaluate the association between parents' beliefs about vaccines and their decision to delay or refuse vaccines for their children. The results of the survey showed that approximately 26% of parents delayed one or more vaccine doses, 8% refused, and almost 6% both delayed and refused. Delays and refusals were associated with parental beliefs that children receive too many vaccines (58.6% vs. 29.1%, $p<0.05$), too many vaccines can overwhelm a child's immune system (48.6% vs. 28.3%, $p<0.05$), and that vaccines have serious side effects (63.1% vs. 30.9%, $p<0.05$). Delays and refusals were more likely among parents with higher socioeconomic status (SES), and among children with lower coverage for all 10 recommended vaccines that were assessed [Smith P. et al *Public Health Rep.* 2011].

According to the results of 2010 HealthStyles Survey, from the top concerns reported by parents or guardians of children less than 6 years of age, 38% reported concern that "it is too painful for the children to receive so many shots," 36% reported that their child is receiving too many shots, and 34% believed that overall children get too many vaccines in their first year of life [Kennedy et al *Health Affairs* 2011].

A cross-sectional internet-based survey of a nationally representative sample of parents of children 6 months through 6 years of age found that more than 1 of 10 parents of young children currently use an alternative vaccination schedule, non-black race and not having a regular provider were associated with increased odds of alternative schedule, a large proportion of parents currently following the recommended schedule seem to be "at risk" for switching to an alternative schedule, 28% believed that delaying vaccine doses was safer than the schedule they used, and 22% disagreed that the best schedule to follow is the one recommended by the experts. This study also found that among parents who reported refusing some vaccines, 31% refused PCV. Among parents who reported delaying some vaccines, 10% delayed PCV to older age than recommended. Among parents who prolonged dosing intervals for some vaccines, 33% did so for PCV [Dempsey et al *Pediatrics* 2011].

Overall, the studies on parental acceptance of vaccines reviewed support the following conclusions:

- The majority of parents surveyed adhere to and do not have concerns about the recommended schedule.
- Parent decisions do lead to delays (13%-25%) or refusals (6%-10%) for one or more recommended vaccine doses.
- Parents who delay and refuse vaccine doses are more likely to have concerns about vaccine safety or multiple injections at each visit
- Parents who follow the recommended schedule also report exhibiting doubts and have considered alternative schedules or refusing vaccine doses in the future.
- It is unclear whether removing a PCV dose at 6 months (2+1) or 12-15 months (3+0) will help reduce refusals or delays of other recommended vaccines.

With regard to the WG conclusions, the GRADE review suggests that 3-dose schedules are likely equivalent to a 4-dose schedule. Evidence from countries using 3-dose schedules is reassuring. An acceptable schedule in the setting of a mature immunization program and strong herd effects may not need to be the same as that chosen at the time of licensure. A 3-dose PCV13 schedule for infants is likely appropriate to maintain already observed benefits from 13 years of PCV use in the US. The WG was not prepared to make a specific policy recommendation at this time. Including a 3-dose PCV13 schedule for routine use among infants requires careful consideration of implementation issues. Further discussion is needed to define groups to be excluded from potential policy change and potential impact on non-adherence.

As the next steps, the WG will define the groups that should be excluded from the potential policy change and the rationale for exclusion of these groups. Discussions have begun related to American Indian and Alaska Native (AI/AN) populations. A group of experts working with these populations has shared data with the WG on disease burden and disparities in rates of pneumococcal disease in these populations compared to general US population. There is a history of ACIP recommendations made specific to AI/AN populations. Discussion is still needed to identify exactly which population groups to exclude if ACIP changes the recommendations for the general population of US children. In addition, the WG will clearly define which underlying medical conditions would be indications to continue receiving a 4-dose schedule. This decision will be based on known disparities in disease burden, lower PCV effectiveness or reduced immune response observed compared to that among healthy children. Careful consideration should be given to implementation issues related to timing of diagnosis for the medical conditions and schedule selection.

Listed in no particular order of preference, the WG agreed to give further consideration to the following policy options:

- Option 1: 2+1 for routine use, 3+1 for high-risk groups (to be defined)
- Option 2: 3+0 for routine use, 3+1 for high-risk groups (to be defined)
- Option 3: 3-dose schedules (2+1 or 3+0) for routine use, 3+1 recommended at provider discretion for healthy infants, 3+1 for high-risk groups (to be defined)
- Option 4: 3+1 for routine use, 3-dose schedules (2+1 or 3+0) optional for healthy infants, 3+1 for high risk groups
- Option 5: Status quo

In conclusion, the following questions were posed to the full ACIP committee for consideration and discussion:

- What are the gaps in information to consider including a 3-dose PCV13 schedule?
 - Provider/practice level issues
 - Public health program level issues
 - Parent considerations
- What specific concerns does the committee have about potentially including a 3-dose PCV13 schedule for routine use among infants?

Discussion Points

Regarding the population level impact across all serotypes for introduction of various 3-dose schedules in a number of countries, Dr. Karron wondered whether there were any serotype differences or any signals that stood out for particular serotypes to suggest that one schedule might be better than another, or if the data mirrored what was shown for the composite.

Dr. Pilishvili replied that there were some differences by population in terms of the serotype distribution, but clarified that the data she presented focused on PCV7 serotypes. Within the PCV7 types, there is less variation in terms of the distribution of those serotypes across the populations for which data were presented. There is more variation for additional serotypes like serotypes 1 and 5 that are included in PCV13, but not in PCV7. The data in ABCs for the US have been assessed by serotype, and there is sufficient power for certain populations to evaluate the individual serotypes, so some of those data could be reviewed. However, there is insufficient power for most of these studies to assess the individual serotype data.

Referring to Slide 18, Dr. Karron thought it would be great to have data from additional years to increase the numbers to determine whether the distributions are the same. With regard to this and the 12-month and up dose and whether children receive vaccine on time, there always seems to be a problem with the 4th dose. It was approximately 50% to 70%. A 2+1 schedule concerns her because she does not believe the 4th dose will be administered any sooner if it were a third dose in a 2+1 schedule. If the delay is too long, there is invasive disease in the 12- to 18-month age range. She wondered if the existing data offered any insight about a 2+1 versus a 3+0 schedule.

Referring to the HPV vaccine, Dr. Doskey (AHIP) reminded everyone of the quagmire regarding permissive recommendations. He spoke against Options 3 and 4, given that they would open a quagmire. He foresaw a potential for scattered coverage across the country. The data were either strong enough to recommend it, strong enough to not recommend it, or strong enough to recommend it for certain groups.

Dr. Pilishvili responded that several members of the WG shared Dr. Doskey's concerns.

Dr. Temte asked Dr. Fryhofer how good internists are in terms of adhering to pneumococcal recommendations for high-risk patients.

Dr. Fryhofer (AMA/ACP) responded that this was a work in progress.

Dr. Warshawsky (NACI) commented that Canada uses a 2+1 schedule in most provinces. They have tried to encourage the +1, the booster, be administered at 12 months. It is not at a range of 12 to 15 months, it is at 12 months. Regarding the failures shown on Slide 23, she wondered if it were known when the failures occurred for the 2+1 and 3+0 schedule (e.g., how old the child was when they failed) and whether that would have been prevented by a booster at 12 months.

Referring to Extra Slide 44, Dr. Pilishvili said it was important to keep in mind that the interval between the last dose and the occurrence of disease were assessed. There is a pretty wide range for each schedule. It may have been soon after the vaccine was given or delayed. Because the number of cases were low (n=5), it was not possible to draw any conclusions based on whether it was worse after 2+0 or 3+0.

Dr. Warshawsky (NACI) said she had heard this type of data before when Quebec went to a 2+1 schedule. They talked about the number of cases that would potentially have failed in that type of schedule. It may be helpful to say, of the 2+0, how many would have failed in a 2+1 so that the true number of failures is known for that scenario—not just the average, but the actual number of cases that might have failed under a 2+0 schedule.

Dr. Bocchini expressed concern with the groups being excluded for potential policy change. They would essentially wind up creating three policy recommendations: 1) for healthy children with no increased risk; 2) high risk children; and 3) patients who would maintain the 3-dose primary schedule and the booster as opposed to a 2+1 or 3+0. He believes this will add confusion and it will be very difficult to define those groups effectively for the practitioner. There are also subgroups such as children who attend childcare who are under a year of age, and others who had a higher risk for pneumococcal invasive disease in the past that disappeared under the current vaccine regimen.

Scanning through the various studies, it appeared to Dr. Harriman that the 2+1 schedule had better efficacy than the 3+0 schedule in most of the studies.

Dr. Vazquez wondered what would happen with coverage by insurance companies if Option 3 or 4 were selected.

Dr. Doskey (AHIP) emphasized that HPV was permissive and people could choose, so plans chose. He likened what would happen to the big marsh mellow man in “Ghost Busters.”

In terms of permissive recommendations, Dr. Schuchat pointed out that essentially, the Affordable Care Act (ACA) requires insurers to cover vaccines that are recommended by ACIP. It is all about what is in the schedule and in the footnotes of the schedule. During the first calendar year after the vote, insurers have to cover what is in the schedule and footnotes if given by an in-network provider. That means footnotes are where the action is.

Dr. Middleman (SAHM) wondered whether there were any data regarding the potential message of decreasing the number of doses and making it appear as though this vaccine may be expendable or perhaps not important for children, and the effect that may have on immunization rates. She found this very concerning.

Dr. Pilishvili responded that she was not aware of any data.

Dr. Schuchat added that there are many different subsets of parents and attitudes. It is important not to over-generalize. People who vaccinate their children regularly express questions and concerns about the number of shots at a single visit. Some of the people who want to vaccinate want to not have so many shots during the same visits. People do question whether all of those shots are really needed. The theoretical implications of a policy change are very difficult to predict, but there is certainly a stewardship of the immunization schedule that ACIP holds to carefully review the risks, benefits, value, and need for each dose recommended. The point of this review was that there is a lot of evidence about ways to give the pneumococcal vaccine, and it is one of the vaccines that is given with many other vaccines.

Dr. Harrison said he was fairly troubled by the immunogenicity data of a 3+0 schedule. The GMC ratios are only 0.2 to 0.6 compared to the 3+1 schedule. He questioned the durability of protection. He wondered what the work group's thoughts were about that.

Dr. Kempe pointed out that there was plenty of evidence showing that primary care and pediatricians cannot and do not identify high risk children. She expressed concern not about dropping a dose, but about offering it as an option. She was worried about having either optional or multiple possibilities.

Dr. Campos-Outcalt said he was not convinced that a change should be made. The schedule is confusing for providers and patients. There is something synchronous about having 2, 4, 6 and then afterwards that goes with other vaccines and fits in nicely with the schedule. Everybody gets the same recommendation. Parsing out by risk and other criteria just confuses the schedule more, which is a major problem. He would prefer a 3-dose schedule or a 4-dose schedule—nothing in between. To convince him to choose a 3-dose schedule, he would have to be convinced that it would be equal to a 4-dose schedule. He did not see that in the GRADE evidence.

Dr. Temte pointed out that consideration must also be given to putting this into immunization information systems. If a dose is made optional, physicians do a notoriously poor job of capturing high risk conditions in the systems to inform them what to do. This is observed repeatedly with high risk conditions for hepatitis B and pneumococcal in adults and HPV in optional groups. He concurred with the sentiment that it would be better to have something fixed versus variable.

Dr. Bennett said the laborious GRADE work the WG did convinced her that these schedules are equal in efficacy. She was not happy that they did not convince all of the ACIP members of that. She also thought it was important to remember that it is ACIP's obligation morally to review any recommendations the committee makes. If that means that removing a dose is complicated, that is too bad, but it is the right thing to do. The situation is currently very different from when this vaccine started being administered. Very little disease is now circulating related to the serotypes in the vaccine. The WG views all of the concerns raised as very serious and is trying to work its way through this to think about all of the possible unintended consequences of changing this schedule, and how this can be communicated so that people understand that ACIP is really just trying to do the right thing for children and parents. That does not undermine this vaccine. It simply says that this vaccine has done such a great job, one fewer dose can be given. She believes this message can be conveyed with confidence.

Dr. Brady (AAP) emphasized that there are 3 studies for the 3+0 schedule, and it may be methodological because the time between them was not appropriate, but those are the only data available and they are not convincing that a 3+0 schedule works. The comparison of 3+1 to 2+1 is low evidence. They did a really bad job when risk factors were used for influenza vaccine in children. Now they were going to say that children at high risk need 3+1 and others can use another schedule. This will result in a real problem because this will not happen the way the recommendations are stated, and children at risk will get too few doses. Then there will be more disease. He believes that the status quo currently provides the best protection and creates the opportunity to minimize risk.

Ms. Pellegrini thought a potentially compelling argument could be made to say that a great job has been done with this vaccine, the cases of disease have decreased, and perhaps a dose could be removed. However, if they are going to do that, they must also be prepared to say why that is not the case for every other vaccine in the schedule. The last naturally occurring case of polio was in 1979; however, polio vaccine is still given to every infant. This pertains to some of the basic education issues and communication problems that exist for vaccines.

Dr. Loehr (AAFP) noted that there are already variations mixed into the schedule. While there are likely to be more cases with a change in the schedule, that might be appropriate given the amount of resources being put into this. He has a large number of vaccine-hesitant parents in his practice. CDC and ACIP consciously stating that they do not believe all of the vaccines are needed because they have done such a good job shows that they are not just adding vaccines, but that they also take them away when they are no longer necessary. He thought that would be a very valuable signal to send.

As an epidemiologist, Dr. Reingold felt that based on the data he had seen from other countries, including countries comparable to the US that either began with a 3-dose schedule in the first schedule or moved to a 3-dose schedule, the impact other countries have observed is identical to the impact the US has observed. A 3-dose schedule costs 25% less. While this may be attributable to better coverage in other countries, he thought there was convincing evidence from a variety of comparable countries that the same results could be accomplished with a 3-dose schedule.

Dr. Kelly Moore (AIM) concurred with those who expressed operational concerns. Although she did not yet know what the right answer was, she thought it was incumbent upon them to avoid unintended consequences by carefully thinking through the operational implications of a split schedule where high risk children still need more vaccine than healthy children. It is known that risk-based recommendations are not implemented effectively. If such a recommendation is going to be made, they must work out the registries, electronic health records, and other operational issues from a programmatic standpoint to ensure that mistakes are not made by introducing a risk group into this consideration who was not there as a special consideration before.

Regarding a delayed last dose in the context of Dr. Reingold's comments, Dr. Sawyer thought it was important to assess coverage rates in other countries that have had success. They likely do a better job at a more prompt or tighter interval around the recommended age in delivering the vaccine. He is very concerned about a 2+1 schedule turning into either a 1+1 or 2+0 schedule in a significant number of children.

Rebecca Coyle (American Immunization Association) thought this highlighted a major issue for those who work in the electronic health record and information system arena. When high risk conditions are added or schedules are separated, it becomes very difficult for electronic systems to translate that information into an appropriate clinical decision support for the clinician or whomever is making that decision. She emphasized the importance of how cumbersome the decisions ACIP makes can be to implement on the technology side as well.

Dr. Sun (FDA) indicated that the FDA is very concerned about the possibility of a recommendation that differs from the label, because in the absence of data presented by manufacturers to support a change in the label, FDA will not make any changes in the package insert. This would present a lot of ambiguity for health care providers, parents, insurers, and vaccine manufacturers.

Dr. Luis Jodar (Pfizer) indicated that he had a number of technical concerns with GRADE. It is somewhat ambiguous to state that there is a mature PCV program, when it really is a mature PCV7 program. What they are judging is whether to change a PCV13 dosing schedule, which includes 6 different serotypes from PCV7. In all of the world, PCV13 was only introduced 3 years ago. Extrapolating the conclusions being observed after 14 years of PCV7 to PCV13 is risky. Pfizer is very encouraged with the effectiveness presented, but this is the first year that serotype-specific effectiveness data have been presented. There may be variability in serotype-specific effectiveness in those countries that have introduced 2+1 PCV13. His concern regarded whether PCV13 could really be considered a mature program after only 3 years and only after just starting to learn about serotype-specific effectiveness. He did not think that anyone there believed that all serotypes were equal. His other question about GRADE was that they were thinking all conjugate vaccines are created equal. When evidence is presented about IPD efficacy, for instance for a 2+1 schedule, the efficacy is for a 10-valent vaccine with 3 different carrier proteins, which is not even licensed in the US. The 3+0 evidence regards PCV9, which was discontinued. PCV11 was discontinued for development for pneumonia. ACIP was considering a change for PCV13, which is a completely different vaccine, based on evidence for other vaccines. He was surprised that the GRADE assessment of immunogenicity was not done with PCV13. A study was published in the *Journal of the American Medical Association (JAMA)* in 2013 comparing different schedules with PCV13 at 2, 4, 6 / 2, 3, 4 / 2, 4 / 3, 5. It is true that intervals are different. 2, 4 for some serotypes like 6b and 23f are worse than 3, 5. Those are worse than 3 doses. Consistently, 6b and 23f have lower percentages of individuals reaching the 0.35 µg/ml than 3 doses. That would have been better evidence than what was being discussed.

Dr. Temte noted that another piece of evidence that might be useful for the committee in general would be to know whether resurgence of disease was observed in any of the national programs that changed from a 4-dose to a 3-dose schedule.

Dr. Jenkins said she would like to know whether there are disparities in the vulnerability of children either based on ethnic diversity or poverty status. She applauded what they were doing in terms of assessing the resources to determine whether they are being used optimally. But they must also ensure that other children are not placed at greater risk as a result of those types of decisions, and that disparities are not created again.

Given the importance of the ACIP and AAP being harmonized, Dr. Duchin encouraged AAP to carefully consider this issue and present ACIP with an official AAP opinion.

Dr. Schuchat indicated that the Healthy People 2020 targets are 90% for 4-dose coverage of pneumococcal conjugate vaccine. Dr. Frieden is very keen to measure and achieve impact. He noted that coverage is approximately 80% with 4 doses of pneumococcal conjugate vaccine, and asked her how much additional impact could be achieved with 90% coverage. She told him zero. It is important to consider what programs and providers are doing in terms of Healthcare Effectiveness Data and Information Set (HEDIS) measures in trying to achieve a 4-dose completion, and whether there are other considerations beyond the question of whether the recommendations should change.

Dr. Pickering pulled up the new 2014 Childhood Immunization Schedule and suggested that everyone read the 3 pages of footnotes, particularly with regard to pneumococcal, to think about whether there are other ways to potentially simplify things. The reasoning behind making recommendations is to have them implemented.

Dr. Temte said he thought he heard clearly in the discussion that it would be very difficult to slice -and-dice the recommendation, and have a recommendation with different schedules for various groups. This is not about small groups of high risk children, such as those with immunocompromising conditions. Rather, this is about fairly large demographic groups and that certainly could be problematic for implementation, especially those groups who may not be captured in information systems. In general, the group did not seem to want to recommend a 2+1 schedule for most children, but a 3+1 schedule for African American or Native American children and other issues, because of risk factors make this very hard to implement efficiently.

Dr. Bennett said the WG heard what everyone was saying about the complexity and about a permissive recommendation. However, she thought it was fair to say that if a recommendation was made to reduce the number of doses, there would have to be different recommendations for certain high risk groups. She did not think this had to be super complicated. To say that they could not have a high risk group would be to say that they could not reduce the number of doses for anyone. This would result in giving a lot of extra shots to healthy children just to be sure other children receive enough.

Dr. Temte stressed that simply by living in poverty, there is a risk factor for not completing the schedule. A dose reduction also introduces the possibility of not completing the new schedule, and dropping instead of a 2+1 down to a 1+1. Unfortunately, many children in the US live under the poverty line.

Dr. Bennett said she distinguished between immunologic concerns with a reduced dose schedule and programmatic, practical issues. The WG is taking both of these very seriously, but she would put them in two different categories as they are making decisions.

Dr. Harrison inquired as to whether there were any concerns among the WG members regarding the immunogenicity data for the 3+0 schedule.

Dr. Matt Moore (SME) said he did not remember there being tremendous concerns about immunogenicity. From a programmatic perspective, some of the WG members seemed to think that perhaps a 3+0 schedule would be somewhat easier to implement than a 2+1 schedule. From an immunogenicity standpoint, there were not great concerns.

Dr. Pilishvili added that timing of the assessment of the antibody response was considered. Some of the studies included followed the most recent dose. The comparisons that Ms. Tomczyk presented as part of GRADE were antibody responses following the 3rd third dose in a primary series in a 3+0 schedule, and then following a booster dose in the 3+1 schedule. They know this is not a fair comparison because of the boosting effect with the last dose administered. At the same time, they assessed a subset of studies that considered the comparison at 13 months of age for both schedules. The differences were smaller in terms of the number of serotypes that showed differences. In other words, by waiting longer, the antibody response declines in all groups. The immediate effect of the boosting goes away, but it is unclear what that means in terms of clinical protection.

Dr. Kempe emphasized that the data are not perfect. There was the graph showing that between 6 months and a booster, 2+1 looks better, but those were old data. One study suggested that that was better now because of baseline, but those are limited data. She could not say as a WG member that she was totally sanguine about that leap.

Dr. Bennett expressed the work group's appreciation for the time everyone had put into reviewing these data, and speaking with the work group about the implications of any possible change.

Frankie Milley: Hi. I am Frankie Milley and I am the Founder/National Director, Meningitis Angels), which represents hundreds of families across this country. Many of them are pneumococcal families. You've met a couple of them over the last months. By the way, I vote for Option 5. You know, I'm often reminded as I look at the Angels within our network, one of my favorite but yet most painful photos of all of our families is of a young mother who held her very young toddler in her arms as they took her off of life support because she didn't get that 4th dose of Prevnar[®]. This is awful. This is just awful. I made notes. I normally don't come with notes, but I didn't want to forget it. I think we've seen in the past when we requested or required or recommended a certain amount of doses—if you recommend 3, they're going to get 2. If you recommend 4, they're probably going to get 3. We see that with HPV, the hepatitis vaccine, all of them we see that. We know that that happens. Also, I think when you start changing the schedules again, especially when you're downgrading the requires or recommendations, I think that says to those parents, "Well, maybe we can downgrade some of the rest of them." I realize that we need to be very careful what we put into our children, but again, as I said in October, "if it ain't broke, don't fix it." I've worked really hard around this country for daycare entry requirements, which require pneumococcal vaccine. I think if you start changing those recommendations, you need to think and consider if that's going to change all of those daycare requirements that we've worked for years on. Are we going to have to go back to those policy makers, to those states where we've worked really hard to save those kids and get those kids immunized, especially in states where we do have a high minority rate? I know in Texas when we've worked with our legislators, one of the things that I said to them when we were trying to get daycare entry was, "We are depriving the most at-risk children in this state of this vaccine," and that was our African American and American Indian populations. Without strong recommendations, it doesn't get paid for. We all know that. So, I think we just have to be very, very careful. I work with a lot of families out there—a lot of parents. I have a lot of young parents that call me all the time. A lot of them I know, a lot of them I don't know. I tell them that you guys work very, very, very hard to make sure that the recommendations you put out are the best and the safest for their children. But you know what? I am begging you guys. I was really hoping that this would just be gone, but I can see that it's not. We have so many immunization issues, and problems, and diseases, and things that we need to be looking at and deciding how we should recommend those vaccines. But, I don't think Prevnar[®] is one of them. I think we need to move forward, not backwards. You've met several of my kids. I don't want my group to grow anymore with pneumococcal kids, and I'm afraid with a change, that's exactly what's going to happen. But, I want to tell you that I appreciate the work that all of you guys do. You volunteer. You have to have a passion for what you do. I appreciate it. Thank you.

Yellow Fever Vaccine

Introduction

Joseph A. Bocchini, Jr, MD
ACIP, Workgroup Chair
Japanese Encephalitis (JE) and Yellow Fever (YF) Vaccines Work Group
Professor and Chairman, Department of Pediatrics
Louisiana State University Health Sciences Center

Dr. Bocchini reminded everyone that the Japanese Encephalitis (JE) Work Group became the JE and Yellow Fever (YF) Vaccines Work Group to address issues with respect to the potential change in the recommendation for a booster dose for YF vaccine, based on the Strategic Advisory Group of Experts (SAGE) recommendation that booster doses are no longer needed for YF vaccine every 10 years. This will certainly affect travelers and laboratory workers who work with YF virus. The objectives and plans for the JE and YF Vaccine Work Group are to develop recommendations regarding YF vaccine booster doses in travelers and laboratory workers; and use the GRADE approach to assess YF vaccine data pertaining to long-term immunogenicity, vaccine failures, and serious adverse events. The work group has met on a number of occasions, and is in the process of a GRADE approach to assess YF vaccine data.

With regard to the timeline, the JE and YF Vaccine Work Group has conducted a number of teleconferences and has discussed vaccine immunity and booster dose data. The purpose of this session was to provide background data on YF, YF vaccine, and the recent change in recommendations. Subsequent to that, the work group will continue to complete the GRADE analysis, establish recommendations, and bring forward to ACIP in June 2015 the work group's booster dose recommendations for a vote. If completed, the work group will develop a final document to be published in the *Morbidity and Mortality Weekly Report (MMWR)*.

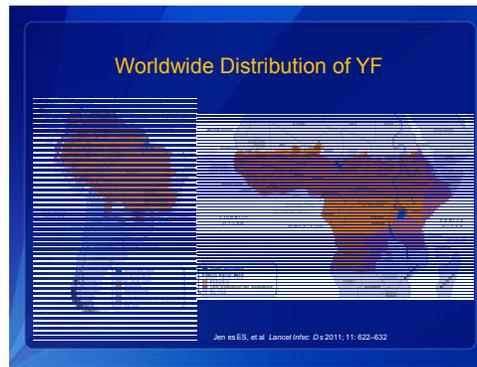
Background of YF Disease, YF Vaccine, and Recent Vaccine Developments

J. Erin Staples, MD, PhD
Arboviral Disease Branch
Division of Vector-Borne Diseases
Centers for Disease Control and Prevention

For those not familiar with the Arboviral Disease Branch, Dr. Staples explained that this group is located in Fort Collins, Colorado in the Western US. This branch is responsible for over 100 mosquito- and tick-borne viral disease, such as YF, Japanese Encephalitis (JE), and West Nile Virus. She then provided background information on YF disease.

YF is caused by YF virus (Flavivirus). The virus is transmitted predominantly by *Aedes* species mosquitoes. It is endemic in equatorial Africa and South America, causing an estimated 200,000 cases and 30,000 deaths annually. There are three transmission cycles for YF: jungle/Sylvatic, intermediate/Savannah, and urban. In the jungle/Sylvatic cycle, the virus circulates between non-human primates and tree-top dwelling mosquitoes, either *Aedes africanus* in Africa or *Haemagogus* and *Sabethes* species in South America. Humans are incidentally affected when they come into contact with these mosquitoes. This is the main

transmission cycle in South America. The intermediate, or Savannah cycle, occurs only Africa where it is the main transmission cycle. In this cycle, the virus circulates between semi-domestic *Aedes* species mosquitoes and humans or non-human primates who live on the edge of the forest in the Savannah region. In the urban cycle, humans are the primary reservoir and *Aedes aegypti* mosquitoes that live in or around homes are responsible for transmitting the virus among humans. The follow maps illustrate the worldwide distribution of YF:



The areas in orange on the map are considered endemic and are areas that have recurrent human disease. These areas also have the vectors and non-human primates needed to maintain the virus in the environment. Areas in yellow are considered transitional where the virus is active periodically and only causes cases every few decades. Low-risk areas are shown in red. In these areas, humans have been found to have antibodies to YF virus. There are the right vectors and non-human primates to transmit the virus, but the areas have never documented any human disease cases. The areas in gray are not considered to be at risk for YF.

Following the bite of infected mosquito, most persons will be asymptomatic or do not develop disease. For those who develop symptoms, the incubation period is approximately 2 to 6 days. Most symptomatic persons will develop a non-specific febrile illness that is often not recognized or cannot be distinguished from several other disease conditions that have the same presentation. Only a small proportion of those infected will develop fever with jaundice or hemorrhage, and approximately 20% to 50% of those persons with severe disease will die. It is only the cases with jaundice, hemorrhage, and death who are usually recognized and reported.

There is no specific anti-viral treatment for YF. Therefore, the mainstay of treatment is supportive therapy or care. Given the current lack of treatment, the best way to lower disease morbidity and mortality is to prevent the infection either through mosquito control measures or vaccination.

YF vaccine was developed from a strain of YF virus collected in 1927 from a patient named Asibi. That strain was passed more than 200 times to develop a live attenuated viral vaccine known as 17D Vaccine. 17D Vaccine is the basis for all vaccines and production today, which includes two distinct substrains used in vaccines today: 17DD, which is produced in Brazil and 17D-204, which is the substrain used by manufacturers outside of Brazil. There is one more substrain, 17D213, which is maintained by WHO as a reference strain stock. All YF vaccines are produced in embryonated eggs and differ in substrain, passage level, and stabilizers.

There are 4 prequalified YF vaccines that can be procured and distributed by United Nations (UN) agencies. These include vaccines made in Brazil (Bio-Manguinhos, 17-DD), France (Sanofi Pasteur, Stamaril[®], 17D-204), Senegal (Pasteur Institute Dakar, 17D-204), and the Russian Federation (Chumakov Institute, 17D-204). There are also vaccines that are made for local uses, including the vaccine manufactured by Sanofi Pasteur US that is used in the US and Canada called YF-Vax[®]. There is also a vaccine produced and distributed locally in China (China National Biotech Group, 17D-204).

From 1937 through 2013, over 600 million doses of YF vaccine have been administered worldwide. However, no placebo controlled studies of efficacy were ever performed for the vaccine. Following the introduction of the vaccine in the late 1930s, the incidence of YF among laboratory workers and endemic areas declined, suggesting it was efficacious. In clinical trials, more than 99% of vaccinated persons develop antibody response at 28 days post-vaccination.

Some of the common adverse events observed for YF vaccine include fever, headache, backache 3 through 7 days after vaccination in 5% to 15% of recipients; and injection site inflammation 1 through 5 days after vaccination in 1% to 30% of recipients. The overall reporting rate for SAEs following YF vaccination in the US population is 4.7 per 100,000 doses distributed. Three SAEs have been clearly described following YF vaccination. This includes anaphylaxis that occurs at a rate of 0.8-1.4 per 100,000 doses. Anaphylaxis is usually seen in persons with pre-existing allergies, and can be the result of a reaction to the egg or chicken proteins, gelatin, or latex. The other two SAEs are neurologic disease (0.4-0.8 per 100,000 doses) and viscerotropic disease (0.3-0.4 per 100,000 doses) [Lindsey et al. *Vaccine* 2008; 26: 6077–6082].

YF vaccine-associated neurologic disease is a spectrum of illnesses related to either direct viral invasion of the central nervous system (CNS) or autoimmune mediated. The most common presentation is meningoencephalitis. Guillain–Barré Syndrome (GBS), acute disseminated encephalomyelitis (ADEM), bulbar palsy, and Bell’s palsy have also been temporally associated with YF vaccination. The absolute number of cases worldwide is unknown, but is likely several hundreds of cases. Illness onset usually occurs at a median of 11 days post-vaccination, with a range of 2 to 28 days. These events are rarely fatal, with five deaths noted to date. These events have been reported predominantly after initial vaccination with YF vaccine.

YF vaccine-associated viscerotropic disease is a severe illness similar to the disease caused by wild-type virus, with vaccine virus proliferating in multiple organs causing multi-system organ dysfunction or failure. To date, over 60 cases have been identified since the event was first recognized in 2001. The illness onset is a median of 3 days post-vaccination, with a range of 1 to 8 days. Viscerotropic disease tends to affect younger females and older males, though the age range between sexes is similar. Of the cases with a known outcome, 63% were fatal. This event has only been reported after initial immunization with YF vaccination.

Most endemic countries require proof of vaccination for all travelers from endemic areas. Certain countries with vectors but without disease, such as India or Australia, require proof of vaccination for all travelers from endemic areas. The US has no vaccine requirements for entry for YF vaccine. YF vaccine is the only vaccine covered by International Health Regulations (IHR). Per these regulations, countries can detain traveler without proof of vaccination for 6 days.

Turning to a status update of YF vaccine recommendations, the last ACIP YF Work Group was formed in 2008 to update previous ACIP recommendations. The work group focused on updating YF epidemiology, including information on the updated IHR from 2005, updating information on vaccine safety, and adding and improving the wording for vaccine precautions and contraindications. The updated recommendations were published in July 2010. Under current ACIP recommendations for the use of YF vaccine in travelers, the vaccine is recommended for persons aged 9 months and above who are traveling to or living in areas at risk for YF virus transmission. Because of the risk of serious adverse events, health-care providers should vaccinate only persons who are at risk for exposure to YF virus or require proof of vaccination for country entry. The vaccine is administered as a single subcutaneous dose, and IHRs allow countries to require revaccination at intervals of 10 years to boost antibody titers. The current contraindications and precautions to YF vaccine administration per the ACIP recommendations are shown in the following table:

Contraindications	Precautions
Allergy to vaccine component	Age 6-8 months
Age <6 months	Age ≥60 years
Symptomatic HIV infection or CD4+ counts <200/mm ³	Asymptomatic HIV and CD4+ counts 200-499/mm ³
Thymus disorder	Pregnancy
Primary immunodeficiencies	Breastfeeding
Malignant neoplasms	
Transplantation	
Immunosuppressive and immunomodulatory therapies	

The Strategic Advisory Group of Experts (SAGE) formed a YF Vaccine Work Group in 2011 to update the World Health Organization's (WHO) YF vaccine recommendations. The group focused on the need for a booster dose every 10 years to maintain protection against YF. The safety of YF vaccine in selected special populations, and co-administration of YF and other vaccines. The updated position paper was published in July 2013. The primary change to the recommendation was the removal of YF vaccine booster doses.

Dr. Staples reviewed the presentation given by the SAGE work group on YF vaccine booster doses as presented to SAGE during their April 2013 meeting. In terms of the overview of YF vaccine immunity as presented to SAGE, no YF vaccine efficacy studies have been performed. Several observations supported the protective effect of the vaccine, including reduction of laboratory-acquired infection in vaccinated workers, development of disease only in unvaccinated persons following vaccine introduction, disappearance of cases in outbreaks when campaign conducted, and protection of monkeys against virulent virus challenge by neutralizing antibodies generated in response to vaccination. These monkey studies have established a log₁₀ neutralization index (LNI) of ≥0.7 correlates with protection¹. However, the correlate of protection using the more common plaque reduction neutralization test (PRNT) has not been established [¹Mason. Appl Microbiol. 1973; 25: 539].

More than 99% of vaccinated persons develop neutralizing antibodies at 28 days post-vaccination. The 10-year booster dose interval was established in 1965 based on two studies documenting roughly 80% of recipients with detectable neutralizing antibodies around 10 years post-vaccination.

A systematic review conducted for the SAGE work group regarding YF vaccine booster doses found that 10 to 20 years post-vaccination, a high proportion of greater than 90% of vaccine recipients had neutralizing antibodies. Of persons vaccinated more than 20 years previously, approximately 80% had detectable neutralizing antibodies. Neutralizing antibodies were detected, at least in one person, as long as 60 years post-vaccination. Twelve vaccine failures were documented within 5 years of initial vaccination out of the over 600 million doses of the vaccine that have been administered to date.

Additional considerations that the SAGE work group discussed included YF disease noted only in unvaccinated persons during outbreaks, such as in Nigeria during the outbreaks that occurred in the 1980s. Data suggest a role for innate and cell-mediated immunity in initial and memory immune response. The SAGE work group also had some issues and concerns with YF vaccine booster dose data, including different PRNT levels used in published studies, making comparability difficult; lack of understanding of protective immunity other than neutralizing antibodies associated with protective immune response, but the level of protective titers is unknown; unknown significance of innate and cell-mediated immunity; natural boosting likely to occur in endemic areas; lack of clarity regarding whether travelers, laboratory personnel, and endemic populations are the same in terms of the need for a booster dose; and limited data suggesting that certain populations might have lower seroconversion rates, such as children, or more rapid antibody decay as observed with HIV-infected persons. Therefore, certain populations might benefit from a booster dose.

To summarize the key findings of the SAGE Work Group on YF Vaccine Booster Doses, no efficacy studies have been performed, and neutralizing antibodies are used as surrogate. The current booster dose recommendation of every 10 years was established under IHR in 1965 and was based on limited data. Most vaccine recipients develop antibody titers and will maintain titers for several decades, possibly life-long, following YF vaccination. Very few primary vaccine failures have been reported, and no secondary vaccine failures have been reported, meaning that no vaccine failures have been noted due to waning antibody levels over time. Both innate and cell-mediated immunity contribute to the initial and memory immune responses. Following this presentation, SAGE issued the following wording regarding YF vaccine booster doses:

“A single dose of YF vaccine is sufficient to confer sustained life-long protective immunity against YF disease; a booster dose is not necessary.”

This recommendation now makes ACIP and WHO YF vaccine recommendations discordant regarding the need for a booster dose. As presented by Dr. Bocchini at the beginning of this session, the focus of the ACIP work group is to develop recommendations regarding YF vaccine booster doses that will be presented to ACIP during an upcoming meeting for a vote.

Discussion Points

Dr. Reingold inquired as to whether travelers will be able to travel to other countries if they are not in compliance with the booster dose, whether there would be changes to the IHR, and whether countries would recognize the new recommendations or if they would still force travelers to acquire a booster dose.

Dr. Staples responded that there have been several discussions, even when SAGE was considering making the change to drop the booster dose recommendation, because IHR is also at WHO. The current IHR have not been addressed at this time, so countries still can require

proof of booster doses. Some countries have indicated that they will continue to require the booster dose. It appears that those who work in the IHR group will be approaching each country individually to ask them to potentially provide waivers about the booster dose requirement or to change their personal requirements for need for a booster dose.

Dr. Plotkin (Vaccine Consultant) said that he was comforted by the SAGE recommendations, but it seemed to him that some things remain missing from our knowledge. For example, he would like to see a study of adverse effects in a population that is receiving vaccine routinely. That would be primarily the African and Brazilian populations. In addition, this is a vaccine that is accompanied by viremia regularly. The viremia is very likely responsible for the viscerotropic and neurotropic reactions. One means that was used years ago was to give gamma globulin with the vaccine. A recent study was published regarding viremia after administration of the vaccine co-administered with immunoglobulin G (IgG) that concluded that IgG did not influence viremia. Dr. Plotkin thinks that result is questionable because the IgG very likely contained little or no YF antibody. One possible study that could be conducted, in animals and humans, is to use gamma globulin obtained from vaccinated individuals, which would have antibody. It would be useful if the vaccine could be given to the elderly together with gamma globulin to prevent the possible reactions by reduction of viremia. Finally, he would be comforted if there was an immunologic study of booster vaccination in individuals who have received a dose of YF vaccine many years previously to determine what type of anamnestic response they have, because the incubation period of YF is not very long. Therefore, one needs the booster response fairly promptly. Although one can discuss innate immune and cellular responses, it is pretty clear that antibody is protective. Although 80% of travelers may have long-lasting antibody, there remain 20% to be concerned about.

Dr. Fryhofer (AMA/ACP) inquired as to whether anyone could update them on what various countries are recommending. Many of her patients have had YF vaccine more than 10 years previously, and many of them are over 60. This is a very expensive vaccine.

Dr. Staples replied that there is some information available. In general, different groups have suggested or supported the SAGE recommendations. The Pan American Health Organization (PAHO), an extension of WHO, has supported and endorsed the SAGE recommendation and many countries have begun to remove the booster dose. Based on a review of their current data, Brazil is continuing to recommend booster doses every 10 years to its population. These data were not available to SAGE, although the ACIP work group is hoping that these data will be available for ACIP, because that swayed Brazil to continue with booster doses.

Dr. Fryhofer (AMA/ACP) noted that while Africa removed the booster dose requirement, it is still shown on the ACIP website as being a requirement.

Dr. Staples responded that there are differences between IHR and requirements versus what a country will choose to recommend for their own population. A country may choose not to recommend booster doses. But for instance, if Columbia removed the booster dose requirement, a person still could be required when traveling to another endemic place in Africa, South America, or India to show proof of a booster dose even if that country does not recommend it anymore. That is a discrepancy between regulations and recommendations.

Dr. Karron emphasized that people lose their YF immunization cards. They might keep them for 10 years, but many people will not keep them for their lifetime. She wondered whether an antibody test would be developed, not to assess protective levels of antibody, but essentially to substitute for the immunization card.

Dr. Staples indicated that there has been some discussion about this among the SAGE work group members in terms of having proof of vaccination. Ultimately, it was determined that having some sort of test that is readily available is not on the horizon in the near future. Unfortunately, IHR requires that whomever issued the original yellow card be the re-issuer if a person loses it.

Dr. Decker (Sanofi Pasteur) said he thought this would remain a confusing area for a while, because unless he was mistaken, the World Health Assembly (WHA) has not yet voted to adopt the SAGE recommendation. That is the first global legal step that has to occur. Then they have to promulgate new IHRs. Then the corresponding countries throughout the world will have to modify their national regulations to reflect the new IHRs. All of that will take a while, and until that all works through the system, this will stay confusing and websites will not quite be up to date. There is no way around that, but eventually, this will probably be adopted worldwide. It has been long recognized that there is life-long immunity from a single effective YF vaccination. The main reason the regulations did not reflect that was administrative. That is, if it is lifetime, how do you handle the paperwork issue? Perhaps now, in the day of computers, a way will be found around that. In any event, once this all works through the system and ACIP modifies the YF recommendations for the US, there will once again be a situation such as that which arose a couple of years ago when ACIP modified the rabies recommendation for the US, and the same situation that Dr. Sun mentioned earlier with regard to possibly dropping a pneumococcal dose, which is that there will be perfectly founded and correct public health national recommendations that are at variance with the package insert. That variance will probably never be reconciled. Dr. Decker said that this was not a reason not to do the right thing, but that he was just pointing it out. With respect to rabies and YF, it is intuitively obvious that giving less vaccine will not result in non-inferior antibody levels. Therefore, there is no way to prove that doing less is not inferior to doing more immunologically, which means under US regulations the only way to modify the package insert is by a randomized, blinded, active controlled clinical trial to show that on the one hand people who do not get a 10-year booster of YF vaccine do not have higher rates of YF disease than people who do get a booster, or people who get 4 doses of rabies vaccine do not have higher rates of rabies following exposure to a rapid animal than people who get 5 doses. Those studies are not going to be done. It is important to recognize that this is going to be a growing dilemma. It is already a dilemma, because when anyone calls Sanofi Pasteur, they are legally required to tell them that they need 5 not 4 doses. It would be really nice if the interagency work group would have a discussion about this, because there ought to be a way for the regulatory authorities in various countries around the world to have an administrative mechanism for reconciling new public health recommendations that are based on valid global experience with the package insert. For example, if the package insert could say what it says now but add, "More recently, ACIP or WHO has recommended . . ." which at least would reduce the level of conflict.

Dr. Temte inquired as to how many doses are administered each year to the US civilian population.

Dr. Staples responded that Dr. Decker could best respond, as Sanofi Pasteur is the sole provider for the US. The military is the largest consumer of the vaccine in the US.

Dr. Decker (Sanofi Pasteur) responded that he would have to check with someone and report back to the committee.

Dr. Schuchat indicated that the program conducted a survey of travel medicine clinics and estimated that approximately 200,000 to 250,000 doses are administered in the US per year to the civilian population.

Dr. Temte indicated that in his state, providers are required to have a YF certificate. He wondered whether that was true across the country.

Dr. Staples responded that this is true across the country. While states control licensure, there is a process for providers to obtain a YF stamp that is necessary to make the yellow cards valid.

Vaccine Supply

Dr. Jeanne M. Santoli
Immunization Services Division
National Center for Immunization and Respiratory Diseases

During this session, Dr. Santoli reported on the vaccine supply status of pertussis-containing vaccines. She indicated that Sanofi Pasteur resumed shipping their pertussis-containing vaccines, Daptacel[®] (DTaP), Pentacel[®] (DTaP-IPV-Hib), and Adacel[®] (Tdap) in mid-October 2013. While product availability continues to increase, supply is expected to remain constrained over the next several months as inventories rebuild.

GlaxoSmithKline (GSK) has taken steps to meet increased demand for pertussis-containing vaccines and anticipates being able to address gaps related to constrained supply, using a combination of products and presentations. However, during this time period, backorders and delays in deliveries may occur related to Tdap vaccine, but these are expected to be short in duration. Also, provider preference for vaccine presentation (syringes/vials) may not be able to be accommodated at all times during this period.

CDC's Vaccine Supply/Shortage Webpage can be found at:
<http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm>

Discussion Points

Dr. Grogg (AOA) inquired as to whether there were any supply problems with YF vaccine.

Dr. Santoli replied that there is a supply issue with regard to YF vaccine. CDC's focus is on the vaccine contracts for routine vaccines for which the agency is responsible, so she was unable to discuss any data there may be for YF vaccine. She called on the manufacturer to address this question.

Dr. Hosbach (Sanofi Pasteur) indicated that they were still working to determine for ACIP the total number of doses distributed annually. During the first quarter of 2014, there was a manufacturing delay. While there are constraints, vaccine is still available. Normal supply is anticipated to resume by April.

Day 1: Public Comment

No public comments were offered during this session.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Schuchat announced that the week of April 28th would be the next National Infant Immunization Week. This year, CDC plans to mark the 20 years since the Vaccines for Children (VFC) Program was implemented as a special highlight to that week. In addition, a recent issue of *The Pediatric Infectious Disease Journal* highlighted the rotavirus burden in Africa as a way to promote the introduction of rotavirus vaccines throughout Global Alliance for Vaccines and Immunisation (GAVI)-eligible countries. Also, an intergovernmental board that is somewhat like ACIP has been established to advise CDC on immunization information systems and the agency's strategic plan, in order to acquire the best of state and local governmental IT thinking about how to best improve immunization systems information technology underpinnings.

Centers for Medicare and Medicaid Services (CMS)

CMS has a couple of updates that Dr. Temte has graciously agreed to share. CMS is sorry that we are not able to attend the meeting in person. However, we are participating by phone and will address any issues that come up during the meeting.

Medicare Flu Vaccine Data: CMS has worked with the Health Resources and Services Administration (HRSA) and the National Vaccine Program Office (NVPO) to post Medicare flu vaccination information for those in fee-for-service on the NVPO website. The website is <http://www.hhs.gov/nvpo/flu-vaccination-map> and is updated weekly.

Coverage of Preventive Services for Adults Currently Enrolled in Medicaid. While the benefit package for adults who receive health care coverage under the Affordable Care Act (ACA) is required to include coverage of preventive services, including coverage of all ACIP recommended vaccinations, states continue to have the option to cover preventive services for adults currently enrolled in Medicaid. The Affordable Care Act addressed this by including a provision (section 4106) that provides an incentive to states that provide coverage of all ACIP recommended vaccines and their administration as well as the Grade A/B US Preventive Services Task Force (USPSTF) recommended services. To date, eleven states have submitted a request to CMS to cover these services and receive the incentive and 8 states have been approved (California, Colorado, Kentucky, Nevada, New Hampshire, New Jersey, New York, and Ohio). CMS continues to work with all states to encourage coverage of preventive services.

Ms. Pellegrini noted that this really does have meaningful impact for many people. In particular, March of Dimes is working with a number of states. For example, Louisiana is not currently covering tetanus and reduced diphtheria toxoids (Tdap) for pregnant women.

Department of Defense (DoD)

Dr. Geibe reported that DoD service members (e.g., Active Duty, Reservists, National Guard) reached a 90% influenza vaccination rate as of December 2013 and was at approximately 95% at the time of this meeting. The challenge always seems to be catching up with Reservists and others because they are spread out. He quipped that while he was in great competition with the Veteran's Administration (VA) and Indian Health Services (IHS), DoD can force its members to get their shots a little quicker, so it always works out. Regarding Japanese encephalitis vaccine, there have been ongoing efforts in Japan and Korea to expand screening and vaccination based on areas of risk, which continues to be a challenge. DoD is offering human papillomavirus (HPV) to males and females during their routine appointments, and is working to target the adolescent population to help improve completion rates as well. Regarding smallpox vaccine, DoD recently updated its screening forms to clarify questions and ensure safety based on customer feedback, but made no real changes in the program. Vaccination against adenovirus types 4 and 7 continues, which was instituted in all military basic training centers in November 2011. Since then, febrile respiratory illness rates and the proportion of febrile illness related to adenovirus among the recruit population has decreased dramatically. In 2013, there were only a few rare sporadic cases in the recruit population, so this has proven to be a success.

Department of Veteran's Affairs (DVA)

Dr. Kinsinger reported that the DVA has recorded nearly 2 million influenza doses administered to its veteran patients thus far, and continues to promote the delivery of influenza vaccine. The DVA's influenza surveillance data matches very closely with national trends in terms of the number of cases and proportion of Influenza A, and the largest number of hospitalizations are in the 45 through 64 year old age group just as in the national data. DVA is working on a number of immunization IT-related projects to improve data collection and data records so that they are easier to use. DVA's wonderful electronic medical record (EMR) was built over the years locally and has been in place for a long time; however, it needs to work much more carefully together. DVA is working on a number of projects with the Indian Health Service and CDC to develop a composite influenza vaccine measure. To improve information for its providers, DVA has developed two algorithms—one for pneumococcal vaccines and the other for meningococcal vaccines. Given that those are such complicated vaccines, the decision was made to develop visual graphics to walk providers through when to administer each vaccine.

Food and Drug Administration (FDA)

Dr. Sun indicated that since the last ACIP meeting, FDA approved Q-Pan H5N1, which is an adjuvant influenza vaccine that has an indication for those 18 years of age and older. Q-Pan H5N1 is a 2-dose vaccine that is mixed prior to administration and is given 21 days apart. The FDA also has been working very closely with CDC and the sponsor to address the use of meningococcal B vaccines for the outbreaks on college campuses. Dr. Sun also indicated that on February 28, 2014, the FDA advisory committee would meet for the 2014-2015 influenza strain selection meeting.

Health Resources and Services Administration (HRSA)

Dr. Houston indicated that the Notice for Proposed Rule Making to amend the Vaccine Injury Compensation Table to add intussusception as an adverse event associated with rotavirus vaccines was published July 24, 2013. The public comment period has ended, and a second public comment hearing will be scheduled soon. The Advisory Commission on Childhood Vaccines (ACCV) made recommendations to amend the Vaccine Injury Compensation Table during the September 5, 2013 and December 5, 2013 meetings based on the Institute of Medicine's (IOM) review of the scientific literature on vaccines and adverse events. These recommendations are being considered. Finally, increasing numbers of petitions are being filed with the National Vaccine Injury Compensation Program each year. In fact, this has increased by 100 petitions from 2012 to 2013, and more claims are being compensated each year.

Indian Health Services (IHS)

Ms. Groom shared preliminary data on influenza vaccination of IHS's healthcare personnel, reporting that after four years of stagnating and remaining at about 74%, there has been a slight increase to approximately 78%. Though still far short of the Health People 2020 goal, at least IHS is making some progress. In addition, IHS has been working in collaboration with the VA on a developmental performance measure for the IHS that would be a composite measure to assess what proportion of adults have been appropriately vaccinated for age with the routinely recommended vaccines. Consideration is being given to rolling that out to IHS sites, and developmental data will be collected on that.

National Institutes of Health (NIH)

Dr. Gorman highlighted three efforts underway at the National Institutes of Health (NIH). There is a new series of efforts to develop a vaccine to protect against respiratory syncytial virus (RSV), which is a leading cause of illness and hospitalization among very young children. A recent report was published in *Science* from an National Institute of Allergy and Infectious Diseases (NIAID) researcher. Two pharmaceutical companies are also working on early stage RSV vaccines, and they will soon be moving into early clinical trials. In terms of partnerships, NIH has entered into the Accelerated Medicines Partnership, which is a venture between NIH and 10 biopharmaceutical companies and several non-profit organizations that hopes to transform the current model for developing new diagnostics and treatments by jointly identifying and validating promising biological targets of disease. The ultimate goal is to increase the number of diagnostics and therapeutics for patients, and reduce the time and cost of developing them. For each pilot that NIH and industry select, research plans will be developed aimed at characterizing effective molecular indicators of disease called "biomarkers," and distinguish biological targets most likely to respond to new therapies. Third, a report was recently published on the NIAID Bacterial Resistance Program that describes the ongoing research portfolio of the basic translation and clinical research in antibacterial resistance, and the combination of innovation approaches based on the latest scientific advances to be pursued. These strategies draw on the multidisciplinary partnerships which are essential for receiving a coordinated and nimble approach to addressing antibacterial resistance threats as they emerge. Since that report was published, NIH has been approached by another consortium of pharmaceutical companies to create a "Living Protocol," which Dr. Gorman hopes to be able to report on during the June 2014 ACIP meeting.

National Vaccine Advisory Committee (NVAC)

Dr. Orenstein reported on a couple of issues pertaining to the last National Vaccine Advisory Committee (NVAC) meeting on February 11-12, 2014. There was a forum on vaccine research, development, and innovation. This included a demonstration of the IOM-developed “Smart Vaccines” tool, and assessing various values of cost, health burden, effectiveness, safety, and public demand and how that influences vaccine priorities and ranking. In addition, Biomedical Advanced Research and Development Authority (BARDA) discussed how it incentivizes development of products that it considers to be high priority. There was a stimulating talk by Dr. Stanley Plotkin dealing with issues of motivating development of new and high priority products, which NVAC will continue to follow. *Standards for Adult Immunization Practices* is now published in *Public Health Reports*, and plans were discussed to implement these standards and track implementation. NVAC has three ongoing work groups, including: 1) Vaccine Acceptance and Confidence, 2) HPV Vaccines, 3) Maternal Immunization. There is a cancer panel that is trying to improve HPV vaccine uptake, and that report is available on the NIH website. The Maternal Immunization Work Group is dealing with how to improve implementation of ACIP recommendations for vaccination of pregnant women. This group is reviewing NVAC comments and expects to put that out for public report sometime during the second week of March 2014, with a final vote on recommendations expected during the June 2014 NVAC meeting. The report urges ACIP to consider developing a statement for pregnant women so that for obstetrical providers and others, there would be one place to turn to obtain information.

National Vaccine Program Office (NVPO)

Dr. Gellin noted that the CMS report included highlights about FluMap, and he encouraged everyone to look at this. The map enables users to drill down to view influenza in the CMS population at the community level. There has been great feedback from the National Association of County and City Health Officials (NACCHO) on how helpful this is at the local level. Related to that, the National Vaccine Program Office (NVPO) has also been working with the HealthMap group at Harvard. This was initially the HealthMap Flu Vaccine Finder, which has now morphed to the Adult Vaccine Finder. This is part of a larger effort to encourage adult vaccination more broadly. In addition, an effort is being made to have IOM demonstrate the “Smart Tool” during the June 2014 ACIP meeting. The first annual report on *The State of the National Vaccine Plan* is on the NVPO website. This report offers an update on progress toward that plan. Dr. Gellin said he was particularly excited about having outside commentaries from a number of people in the field who offered their perspectives. He also reported that a funding opportunity announcement (FOA) had been published titled “Mobilization for Health: National Prevention Partnership Awards (NPPA),” which recognizes the importance of partnership. This FOA is located on the Assistant Secretary for Health’s website for those who are interested. Dr. Gellin emphasized that the application deadline would be March 3, 2014 by 5:00 pm Eastern Time (ET). Finally, in late March 2013, NVPO convened a meeting on pertussis. A report on this meeting is anticipated to be published in a *JID* supplement in March 2014.

General Recommendations

Introduction

Dr. Jeff Duchin ACIP General Recommendations Working Group Chair

Dr. Duchin reminded everyone that the General Recommendations document is published by the *MMWR* every 3 to 5 years, and addresses a broad range of clinical practice issues that are relevant to all vaccines as opposed to the vaccine-specific publications. The General Recommendations are intended to address topics that cannot be attributed to a single vaccine, but that are germane to the practice of immunization in general. A number of topics have been or are being revised, including the following:

- 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

The topic addressed during this session was *Storage and Handling of Immunobiologics*. The remaining sections to be revised and discussed in future meetings include:

- Altered Immunocompetence
- Vaccination Programs
- Vaccination Information Sources

Dr. Duchin encouraged ACIP members and others to review the proposed revisions and provide feedback. He also called attention to a recent publication that Dr. Rubin led for the Infectious Disease Society of America (IDSA) pertaining to guidelines for the vaccination of immunocompromised hosts. This topic is also addressed in the General Recommendations, but the IDSA guidelines go into a lot more detail and provide guidance for clinicians based on a variety of levels of evidence from high quality down to expert opinion on various areas, some of which are not addressed by ACIP. There are some conflicting recommendations between ACIP and IDSA, so it would be helpful for ACIP members to review the IDSA guidelines so that the General Recommendations Work Group can be made aware of those.

Storage and Handling of Immunobiologics

Dr. Andrew Kroger

General Recommendations Working Group

During this session, Dr. Kroger provided an update on the proposed changes to the *Storage and Handling of Immunobiologics* section of the General Recommendations. The following topics were covered in the 2011 General Recommendations document, which is brief:

- Storage Temperature
- Storage Units
- Temperature Monitoring
- Response to Out-of-Range Temperature Reading
- Expiration Dates and Windows
- Multidose Vials

Since the General Recommendations were published in 2011, CDC's Storage and Handling Toolkit, which is posed on CDC's website, has been extensively revised. This tool contains best practices information for both public and private providers, and includes precise and exhaustive details on the following topics:

- Storage Units
- Temperature Monitoring
- Expiration Dates and Windows
- Multidose Vials

The website link for the toolkit is: www.cdc.gov/vaccines/recs/storage/toolkit/default.htm Dr. Kroger noted that in the draft of the General Recommendations supplied to the ACIP members, there were extensive strikeouts because the General Recommendations Work Group believes that these topics are adequately covered in the toolkit and do not need to be in the ACIP recommendations. Topics in the Storage and Handling Toolkit include the following:

- Best Practices, which breaks down into the following:
 - Equipment considerations for storage units and thermometers
 - Maintaining the cold chain
 - Routine storage and handling practices
 - Inventory management
 - Emergency procedures for protecting vaccine inventories
 - Equipment considerations for storage units and thermometers
 - Stand-alone units preferred
 - Use of glycol-buffered probes
 - Maintaining the cold chain
 - Required temperatures
 - Routine storage and handling practices
 - Positioning of vaccine
 - Labeling trays and containers
 - Inventory Management
 - Interpreting expiration dates
 - Emergency procedures for protecting vaccine inventories
 - Transporting to off-site facilities

The Storage and Handling Toolkit is CDC-cleared, and it represents best practices for the public and private sectors. It is harmonized with the VFC regulations described in the VFC Operations Manual.

The following topics will be retained in the ACIP General Recommendations:

- ❑ Retaining the table of temperature ranges (Draft, Page 4)
- ❑ Categories of vaccine
 - Nonlyophilized, aluminum-adjuvanted vaccines
 - Lose potency when exposed to freezing temperatures
 - Nonlyophilized non-aluminum adjuvanted vaccines
 - Might lose potency if exposed to freezing temperatures
 - Lyophilized (nonvaricella) vaccines
 - Do not need to be frozen (but lyophilized pellet can be with exception of MenHibrix pellet)
 - Varicella-containing vaccines
 - Must be kept frozen or vaccine virus will degrade
 - Noninjectable vaccines
 - Do not freeze
- ❑ Response to Out-of-Range Temperature Reading (not specifically covered in the toolkit, so it is important to maintain in the General Recommendations)
 - Have a plan ahead of time
 - Mark vaccine “do not use”
 - See if temperature deviation has a resolvable solution
 - Door left open
 - Unplugged
 - Move vaccine to alternate site
 - Contact state/local health department or manufacturer to determine if vaccine is viable (this is not new language)
 - If doses already administered, contact state/local health department
 - Sample language: As a general rule, vaccines that have been stored at inappropriate temperatures should not be administered unless public health authorities or the manufacturer determine it is safe to do so. (Draft, Page 3, Line 28)
 - Sample language: If such vaccines already have been administered, vaccine exposed to inappropriate temperatures that is inadvertently administered should generally be repeated. Clinicians should consult promptly with state or local health departments in these situations. Consultation with CDC is available when necessary. (Draft, Page 3, Line 31)
- ❑ Table of Storage Temperatures
 - Added PRP-T Hib-MCV2 (MenHibrix[®])
 - Added new minimum temperatures for all varicella containing vaccines (negative 58 degrees Fahrenheit, negative 50 degrees Celsius)
 - Most storage units cannot reach this temperature
 - The cutoff is emphasized because transport on dry ice can cause variations in temperature, perhaps as low as negative 58 degrees Fahrenheit
 - Lead to increased gas permeability of rubber vial, theoretically compromising sterility (especially in presence of water vapor (dry ice))

- Removed the “Comments” column, given that the most precise information on light sensitivity and degree of thermostability can be found in the FDA product information
- A snapshot of the Vaccine Storage Temperature Recommendation Table (Page 6) is as follows, although the column labels are not shown and are Vaccine, Storage Temperature, and Diluent Storage Range from left to right:

Varicella-containing vaccines		
MMRV [†]	-58°F--5°F (-50°C to -15°C)	35°F--77°F (2°C--25°C) Can be refrigerated or stored at room temperature
Varicella [*]	-58°F--5°F (-50°C to -15°C)	35°F--77°F (2°C--25°C) Can be refrigerated or stored at room temperature
Herpes zoster [*]	-58°F--5°F (-50°C to -15°C)	35°F--77°F (2°C--25°C) Can be refrigerated or stored at room temperature

- ❑ Updated Temperature Logs (borrowed from the Immunization Action Coalition; shown in the samples below)
 - One for refrigerator storage, one for freezer storage
 - Has spaces to log the maximum and minimum temperature of the day (per new best practice recommendations)
 - Does not have spaces to check off a box if the temperature is out of range
 - Emphasizes the need to take immediate action if temperature is out-of-range

Discussion Points

Dr. Rubin noted that his hospital, a multi-dose vial expires after 30 days regardless of the expiration date on the vial. He did not know where that came from, or how that conflict is resolved in other places.

Dr. Kroger responded that this is an inventory issue and reading the expiration date on the vial. That is in the toolkit, but will not be mentioned in detail in the General Recommendations any longer. United States Pharmacopeial (USP) was one of the first organizations to post information about the 30-day open rule. There are certain vaccines for which the package insert states a longer period of time for multidose vaccines that need to be entered and reconstituted. The meningococcal polysaccharide vaccine was one of these. Most vaccines in use are in single dose vials that have the 30-day recommendation. Therefore, this is not believed to be a major issue. The details will be in the Storage and Handling Toolkit.

Ms. Hayes (ANA) added that she was fairly certain that it was a Joint Commission requirement in hospitals to discard a product after 28 days, which probably does not apply in the outpatient setting.

Regarding the response to an out-of-range temperature, Dr. Hahn (CSTE) suggested that perhaps the language should read “should not be administered unless determined to be safe and effective to do.” Usually, the concern is more about loss of efficacy than safety. Regarding the diluent temperature, she wondered whether there could be confusion in terms of the third column for varicella vaccines and whether people may misinterpret that as being the vaccine temperature range. Perhaps it should be separated more clearly.

Dr. Kroger responded that this revision could be made, and that he would ensure that this would not be too redundant with other language that appears later. Regarding diluents temperature, he emphasized that what he showed was a snapshot of the table. The top header of the entire table that contains all of the vaccines will indicate what the columns stand for. He will review the table to ensure that it is clear that one table is vaccine temperature and the other is diluent temperature.

Dr. Temte inquired as to what type of ongoing training VFC and non-VFC sites receive, and how the recommendations are translated into action. He also wondered about the percentage of VFC versus non-VFC sites.

Dr. Moore (AIM) responded that immunization programs work with the VFC providers very carefully. Extensive training is conducted using CDC materials, and AIM is extremely appreciative of the newest materials that have been developed, including the more detailed toolkit. People can also complete online modules on their own, and there are requirements for all VFC providers to undergo education in storage and handling annually that have recently begun to kick in. Site visits are conducted at least every other year, if not more often, with VFC providers. There is no direct involvement of programs in supervision of those who administer vaccines outside of the VFC program. However, tools are available for them to acquire training on their own through the CDC website. In terms of the breakdown of VFC versus non-VFC sites, while she did not have specific numbers, Dr. Moore noted that most pediatric practices and a good number of family physicians participate in VFC. The VFC would not comprise a large component of adult vaccines and vaccines administered through pharmacies.

Dr. Schuchat added that most VFC providers are also providing vaccines to publicly insured people. There are over 40,000 VFC provider sites. CDC has also made efforts to be clear that pharmacies can be VFC providers if they follow the requirements; however, site visits are not being conducted to the adult only providers. There are potentially other oversight groups that address that.

Dr. Temte said his impression was that because pharmacies are used to maintaining inventory at appropriate temperatures and so on, that is not as much of a concern as it would be in the private adult practice that has some inventory, but does not participate in VFC.

Dr. Foster (APhA) replied that APhA monitors storage and handling quite carefully. However, there is probably not 100% compliance with all of the rules of the toolkit. The toolkit has been distributed to pharmacists, but this remains a corporate decision for many pharmacies in terms of what they do. Some comply and some do not, given that there really has not been any enforcement. Pharmacies do have other medications and requirements, and those are well-monitored.

Dr. Schuchat added that the Office of the Inspector General reviewed storage and handling in the VFC program a couple of years ago and found a number of concerns. CDC issued a corrective action plan, and much of the training and toolkit are in response to these findings. There has been a major uptick in accessing the toolkit and training, which reflects the work that CDC programs and states have been doing in terms of training materials.

Safety of Tetanus, Diphtheria, and Acellular Pertussis (Tdap) Vaccine

Introduction

Art Reingold, MD Chair, ACIP Pertussis Vaccine Work Group

Dr. Reingold reminded everyone that the current ACIP recommendations for Tdap and Td are for a single Tdap dose for all persons aged 11 years and older, with preferred administration at 11 or 12 years of age. Pregnant women are recommended to receive Tdap with every pregnancy. A decennial Td booster is recommended for those who have received 1 Tdap 5 years for wound management.

The Pertussis Vaccine Work Groups (WG) terms of reference are to:

- Review existing statements on infants and young children (1997), adolescent (2006), adults (2006), and pregnant and postpartum women and their infants (2008) and consolidate into a single statement.
- Review new data on Tdap including:
 - Effectiveness of ACIP recommendations
 - Interval between Td booster and Tdap
 - Use of Tdap in adults ages 65 yrs and older
 - Pregnant and breastfeeding women
 - Use of Tdap
 - Cocooning strategies
 - Vaccinated HCP and need for postexposure prophylaxis
 - Tdap revaccination
 - Pregnant women
 - Healthcare personnel
 - “Cocooning”
- Review updated epidemiology of tetanus and diphtheria

Recent WG activities have included reviews and discussion of the following:

- ❑ Pertussis in healthcare personnel, including a review of epidemiology, post-exposure prophylaxis practices, Tdap coverage, and cost-effectiveness models and discussion regarding the need for additional Tdap boosters
- ❑ Epidemiological and clinical significance of pertactin deficient *B. pertussis*
- ❑ Baboon model data on pertussis transmission and infection after vaccination
- ❑ Vaccinating pregnant women, including information about ACOG and CDC activities, and Tdap safety in pregnancy (VAERS, VSD)

With regard to the context for this session, in June 2011 ACIP recommended a single dose of Tdap for pregnant women who previously have not received Tdap. In October 2012, ACIP recommended a dose of Tdap during each pregnancy, irrespective of the patient's prior history of receiving Tdap. ACIP supported ongoing safety monitoring and requested that CDC commit to safety studies for Tdap given during pregnancy, especially to women who have previously received Tdap.

There are a number of monitoring activities underway for maternal Tdap safety, including ongoing monitoring through VAERS, coverage data and safety studies through VSD, and a clinical study of Tdap safety in pregnant women to be implemented during 2014 through CISA. During this session, the CDC ISO presented updates from VAERS and VSD on the safety of Tdap vaccine during pregnancy.

Safety of Tdap During Pregnancy: Enhanced Surveillance in VAERS

Pedro L. Moro, MD, MPH
Immunization Safety Office
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention

Regarding background, Dr. Moro reminded everyone that on October 11, 2011, ACIP voted to recommend that unvaccinated pregnant women should receive a dose of Tdap. On October 24, 2012, ACIP voted to recommend the use of Tdap during every pregnancy irrespective of the patient's prior history of receiving Tdap. The optimal timing for Tdap administration is between 27 and 36 weeks gestation. Tdap is not approved for repeat doses, and ACIP has not previously recommended repeat doses in other populations. No pre-licensure trials for Tdap were conducted in pregnant women.

In a review conducted in VAERS for the period 2005 through 2010 before the routine recommendation, 132 reports to VAERS in women who received Tdap^a during pregnancy or infants exposed in utero were reviewed.^b In this study 77% of reports had Tdap during first trimester, many of which were inadvertent exposures, and 42% described no adverse events. There were no unusual or unexpected patterns of maternal, fetal, or infant outcomes. Some selected outcomes identified in that study included 22 spontaneous abortions, 2 fetal deaths, 2 preterm births, and 1 major birth defect (gastroschisis) [^aZheteyeva et al. Safety of Tdap in pregnancy. *Am. J. Obstet Gynecol.* 2012;207:59.e1-7.; ^bBefore routine recommendation for Tdap in pregnant women].

The objective of the review was to describe adverse event reports submitted to VAERS of pregnant women or their infants who received Tdap during the time period 10/2011 through 01/2014, since the ACIP recommendations. In terms of the methods, enhanced surveillance was initiated on November 26, 2012. A search was conducted in the VAERS database for reports of pregnant women or infants exposed in utero after administration of Tdap during the time period 10/11/2011 through 01/31/2014. "Exposure during pregnancy," "drug exposure during pregnancy," "maternal exposure during pregnancy," and other specific pregnancy MedDRA codes were used to search for these reports. Serious reports classified based on the Code of Federal Regulations included death, life-threatening, hospitalization, prolonged hospitalization, and permanent disability (exception: hospitalization for normal delivery was not considered to be a serious report).

As a reminder, VAERS is a spontaneous reporting system that is co-administered by the FDA and CDC. Its strengths are that it allows for rapid signal detection, can detect rare adverse events, generates hypotheses, encourages reports from healthcare providers and accepts reports from patients and others, and data are available to the public. VAERS' limitations include reporting bias (e.g., underreporting, stimulated reporting), inconsistent data quality and completeness, inability of the design to assess whether a vaccine caused an adverse event, lack of an unvaccinated comparison group, and lack of a field for pregnancy (making it difficult to search for reports).

Medical records were requested and reviewed for all pregnancy reports associated with Tdap. Reports describing maternal and infant events in the same report were treated as separate reports. The records were queried for prior administration of tetanus-containing vaccines. In addition to vaccination records, the provider or patients were queried regarding whether they were exposed to Tdap in the past. A descriptive analysis of adverse events reported was conducted.

In terms of the preliminary findings, thus far a total of 90 reports have been received. Of these reports, 22% describe an adverse event of which 16% were serious. The main type of reporter was the provider (38%), followed by the manufacturer (38%), other (14%), and the patient/parent (11%). Tdap was the only vaccine administered in 62% of the reports. Most women (55%) received Tdap vaccine during the third trimester. Some of the pregnancy-specific adverse events that were reported included premature delivery at < 37 weeks (n=5), spontaneous abortion at < 20 weeks gestation (n=4), stillbirth (n=4; one with trisomy 12), gestational diabetes (n=2), oligohydramnios (n=2), preeclampsia (n=2), chorioamnionitis (n=2), polyhydramnios/macrosomia (n=1), placenta previa (n=1), abruptio placentae (n=1), nausea and vomiting (n=1), and increased blood pressure (n=1).

There were 6 infant or fetal adverse events, with 1 each of the following: ectopic kidney in newborn (pregnant patient vaccinated at 17 weeks; major birth defect), hypoplastic left heart syndrome (pregnant patient vaccinated at 1.4 weeks; major birth defect), polydactyly (pregnant patient vaccinated at 28 weeks), intrauterine growth restriction, neonatal respiratory disorder, and lockjaw in infant (patient required hospitalization). Non-pregnancy-specific adverse events included injection site reactions and pain in extremity/myalgia (n=19); thrombocytopenia (n=4); non-anaphylaxis allergic reaction (n=4); systemic reactions including fever, chills, and headache (n=4), and 1 each GBS, transverse myelitis, anaphylaxis, hypothyroidism, pyrexia, chronic hypertension, and urinary tract infection. VAERS received 10 reports of pregnant women who were exposed to Tdap in the past. The interval between the current and previous Tdap vaccines for the adverse events reported ranged from 7 days to 3.8 years.

In terms of a comparison of the safety data in VAERS before and after the routine recommendations for Tdap during pregnancy, before the routine recommendation most women (77%) received Tdap during the first trimester. Many of these exposures were inadvertent. After the routine recommendation, most women (55%) received Tdap during the third trimester. The proportion of serious reports increased from 5% before to 16% after the routine recommendation. There also has been an increase in the proportion of some adverse events (preterm birth, stillbirth, major birth defects, injection site reactions). These are changes that were expected to occur due to the new recommendations.

In summary, compared to the period prior to the routine recommendation for Tdap during pregnancy, an increase was observed in the proportion of serious reports; pregnancy-specific outcomes that occur after the first trimester (e.g., stillbirths, preterm deliveries); and non-pregnancy specific outcomes (e.g. injection site reactions) following the routine Tdap recommendation during pregnancy in VAERS. In addition, there was a decrease in the number of reports describing no adverse events. Most vaccinations were administered during the second and third trimesters. Changes in reporting patterns are likely due to the new routine Tdap recommendation, increased awareness, and differences in the trimester of vaccination.

In conclusion, no new unexpected vaccine safety concerns have been noted among pregnant women who received Tdap or their infants. A limited number of pregnancy reports with repeat Tdap doses have been received by VAERS. CDC will continue to monitor the safety of Tdap vaccine during pregnancy, with special emphasis on repeated doses of Tdap.

Discussion Points

Dr. Temte reminded everyone that with the October 2012 vote to recommend Tdap for every pregnancy, there was a request to have updates on safety at every subsequent ACIP meeting until such time as there is sufficient accumulated wisdom on this program.

Dr. Reingold thought it would be fairly simple to add an indicator on the VAERS form regarding whether a woman is pregnant, and was curious as to whether consideration has been given to doing so.

Dr. Moro replied that the VAERS form is in the process of being changed, and will include a field for pregnancy and perhaps some additional information (e.g., gestational age or LMP). However, it could take two to three years for this process to be completed.

Ms. Hayes (ANA/ACNM) asked whether the rate of adverse events was calculated for the pre-recommendation timeframe based on the number of pregnancies that were completed to full-term. The rate of miscarriage during the pre-recommendation phase was quite high compared to the post-recommendation timeframe. Therefore, the number of full-term pregnancies differed in the two study group populations. She recommended that consideration be given to assessing those data differently. Regarding the rate of these occurrences overall in all pregnancies, it is helpful to look at how often these events occur in the normal pregnancy population compared to this population, because for most of these adverse events, the rate is no different.

Dr. Moro replied that the proportions shown were based on the total number of Tdap pregnancy reports received, and are not representative of the population and should not be thought of in comparison to the background rate in the general population.

Ms. Hayes (ANA/ACNM) clarified that she was recommending that a comparison be made to the background rate in the general population.

Dr. Temte inquired as to whether brand-specific information was being received with the VAERS reporting, and to whether any differences were being observed between the two.

Dr. Moro responded that certain adverse events could be assessed by brand, but this has not yet been done. Most of the reports (57) have been Adacel[®], and about a third have been Boostrix[®].

Dr. Riley (ACOG) inquired as to whether there was a sense of how many women received influenza vaccine and Tdap simultaneously out of this population.

Dr. Moro replied that the most common vaccine given along with Tdap was TIV in about 21% of the reports.

Dr. Harriman pointed out if the trimester the vaccine was given was known, along with certain adverse events in a fetus that occur at a certain developmental phase of pregnancy, if a vaccine was given in the third trimester and an adverse event was known to occur during the first trimester, it would be nice to tease that out.

Dr. Moro responded that for these reports, this information was provided. For example, for the ectopic kidney event in the newborn, the pregnant patient was vaccinated at 17 weeks. For the infant with hypoplastic left heart syndrome, the pregnant patient was vaccinated at 1.4 weeks.

Dr. Duchin wondered whether the numbers shown for various conditions for women who received Tdap in the third trimester were any different from those who received TIV alone without Tdap in the third trimester. The concern was that there may be some unique potential adverse events associated with the administration of Tdap to women repeatedly in the third trimester. Influenza is also believed to be a very safe vaccine that has been recommended for administration in pregnant women as well. So he was curious as to whether the spectrum of adverse events being reported for Tdap were any different than those report among women who receive just TIV in the third trimester.

Dr. Moro indicated that for the current season, for some of the events TIV was comparable to Tdap. For example, the rate of spontaneous abortions is similar for TIV and Tdap. This is also very comparable in previous seasons. Nothing of concern has been observed.

Dr. Schuchat reminded everyone that VAERS data do not provide rates. The analysts are assessing the proportion of VAERS reports that have a particular conditions. It is really helpful for the ACIP members to suggest additional analyses they would like to see with these passive data that they believe would be useful, and she thought the next presentation regarding the VSD would be helpful with regard to information about rates. The point of VAERS is just for signal detection.

Dr. Plotkin (Vaccine Consultant) was troubled by the fact that 45% of women were receiving Tdap before the third trimester. This is not influenza. In the case of influenza, the goal is to protect the pregnant women. In the case of Tdap, the goal is the transmission of passive antibody to the infant. Vaccinating with Tdap in the first or second trimester is not deriving the maximum benefit from the vaccination. There is also the issue of confusion with congenital anomalies if vaccine is given in the first trimester, which could damage the idea of safety of

vaccinations during pregnancy. Thus, it seemed to him that the ACIP recommendation should be stronger for third trimester vaccination than for earlier vaccination.

Dr. Schuchat pointed out that these data do not indicate in what trimester women are getting Tdap. These are reports of adverse events and what the circumstances were, but this is not the denominator of when women are getting vaccine in pregnancy. The comment about ensuring high antibody levels at birth is important, but it should not be assumed that 45% of the Tdap doses are being given before the third trimester because that is not what VAERS can tell us.

Dr. Moore (AIM) is already receiving many questions in her state about how adverse event reporting will be dealt with, given the goal for as many women as possible to receive Tdap and influenza vaccine. During pregnancy, almost anything is going to be temporally associated with administration of those vaccines because of the narrow windows in which they are given. Adverse events occur naturally during pregnancy, and that correlation is going to be a challenge. She wondered whether there were any signals in the VAERS data that warrant further attention based on the data presented during this session.

Dr. Moro replied that no signals have been detected in VAERS. Of course, these adverse events will continue to be monitored.

Dr. Reingold noted that several women had received a Tdap vaccine fairly recently before the dose in question. One received the dose 7 days before, another 29 days before, and another 159 days before. He was curious as to whether a minimum is given in the recommendation that indicates that if a woman has had a dose within a certain time period, she does not need yet another dose during pregnancy.

Dr. Temte clarified that the recommendation is for a dose during pregnancy, preferably between 27 and 36 weeks.

Dr. Tom Clark (SME) clarified that it is one dose with each pregnancy, preferred in the third trimester. It would be odd for a woman to discover that she was pregnant in the third trimester 7 days after the previous dose, but the recommendation would still be one dose even if it was somewhat too early.

Dr. Karron inquired as to whether there was a mechanism to know when in pregnancy women are getting vaccine.

Dr. Schuchat indicated that the next presentation would give the details of a managed care population denominator and numerator. In addition to that, CDC is periodically conducting national surveys of Tdap coverage, which would include timing for those who are pregnant. That is not going to be done annually at this point, but that information will be periodically updated. The National Health Interview Survey (NHIS) of adult immunization is one of the ways that Tdap in adults is monitored. There is only one time point so far on that, but there will also be data monitoring through the Pregnancy Risk Assessment Monitoring System (PRAMS) and some other systems.

Tdap During Pregnancy: Safety and Coverage Data from the VSD

Elyse Olshen Kharbanda, MD, MPH
Health Partners Institute for Education and Research

During this session, Dr. Kharbanda presented updated estimates of Tdap coverage during pregnancy within 7 of the VSD sites, as well as data on Tdap safety during pregnancy from the VSD's large observational cohort. All 7 VSD sites contributed data for this study, and all 7 sites contributed data on Tdap coverage. The safety data are only from the California VSD sites, given that for the time period studied, the majority of Tdap vaccinations during pregnancy occurred in California. For this cohort, pregnancies from the 7 VSD sites were identified from claims and electronic health record data using an automated, validated algorithm.

Using standardized VSD vaccine files, all vaccines administered to pregnant women in the cohort starting in 2005 and ending at 6 weeks postpartum were included. In the coverage data, Tdap administrations were assigned as pre-pregnancy, during pregnancy, or postpartum. For the safety study, in order to reduce the potential for misclassification of exposure status, women vaccinated in the 7 days following their last menstrual period (LMP) or in the 7 days prior to delivery were excluded.

As a reminder, data regarding Tdap coverage during pregnancy through 2011 were presented to ACIP during the June 2013 meeting. The updated estimates provided during this session pertained to receipt of Tdap for pregnancies ending between 1/1/07 and 11/15/2012. The cutoff of November 15th was to allow 6 weeks of postpartum observation. As mentioned previously, pregnancies (including pregnancy outcomes and start and end dates) were identified using a validated algorithm, and receipt of Tdap was pulled from the electronic health record. Thus, the coverage data reflect the 2010 California Department of Health recommendations and the 2011 ACIP recommendations to administer Tdap to women who were not previously vaccinated, preferably after 20 weeks gestation.

Regarding the findings for all pregnancies identified from the 7 VSD sites for the years 2007 through 2012, the full cohort includes nearly 400,000 women with pregnancies ending in a live birth, of whom 9.5% received Tdap during pregnancy and 14.4% received Tdap postpartum. In 2010, for all women in the cohort, 9.2% received Tdap during pregnancy. This increased to 17.1% in 2011, but decreased in 2012 back down to 13.7%. In terms of Tdap coverage among live births in the California VSD sites, coverage during pregnancy increased starting in 2010. In 2011, coverage was up to 30%, but decreased in 2012 to 19.5%. However, this is believed to be due to the marked increase in pre-pregnancy receipt of Tdap.

By 2012, more than half of women in the cohort at the California sites had received Tdap prior to pregnancy. Consistent with recommendations at that time, these women were not recommended to receive a dose during pregnancy. With respect to data from live births occurring at the VSD sites (e.g., Minnesota, Washington, Oregon, Colorado, and Wisconsin), the first real increase in Tdap coverage during pregnancy occurred in 2012 when 16% of women were vaccinated. Similar to California, at these sites more than half of women received Tdap prior to pregnancy and an additional 10% received within 6 weeks Tdap post-partum.

In summary of Tdap coverage from 2007-2012 at the California VSD sites, Tdap coverage increased substantially in 2010 and 2011, but decreased in 2012. This is likely because many women had received Tdap pre-pregnancy. At the Minnesota, Washington, Oregon, Colorado, and Wisconsin VSD sites, Tdap coverage during pregnancy increased in 2012, with approximately 16% of women vaccinated in response to the 2011 ACIP recommendations.

Turning to preliminary findings from the Tdap safety study, an observational cohort study was conducted of pregnancies with live birth outcomes between January 2010 and November 2012 from the two California VSD sites. Women were required to have continuous insurance enrollment 6 months prior to the start of pregnancy, continuing through pregnancy, and through 6 weeks postpartum. Multiple gestation pregnancies, women with no medical care during pregnancy, and women who received a live virus vaccine were excluded.

The safety outcomes included two late pregnancy complications and two birth outcomes. Late pregnancy complications were identified from diagnoses or ICD-9 codes occurring at medical visits. Hypertensive disorders in pregnancy were defined as having a new diagnosis of either gestational hypertension, preeclampsia, or eclampsia. The second pregnancy complication studied was chorioamnionitis. While these ICD-9 codes have been shown to be valid, in order to increase specificity, both eclampsia and chorioamnionitis were required to be inpatient diagnoses. The two birth outcomes were preterm delivery and small for gestational age (SGA) births. These birth outcomes came from EHR data. Gestational age at delivery was specifically based on clinician assessment at delivery. Preterm delivery was defined with a single cut-off of delivery before 37 weeks gestation, and SGA was defined as having a weight for gestational age at less than the 10th percentile.

Adjustment was made for multiple covariates in the models using a propensity score. The propensity score was created with logistic regression to estimate the likelihood of receiving Tdap during pregnancy. Variables included in the propensity score included age, race, SES, pre-existing medical conditions, and prenatal care index. Site and receipt of other vaccines during pregnancy were also adjusted for. The analytic approach varied for each outcome, accounting for the expected timing of the outcome in pregnancy and presumed pathophysiology. For hypertensive disorders, women vaccinated before 20 weeks were compared to unvaccinated women. This was done for two reasons. First, as the current analyses were not matched, there was not an index date for the unvaccinated population. Looking at vaccination prior to 20 weeks offered assurance that all vaccination occurred before the hypertensive disorder could be diagnosed. A second reason was that although hypertensive disorders of pregnancy by definition occur at 20 weeks gestation or later, they are thought to be due to insults that occur early in pregnancy and relate to abnormal placental growth. A Poisson model was used with robust variance estimate to compare rates of hypertensive disorders between vaccinated and unvaccinated women.

When conducting an observational cohort to study vaccination and preterm delivery, there is potential for bias as women who deliver early have less time during pregnancy when they can be vaccinated. This bias may be especially pronounced for a vaccine such as Tdap that is preferentially administered in the 3rd trimester. Strategies applied to reduce this bias included evaluating only vaccination occurring at 36 weeks or earlier for preterm deliveries, and use of a time-dependent exposure Cox model in the analyses. For the other two outcomes, chorioamnionitis and SGA births, all vaccinated women were compared to all unexposed women, and a Poisson model with a robust variance estimate was used. It is important to note that "unvaccinated" refers only to women who did not receive Tdap. Women in both groups could have received influenza vaccine.

In terms of baseline characteristics, the safety cohort included 26,224 women who received Tdap during pregnancy and had a live birth delivery and 97,265 unvaccinated women. Most vaccination occurred in the 2nd and 3rd trimesters. Most women were between 25 through 34 years of age. Prior to any adjustments, the cohorts were well-matched in terms of age distribution and race/ethnicity. There were some additional baseline characteristics. Of note, women who received Tdap during pregnancy were slightly more likely to have received adequate or adequate plus prenatal care index, and were much more likely to have received another vaccine during pregnancy. However, whether it was the same day as Tdap or a different day was not determined. Of note, 4% of vaccinated and more than 45% of unvaccinated women had received Tdap pre-pregnancy.

With regard to the preliminary results, among more than 26,000 women who received Tdap during pregnancy, 6.1% developed chorioamnionitis. Among nearly 100,000 unvaccinated women, only 5.5% developed chorioamnionitis. This gave an adjusted rate ratio of 1.19, with a 95% confidence interval of 1.13 to 1.27. In contrast, the rates for delivery before 37 weeks gestation were lower among women who received Tdap during pregnancy, with an adjusted hazard ratio of 0.88 (95% CI 0.83-0.93). There were no significant differences in rates of small for gestational age births between vaccinated and unvaccinated women. Rates were evaluated for hypertensive disorders between women who received Tdap before 20 weeks gestation and unvaccinated women, which found an adjusted rate ratio of 1.09 (0.99-1.20). In secondary analyses, women who were vaccinated between 27 through 36 weeks gestation were evaluated, which is similar to current Tdap recommendations. Again, a very small increased risk was found for chorioamnionitis, with an adjusted rate ratio of 1.11 (1.03-1.21). Also found were reduced risk for preterm delivery and no association between Tdap vaccination and SGA births.

Chorioamnionitis is thought to be an acute process due to a polymicrobial infection of the amniotic fluid, fetal membranes, placenta, and/or uterus. It is usually diagnosed during the course of labor, and occurs in up to 8% of full-term deliveries and 30% to 40% of preterm deliveries. Chorioamnionitis is an important outcome as it can result in adverse consequences for mothers and infants, most notably as a risk for preterm birth and cerebral palsy. There are many known risk factors for chorioamnionitis, including prolonged labor, use of internal monitoring, prolonged rupture of membranes, urogenital infections, multiple exams, previous diagnosis, substance abuse, and obesity.

While most prior studies of vaccination during pregnancy have not evaluated chorioamnionitis as an outcome, it was included in a recently published study on inactivated influenza vaccine during pregnancy and risks for adverse obstetric events. This study found vaccination at 20 weeks gestation or greater to be associated with adjusted hazard rate ratio of 1.08 (1.02-1.15). In this study, due to multiple comparisons, a threshold was set for significance of .005 a priori so the observed risk was considered non-significant [Kharbanda, Elyse; Olshen MD, MPH; Vazquez-Benitez, Gabriela; Lipkind, Heather; MD, MPH; Naleway, Allison; Lee, Grace; MD, MPH; Nordin, James; MD, MPH; *Obstetrics & Gynecology*. 122(3):659-667, September 2013. DOI: 10.1097/AOG.0b013e3182a1118a].

In summary, receipt of Tdap during pregnancy was not associated with increased risk for adverse birth outcomes. The chorioamnionitis findings merit further discussion and possibly further investigation. First, the slight elevated risk persisted despite adjustments. For example, maternal age and comorbidities were both included in the propensity score and thus should have been well-balanced between vaccinated and unvaccinated women. However, no data

were available to evaluate and adjust for many other chorioamnionitis-specific risk factors, such as urogenital infections or prior occurrence of chorioamnionitis. It is also important to note that the magnitude of the risk detected is small. Although due to time limitations Dr. Kharbanda did not present the data by year, the risk reported was primarily due to differences between vaccinated and unvaccinated women in their rates of chorioamnionitis in a single year (2012). Finally, it should be noted that chorioamnionitis is a leading cause of preterm birth. It is reassuring that although a small increased risk has been observed for chorioamnionitis, no increased risk for preterm birth was observed.

Discussion Points

Dr. Duchin noted that during 2010-2011 and 2011-2012, a Bordetella tsunami was striking the West Coast. There were huge outbreaks occurring in California and moving North to Oregon and Washington. He wondered how that and the associated exhortations from public health officials about vaccination and the press about pertussis epidemic in the community may have impacted the data Dr. Kharbanda shared, and what might be observed in communities not in the midst of large scale epidemics.

Dr. Kharbanda indicated that the data were pulled by site for all of the VSD sites. The numbers were pretty small, but increased Tdap coverage rates were observed outside of California, Oregon, and Washington.

Dr. Schuchat wondered whether the data had been analyzed adjusted by first pregnancy. Thinking about the managed care population and that half of those who were non-vaccinated had previously received Tdap, she wondered whether those were often second pregnancies and the vaccinated were first pregnancies.

Dr. Kharbanda replied that the way the data are received, each pregnancy is a unique data point, and women cannot be linked to prior pregnancies. It is unknown for each pregnancy whether it was the first pregnancy or they were pregnancy before. A request has been made for additional pregnancy files within the VSD files, but this information is not currently easily retrievable.

Dr. Schuchat suggested that in the future, for pregnancy-related analyses, it may be worth obtaining input from obstetricians about key parameters. Some of the risk factors mentioned are difficult to get from a medical record, but some like number of pregnancies is on every labor and delivery file.

Dr. Kharbanda responded that this information is in the EHR, but is not in the standard VSD files. However, work is being done to expand the VSD files in order to assess some of these other issues.

Dr. Kempe inquired as to whether there was any information about pregnancies that did not result in live deliveries. She also requested further information about the rationale for the choice of safety outcomes, which seemed somewhat arbitrary to her.

Dr. Kharbanda replied that the only data available on spontaneous abortions and stillbirths was coverage data. Only 1.2% of women who had a pregnancy ending in spontaneous abortion, stillbirth, and therapeutic abortion received Tdap during pregnancy. Those numbers are not expected to increase much, given that the current recommendation is to vaccinate late in pregnancy. There have not been that many exposures. Again, with the way the data structure

works, it is much harder to time the pregnancy for these outcomes. Most of the gestational age data are based on clinician assessment at delivery, which is well-validated. Within the VSD files, it is difficult to know whether it was a stillbirth at 20 weeks, 30 weeks, et cetera, so it is difficult to know when the pregnancy started or whether the Tdap was really administered when the woman was pregnant. The investigators do not feel comfortable doing further analyses using the current data files.

Ms. Hayes (ANA/ACNM) noted that while chorioamnionitis is a link for preterm birth, the data were not stratified by gestational age at birth or full-term and pre-term pregnancies with chorioamnionitis at birth. She wondered whether this had been or could be done, and why the investigators selected chorioamnionitis as an outcome since it seemed like such a bizarre outcome to assess for vaccines.

Dr. Kharbanda responded that while this had not yet been done, it can be and is a good suggestion. In terms of the selection of chorioamnionitis, in picking outcomes the investigators tried to focus on input and outcomes in terms of women's and infants' health. These outcomes were also studied previously with influenza vaccine, so the investigators felt comfortable that the diagnoses were in the data. There has been some validation work on the outcomes. An OB consultant from Yale University, Dr. Heather Lipkind, has been part of the study team. She raised the point as well that in maternal-fetal medicine, often chorioamnionitis is on the pathway to preterm delivery, but is not considered an outcome in itself. They were trying to assess the common diagnoses that occur in pregnant women, and this is a common diagnosis.

Dr. Campos-Outcalt noted that as time goes on, there will be increase interest in repeat vaccination and repeat pregnancy, so consideration must be given to that design. It was unclear why .005 was selected. He thought with 20 variables, most people would go to .001 in which case the finding would have been significant.

Dr. Kharbanda replied that a protocol has already been written for repeat vaccination and repeat pregnancy, and is being led by CDC investigators. Selection of .005 was for the other study on influenza vaccine safety during pregnancy, for which there was a cohort of nearly 80,000 women who received TIV during pregnancy and 300,000 who did not. There were about 20 to 25 different comparisons, so the investigators were really worried about error if a .05 cutoff was used.

Dr. Sawyer (PIDS) requested clarification about the comment that the investigators felt that the risk of chorioamnionitis was largely attributable to rates in differences of chorioamnionitis in 2012, and whether they meant in the VSD population.

Dr. Kharbanda replied that this was within the VSD data files. She presented these data last fall during the VSD annual meeting, and that time they only had pregnancies from 2010 and 2011. No increased risk was detected at that time. The 2012 data were added in January, and when they looked by year, it was mostly due to differences in chorioamnionitis diagnosed in 2012. There was a bigger differential between vaccinated and unvaccinated women just in that year.

Dr. Riley (ACOG) said that while she hated to beat on chorioamnionitis, it was probably the worst diagnosis in obstetrics ever because it is a clinical diagnosis. As a practicing obstetrician, she could attest that if a mom gets a fever, she will receive antibiotics and a diagnosis of chorioamnionitis and that is what will be on the medical record. This is tough, because depending upon how many people receive an epidural, there will be more diagnoses of chorioamnionitis because 15% of women who get an epidural are going to get a fever. This is

probably the messiest diagnosis there is, and it is very hard to make any sense out of what it really means. It is one of those diagnoses where all information needs to be known, and then there are more risk factors such as anesthesia. Therefore, she was not sure what she would do with this information.

Ms. Pellegrini said she assumed that the exclusion of women who received Tdap within 7 days of the end of pregnancy meant regardless of when pregnancy ended, and she wondered whether that would capture a case in which a woman received her Tdap at 29 weeks and then had a preterm birth 5 days later. Could that have potentially masked a serious signal?

Dr. Kharbanda responded that only about 300 women were excluded because their vaccine was within 7 days of delivery. The reasons the exclusions were done is because once a woman is in the hospital, all of their vaccinations may show up on the VSD records on the day they were admitted to the hospital even if they were really administered post-partum. This is in order to make the data cleaner and that it really was a pregnancy vaccine and not a post-partum vaccine. Very few women are thought to have received their vaccine in that window.

Dr. Harriman wondered whether there was any biological plausibility to suggest that chorioamnionitis could result from either influenza or Tdap vaccine, and she suggested assessing different outcomes. Also of importance were the low rates of Tdap administered during pregnancy that were shown with these data. A survey was conducted of California birth hospitals during the fall in which the hospitals were to ask every woman delivering on a single day whether they received Tdap during pregnancy. This was not validated, but about 25% stated that they received Tdap. To her, that was disappointing. Anecdotally it has been said that if Tdap is mentioned at all, women are told to get it at the drug store. While there may be the best intentions, there is not follow through. ACOG has done a lot of work to educate its providers about this, but Tdap is not being offered as often as it should be. Certainly, there are some women who will not accept it, but it at least has to be offered.

The decreased rates of preterm delivery suggested to Dr. Bennett that there was some uncontrolled confounding. She wondered whether that might be related to the diagnosis of chorioamnionitis.

Dr. Kharbanda replied that the investigators believe that the preterm delivery and the reduced risk are still just bias that they are unable to eliminate in this observation cohort. Women who delivered at 24, 25, 26 weeks were not recommended to receive Tdap vaccine based on current recommendations. They will all end up in the unvaccinated group. Similarly, as they get closer, they just have less time. An attempt was made to adjust for that, that bias cannot be fully adjusted for. A lot of work has been done on this with influenza vaccine, and they just keep seeing that when there is a vaccination that is supposed to be given toward the end of pregnancy, this bias occurs in observational studies. For influenza, this was not observed for first and second trimester vaccinations.

Dr. Riley (ACOG) put in a plug for OBs, because she was hopeful that 2013 would look better. ACOG has put a lot of time and energy into increasing the rate. She has unpublished data from her own institution, which assesses February 2013 through June 2013—a short period of time. Their vaccination rate for Tdap was 81.6%. Obviously, that is an institution where there is a vaccine champion. However, practicing in a very big place, this shows that with persistence uptake can be increased. The interesting thing they found in their data is that even though they got 81.6% of women, there were low rates for African American women, which was very disappointing. There was a high correlation with those women who were willing to take

influenza vaccination being the same women who were willing to take Tdap vaccination. She is very hopeful, because their numbers did not look that great in 2012 either.

Dr. Temte noted that the increase in rates of vaccine coverage during pregnancy in the other sites from 2% to 16% was somewhat of a tsunami of providers. That is an 8-fold increase in a year, which is incredible. He was curious about comments from AAFP and ANA/ACNM about acceptance within their organizations.

Dr. Loehr (AAFP) replied that the family physicians who practice obstetrics are also trying to push Tdap vaccine.

Carol Hayes (ANA/ACNM) indicated that ACNM has a grant from ASTHO to increase vaccination rates among pregnancy women, and to improve the perception about vaccines among nurses.

Dr. Orenstein (NVAC) pointed out that everyone keeps lumping Tdap vaccines together, but there are differences in formulations, antigens, and the quantity of antigens. He wondered if any analyses had been done with regard to whether there are any differences between the available Tdap preparations. He also emphasized that NVAC is taking this on as a major effort, which includes the desire to have an ACIP pregnancy issue so that it makes it easier for people to go to one place for all of the issues pertaining to pregnant women. He presumed this could be distributed to everybody when it goes out for comments in March, and NVAC is trying to finalize the recommendations during the June meeting to cover topics such as enhancing communications, maximizing obstetrics provider recommendations, improving financing for services, linking electronic records, and dealing with issues of that nature. This is not Tdap-oriented. It is vaccines ACIP recommends for pregnant women. After this is finished, the Maternal Immunization Working Group will take on the issue of how to incentivize development of more vaccines that could be used for dealing with issues that affect pregnant women or young newborns.

Dr. Kharbanda replied that while analyses on various formulations have not yet been done, they can be.

Dr. Temte noted that for follow-up to NVAC, Dr. Pickering sent the draft Maternal Immunization Working Group report out to all of the ACIP members. Pages 20-22 deals with ACIP.

Dr. Salisbury (UK DOH) said he had an overwhelming sense of déjà vu washing over him, because he believed during the June 2013 ACIP meeting he presented on exactly this topic with 20,000 pregnant women collected through a database where all health details were available. A specific assessment was done of stillbirth rates and prematurity and nothing was found. Efficacy was also analyzed, and extraordinarily high efficacy was found in women who were vaccinated between 28 and 38 weeks of pregnancy. Many of the questions just raised were answered in that presentation 8 months ago, and the report is in the ACIP meeting minutes.

Human Papillomavirus (HPV) Vaccines

Introduction

Joseph A. Bocchini, Jr, MD
Chair, ACIP HPV Vaccine Working Group

Dr. Bocchini indicated that this human papillomavirus (HPV) vaccine session would include the following topics:

- ❑ Continued review of the investigational 9-valent HPV vaccine, which is directed against 9 HPV types, including 5 additional high risk types that are not in the quadrivalent vaccine
- ❑ Completion of the review and approval of the updated, combined ACIP statement, which includes recommendations for currently licensed bivalent and quadrivalent vaccines and for females and males

To review, during the October 2103 ACIP meeting HPV session, an update was presented on HPV vaccination coverage in the US; the review of 9-valent HPV vaccine was begun, with a presentation from Merck on the clinical development program; and the draft updated ACIP statement was reviewed and discussed. Since the October 2013 ACIP meeting, the WG has had regular conference calls to review and discuss a variety of data, including the 9-valent HPV vaccine clinical trials and HPV type attribution in HPV-associated disease, and to initiate discussion of GRADE considerations.

In terms of the overall proposed timeline for consideration of the investigational 9-valent vaccine, clinical trial data are to be presented during this session. In June 2014, there will be a presentation of additional clinical trial data, along with health economic data. GRADE will be discussed in October 2014, and a vote is anticipated to occur in February 2015.

With respect to the two presentations to be given during this session regarding type attribution, Dr. Bocchini pointed out that understanding HPV-associated disease attributable to HPV types is important to assessing the potential impact and cost-effectiveness of HPV vaccines. Of note, detecting HPV in a cancer tissue does not necessarily indicate a causal relationship. The International Agency for Research on Cancer (IARC) defined some cancers to have strong evidence for causal etiology. These HPV-associated cancers include cervical, vaginal, vulvar, anal, penile, and oropharyngeal cancers. Therefore, finding HPV in these tissues is a good indication of causality. However, determining types responsible for HPV-associated disease depends on a variety of factors, including quality of the specimen, the assay used to detect HPV, and the algorithm to assign type attributable if multiple types are discovered in the same preparation. This can vary by the population sampled.

HPV Type Attribution in Cervical Precancers

Susan Hariri, PhD

**National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention**

During this session, Dr. Hariri presented data on HPV type attribution in high grade cervical lesions in the US. She began with a brief summary of the natural history of cervical HPV infection and associated outcomes; reviewed the published data on the distribution of HPV types in non-invasive high grade cervical lesions in women from different regions of the world; briefly reviewed the methods used to estimate individual HPV type attribution and the reasons for them; and presented data from the US on HPV type attribution to high grade cervical lesions.

Infection with genital HPV is responsible for a spectrum of cervical abnormalities. The majority of these abnormalities are benign and do not progress to disease. In fact, approximately 90% of infections become undetectable within 2 years without causing any symptoms. However, infection with high-risk HPV types can persist, which could lead to mild cervical abnormalities that tend to regress without treatment or to high grade lesions that are more likely to progress to invasive cervical cancer if they are not treated. Routine cervical cancer screening with Pap and HPV-based tests is recommended to detect and treat pre-cancerous lesions as a secondary cervical cancer prevention strategy.

The focus of this presentation was on non-invasive high grade cervical lesions, specifically cervical intraepithelial neoplasia grade 2 and higher and adenocarcinoma *in situ* (CIN2+). CIN2+ lesions are associated with high-risk or oncogenic HPV types that are the most likely to persist among all genital HPV infections. About 30% of CIN2+ lesions are estimated to progress to cervical cancer. HPV16 is the most frequent type detected in CIN2 and 3, which are squamous lesions. HPV 18 is the most common in AIS lesions, which are glandular. CIN2+ lesions were used as the main endpoints for HPV vaccine efficacy trials, and are also used as intermediate endpoints to monitor post-licensure vaccine impact in some countries that have established screening programs.

Using data from a meta-analysis of international studies conducted to determine HPV type relative contribution in non-invasive high grade cervical lesions in women around the world, relative contribution of groups of oncogenic HPV types were presented for 2 groups: HPV16/18 and HPV 31/33/45/52/58 that are the 5 additional types included in the candidate 9-valent vaccine. There was wide variation globally in the proportion of HPV16/18 detected in high grade cervical lesions, from greater than 60% of lesions in women in North America, Europe, and South or Central America to less than 50% in lesions from women in East Asia and Africa. There was less variability in the distribution of the additional 5 additional types, which were detected in about 40% of women across all regions except in East Asia where the prevalence was much higher at 60% [Guan et al. Int J Ca 2012].

The objective of this analysis was to estimate high-risk HPV type attribution to CIN2+ lesions among US women aged 21 through 39 years who were diagnosed from 2008 to 2011; and to examine whether HPV type attribution differed by age and race and ethnicity. Data came from the HPV-IMPACT project, a population-based sentinel surveillance system that was established in 2008 to monitor HPV vaccine impact on high grade cervical lesions and HPV types associated with them. This project is a CDC collaboration with 5 Emerging Infections Program (EIP) sites and includes equally sized catchments of approximately 300,000 adult females in each catchment in California, Connecticut, New York, Oregon, and Tennessee. At each site,

histopathology laboratories serving the catchments are enumerated and asked to report histologically confirmed CIN2+ diagnoses in adult residents of catchment 18 years of age and older; and to submit archived diagnostic tissue from women who were diagnosed before age 40 years of age for HPV DNA typing.

Depending on the number of women reported and resources available, sites request all or a sample of specimens from age eligible women from each reporting lab. Labs are asked to select tissue that is most representative of the diagnostic lesion, and to cut and process the tissue which is formalin fixed and paraffin embedded using a standard protocol. Processed specimens are sent to CDC where they are reviewed by a pathologist to ensure adequate tissue is present for typing. If it is, DNA is extracted and tested for 37 individual HPV types with the Roche Linear Array Genotyping assay. Specimens that are negative on Linear Array or fail to amplify control are re-tested with the Inno-Lipa genotyping assay, which represents about 10% of the specimens overall.

Between 2008 through 2011, there were adequate typing results for over 5000 specimens. Almost all, 97%, were positive for HPV with only a single HPV type detected in 79% of specimens. HPV 16/18, which are the types targeted by current HPV vaccines, were detected in slightly more than 50%. The additional 5 types (31, 33, 45, 52, and 58) that are included in the candidate 9-valent vaccine were detected in 31% overall. In terms of the typing results broken out by severity of lesion into CIN2 (lowest histologic grade) and CIN3/AIS (highest grade), there were about 900 specimens in which histologic grade was not discriminated. Dr. Hariri did not show these, but they do represent a combination of the 2 grades. AIS was combined with CIN due to small numbers since AIS represented less than 2% of reported cases. CIN2 accounted for a bigger fraction of the lesions overall compared to higher grade CIN3/AIS lesions. HPV 16/18 typed were more common in CIN3/AIS compared to CIN2, 66% vs. 40%, whereas, the 5 additional types were more common in CIN2 than in CIN3/AIS lesions.

In terms of prevalence of individual HPV types by histologic grade, most notably HPV 16 was by far the most common of any high-risk type in all grades, but a big difference was observed in HPV16 prevalence by grade from 35% in CIN2 to 60% in CIN3/AIS. HPV 18 was relatively uncommon and accounted for about 4% to 5% of lesions. In the group of the 5 types in the candidate 9-valent vaccine, types 31 was the most common in all histologic grades, types 52 and 58 were next, and both were more common in CIN2 lesions. HPV types 33 and 45 were detected in less than 5% in all grades. With regard to oncogenic HPV types that are not included in any vaccine, types 35 and 51 were most common. The rest were detected in 5% or less of specimens across all histologic grades.

For the purpose of HPV type attribution to cervical lesions, generally, if only a single HPV type is detected in a CIN2+ lesion that type is considered to be causally associated with the lesion. However, more than 1 HPV type is detected in about 20% of lesions and the role of each type in co-infected lesions is less clear. So different methods are used to quantify the degree to which individual types or groups of types contribute to cervical lesions with multiple HPV types, and individual type attribution is used to evaluate the potential impact of HPV vaccines. In this analysis, two methods were used that are most commonly used to determine individual type attribution in lesions with multiple HPV types. The first method was hierarchical and attributed a co-infected lesion to the most oncogenic type. For example, in a CIN3 specimen with 16 and 31, 100% was attributed to 16. This method tends to overestimate attribution of types 16 and 18 because they are the most oncogenic types of all of the high risk types. The second method assigned weights to each type that were proportional to their frequencies as single infection in a given histologic grade, for example, the same specimen. Here, the proportion was calculated of

CIN3 lesions in which each type is detected as a single infection (61% for HPV16 and 9% for HPV31) and each by sum was divided by the proportions of both types in lesion. A less than 2% difference was found using the two methods, so the results Dr. Hariri presented were based on the proportional attribution method.

Regarding the proportional type attribution for the 3 HPV type groups by histologic grade, 38% of CIN2 lesions were attributable to 16/18 types, and the percentage of 16/18 attribution increased with severity of lesion, up to 64% in CIN3/AIS. Of CIN2, 28% and slightly less (23%) of higher grades were attributable to the 5 additional types in the candidate 9-valent vaccines. Other high risk type attribution ranged from 21% in CIN2 to less than 10% in CIN3/AIS. HPV16/18 accounted for the highest proportion of lesions across age groups, although there was a decline in 16/18 attribution in the oldest age group and an increase in the additional 5 types. Proportional attribution of other oncogenic types was similar across age groups. With regard to type by race and ethnicity, the highest proportion of CIN2+ lesions were attributable to HPV16/18 across all racial groups. However, HPV16/18 attribution was significantly higher in non-Hispanic whites compared to all other race and ethnicity groups. Conversely, the additional 5 types were more common in racial/ethnic minorities compared to non-Hispanic whites. A significantly higher proportion of lesions were attributable to other oncogenic or high-risk HPV types among non-Hispanic blacks compared to other groups. Looking at the age distribution within each group, the median age was similar across the groups. Breaking out the attribution of individual high-risk types groups by the different race and ethnic groups, HPV16 predominated across all race and ethnic category, although to a lesser extent in black and Hispanic women compared to whites. There were some race differences in attribution of HPV45, 52, and 58 in the candidate 9-valent vaccine. There were two high-risk types (35 and 51) with at least 5% attribution in one or more histologic grade.

In summary, these data from a large population-based sample of women in the US showed that 50% of CIN2+ lesions were attributable to HPV16/18 overall, and the attribution ranged from 40% in CIN2 to >60% in CIN3/AIS lesions. An additional 25% of CIN2+ lesions were attributable to the 5 additional types included in the candidate 9-valent vaccine. A higher proportion of lesions were due to HPV16/18 in women under age 35. This is consistent with evidence indicating that these 2 types are stronger carcinogens compared to other high risk types, and are more likely to progress faster to disease. The highest proportion of CIN2+ lesions was attributable to HPV16/18 across all racial and ethnic groups. However, a higher proportion was attributable to HPV16/18 in non-Hispanic whites compared to other racial/ethnic groups. The reasons for racial differences are not clear, but may be due to differences in the underlying prevalence of HPV types in the populations or to differences in screening and treatment of the lesions.

HPV-Associated Cancers and Type Attribution

Mona Saraiya, MD, MPH

**National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention**

Dr. Saraiya first reviewed data from the *Annual Report to the Nation* that was published last year showing the incidence rate of cervical, vaginal, and vulvar cancers from 2005 through 2009. Based on these data, black and Hispanic women have the highest rates of cervical cancer, and black women also have the highest rate of vaginal cancer. In terms of the rates of oropharyngeal and anal cancers by race, black males and females have the second highest rate

of oropharyngeal cancer. For anal cancer, black males have the highest rate [Jemal et al, J Natl Cancer Inst 2013].

International data of archived invasive cervical cancer specimens were collected from convenience samples around the world and typed by one lab to determine what percentage had HPV 16/18, and the additional types in the candidate 9-valent HPV vaccine. The important issue to highlight here is that the majority of cancers, whether they are in Africa Asia, Europe, et cetera, usually have HPV 16/18 attribution-usually in the range of 70%. An additional 17% to 20% are attributed to the other 5 types. Another point to note is that very few cases have been analyzed from North America from this comparative study, which is why the CDC study was conducted. The same international group in Barcelona is conducting a similar study worldwide for all the other HPV cancers globally [Serrano et al, Infectious Agents and Cancer, 2012].

The results from a summary of the literature from various US studies conducted around 2006 that examined tissues from these cancers attributed it to HPV are shown in the following table:

Cancer	HPV	HPV 16/18
	Attributable % (95% CI)	Attributable % (95% CI)
Cervical	96 (95-97)	76 (NA)
Vaginal	64 (43-82)	56 (35-76)
Vulvar	51 (37-65)	44 (30-58)
Anal	93 (86-97)	87 (82-91)
Penile	36 (26-47)*	31 (22-42)
Oropharyngeal	63 (50-75)	60 (47-72)

© Simon Cancer 2008
 *% Any HPV is percent age HPV detected in a cancers
 **% HPV or penile cancer is % where any oncogen c HPV type detected
 % HPV 16/18 is percent age HPV 16/18 detected among a cancers

The first column summarizes the attribution of any HPV and the second column summarizes the HPV 16/18 attribution. This percentage is usually combined with the number of actual cancers from these sites to estimate the burden of HPV-associated cancers. It is important to note here that the HPV DNA prevalence/HPV positivity has been considered a proxy for HPV attribution but it doesn't mean that HPV caused all of these cancers as noted by Dr. Bocchini [Gillison, Cancer 2008].

The objectives of the CDC analysis were to establish a systematic population-based approach to monitoring HPV types in cervical cancer and other HPV-associated cancers in the US; determine attribution of HPV 16/18 and additional types in candidate 9-valent vaccines; and determine HPV type attribution by race/ethnicity. For the study design, cancer registries were used to collect data, most of which were collected from 2004 through 2005 right before the HPV vaccines were licensed, to help establish a baseline. The registries have information about the cancer diagnoses, but in order to get the actual tissue specimens, four cancer registries went to pathology labs to get the most representative specimens, and three cancer registries used existing biorepositories. Most of the cancers that were collected were invasive cancers, but there were a few *in situ* cancers because the registries had legal authority to collect these data. The HPV genotyping was done by the CDC lab-as described by Dr. Hariri and the attribution method was the same. HPV cancers were grouped into the following categories: HPV 16/18, additional 5 types other HPV (which includes low risk), and HPV negative. The denominator included all cancers.

Four cancer registries (Michigan, Louisiana, 3 Florida counties, Kentucky) generated a list of all eligible cervical cancer/precancer cases, sampled randomly, and then requested the local hospital or pathology lab with the tissue specimen to prepare and send the tissue to the CDC HPV lab for genotyping analysis. Three cancer registries (Hawaii, Iowa, Los Angeles) had Residual Tissue Repositories which store their own tissue specimens, and here eligible cases were identified in-house and sent directly to the CDC HPV Lab. In all states, tissue specimens were prepared according to a common protocol. Complete genotyping results were then linked with demographic information collected by each cancer registry, and results were shared with each cancer registry. While 3017 tissue samples were submitted to the CDC HPV lab, due to specimen inadequacy and other issues the final sample size was 2670 cancers.

Assessing the percentage of any HPV detection by cancer site, HPV DNA was detected in 91% of cervical cancers, 99% of *in situ* cervical cancers, 69% of vulvar cancers, 75% of vaginal cancers, 91% of anal cancers, 63% of penile cancers, and 70% of oropharyngeal cancers [Saraiya et al, presented at International Papillomavirus Conference 2012, Puerto Rico].

In terms of the top 5 cancer-causing types in these select cancers, the theme is that HPV 16 is the most common in all cancers. Regarding the attribution by the 4 HPV groups, for cervical cancer 66.2% had 16/18 detected compared to 14.7% for the additional 5 types. Anal cancer had the higher proportion of 16/18 detected. The cancer with highest attribution due to the 5 types were *in situ* cervical cancer, vaginal cancer, and vulvar cancer. Regarding the general findings of a number of analyses that were conducted for this study, by age there was definitely a higher proportion of cancers in younger age groups attributable to HPV 16/18. By race/ethnicity, there were no differences for cancers except for *in situ* cervical cancers and oropharyngeal cancers. By gender, there were no differences for cancers except oropharyngeal cancers. With respect to the racial differences for *in situ* versus invasive cervical cancer, there was a lower proportion of *in situ* cancers that had HPV 16/18 detected among Black and Hispanic populations. But it should be noted that for *in situ* cervical cancers, the numbers are quite small. In contrast, when the invasive cancers were examined when there was a good sample size for each racial group, the proportion of HPV negative cancers were lower among blacks and Hispanics than Whites. More importantly, there were no significant differences in the proportion of 16/18: White Non-Hispanic 67%, Black Non-Hispanic 68%, and Hispanic 64% [Saraiya et al, presented at AACR Health Disparities in Cancer, 2013].

This raises the question, "How can cervical cancers be negative?" The classic study by Wallboomers/Bosch et al found that 99.7% of cervical cancers were HPV positive. However, it is important to keep in mind that that study was based on multiple HPV assays and cancers that met select criteria. The Saraiya et al study is based on a population-based surveillance study. There may be misclassification of the actual anatomic site in that lower segment uterine cancers are not distinguishable from upper segment cervical cancers. There may be false negatives in that there may be HPV that could not be detected with the current assays or the specimen/tissue is not well-preserved. There may be true HPV negative cervical cancers, albeit these are rare histologies and represent perhaps 1% to 2% at the most of all cervical cancers.

For anal cancer, there were few differences by race/ethnicity. About 80% of anal cancers were attributed to types 16/18. There were also no difference by gender, with 79% of HPV 16/18 among males compared to 80% of HPV 16/18 among females. Although it appeared that females had a higher percentage of additional HPV types in the candidate 9-valent vaccine, this difference was not significant. Regarding oropharyngeal cancer and HPV attribution by race/ethnicity and gender, a higher proportion (50%) of HPV negative cancers was observed among blacks compared to 25% among whites and 27% among Hispanics. A lower proportion was observed of 16/18 cancers overall among blacks, even though the cancers were limited to

HPV positive cancers. By gender, there was also a higher proportion of HPV negative cancers among females, and a lower proportion of HPV 16/18 cancers as well.

Using the data from this particular study to revise the estimated percentages of cancers attributed to HPV in the US, it can definitely be said with more authority using population-based and consistent assays that the prevalence of HPV positivity would be slightly revised. For example, for cervical cancer 91% were attributable to HPV, 66% were attributable to 16/18, and 15% were attributable to the additional 5 types in the candidate 9-valent vaccine. Also important to note for oropharyngeal cases for males is that 72% were HPV-attributable, which is much higher than the previous estimates; 63% had 16/18; and 4% had the additional 5 types in the candidate 9-valent vaccine.

In summary, 62% of invasive cancers were attributable to HPV 16/18. This was a range from 48% of penile cancers to 79% of anal cancers. Among females, approximately 62% of cancers were attributable to HPV 16/18 compared to 63% for males. This translates overall to approximately 25,500 cases annually. Of the invasive cancers, 11% were attributable to the 5 additional types in the candidate 9-valent vaccine. Based on the cancer type, this is a range from 6% for oropharyngeal cases to a high of 18% for vaginal cancers. There was also a difference by gender, with 14% of female cancers being attributable to the additional 5 types in the candidate 9-valent vaccine compared to 5% of male cancers. Overall, this translates to 4000 cases annually. In terms of racial ethnic differences, HPV 16/18 attribution did not differ for invasive cancers except oropharyngeal cancers. A lower percentage of oropharyngeal cancers was attributable to HPV positive (or HPV 16/18) among blacks. These data will be useful in estimating the impact of candidate 9-valent vaccine on cancers and for cost-effective analyses.

Discussion Points

Given that the cases assessed spanned a time range from before and after HPV vaccine use, as well as what is known about fairly low coverage and latency, Dr. Reingold wondered whether the amount attributable to 16/18 may be underestimated.

Dr. Hariri responded that this is possible. An attempt is made to collect HPV vaccination history on all of the cases reported to the HPV-IMPACT project, but sometimes vaccination history cannot be found for everybody. However, vaccination history was collected on about 50% of the cases. Among those, a fairly sizeable proportion of 18 through 20 year old females with CIN2+ were vaccinated. Fewer 21 through 29 year olds were vaccinated. However, excluding cases with known receipt of at least 1 dose from the analyses did not significantly change the results. It is possible that there is some impact, but because there is no vaccination history for 50% of the cases, it is very difficult to tease that apart.

Dr. Karron requested a reminder about cross protection against non-16/18 serotypes from the vaccines in terms of which serotypes there may be protection against, and whether the vaccines differ in their ability to do that.

Dr. Hariri replied that some cross protection has been shown for both vaccines, mostly in types 31, 33, and 45. Cross protection has been somewhat stronger for the bivalent vaccine, although it is really difficult to compare the two vaccines head-to-head. Though some cross protection has been demonstrated, the duration of protection is unknown.

Regarding Dr. Hariri's slides 11 and 17, Carol Hayes (ANA/ACMN) said that when she looked at the data, there appeared to be two strains of HPV that seemed to be higher than those used in the new 9-valent vaccine. She was confused by that. For those on the right, 51 and 35 were higher than 33 and 45. It was unclear why 35 and 51 were not included in the vaccine and why were 33 and 45 included.

Dr. Hariri pointed out that the prevalence was very low compared to type 16 across the board for all of the types. While it was correct that 35 and 51 were more common, that was mostly in the CIN2 lesions which are a lower histologic grade and are probably not the true precancers. The prevalence is significantly lower in the CIN3 and AIS lesions that are most likely to progress to invasive cancer. She said she could not really speak to the decision about which types were included in the vaccine.

Dr. Markowitz clarified that these were precancers, and most decisions were made based on the types in the cancers. Many of these, even if they are oncogenic types, are less likely to progress to cancers than 16/18.

Barbara Kuter (Merck) indicated that the decision Merck made in terms of what additional types would go into the vaccine was based on their global data that assessed the prevalence of all of these types around the world. The decision was based primarily on the oncogenic cancer types, which is why 31, 33, 45, 52, and 58 are in the current vaccine. There is some difference in the epidemiology between the US data shown during this session and the global rates.

Dr. Bennett said she was very interested in the racial differences shown in Dr. Hariri's data, and requested a reminder regarding what was shown in the carriage data from National Health and Nutrition Examination Survey (NHANES) and whether there were racial differences in those data as well.

Dr. Hariri responded that HPV prevalence is being monitored in the US population in the NHANES. HPV type prevalence in NHANES over time has been assessed, and it is true that there are racial differences. However, there is a higher prevalence of all types in non-Hispanic blacks compared to non-Hispanic whites. Though a closer assessment of the data is underway, there does not seem to be a differential increase or decrease in the prevalence of the oncogenic types.

Dr. Bennett inquired as to whether there were any thoughts about why that pattern would be found in the early lesions and not in the invasive cancers or NHANES data either for 16/18 differences.

Dr. Hariri replied that 16/18 have more oncogenic potential than the other oncogenic types. As shown in Dr. Saraiya's presentation, no differences are seen by race in terms of the invasive lesions. It is not clear what to attribute the racial differences to, but it could have something to do with the prevalence combined with the differential oncogenic potential of the types. Again, that needs further investigation.

9-Valent HPV Vaccine Clinical Trial Data

Alain Luxembourg, MD, PhD
Director, Clinical Research
Merck & Company, Inc.

Dr. Luxembourg reminded everyone that a presentation regarding program design was given to ACIP during the October 2013 meeting. During this session, he discussed some of the key data from the clinical program for the 9-valent vaccine. He explained that 9vHPV vaccine is the investigational 9-valent HPV vaccine, while qHPV vaccine is the licensed quadrivalent vaccine Gardasil®.

In terms of the relative contribution of HPV types worldwide, the existing qHPV vaccine covers types 16/18, which cause approximately 70% of cervical cancers worldwide. By adding the 5 next most frequent HPV types in cervical cancers, there is a potential to reach approximately 90% cervical cancer prevention. To answer the question that was asked following the previous presentation, the selection of the 5 additional HPV types was based on the frequency in cancer worldwide—not in precancer or dysplasia. The 5 high-risk HPV types that were not included in the vaccine represent 5% to 6% of cervical cancer cases worldwide. Looking at precancers worldwide, there is also a potential for additional coverage with the additional HPV types. With CIN2/3 lesions, there is a potential to increase protection from 50% with the existing vaccine to 80% with the 9vHPV vaccine, which would exceed the best cervical cancer screening programs. This is an exciting possibility. The contribution of the additional HPV types in cancer is slightly lower than in precancer, which most likely reflects a generally faster progression to cancer with HPV types 16/18 than with HPV types 31/33/45/52/58. Overall, the potential benefit with the 9vHPV vaccine is not only a substantial increase in prevention of cervical cancer worldwide, but also for the prevention of precancerous cervical lesions. This means that in countries with cervical cancer screening programs there will be a lower need for invasive procedures, because precancers are treated by surgery, and lower costs, better quality of life, and lower risks. A wide range of benefits could be estimated from the 9vHPV vaccine.

The qHPV vaccine is a virus-like particle (VLP)-based vaccine that contains L1 VLPs for HPV types 6, 11, 16, and 18. Types 6 and 11 are responsible for 90% of genital warts, and are generally responsible for benign lesions. Types 16 and 18 are responsible for most cervical cancers. The 9vHPV vaccine contains these same 4 types plus the 5 additional high-risk HPV types (31, 33, 45, 52, and 58). The aluminum-based adjuvant is the same in both vaccines, but the amount of adjuvant has been increased in the 9vHPV vaccine to keep the adjuvant to antigen ratio the same as in the qHPV vaccine. The amount of antigen for the original types has also been increased to preserve immunogenicity compared with the qHPV vaccine. Thus, the dose selection process was data-driven.

The aim is to transition from the clinical program was designed to support full transition from the qHPV vaccine to the 9vHPV vaccine. One goal of the program is to show that for the original 4 types, the two vaccines perform the same. A second goal is to demonstrate that the new vaccine is highly protective against infection and disease due to the additional types. A third goal pertains to adolescent populations. HPV vaccine efficacy cannot be assessed in adolescents because they are not frequently exposed to HPV. Therefore, similar to what was done in the qHPV vaccine program, the efficacy findings in young women exposed to HPV will be extended to adolescents based on similar immunogenicity. So the program is designed to demonstrate non-inferior immunogenicity in adolescents versus young women (e.g., immunobridging). A fourth goal is to demonstrate is that the safety profile for the 9vHPV

vaccine is acceptable. If these 4 goals can be demonstrated, it will show value for the new vaccine.

Six Phase 3 studies have been conducted and were included in the initial filing. Three pivotal studies support the key indications. Protocol 001 is the only efficacy study. It was conducted in young women ages 16 through 26, and has been completed. A long-term extension of this study is ongoing to assess long-term effectiveness and long-term immunogenicity. There were two immunobridging studies in adolescents. Protocol 002 provided adult-to-adolescent immunobridging. This study is completed and an extension is ongoing to assess long-term effectiveness and immunogenicity up to 10 years post-dose 3. The purpose of protocol 009 was to assess whether the qHPV and 9vHPV vaccines induce the same immunogenicity in adolescents. Three additional studies were included in the initial filing, and the data regarding these studies will be presented during the next ACIP meeting. Two of these were concomitant use studies to assess vaccines commonly used in adolescents, co-administered with the 9vHPV vaccine. Protocol 005 assessed Menactra[®] (meningococcal vaccine) and Adacel[®] (Tdap vaccine). two vaccines commonly used in the Americas, and Protocol 007 assessed Repevax[®] (Tdap-IPV vaccine), a vaccine commonly used in the European Union. These two studies have been completed. Protocol 006 was a study conducted to assess the 9vHPV vaccine in prior qHPV vaccine recipients. Recognizing that millions of individuals have been vaccinated with qHPV vaccine, and that even if among them a small fraction is interested in a fuller vaccination with 9-valent, Merck feels obliged to provide data to help providers and individuals make those choices. Though no indication was sought in this case, Merck believes this will be an important study to discuss. The initial filing was in boys 9 through 15 years of age and girls and young women 9 through 26 years of age. Protocol 003, the young men study, is ongoing. It started a little later than the other phase 3 studies and the results will be available later in 2014.

These are not the only studies ongoing for the 9vHPV vaccine, but for the sake of time, everything could not be presented. Of potential interest to ACIP, Merck recently started an evaluation of a 2-dose regimen for the 9-valent vaccine. A full transition from the qHPV to the 9vHPV vaccine is expected to be very rapid in the US, so the focus for the 2-dose study is on the 9vHPV vaccine. An initial immunogenicity study was begun to evaluate the question of feasibility and value. Merck recognizes that long-term effectiveness information will be needed as well.

During this session, Dr. Luxembourg discussed study results data for the following studies:

- ❑ Evaluation in young women (16 through 26 years of age)
 - Protocol 001 (pivotal efficacy study)
 - Efficacy and immunogenicity
 - Safety
- ❑ Evaluation in adolescents (girls/boys, 9 through 15 years of age)
 - Protocol 002 (adult-adolescent immunobridging)
 - Immunogenicity
 - Safety
 - Protocol 009 (qHPV-9vHPV immunobridging)
 - Immunogenicity
 - Safety

Protocol 001 is a large international study comprised of more than 14,000 young women ages 16 through 26. It is a double-blinded study in which young women were randomized to 9vHPV or qHPV vaccine. Placebo was not used for ethical reasons: the qHPV vaccine is widely recommended and widely available, and it would not be acceptable to let study participants develop precancers that can be prevented by the licensed qHPV vaccine. The study was started in 2007 one year after qHPV vaccine was licensed as a 3-dose regimen vaccine. Since the goal was to bridge from qHPV to the 9vHPV vaccine, both vaccines were administered as a 3-dose regimen. A key goal of the study is to assess 9vHPV vaccine efficacy. Women are followed by genital gynecological examinations. Every 6 months, genital swabs are used to assess for the presence of HPV and a Pap test is done. For any subject with an abnormal Pap test, there is a protocol-mandated triage to assess for disease endpoints. Immunogenicity is also assessed Day 1 and Month 7 for antibody titers for all 9 vaccine HPV types. Safety is also assessed through standard methods.

This large efficacy trial has been underway for almost 6 years. Subjects have had follow-up for up to 4 years post-vaccination. The intensive screening (every 6 months) ensures that no lesions are missed, so the data package is very high quality. Again, there is no placebo control. The control is the licensed qHPV vaccine, which is highly efficacious. For this reason, no disease endpoints are expected for the original types in the qHPV vaccine group. If the 9-valent vaccine is successful, very few to no disease endpoints are expected for the original types in the 9vHPV vaccine group as well. This means a head-to-head comparison based on efficacy endpoints is not feasible, because there will be too few disease endpoints to conduct a statistical comparison. Given that, the primary demonstration of efficacy for the original types is based on the demonstration of non-inferior immunogenicity. The goal is to bridge the efficacy findings with the qHPV vaccine to the 9vHPV vaccine based on non-inferior immunogenicity. For the additional types, a difference is expected between the two vaccines in terms of these endpoints. As mentioned, there is some cross-reactivity and some cross-protection, though this is still insufficient to cover all of the types. So the qHPV vaccine cohort will be assimilated to an unvaccinated cohort for the additional types. If anything, this would mean an underestimation of the true efficacy of 9vHPV vaccine.

Two different primary objectives are being followed for the original and additional types. The primary analysis population for efficacy is the susceptible population, consisting of women who are seronegative for the relevant HPV type at Day 1 and PCR negative for the relevant HPV type on all swabs/biopsies from Day 1 through Month 7. This definition is similar to the one used previously in the qHPV vaccine clinical program. In addition subjects in the primary analysis population received all 3 vaccinations within 1 year, and had no protocol violations. The primary analysis population for immunogenicity has a similar definition.

Compliance was very good. Most subjects received 3 doses and most of them stayed in the study. There was no difference between the two vaccine cohorts. Over 96% of subjects continued in the efficacy evaluation phase. Month 7 antibody titers were measured by the 9-valent HPV competitive Luminex Immunoassay (HPV-9 cLIA), which is based on the same principle as the HPV-4 cLIA, the immunoassay which was used previously in the qHPV vaccine program. Non-inferiority was demonstrated for all 4 types with GMT ratios with a p value <0.001. Seroconversion rates were also comparable between the two vaccine groups. Based on these results efficacy with respect to HPV types 6, 11, 16, and 18 is inferred.

To evaluate efficacy with respect to the additional types, composite endpoints were assessed for disease or infection caused by any of the 5 additional types. The key endpoints were (1) high-grade cervical, vulvar, and vaginal disease due to any of the additional types, (2) cervical, vulvar, and vaginal disease of any grade due to any of the additional types, and (3) 6-month persistent infection due to any of the additional types. What is remarkable is that the efficacy is very high at greater than 96%, and is very consistent across all endpoints. This demonstrates that the vaccine is highly efficacious in reducing the risk of disease and infection due to the additional types. In addition, these very high numbers are reminiscent of the numbers for efficacy found in the qHPV vaccine program where the efficacies were in the high 90s. Now there are two vaccines based on the same technology, VLP, that in two different clinical programs were shown to be highly efficacious.

Looking at cervical and vulvar disease separately, the study results show that 9vHPV vaccine is highly efficacious for high-grade cervical, cervical disease of any grade, high-grade vulvar and vaginal disease, and vulvar and vaginal disease of any grade. There was one case of high grade cervical disease in the 9-valent group. This case was co-infected with a non-vaccine high-risk HPV type, type 56. Most likely, type 56 is the causal virus because this subject was infected by Type 56 from Day 1 and through at least the first two years of the study; whereas, type 58 was found only at the time biopsy was done. Type 58 was mostly likely a transient infection. In terms of invasive procedures related to the additional types, the risk of biopsies and definitive therapies was substantially decreased. This suggests that not only does the vaccine have the potential to prevent a lot of disease types, but also the potential to prevent a lot of procedures.

Regarding safety for Protocol 001, Dr. Luxembourg showed a summary of the vaccine-related experiences comparing two vaccines. Essentially the profiles were similar, with very few vaccine-related SAEs on days 1 through 15 following vaccination. There were no vaccine-related deaths and very few discontinuations. The only difference was a higher frequency of injection site SAEs among 9vHPV recipients. This was not a surprise, given that there are more adjuvant and more antigen in the 9vHPV vaccine than in the 4vHPV vaccine. Looking more closely at the injection-site adverse experiences from Days 1 through 5 following each dose of vaccination in the safety set, it is clear that there was a difference for all three types of injection site adverse events (erythema, pain, swelling) and that the difference was statistically significant. Due to the very high numbers of subjects, the difference can be demonstrated. From a clinical standpoint, most injection site adverse events were of mild or moderate intensity in both vaccine groups. Thus, it is anticipated that the clinical significance of this difference will be minimal.

Looking at systemic vaccine-related adverse events with an incidence of more than 2%, there were only 5 types of events (headache, pyrexia, nausea, dizziness, fatigue) within a study of 14,000 subjects. All of these events are everyday life events that are commonly used in vaccine studies. There was no substantial difference between the two vaccines. Four serious vaccine-related adverse events were observed, 2 in the 9-valent group and 2 in the qHPV vaccine group. None of these required hospitalization except for one day for the event of headache in the qHPV vaccine group. The adverse event terms were seen previously in the 4-valent clinical program, and all events were promptly resolved.

In conclusion of Protocol 001, non-inferior immune responses were demonstrated for the original types. An approximately 97% reduction in disease was demonstrated for the additional types. Regarding safety, the 9vHPV vaccine was generally well-tolerated in more than 7,000 young women. The adverse experiences profile was generally comparable between 9vHPV

vaccine and qHPV vaccine. A higher frequency was noted of injection-site adverse events with 9vHPV vaccine, but most were of mild or moderate intensity.

Turning to Protocol 002, the international adult-adolescent immunobridging study, the immunogenicity goal was to demonstrate non-inferior immunogenicity of 9vHPV vaccine in adolescents 9 through 15 years of age versus young women 16 through 26 years of age. The safety goal was to evaluate the safety and tolerability of the 9vHPV vaccine in adolescent boys and girls and young women. The study population was comprised of 1800 girls, 600 boys, and 400 young women. This was an open-label study in which subjects received a 3-dose regimen of 9-valent vaccine. Immunogenicity was assessed at Day 1 and Month 7, while safety was assessed at Day 1 through Month 12.

In terms of GMTs in girls versus young women, non-inferiority was met in that the GMTs were higher in girls compared to young women. This is reminiscent of what was seen in the 4-valent program where a similar comparison was made for the 4 original types, and the GMT ratio was about 2. Once again, there was similarity between the two vaccines. Regarding seroconversion rates, most subjects became seropositive for 9 types after a 3-dose regimen both in the girls and young women cohorts. Like the comparison between the girls and the young women, the boys had a higher immunogenicity and GMT ratios of approximately 2 and close to 3 for some types. There was clearly superior immunogenicity in this group as well. Seroconversion rates were very good in male subjects, all of whom converted to all 9 types. With regard to safety during Days 1 to 15 following any vaccination, the safety profile was similar between the three demographic groups. Safety may even look slightly more favorable for the boys, which is similar to what was observed in the 4-valent vaccine clinical program.

In conclusion for Protocol 002, non-inferior immunogenicity was demonstrated in adolescents compared to adults. This supports bridging of efficacy findings in young women to the adolescent population. Immunogenicity was comparable in boys versus girls. In terms of safety, 9-valent vaccine was generally well-tolerated in all 3 demographic groups.

Moving to Protocol 009 (qHPV-to-9vHPV immunobridging), the immunogenicity objective was to compare anti-HPV 6, 11, 16 and 18 GMTs in adolescent girls who received qHPV vaccine compared to adolescent girls who received 9vHPV vaccine. The safety objective was to evaluate the safety and tolerability of the qHPV and 9vHPV vaccines in adolescent girls. Protocol 009 was a double-blinded study in which subjects receive 9vHPV or qHPV vaccine. The study was comprised of 600 girls who were equally randomized to 9vHPV vaccine or qHPV vaccine. The key endpoints included immunogenicity at Day 1 and Month 7, and safety for Day 1 through Month 7. Compliance was very good. Most subjects who completed the study received the 3-dose regimen. Non-inferiority of GMTs was demonstrated. The immunogenicity was comparable between the two vaccines for the two oncogenic Types 16 and 18. This mirrors the data in young women, and adds confidence that the two vaccines have the same profile. There was similar immunogenicity for Types 6 and 11, the non-oncogenic genital wart causing types. Of the subjects, 100% seroconverted after a 3-dose regimen in both vaccine groups, which shows that the vaccine was highly immunogenic.

In conclusion for Protocol 009, for the immunogenicity endpoint, anti-HPV 6/11/16/18 GMTs were comparable in adolescent girls who received 9vHPV vaccine compared to adolescent girls who received qHPV vaccine. This supports the bridging of efficacy findings with qHPV vaccine to 9vHPV vaccine. The safety profile was comparable between 9vHPV vaccine and qHPV vaccine, with most injection-site reactions being of mild or moderate intensity with both vaccines.

With respect to the overall conclusions, the 9-valent clinical development program is believed to be successful. All efficacy and immunogenicity objectives were met for the key pivotal studies. Non-inferior immunogenicity was demonstrated for anti-HPV 6, 11, 16, 18 responses compared to qHPV vaccine. Approximately 97% protection was demonstrated against disease caused by the additional types (HPV 31, 33, 45, 52, 58). Non-inferior immunogenicity was demonstrated in adolescents versus adults. The 9-valent vaccine is generally well-tolerated. There were over 10,000 subjects in protocols 001, 002, 009. The adverse event profile was generally similar to that of qHPV vaccine. Additional information to be presented during future ACIP meetings includes data on concomitant use; prior qHPV vaccine recipients; and young men 16 through 26 years of age. Presently, the 9-valent vaccine is still an investigational product even though the studies have completed. The product is currently under standard FDA review, and regulatory action is expected within the next few months.

Discussion Points

In terms of adverse events, Dr. Jenkins noted that for the 4-valent vaccine recipients experienced syncope following vaccination. She did not hear that mentioned in terms of these studies.

Dr. Luxembourg replied that Merck monitored all systemic adverse events, but he showed only the most frequent events. Syncope and syncope with fall was monitored, and there was no event of syncope with fall during the study. Precautions were also taken to observe subjects during the study, and there were no events like that. There was one event of syncope prior to vaccination.

Dr. Riley (ACOG) inquired as to what this looked like in HIV-positive women.

Dr. Luxembourg responded that HIV-positive women have not been studied. All of the studies were conducted in healthy subjects, as is common in vaccine studies. An academic study was conducted in HIV-positive children 7 through 12 years of age for the 4-valent vaccine. Given that the immunogenicity profiles of the two vaccines are very similar and consistent, the same safety and immunogenicity profile would be expected in that population as when 4-valent was administered to that subgroup.

Dr. Temte asked whether there were any differences in side-effects between the first, second, and third doses in terms of the profile.

Dr. Luxembourg indicated that there were differences. The main difference was in terms of frequency of injection site swelling and injection site erythema. The frequency increases by dose, and it is similar to what has been observed previously with the 4-valent vaccine.

Dr. Pickering asked whether there were any data on women who may have received 3 doses of HPV 4-valent with regard to injection site reactions in these women if they received HPV 9-valent.

Dr. Luxembourg responded that Merck has conducted one study, Protocol 006, with one of the primary goals being to assess 3 + 3. The safety profile was found to be acceptable, and there was no major increase in terms of injection site adverse experiences.

Dr. Neuzil (IDSA) noted that there was a press release earlier in the day that reported that Gardasil® received a favorable opinion from the EMA for a 2-dose schedule. She wondered what Merck's clinical development plans were for the 9-valent 2-dose schedule.

Dr. Luxembourg indicated that Merck is interested in and recognizes the importance of this topic. A 2-dose study has been initiated for the 9-valent vaccine. Merck first wants to demonstrate the feasibility, value, and immunobridging of the 9-valent vaccine. Merck also recognizes that follow-up is important with regard to long-term effectiveness and duration of protection conferred by 2 doses versus 3 doses. It is a somewhat premature to discuss more about the plans at this stage, but an immunogenicity study has been started.

Dr. Sawyer (PIDS) inquired as to how long Merck's long-term follow-up of the quadrivalent 2-dose series has been and, therefore, what could be expected for the 9-valent.

Dr. Luxembourg responded that Merck has long-term follow-up for a 3-dose regimen for the 4-valent vaccine. At this time, there is no evaluation of long-term effectiveness for a 2-dose regimen.

Summary and Next Steps

Lauri Markowitz, MD
HPV Vaccine Working Group
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Dr. Markowitz began with a brief summary of some of the data presented during this session about HPV type attribution. Of the CIN2+ lesions, about 50% are attributable to HPV16/18 and about 25% are attributable to 5 additional types in investigational 9-valent vaccine. The largest percentage of lesions in all racial/ethnic groups is attributable to HPV16/18. A larger percentage of lesions is attributable to HPV16/18 among non-Hispanic white compared with non-Hispanic black and Hispanic women. For HPV-associated cancers, approximately 62% (range, 48% penile - 79% anal) are attributable to HPV16/18, and 11% (range, 8% anal - 18% vaginal) are attributable to the 5 additional types. The largest percentage of HPV-associated cancers in all racial/ethnic groups is attributable to HPV16/18. No differences have been observed by race for cervical, vaginal, vulvar, penile or anal cancers. A smaller percentage of oropharyngeal cancers are attributable to HPV among non-Hispanic blacks. Among HPV positive oropharyngeal cancers, a smaller percentage is attributable to HPV16/18. The Pivotal efficacy study among females aged 16 through 26 years of age found non-inferior HPV 6/11/16/18 immunogenicity versus HPV4, and approximately 97% protection against HPV 31/33/45/52/58-related disease. The immunobridging studies in adolescents demonstrated non-inferior immunogenicity in adolescents versus adults.

As a reminder about the HPV WG timeline, further trial data will be presented to ACIP during the June 2014 meeting, specifically data from concomitant administration and 9-valent vaccine among prior HPV4 recipients. There are also plans to discuss health economics at that time. In October 2014, GRADE results will be presented and recommendation options will be discussed. If data are available from the ongoing immunogenicity trial in males 15 through 26 years, those data will also be reviewed during the October ACIP meeting. If 9-valent vaccine is licensed, a vote can be anticipated on the recommendations during the February 2015 ACIP meeting.

A variety of issues will be considered by the HPV vaccine WG with regard to 9-valent vaccine including the following:

- Routine vaccination of females and males at age 11 through 12 years of age
- Vaccination of older females and males who were not vaccinated at the recommended age; the timing for consideration of males age 16 through 26 years will be discussed by the work group, because it is anticipated that the vaccine will not be licensed in this age group at the time of first licensure
- Vaccination of persons fully or partially vaccinated with HPV4

While the ACIP HPV vaccine WG is focusing on review of data relevant to the investigational 9-valent vaccine, other issues are being considered. As always, there is ongoing review of post-licensure safety and coverage data. The WG is also keeping abreast of data on reduced dose schedules for HPV vaccination and plans for a future review of these data. With regard to the issues related to a reduced number of doses or simplified schedules, there is global interest in simplified schedules for HPV vaccine. This would reduce logistical challenges for delivery and decrease resources and costs. There are available data on 2-dose schedules for the bivalent and the quadrivalent vaccines. These are primarily immunogenicity studies, but there are post-hoc evaluation of data from the efficacy trial for the bivalent vaccine, and post-licensure effectiveness data for the quadrivalent vaccine. Some jurisdictions are using 2-dose schedules in their national or provincial immunization programs around the world. The EMEA granted marketing authorization for Cervarix[®], the bivalent vaccine produced by GSK, as a 2-dose schedule given at 0 and 6 months for girls aged 9 through 14 years in December 2013. Merck has submitted an application to the EMEA for a 2-dose schedule as well. The 9-valent vaccine is currently in immunogenicity trials. The HPV Work Group will be keeping abreast of these data, and can report back to ACIP.

Updated ACIP Statement for Bivalent & Quadrivalent Vaccines

Lauri Markowitz, MD
HPV Vaccine Working Group
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Regarding the updated HPV vaccine ACIP statement, Dr. Markowitz reminded everyone that the first recommendation was in 2006 and the most recent for routine vaccination of males in late 2011. Because of the evolving recommendations, after the original 2007 ACIP statement, short Policy Notes were published with updated recommendations. The 2011 Policy Note was published for the recommendation for routine vaccination of males. This last recommendation was the only one in which GRADE was used, as this was after GRADE adoption by ACIP. To review, the following are published ACIP recommendations for HPV vaccines:

- 2007 ACIP Statement [*MMWR* Recomm Rep 2007;56:1-24]
 - Recommendation for routine vaccination of females at age 11 or 12 years with quadrivalent HPV vaccine
- 2010 Policy Note [*MMWR* 2010;59:626-9]
 - Recommendation for routine vaccination of females with bivalent or quadrivalent HPV vaccine

- ❑ 2010 Policy Note [*MMWR* 2010;59:630-2]
 - Quadrivalent HPV vaccine may be given to males 9 through 26 years
- ❑ 2011 Policy Note [*MMWR* 2011;60:1705-8]
 - Recommendation for routine vaccination of males at age 11 or 12 years with quadrivalent HPV vaccine
 - This was the only recommendation for which GRADE was used, because GRADE had just been adopted by ACIP before that time

The objectives of the updated HPV vaccine statement are to consolidate recommendations for females and males; consolidate information and recommendations for bivalent and quadrivalent vaccines; harmonize wording that differ in policy notes and the statement; and update background information and data regarding efficacy, safety, immunogenicity, impact monitoring, et cetera. This overlaps with consideration of the 9-valent vaccine, but the work group believes that the updated ACIP statement will facilitate efforts for development of future policy. All members have reviewed the statement.

The new statement has many of the same sections as the 2007 document. These include:

- ❑ Background on biology, immunology, epidemiology, and natural history
- ❑ Clinical sequelae
 - Cancers
 - Anogenital warts
 - Recurrent respiratory papillomatosis (RRP)
- ❑ Prevention, treatment, and cervical cancer screening
 - Prevention of sexual transmission of HPV, non-vaccine
 - Cervical cancer screening
 - Treatment of HPV related disease
 - Selected health care and research laboratory workers (non-vaccine prevention measures)

The updated ACIP statement sections include the following:

- ❑ Vaccines
 - Clinical trial data for quadrivalent and bivalent vaccines
 - Post licensure safety data
- ❑ Economic burden of HPV disease and cost-effectiveness
- ❑ HPV vaccination program in the US
- ❑ Summary of rationale for HPV vaccination recommendations
- ❑ Recommendations
 - Routine
 - Administration: intervals, concomitant administration, interchangeability
 - Special populations
 - Precautions and contraindications

In the first updated draft statement discussed during the October 2013 ACIP meeting, the recommendation section was divided into recommendations for females and males. In the current version, the female and male recommendations are combined as follows:

- ACIP recommends routine vaccination at age 11 or 12 years with HPV4 or HPV2 for females and with HPV4 for males (male GRADE recommendation category: A, evidence type: 2). The vaccination series can be started beginning at age 9 years.
- HPV4 and HPV2 are each administered in a 3-dose schedule. The second dose should be administered 1-2 months after the first dose; the third dose 6 months after the first dose.
- Vaccination also is recommended for females aged 13 through 26 years and for males aged 13 through 21 years who have not been previously vaccinated or who have not completed the 3-dose series. Males aged 22 through 26 years may be vaccinated.

There are also recommendations for special populations and precautions and contraindications, which are as follows:

Special Populations

- Persons with abnormal Pap, genital warts, et cetera
- Immunocompromised persons
- Men who have sex with men (MSM)
- Lactating women
- Children with history of sexual abuse or assault (new in this statement; discussed several times with ACIP)

Precautions and Contraindications

- Hypersensitivity or allergy
- Acute illness
- Preventing syncope
- Pregnancy

The language in the updated HPV vaccine ACIP statement for special populations is as follows:

Immunocompromised Persons

“ACIP recommends routine vaccination at 11 or 12 years with HPV2 or HPV4 for females and with HPV4 for males. Vaccination is recommended through age 26 years for immunocompromised persons who have not been vaccinated previously or who have not completed the 3-dose series.”

Men who have Sex with Men (MSM)

“For MSM, ACIP recommends routine vaccination with HPV4, as for all males, and vaccination through age 26 years for those who have not been vaccinated previously or who have not completed the 3-dose series.”

History of Sexual Abuse or Assault

“While HPV vaccination will not promote viral clearance or protect against disease progression due to types already acquired, vaccination would protect against vaccine-preventable types not yet acquired. ACIP recommends HPV vaccination beginning at age 9 years for children and youth with any history of sexual abuse or assault who have not initiated or completed the 3-dose

series. Adults through age 26 years who are victims of sexual abuse or assault should receive HPV vaccine if they have not already been vaccinated.”

Hypersensitivity or Allergy to Vaccine Components

“HPV vaccines are contraindicated for persons with a history of immediate hypersensitivity to any vaccine component. HPV4 is produced in *Saccharomyces cerevisiae* (baker’s yeast) and is contraindicated for persons with a history of immediate hypersensitivity to yeast. Prefilled syringes of HPV2 have latex in the rubber stopper and should not be used in persons with anaphylactic latex allergy. ~~HPV2 single dose vials contain no latex~~

The language in the updated HPV vaccine ACIP statement for precautions and contraindications is as follows:

Pregnancy

“HPV vaccines are not recommended for use in pregnant women. The vaccines have not been causally associated with adverse outcomes of pregnancy or adverse events in the developing fetus. However, if a women is found to be pregnant after initiating the vaccination series, the remainder of the 3-dose series should be delayed until completion of pregnancy . . .”

Finally, there are sections on monitoring impact of vaccination and areas for ongoing research and future priority activities. A variety of issues are very briefly mentioned here, including the investigational 9-valent vaccine and reduced dose schedules.

A variety of helpful comments were received from ACIP members and other reviewers. These included requests for edits and clarifications and requests for additional data on post-licensure safety evaluations. In the recommendation section, suggestions were received for rewording of the sexual abuse section, as well as other minor wording changes.

The following table is included in the document. It reviews post-licensure safety evaluation in the US and other countries. This was in the last version ACIP members reviewed, but text was added to mention briefly each of these studies, which have all shown reassuring safety profiles:

System or review and Country	Doses evaluated	Description	Methods	Findings
Vaccine Safety Datalink (VSD) ^a USA	600,559	Large data base used for active surveillance and research. Safety assessment of 7 pre-specified health outcomes among HPV4 female recipients.	Cohort design with weekly sequential analyses of electronic medical data	No statistically significant increase in risk for the outcomes monitored.
Post-marketing commitment (to US FDA) ^b USA	346,972	General study assessment of HPV4 following routine administration at two large managed care organizations.	Self-controlled risk interval design supplemented with medical record review	HPV4 associated with syncope on the day of vaccination and skin infections in the two weeks after vaccination. ^c No other vaccine safety signals were detected.
Post-marketing commitment (to US FDA) ^b USA	346,972	Assessment of 16 pre-specified autoimmune conditions following routine use of HPV4 at two large managed care organizations.	Retrospective cohort using electronic medical data, supplemented with medical record review	No confirmed safety signals for monitored conditions.
Register based cohort study ^d Denmark and Sweden	696,240	Assessment of 23 different autoimmune, 5 neurologic conditions and VTE following HPV4 among females aged 10-17 years.	Retrospective cohort using national patient registers	No consistent evidence of causal associations between HPV4 and the events monitored.
Pharmacoepidemiologic General Research Extension ^e France		Assessment of 6 different autoimmune outcomes among 211 cases and 875 controls aged 14-26 years.	Case control study with recruitment of cases and controls through registries	No increased risk of combined endpoint of 6 autoimmune disorders.

In summary, the draft statement updates background information and clinical trial data; consolidates and clarifies existing recommendations; and includes a variety of new sections, including a substantial amount of post-licensure safety data. This still has to finish going through editorial clearance, so there are likely to be a number of additional changes. The hope is that it will be published in the spring. The WG realizes that substantial new data will become available, and understands that recommendations will be updated in the future as more data become available.

Discussion Points

Dr. Temte reminded everyone that it is the goal of ACIP to renew, revise, or retire statements about every 5 years, so this is very timely considering everything that has occurred. The ACIP members received and reviewed this document, and submitted comments on it previously. He asked Dr. Markowitz whether there were any comments from the WG regarding the next steps. He said he was reflecting on the discussion the previous day about how difficult it is to consider making a change for a well-established, very successful vaccine program in terms of trying to reduce doses.

Dr. Markowitz replied that the WG has been closely following the discussions for the pneumococcal vaccine. Currently, the WG does not have plans to bring anything forward to the ACIP. The group is keeping abreast of the data, reviewing what is occurring, and is aware that there is a lot of interest in this area. More information will be available from ongoing studies, and while the work group is happy to present the data, they are considering a motion or consideration by ACIP at this time.

Dr. Tan (IAC) thanked ACIP for consolidating the recommendations. As everyone knows, having consolidated guidance will be very useful to providers to strongly recommend this vaccine. He called attention to a letter and press release provided to ACIP members essentially urging providers to not just give a recommendation for HPV vaccination, but to make the recommendation very strong. The tag line for this "Dear Colleague" letter essentially is "What you say matters, but how you say it matters even more." Dr. Tan said it had been a delight to collaborate with AAP, AAFP, ACOG, ACP, and CDC to create this "Dear Colleague" letter, which was launched two days after the President's Cancer Panel and it is fortunate to be able to collaborate with the President's Cancer Panel to market this letter with their report. This letter has been very favorably received by the media. Any questions can be directed to Dr. Tan.

Dr. Jean Smith (ACIP Medical Officer) noted that in the last two days they had heard mention of two anniversaries, the 50-year anniversary of ACIP and the 20-year anniversary of the implementation of VFC. She informed the audience that this also marked the 10-year anniversary of Dr. Markowitz serving as the WG lead. She has worked with several ACIP members serving as WG chair. Dr. Smith said she could personally say that she was astonished at Dr. Markowitz's fortitude as problems and issues are thrown out repeatedly. She always marches forward with absolute calm.

Vote: Updated HPV ACIP Statement

Dr. Coyne-Beasley made a motion to accept the recommendations as proposed. Dr. Rubin seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

- 15 Favored:** Bennett, Bocchini, Campos-Outcalt, Coyne-Beasley, Duchin, Harriman, Harrison, Karron, Jenkins, Kempe, Pellegrini, Reingold, Rubin, Temte, and Vazquez
- 0 Opposed:** N/A
- 0 Abstained:** N/A

Smallpox Vaccine**Lee Harrison, MD
ACIP, Work Group Chair**

Dr. Harrison noted that numerous occurrences of laboratory-acquired orthopoxviruses infections have been reported. Smallpox vaccine provides cross-protection against all orthopoxviruses (e.g., smallpox, monkeypox, vaccinia, and cowpox). Smallpox vaccine is used to protect clinical and research laboratory workers against these viruses. Dr. Harrison shared several images of ocular, ear, and needlestick vaccinia virus transmissions in laboratory workers.

In terms of background, ACIP recommendations for smallpox vaccination of laboratory workers have not been updated since 2003. A new smallpox vaccine, ACAM2000, was licensed in 2007 and has replaced the previously used smallpox vaccine, Dryvax. The Smallpox Vaccine Work group was established in March 2013, and monthly meetings have been held since that time. The work group's terms of reference are as follows:

1. Review recommendations for smallpox vaccination for lab workers in 2001 statement (and supplements from 2003):
 - a. Review Biosafety in Microbiological and Biomedical Laboratories (BMBL) requirements for work with orthopoxviruses
 - b. Review orthopoxvirus laboratory exposure cases and reports
2. Review data on smallpox vaccine:
 - a. ACAM2000
 - Safety and immunogenicity data
 - Adverse event rates with current stringent prescreening program
 - b. Dryvax: Publications on 2002 through 2004 pre-event smallpox vaccination program
3. Review human safety and animal model efficacy data for attenuated smallpox vaccine IMVAMUNE stored in Strategic National Stockpile and potential role in smallpox vaccination for lab workers (unlicensed product and therefore informational)

4. Review data on recombinant vaccinia viruses in development or under investigation in clinical trials to provide guidance on need for smallpox vaccination in healthcare and/or laboratory personnel working with these viruses
5. Revise existing statement and supplements for smallpox vaccination of laboratory workers into single ACIP Policy Note document

Use of ACAM2000 Smallpox Vaccine in Laboratory Personnel

Brett W. Petersen, MD, MPH
CDC Lead, Smallpox Work Group
Medical Officer, Poxvirus and Rabies Branch, CDC
Lieutenant Commander, U.S. Public Health Service

Dr. Petersen indicated that the goal of his presentation was to provide a general overview of some of the topics and issues that the Smallpox Work Group has discussed to date, as well as some of the data that the WG has reviewed and assessed. The hope is that this information will serve as a foundation for revising and updating the smallpox vaccine recommendations for laboratory workers.

With regard to background, orthopoxviruses are a group of large double-stranded DNA viruses within the family *Poxviridae*. There are four known species that infect humans: Variola (Smallpox), Vaccinia (Smallpox Vaccine), Monkeypox, and Cowpox. Orthopoxvirus virus infection provides cross protection across species. It is this property that has allowed the development of vaccinia as a vaccine for smallpox and other orthopoxviruses and has ultimately resulted in eradication of smallpox as a human disease. However, orthopoxviruses remain an active subject of research.

In particular, vaccinia virus is commonly used in laboratory research. There are many historic vaccine seed stocks and derivatives including the following: New York City Board of Health (NYCBH), Lister, Modified Vaccinia Ankara (MVA), Western Reserve, LC16M8, Copenhagen, among others. Different vaccinia viruses demonstrated varying degrees of attenuation and safety profiles. Recombinant vaccinia viruses are being used increasingly in the laboratory setting as a viral vector for expression of foreign genes using gene therapy or genetic engineering, and are also under investigation as potential recombinant vaccines and as oncolytic or immunotherapy for cancer.

Given the risks to laboratory workers using these viruses, ACIP produced recommendations for vaccinia vaccine in 2001. ACIP recommended vaccinia vaccine for laboratory workers who directly handle cultures or animals contaminated or infected with non-highly attenuated vaccinia virus, recombinant vaccinia viruses derived from non-highly attenuated vaccinia strains, or other orthopoxviruses that infect humans (e.g., monkeypox, cowpox, vaccinia, and variola). Vaccination can be offered to healthcare workers with direct contact with dressings or other infectious material from volunteers in clinical studies where non-highly attenuated vaccinia viruses or recombinant viruses derived from these strains are used. Persons working with vaccinia virus, recombinant vaccinia viruses, or other non-variola Orthopoxviruses should be revaccinated at least every 10 years. Revaccination every 3 years can be considered for persons working with more virulent non-variola Orthopoxviruses (e.g., monkeypox).

Laboratory and healthcare personnel working with highly attenuated poxvirus strains do not require routine vaccinia vaccination. Highly attenuated poxvirus strains include the following:

- MVA: Derived from vaccinia virus Ankara
- NYVAC: Derived from vaccinia virus Copenhagen
- TROVAC: Derived from fowlpox virus
- ALVAC: Derived from canarypox virus

The population at risk is difficult to estimate, given that there is no registry of persons who work with orthopoxviruses. Indirect measures that offer some sense of the size of this population include the following:

- A simple PubMed search revealed that 431 orthopoxvirus-related publications were released in 2013
- A search of the NIH Research Portfolio Online Reporting Tools revealed that there are 185 active projects listed relating to vaccinia virus work (<http://projectreporter.nih.gov/>)
- Clinicaltrials.gov lists 25 open clinical trials involving vaccinia virus
- As of 2013, 31 different sites received 80 shipments of smallpox vaccine from the CDC stockpile in 2013 and over the last 5 years, 96 different sites received 523 shipments

The risk of orthopoxviral disease is difficult to estimate as well, given that surveillance is not ideal and the true burden of disease is not known. Vaccinia and cowpox infections are not reportable conditions, so there is not a comprehensive list of all potential infections. Similarly, orthopoxvirus exposures are not always reported. In addition, the pathogenicity and virulence of the virus may not be well-characterized, particularly with regard to recombinant viruses.

However, CDC has maintained a database of laboratory-related orthopoxvirus exposures and infections that have been reported since 2004. Of the 26 exposure incidents reported, 18 (69%) involved recombinant viruses and 14 (54%) resulted in infections. Of those 14, 12 (86%) involved recombinant viruses, 12 (86%) involved vaccinia infections, 2 (14%) involved cowpox infections, 4 (29%) required hospitalization, and 4 (29%) involved infection with a strain other than that with which they were working (or thought they were working). Of the 26 exposure incidents reported, 7 (27%) met ACIP vaccination recommendations, and 1 of those 7 (14%) resulted in infection. One other infection occurred in an individual vaccinated over 10 years prior, which did not meet the ACIP vaccine recommendations [Adapted from MacNeil A, Reynolds MG, Damon IK. Risks associated with vaccinia virus in the laboratory. *Virology*. 2009 Mar 1;385(1):1-4 and CDC records].

ACAM2000 is currently the only smallpox vaccine licensed and available in the US. It was licensed in 2007 and replaced the previously used smallpox vaccine, Dryvax, which is no longer available. ACAM2000 has been used in laboratory and healthcare workers and select DoD personnel. It is a live vaccinia virus vaccine that is produced in vero cells. It is derived from a clonal isolate of Dryvax, a New York City Board of Health strain used during the smallpox eradication campaign. ACAM2000 is administered in a single dose percutaneously via multiple puncture with a bifurcated needle. Following vaccine administration, a lesion develops at the site of vaccination. During this time, the lesion does contain infectious virus that can be transmitted to others via inadvertent inoculation or to other sites of the body via auto-inoculation. However, this cutaneous response is also referred to as a “take” and is considered a marker of successful vaccination.

Historically, smallpox vaccines have been associated with a number of adverse events, some of which can be severe and life-threatening. Some of those include eczema vaccinatum, progressive vaccinia, and postvaccinial encephalitis. Based on data from primary vaccination with Dryvax from a study conducted in 1968 during the time of routine immunization with smallpox vaccine, the rates ranged from 1.5 cases/million vaccinations to 38.5 cases/million vaccinations. Overall rates for deaths were also reported as approximately 1 death/million vaccinations. The rates for revaccination were much lower than those for primary vaccination [Adapted from Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: results of ten statewide surveys, *J Infect Dis.* 1970 Oct;122(4):303-9 and ACAM2000 package insert].

Based on data from a more recent study evaluating the adverse event rates observed during the DoD and HHS vaccination programs during 2002 and 2005, of note was the absence of any observed eczema vaccinatum or progressive vaccinia cases. This was likely due to the intense screening of persons for risk factors for these adverse events. Also of note was the incidence of myo/pericarditis, which had not previously been recognized as a significant adverse event related to smallpox vaccine [Adapted from Poland GA, Grabenstein JD, Neff JM. The US smallpox vaccination program: a review of a large modern era smallpox vaccination implementation program. *Vaccine* 2005, Mar 18;23(17-18):2078-81 and ACAM2000 package insert].

Using this background, the GRADE method was used to assess the ACAM2000 in laboratory workers utilizing the following steps:

- Development of a policy question
- Identification and assessment of the importance of outcomes
- Review of the literature
- Summarization of the evidence for critical outcomes
- Evaluation of the quality of evidence for outcomes

The policy question formulated by the WG was, "Should administration of ACAM2000 be recommended routinely to persons at risk for orthopoxviral disease?" The population of interest was persons at risk for exposure to orthopoxviruses. The intervention was vaccination with ACAM2000, the currently available vaccine, and the comparison was vaccination with the previously recommended vaccine, Dryvax. A modified Delphi method was used to solicit outcomes assessments from the work group members. The outcomes identified included benefits and harms. Among the benefits were vaccine efficacy to prevent orthopoxviral disease, cutaneous response or take, and neutralizing antibody response. Among the harms were serious adverse events, myo/pericarditis resolved with sequelae, myo/pericarditis resolved without sequelae, inadvertent inoculation, and mild adverse events. Outcomes deemed to be critical were vaccine efficacy to prevent orthopoxviral disease, serious adverse events, and myo/pericarditis resolved with sequelae. All of the outcomes were included in the evidence profile, though data were not available for vaccine efficacy to prevent orthopoxviral disease. Therefore, cutaneous response and neutralizing antibody response were used as surrogates for this benefit outcome.

A systematic literature review was performed to identify studies that met the criteria and addressed the outcomes identified by the work group. A total of 5 RCTs were identified that addressed the benefits outcomes, 4 of which also addressed the harms outcomes. Cutaneous response was best assessed in two studies evaluating this outcome in vaccinia-naïve and previously vaccinated subjects who were vaccinated with both ACAM2000 and the comparator

Dryvax. Of vaccinia-naïve subjects receiving ACAM2000, 96% demonstrated vaccination success. ACAM2000 was found to be non-inferior to the comparator, Dryvax, among this population. Of the previously vaccinated subjects receiving ACAM2000, 84% demonstrated vaccination success by cutaneous response as compared to 98% of Dryvax subjects. A statistical analysis revealed that ACAM2000 did not meet the predefined criteria for non-inferiority to Dryvax among this population. In terms of the neutralizing antibody response, these same studies evaluated the response in both vaccine-naïve and previously vaccinated subjects. Among vaccinia-naïve subjects, the geometric mean neutralizing antibody titer and the Log₁₀ mean were comparable to the comparator, Dryvax, although by the slightest of margins ACAM2000 did not meet the criteria for non-inferiority to the comparator vaccine. In contrast, among the previously vaccinated subjects, the neutralizing antibody titers were again similar and in this instance did meet the criteria for non-inferiority.

Regarding the critical harms outcomes, no serious adverse events were reported in the RCTs reviewed (e.g., death, eczema vaccinatum, progressive vaccinia, or postvaccinal encephalitis). There were 7 cases of suspected myo/pericarditis reported among the 2983 clinical trial participants who received ACAM2000. The best estimate of risk based on detection of 5 cases among 873 vaccinees during Phase 3 clinical trials incorporating active monitoring for myocarditis and pericarditis is 5.7 cases/1000 vaccinees. One case among those reporting myo/pericarditis demonstrated sequelae (e.g., persistent abnormal echocardiogram at one year).

Using the GRADE methodology to assess the evidence, the WG had no concerns for risk of bias or inconsistency for any of the outcomes. However, there were concerns about indirectness in the cutaneous response, neutralizing antibody, and myo/pericarditis resolved without sequelae outcomes. With respect to imprecision, there were concerns regarding the serious adverse events and inadvertent inoculation outcomes. Given these concerns, the evidence type was downgraded for those outcomes. In terms of indirectness, there was concern that the outcomes that were assessed in the RCTs may have differed from those of primary interest. With regard to the benefits outcomes, the cutaneous response and neutralizing antibody response were surrogates for the outcome of primary interest (i.e., vaccine efficacy to prevent orthopoxviral disease). With regard to harms outcomes, the true clinical significance of myo/pericarditis that resolved without sequelae is unclear. Many of these cases represented asymptomatic disease that were only detected due to the intensive cardiac monitoring that was performed during these trials. These included monitoring of EKGs as well as cardiac enzymes. Some of the suspected cases were only transient EKG changes or elevations of cardiac enzymes that had no symptoms whatsoever. Thus, myo/pericarditis that resolved with sequelae was felt to better represent the outcome of primary interest. Regarding imprecision, the work group found that the clinical trials were not adequately powered to detect serious adverse events (e.g., death, eczema vaccinatum, progressive vaccinia, or postvaccinal encephalitis), and was also not powered to detect inadvertent inoculation. Calculations of the probability that these adverse events would not be observed based on the number of participants in the clinical trials, as well as the sample size that would be needed to detect these events certainly support the assessment of imprecision in these cases. Based on this GRADE assessment, the overall level of evidence was determined to be 2. Although the studies evaluated were all RCTs, they did have important limitations.

Regarding next steps, the work group will begin updating and revising the recommendations using the data reviewed and discussed to date. The hope is to present these recommendations to ACIP during a future meeting, and ultimately to publish these recommendations in at least an ACIP Policy Note.

Discussion Points

With respect to nomenclature, Dr. Temte inquired as to whether this should be referred to as an orthopoxvirus vaccine as opposed to smallpox vaccine.

Regarding the serious sequelae shown on Slide 24, Dr. Kempe noted that the comparator was not given for Dryvax and she wondered what those were.

Dr. Petersen replied that the rate of myo/pericarditis in the ACAM2000 group was lower, with 7 cases reported among the ACAM2000 group (5.73 events per thousand vaccinations) and 3 cases among the Dryvax group (10.38 events per thousand vaccinations).

Dr. Campos-Outcalt noted that this was a pretty high rate of myo/pericarditis at about 1/180. He was interested in knowing the rate of autoinoculation and other complications among laboratory workers who have exposures, given that the harms and benefits must be weighed of offering it to someone. He would like to see a comparison the rate of 1/180 to the rates of autoinoculation and other complications from vaccinia exposure in the lab.

Dr. Petersen responded that this could certainly be investigated to see if the rate of autoinoculation among laboratory workers with lab-acquired infections can be determined.

It remained unclear to Dr. Kempe why the GRADE comparison was not being done against nothing versus Dryvax.

Dr. Petersen replied that the previous vaccine was Dryvax, so that was how the WG approached the GRADE assessment. There are no RCTs and there are very little data with which to evaluate the question of a comparison with nothing. Since smallpox vaccine was the first vaccine invented and in some sense has been grandfathered in, there have not been any robust studies to evaluate its actual efficacy against orthopoxviruses.

Dr. Harriman in the 2003 pre-event Dryvax vaccination program, people who got myo/pericarditis were older and often male. She wondered whether there was indication that certain types of people would be more likely to get myo/pericarditis in the ACAM2000 group.

Dr. Petersen indicated that it was correct that persons who experienced myo/pericarditis in recent vaccination campaigns were older. However, overall the population being vaccinated was older as well. In analyses of myo/pericarditis, no significant risk factors have been identified among the population that might predict who would be at higher risk of suffering this adverse event.

Dr. Decker (Sanofi Pasteur) offered some insight on most of the question posed thus far by reporting briefly on one of the post-marketing trials that Sanofi Pasteur is conducting as the licensed holder for ACAM2000 vaccine. When it was licensed as a national imperative at the time, ACAM2000 was licensed in recognition of the data Dr. Petersen described and in association with a family of coordinated post-marketing commitment trials designed to further assess the safety of the vaccine—all but one of which are still underway. One study has been completed and the report is in preparation. All of the studies are being conducted within the DoD, which is where people are receiving this vaccine. Study 004 is being conducted among troops who receive ACAM2000 while being processed to deploy overseas. There are study sites at 6 major military bases in the US that solicit participation of deploying troops into the

study. To date, approximately 130,000 deploying troops have been solicited and about 15,000 have agreed to participate. Of those, approximately 12,000 received ACAM2000 and remainder did not receive it either because they did not need another smallpox vaccination or because they had some type of contraindication such as a close contact who is pregnant. This study population obviously differs from the study population of laboratorians in that these are generally more fit people, and they receive their vaccinations in a highly structured or organized DoD program that has a rigorous list of contraindications. That list of contraindications is, in and of itself, a list issues that put one at higher risk if receiving the vaccination. For example, anyone with more than four signal cardiac risks or cardio-respiratory conditions is not offered vaccination. CDC also operates off of a similar list in giving guidance to who is vaccinated through the civilian program. The study is still underway; therefore, Dr. Decker did not have the detailed results. However, from the administrative management of the study, he was able to say that approximately 3/1000 vaccinees develop signs or symptoms suggesting possible myo/pericarditis that warrants their referral to an independent expert committee that adjudicates based on the complete and available medical data, regardless of whether they have definite, probable, possible, or no myo/pericarditis. Based on that, about 30 so far out of approximately 10,500 have been adjudicated as possible, probable, or definite myo/pericarditis. That is typically based on elevated troponin or abnormal EKG. Virtually none of these people have been symptomatic. There is also an attempt to follow the long-term clinical course, and almost no one solicited has been willing to participate in the study, which perhaps suggests that they do not feel any personal benefit of the study because they do not feel that they have any personal medical problems. However, that is just conjecture.

Day 2: Public Comment

No public comments were offered during this session.



Certification

Upon reviewing the foregoing version of the February 26-27, 2014 ACIP meeting minutes, Dr. Jonathan Temte, ACIP Chair, certified that to the best of his knowledge, they are accurate and complete. His original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

ACIP Membership Roster**CHAIR**

TEMTE, Jonathan L., MD, PhD
Professor of Family Medicine
University of Wisconsin School of Medicine and Public Health
Madison, WI
Term: 07/01/2011-06/30/2015

EXECUTIVE SECRETARY

PICKERING, Larry K., MD
Senior Advisor to the Director
Centers for Disease Control and Prevention
National Center for Immunization and Respiratory Diseases
Atlanta, GA

MEMBERS

BENNETT, Nancy, MD, MS
Professor of Medicine and Community and Preventive Medicine
University of Rochester School of Medicine and Dentistry
Rochester, NY
Term: 07/01/2011-06/30/2015

BOCCHINI, Joseph A., Jr., MD
Professor and Chairman
Department of Pediatrics
Louisiana State University Health Sciences Center
Shreveport, LA
Term: 07/01/2011-06/30/2015

CAMPOS-OUTCALT, Douglas, MD, MPA
Chair
Department of Family, Community and Preventive Medicine
University of Arizona College of Medicine - Phoenix
Phoenix, AZ
Term: 07/01/2011-06/30/2015

COYNE-BEASLEY, Tamera, MD, MPH
Director, NC Child Health Research Network
Associate Director, Community Engagement NC TraCS Institute - Child Health Core
Professor of Pediatrics and Internal Medicine
Division of General Pediatrics and Adolescent Medicine
University of North Carolina School of Medicine
Chapel Hill, NC
Term: 10/04/2010-06/30/2014

DUCHIN, Jeffrey, MD
Chief, Communicable Disease Epidemiology and Immunization Section
Public Health - Seattle and King County
Professor in Medicine
Division of Allergy and Infectious Diseases
University of Washington School of Medicine
Seattle, WA
Term: 10/04/2010-06/30/2014

HARRIMAN, Kathleen, PhD, MPH, RN
Chief, Vaccine Preventable Disease Epidemiology Section
Immunization Branch
California Department of Public Health
Richmond, CA
Term: 07/01/2012 – 06/30/2016

HARRISON, Lee H., MD
Professor of Medicine and Epidemiology
Infectious Diseases Epidemiology Research Unit
University of Pittsburgh
Pittsburgh, PA
Term: 07/01/2012 – 06/30/2016

JENKINS, Renée R., MD
Professor and Chair Emeritus
Department of Pediatrics and Child Health
Howard University College of Medicine
Washington, DC
Term: 10/06/2010 – 06/30/2014

KARRON, Ruth A., MD
Professor and Director
Center for Immunization Research
Department of International Health
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD
Term: 07/01/2012 – 06/30/2016

KEMPE, Allison, MD, MPH
Professor of Pediatrics
Director of Primary Care Fellowship
University of Colorado School of Medicine
Director of Research
Division of General Academic Pediatrics
Director of Children's Outcomes Research Program
The Children's Hospital of Denver
Denver, CO
Term: 07/01/2013 - 06/30/2017

PELLEGRINI, Cynthia
Senior Vice President
Public Policy and Government Affairs
March of Dimes
Washington, DC
Term: 07/01/2013-06/30/2017

REINGOLD, Arthur L., MD
Professor of Epidemiology
Edward Penhoet Distinguished for Global Health and Infectious Disease
Associate Dean for Research
School of Public Health
University of California
Berkeley, CA
Term: 07/01/2013-06/30/2017

RUBIN, Lorry, MD
Director
Pediatric Infectious Diseases
Steven and Alexandra Cohen Children's Medical Center of New York
North Shore-Long Island Jewish Health System
New Hyde Park, NY
Professor of Pediatrics, Hofstra-North Shore LIJ School of Medicine
Hempstead, NY
Term: 07/01/2012 – 06/30/2016

VÁZQUEZ, Marietta, MD
Associate Professor of Pediatrics
Department of Pediatrics
Yale University School of Medicine
New Haven, CT
Term: 07/01/2011-06/30/2015

EX OFFICIO MEMBERS

Centers for Medicare and Medicaid Services (CMS)

HANCE, Mary Beth
Senior Policy Advisor
Division of Quality, Evaluations and Health Outcomes
Children and Adults Health Programs Group
Center for Medicaid, CHIP and Survey & Certification
Centers for Medicare and Medicaid Services
Baltimore, MD

Department of Defense (DoD)

GEIBE, Jesse, MD, MPH, MBA
CDR, Medical Corps
Defense Department Liaison Officer
Centers for Disease Control and Prevention
Atlanta, GA

Department of Veterans Affairs (DVA)

KINSINGER, Linda S., MD, MPH
Chief Consultant for Preventive Medicine
Office of Patient Care Services
National Center for Health Promotion and Disease Prevention
Durham, North Carolina

Food and Drug Administration (FDA)

SUN, Wellington, MD
Director, Division of Vaccines and Related Product Applications
Office of Vaccines Research and Review
Food and Drug Administration
Rockville, MD

Health Resources and Services Administration (HRSA)

CASERTA, Vito, MD, MPH
Acting Director
Division of Vaccine Injury Compensation
Director, Countermeasures Injury Compensation Program
Healthcare Systems Bureau
Health Resources and Services Administration
Rockville, MD

Indian Health Service (IHS)

GROOM, Amy, MPH
Immunization Program Manager
Indian Health Service
Albuquerque, NM

National Vaccine Program Office (NVPO)

GELLIN, Bruce, MD, MPH
Director
National Vaccine Program Office
Department of HHS, Public Health and Science
Washington, DC

National Institutes of Health (NIH)

GORMAN, Richard L., MD
Associate Director for Clinical Research
Division of Microbiology and Infectious Diseases/NIAID
National Institute of Health
Bethesda, MD

LIAISON REPRESENTATIVES**American Academy of Family Physicians (AAFP)**

LOEHR, Jamie, MD, FAAFP
Cayuga Family Medicine (Owner)
Ithaca, NY

American Academy of Pediatrics (AAP)

Chair, Committee on Infectious Diseases

BRADY, Michael T., MD

Professor and Chair, Department of Pediatrics

The Ohio State University and Nationwide Children's Hospital

Columbus, OH

American Academy of Pediatrics (AAP)

Red Book Editor

KIMBERLIN, David, MD

Professor of Pediatrics

Division of Pediatric Infectious Diseases

The University of Alabama at Birmingham School of Medicine

Birmingham, AL

American Academy of Physician Assistants (AAPA)

LÉGER, Marie-Michèle, MPH, PA-C

Senior Director, Clinical and Health Affairs

American Academy of Physician Assistants

Alexandria, VA

American College Health Association (ACHA)

EVEN, Susan, MD

Executive Director

Student Health Center

University of Missouri

Columbia, MO

American College of Obstetricians and Gynecologists (ACOG)

RILEY, Laura E., MD

Associate Professor, Obstetrics, Gynecology and Reproductive Medicine

Harvard Medical School

Maternal Fetal Medicine

Massachusetts General Hospital

Boston, MA

American College of Physicians (ACP)

FRYHOFFER, Sandra Adamson., MD, MACP

Adjunct Associate Professor of Medicine

Emory University School of Medicine

Atlanta, GA

American College of Physicians (ACP) (alternate)

POLAND, Gregory A., MD

Mary Lowell Professor of Medicine and Infectious Diseases

Mayo Clinic

Rochester, MN

American Geriatrics Society (AGS)

SCHMADER, Kenneth, MD
Professor of Medicine-Geriatrics
Geriatrics Division Chief
Duke University and Durham VA Medical Centers
Durham, NC

America's Health Insurance Plans (AHIP)

NETOSKIE, Mark J., MD, MBA, FAAP
Market Medical Executive, CIGNA
Houston, TX

American Medical Association (AMA)

FRYHOFER, Sandra Adamson., MD, MACP
Adjunct Associate Professor of Medicine
Emory University School of Medicine
Atlanta, GA

American Nurses Association (ANA)

BREWER, Katie, MSN, RN
Assistant Director
Patient Care Services
Fairfax County Government
Fairfax, VA

American Nurses Association (ANA) (alternate)

HAYES, Carol E., CNM, MN, MPH
Advanced Practice Nurse
American Nurses Association
American College of Nurse Midwives
DeKalb Board of Health
Decatur, GA

American Osteopathic Association (AOA)

GROGG, Stanley E., DO, FACOP
Associate Dean/Professor of Pediatrics
Oklahoma State University-Center for Health Sciences
Tulsa, OK

American Pharmacists Association (APhA)

FOSTER, Stephan L., PharMD, FAPhA
Professor and Vice Chair, Department of Clinical Pharmacy
University of Tennessee Health Sciences Center, College of Pharmacy
Memphis, TN

Association of Immunization Managers (AIM)

MOORE, Kelly, MD, MPH
Medical Director, State Immunization Program
Tennessee Department of Health
Nashville, TN

Association for Prevention Teaching and Research (APTR)

McKINNEY, W. Paul, MD
Professor and Associate Dean
University of Louisville School of Public Health and Information Sciences
Louisville, KY

Association of State and Territorial Health Officials (ASTHO)

DWELLE, Terry L, MD, MPHTM, FAAP, CPH
State Health Officer
North Dakota Department of Health
Bismarck, ND

Biotechnology Industry Organization (BIO)

LEWIN, Clement, PhD, MBA
Head, Medical Affairs and Immunization Policy
Novartis Vaccines and Diagnostics
Cambridge, MA

Council of State and Territorial Epidemiologists (CSTE)

HAHN, Christine, MD
State Epidemiologist
Office of Epidemiology, Food Protection and Immunization
Idaho Department of Health and Welfare
Boise, ID

Canadian National Advisory Committee on Immunization (NACI)

WARSHAWSKY, Bryna, MDCM, CCFP, FRCPC
Associate Medical Officer of Health
Middlesex-London Health Unit
London, Ontario, Canada

Department of Health, United Kingdom

SALISBURY, David M., CB, FRCP, FRCPC, FFPH
Director of Immunisation
Department of Health, London
London, England, U.K.

Healthcare Infection Control Practices Advisory Committee (HICPAC)

Vacant

Infectious Diseases Society of America (IDSA)

NEUZIL, Kathleen M., MD, MPH, FIDSA
Vaccine Development Global Program (PATH)
Clinical Professor
Departments of Medicine and Global Health
University of Washington School of Medicine
Seattle, WA

Infectious Diseases Society of America (IDSA) (alternate)

BAKER, Carol J., MD
Professor of Pediatrics
Molecular Virology and Microbiology
Baylor College of Medicine
Houston, TX

National Association of County and City Health Officials (NACCHO)

ZAHN, Matthew, MD
Medical Director, Epidemiology
Orange County Health Care Agency
Santa Ana, CA

National Association of Pediatric Nurse Practitioners (NAPNAP)

STINCHFIELD, Patricia A., RN, MS, CPNP
Director
Infectious Disease/Immunology/Infection Control
Children's Hospitals and Clinics of Minnesota
St. Paul, MN

National Foundation for Infectious Diseases (NFID)

SCHAFFNER, William, MD
Chairman, Department of Preventive Medicine
Vanderbilt University School of Medicine
Nashville, TN

National Immunization Council and Child Health Program, Mexico

VILLASEÑOR RUIZ, Ignacio
Directora del Programa de Atención de la Salud de la Infancia y la Adolescencia / Director
General, Child and Adolescent Health
Centro Nacional Para la Salud de la Infancia Y La Adolescencia / National Center for Child and
Adolescent Health
Ministry of Health / Secretaría de Salud
Mexico

National Medical Association (NMA)

WHITLEY-WILLIAMS, Patricia, MD
Professor and Chair
University of Medicine and Dentistry of New Jersey
Robert Wood Johnson Medical School
New Brunswick, NJ

National Vaccine Advisory Committee (NVAC)

ORENSTEIN, Walt, MD
Chair, NVAC
Associate Director, Emory Vaccine Center
Emory University
Atlanta, GA

Pediatric Infectious Diseases Society (PIDS)

SAWYER, Mark H, MD
Professor of Clinical Pediatrics
University of California, San Diego School of Medicine
San Diego, CA

Pediatric Infectious Diseases Society (PIDS) (alternate)

ENGLUND, Janet A., MD
Professor, Department of Pediatrics
Seattle Children's Hospital
University of Washington
Seattle, WA

Pharmaceutical Research and Manufacturers of America (PhRMA)

BRAGA, Damian A.
President, Sanofi Pasteur
Swiftwater, PA

Society for Adolescent Health and Medicine (SAHM)

MIDDLEMAN, Amy B., MD, MEd, MPH
Professor of Pediatrics
Chief, Section of Adolescent Medicine
University of Oklahoma Health Sciences Center
Oklahoma City, OK

Society for Healthcare Epidemiology of America (SHEA)

WEBER, David, MD, MPH
Professor of Medicine, Pediatrics, and Epidemiology
University of North Carolina Schools of Medicine and Public Health
Medical Director, Hospital Epidemiology and Occupational Health, UNC Health Care
University of North Carolina
Chapel Hill, NC