

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

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



**Summary Report
June 25-26, 2014
Atlanta, Georgia**

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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

June 25-26, 2014

	<u>AGENDA ITEM</u>	<u>PURPOSE</u>	<u>PRESIDER/PRESENTER(S)</u>
Wednesday, June 25th			
8:00	Welcome & Introductions		Dr Jonathan Temte (Chair, ACIP) Dr Larry Pickering (Executive Secretary, ACIP, CDC)
8:30	General Recommendations		
	<ul style="list-style-type: none"> • Introduction • Vaccination of persons with altered immunocompetence • Vaccination programs 	Information Discussion	Dr Jeff Duchin (ACIP, WG Chair) Dr Andrew Kroger (CDC/NCIRD) Dr Andrew Kroger (CDC/NCIRD)
9:15	Child/Adolescent Immunization		
	<ul style="list-style-type: none"> • Introduction • Healthcare provider review of 2014 catch-up schedule and supplementary tables 	Information Discussion	Dr Renée Jenkins (ACIP, WG Chair) Dr Andrew Kroger (CDC/NCIRD)
9:35	Yellow Fever Vaccine		
	<ul style="list-style-type: none"> • Introduction • GRADE and Work Group conclusions regarding yellow fever vaccine booster dose 	Information Discussion <u>Vote</u>	Dr Joseph Bocchini (ACIP, WG Chair) Dr Erin Staples (CDC.NCEZID)
10:35	<i>Break</i>		
11:00	Influenza		
	<ul style="list-style-type: none"> • Introduction • Novel Influenza Vaccine Work Group • Influenza vaccine safety update • Assessing fever rates in children following LAIV and IIV • LAIV and IIV vaccine safety • Proposed recommendations 	Information Discussion <u>Vote</u>	Dr Ruth Karron (ACIP, WG Chair) Dr Doug Campos-Outcalt (ACIP, WG Chair) Dr Maria Cano (CDC/NCEZID) Dr Melissa Stockwell (Columbia University) Dr Lisa Grohskopf (CDC/NCIRD) Dr Lisa Grohskopf (CDC/NCIRD)
12:30	<i>Lunch</i>		
1:45	Human Papillomavirus (HPV) Vaccines		
	<ul style="list-style-type: none"> • Introduction • 9-valent HPV vaccine clinical trial data • 9-valent HPV vaccine: overview of WG considerations • 2-dose HPV vaccine schedules: review of data • HPV Vaccines Work Group plans 	Information Discussion	Dr Joseph Bocchini (ACIP, WG Chair) Dr Alain Luxembourg (Merck) Dr Eileen Dunne (CDC/NCHHSTP) Dr Lauri Markowitz (CDC/NCHHSTP) Dr Lauri Markowitz (CDC/NCHHSTP)
3:15	<i>Break</i>		
3:45	Vaccine Safety		
	<ul style="list-style-type: none"> • Introduction • Febrile seizures after administration of trivalent influenza vaccines – PRISM system, 2010-2011 influenza season • Seizures following administration of multiple vaccines: a VSD study • Summary 	Information Discussion	Dr Tom Shimabukuro (CDC/NCEZID) Dr Alison Kawai (Harvard Medical School, Harvard Pilgrim Health Care Institute) Dr Jonathan Duffy (CDC/NCEZID) Dr Tom Shimabukuro (CDC/NCEZID)
5:00	Adult Immunization		
	<ul style="list-style-type: none"> • Introduction • Update on adult immunization coverage • Update on CDC's adult immunization communication activities 	Information Discussion	Dr Tamera Coyne-Beasley (ACIP, WG Chair) Dr Walter Williams (CDC/NCIRD) Dr Kristine Sheedy (CDC/NCIRD)

5:45 **Public Comment**6:00 **Adjourn**

	<u>AGENDA ITEM</u>	<u>PURPOSE</u>	<u>PRESIDER/PRESENTER(S)</u>
<u>Thursday, June 26th</u>			
8:00	Updates <ul style="list-style-type: none"> • Typhoid Vaccines • Agency Updates: CDC and ACIP <i>Ex Officio</i> Members CMS, DoD, DVA FDA, HRSA, IHS, NVPO, NIH 	Information	Dr Brendan Jackson (CDC/NCEZID)
8:15	13-Valent Pneumococcal Conjugate Vaccine <ul style="list-style-type: none"> • Introduction & update on 3-dose schedule for infants • PCV13 efficacy among adults: results of CAPiTA study • Potential public health impact and cost-effectiveness of PCV13 use in adults • Considerations for PCV13 use among adults and policy options 	Information Discussion	Dr Nancy Bennett (ACIP, WG Chair) Dr Rosalind Hollingsworth, (Global Medical Lead, Pfizer) Dr Charles Stoecker (Tulane University, School of Public Health) Dr Tamara Piliishvili (CDC/NCIRD)
9:55	Vaccine Supply	Information	Dr Jeanne Santoli (CDC/NCIRD)
10:00	Measles Update <ul style="list-style-type: none"> • Global update • Domestic update 	Information Discussion	Mr Jim Goodson (CDC/CGH/GID) Dr Greg Wallace (CDC/NCIRD)
10:45	<i>Break</i>		
11:00	Meningococcal Vaccines <ul style="list-style-type: none"> • Introduction • Epidemiology of meningococcal disease outbreaks in the United States • Interim guidance for the use of serogroup B meningococcal vaccines under a CDC-sponsored IND 	Information Discussion	Dr Lorry Rubin (ACIP, WG Chair) Dr Sarah Meyer (CDC/NCIRD) Ms Jessica MacNeil (CDC/NCIRD)
12:00	Hepatitis Vaccines <ul style="list-style-type: none"> • Update: ACIP Hepatitis Work Group 	Information	Dr Art Reingold (ACIP, WG Chair)
1:15	Public Comment		
1:30	Adjourn		

Acronyms

CDC	Centers for Disease Control & Prevention
CMS	Centers for Medicare and Medicaid Services
DOD	Department of Defense
DVA	Department of Veterans Affairs
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRSA	Health Resources and Services Administration
IHS	Indian Health Service
IIV	Inactivated Influenza Vaccine
IND	Investigational New Drug
IHS	Indian Health Service
LAIV	Live-Attenuated Influenza Vaccine
NCHHSTP	National Center for HIV, Hepatitis, STD and TB Prevention [of CDC/OID]
NCIRD	CDC National Center for Immunization & Respiratory Diseases [of CDC/OID]
NCZVED	National Center for Zoonotic, Vector-Borne, and Enteric Diseases [of CDC/OID]
NIH	National Institutes of Health
NVPO	National Vaccine Program Office
WG	Work Group

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core Surveillance
ACA	Affordable Care Act
ACIP	Advisory Committee on Immunization Practices
ACNM	American College of Nurse Midwives
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
AE	Adverse Events
AFP	American Family Physicians
AHIP	America's Health Insurance Plans
AIM	Association of Immunization Managers
AMA	American Medical Association
ANA	American Nurses Association
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research (FDA)
CDC	Centers for Disease Control and Prevention
CGD	Chronic Granulomatous Disease
CHS	Chediak-Higashi Syndrome
CI	Cochlear Implants
CIN	Cervical Intraepithelial Neoplasia
CISA	Clinical Immunization Safety Assessment
CMS	Centers for Medicare and Medicaid Services
COI	Conflict of Interest
COID	Committee on Infectious Disease
COPD	Chronic Obstructive Pulmonary Disease
CSF	Cerebrospinal Fluid
CSTE	Council of State and Territorial Epidemiologists
CUMC	Columbia University Medical Center
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DTaP	Diphtheria, Tetanus, and Pertussis
DVA	Department of Veterans Affairs
ED	Emergency Department
EMA	European Medicines Agency
EMR	Electronic Medical Record
FACA	Federal Advisory Committee Act
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
GMTs	Geometric Mean Titers
GP	General Practitioner
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HR	Hazard Ratio
HCT	Hematopoietic Cell Transplants
HHS	(Department of) Health and Human Services
Hib	<i>Haemophilus influenzae</i> Type b
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
IAC	Immunization Action Coalition
ICD	International Classification of Diseases
IDSA	Infectious Disease Society of America
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
IRR	Incidence Rate Ratio
ISO	Immunization Safety Office
JE	Japanese Encephalitis
LAD	Leukocyte Adhesion Deficiency
LAIV	Live Attenuated Influenza Vaccine
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
NCDPS	North Carolina Department of Juvenile Justice and Delinquency Prevention
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
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
NIS	National Immunization Survey
NMA	National Medical Association
NNV	Number Needed to Vaccinate
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
OM	Otitis Media
PCV	Pneumococcal Conjugate Vaccine
PhRMA	Pharmaceutical Research and Manufacturers of America
PICO	Population, Intervention, Comparison, and Outcome
PIDS	Pediatric Infectious Diseases Society
PRISM	Post Licensure Rapid Immunization Safety Monitoring
PRNT	Plaque Reduction Neutralization Test
QALYs	Quality Adjusted Life Years
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RIV	Recombinant Influenza Vaccine
SAEs	Serious Adverse Events
SAGE	Strategic Advisory Group of Experts (WHO)
SAHM	Society for Adolescent Health and Medicine
SCRI	Self-Controlled Risk Interval
SES	Socioeconomic Status
SME	Subject Matter Expert
SOS	Serious Outcome Surveillance
SSUAD	Serotype-Specific Urinary Antigen Detection
Td	Tetanus-Diphtheria
Tdap	Tetanus and Reduced Diphtheria Toxoids
TIV	Trivalent Inactivated Vaccine
TNF	Tumor Necrosis Factor
UK	United Kingdom
UNC	University of North Carolina
US	United States
VA	Department of Veterans Affairs
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Effectiveness
VFC	Vaccines for Children
VICP	National Vaccine Injury Compensation Program
VIS	Vaccine Information Statements
VLP	Virus-Like Particles
VRBPAC	Vaccine and Related Biologic Products Advisory Committee
VRC	Vaccination Report Card
VSD	Vaccine Safety Datalink
WHA	World Health Assembly
WHO	World Health Organization
YF	Yellow Fever

Welcome and Introductions

Welcome

Dr. Jonathan Temte
Chair, ACIP / CDC

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

Welcome

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

Following Dr. Temte's greeting and call to order, Dr. Pickering welcomed everyone to the June 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: Stephanie Thomas, Natalie Greene, Reed Walton, 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 expressed sincere appreciation to the three ACIP members for whom this would be their last ACIP meeting including Renee Jenkins, Tamera Coyne-Beasley, and Jeff Duchin who would be rotating off the committee at the end of June. He recognized them for their incredible contributions to ACIP over the past four years, stressing that they were members during a transformative time in this committee's history.

Dr. Temte acknowledged the passing of *Ciro de Quadros* who led efforts to successfully eradicate polio and measles in the Americas, as well as smallpox in Ethiopia. Dr. de Quadros died in May 2014 from pancreatic cancer. In an article for *The Huffington Post* in 2013, Dr. de Quadros wrote, "Medicine, sanitation, nutrition, education—all are necessary and interrelated components of preventing and curing sickness, but there is one tool that stands out as the most effective: vaccines. Every child—no matter where he or she is born—has a fundamental right to vaccines." Dr. de Quadros was essential in efforts to eradicate smallpox, polio, and measles across the Americas. His work improved the lives of millions of people, and his commitment to country ownership of health programs helped fundamentally shape the current public health landscape. He served as Director of PAHO, Executive Vice President of the Sabin Vaccine Institute, and Director of Sabin's Vaccine Advocacy and Education Program. Due to his work, a contingency of vaccine experts from Mexico was in attendance at the ACIP meeting through

sponsorship from PAHO and Sabin. Dr. Temte offered condolences to Dr. de Quadros' wife Susan and his two daughters, and recognized his incredible body of work.

Dr. Temte then recognized the following ACIP members who reached the end of their four-year terms and were rotating off of the committee, and presented each of them with a Certificate of Appreciation and a letter from Dr. Frieden, CDC's Director:



Dr. Tamera Coyne-Beasley

Dr. Tamera Coyne-Beasley is an Associate Professor in the Department of Pediatrics and Department of Internal Medicine at the University of North Carolina (UNC), and is trained in both areas. She is also a Senior Fellow for the Center for Prevention of School Violence, and works with the North Carolina Department of Juvenile Justice and Delinquency Prevention (NCDPS). Dr. Coyne-Beasley has served as the Chair of the Adult Immunization Work Group, and has also been very active with the Measles, Mumps, and Rubella Work Group, Influenza Work Group, and HPV Work Group. She has also been very instrumental with the National Adult Immunization Summit. The first publication Dr. Temte could find for Dr. Coyne-Beasley was from 1999 titled, "Epidemiology of Adolescent Homicide in North Carolina from 1990-1995 in the *Archives of Pediatric and Adolescent Medicine*. In 2000, she published "The African American Church: A Potential Forum for Adolescent Comprehensive Sexuality Education." In 2014, she published "Vaccine Intervention Effects from a Social Marketing Campaign to Promote HPV Vaccinations in Pre-Teen Boys." In addition, Dr. Coyne-Beasley is a published poet and in 1995 and 1997 she won the National Library of Poetry Excellence Award.

Dr. Coyne-Beasley said that it had been one of life's greatest pleasures and privileges to serve on and be a part of the ACIP. She expressed her gratitude for the opportunity, which included the opportunity to work with each and every one of her ACIP colleagues, CDC leaders and staff, liaison members, and audience members who share their wisdom and experiences such as Dr. Plotkin and Frankie Milley who has shared her pain and has turned that into a movement that supports vaccination. Dr. Coyne-Beasley said that she had never been so remorseful about rotating off of a committee, particularly one that requires so much work, time, and energy. She emphasized that what ACIP does is so important, as is the opportunity to deliberate extensively and make evidence-based recommendations that are translated into policy and practice within a matter of months or at least within a year. She expressed her hope that she had been able to contribute in some small way, and said that she looked forward to continuing to collaborate with ACIP. She expressed her sincere appreciation to her nominator who was a former ACIP Chair, was the Chair of Pediatrics at Duke when she was there, and also had something to do with the measles vaccine. She said she was eternally grateful for his support and his confidence in her. She also said that one of her greatest joys had been the opportunity to serve with one of her most invaluable and special mentors, Dr. Renée Jenkins.



Dr. Jeff Duchin

Dr. Jeff Duchin is Chief of the Communicable Disease Epidemiology and Immunization Section for Public Health Seattle and King County in Washington State. He is also Associate Professor of Medicine in the Division of Allergy and Infectious Diseases at University of Washington School of Medicine. One of his quotes is, “The GRADE process makes me a low quality judge of the importance of my contributions.” Dr. Duchin has served as Chair of the Zoster, General Recommendations, and Febrile Seizure Work Groups and as a member of the Influenza and Pneumococcal Work Groups. He served as the ACIP liaison for the National Association of County and City Health Officials (NACCHO) from 2006 through 2010, as well as the Chair of the NACCHO Immunization Work Group. He was recently appointed as a member of the National Quality Forum, Adult Immunization Steering Committee, and the Public Health Committee for Infectious Disease Society of America (IDSA). Dr. Duchin has been very active with various efforts, including as an EIS Officer. Some of his publications include “Hantavirus Pulmonary Syndrome: A Clinical Description of 17 Patients with a Newly Recognized Disease” in 1994, “High Prevalence of Multidrug-Resistant *Streptococcus pneumoniae* among Children in a Rural Kentucky Community” in 1995, and “Evaluation of Electronic Ambulatory Care Data for Use in Influenza-Like Illness Surveillance Network (ILINet)” published in 2013. Dr. Temte noted that Dr. Duchin once became hypothermic in Hawaii when he got caught in a storm while biking at 9,000 feet and had to seek aid at a ranger station. Dr. Duchin is an avid biker and often exercises at 3:00 am.

Dr. Duchin said that it was a great honor and pleasure to serve with such a great group of colleagues, and that he had learned a lot from the experience. He looked at himself on the top of Haleakalā and asked himself the same question that he was asking now, “Where do you go from here?” Unfortunately, from Haleakalā one can only go down, so he was hoping the same was not true of his ACIP experience. He thanked his great colleagues on the CDC WGs who helped accomplish so much during his four years on the committee, particularly the Designated Federal Officers (DFO) Dr. Andrew Kroger from the General Recommendations WG, Craig Hales and Rafael Harpaz from the Zoster WG, and Lisa Grohskopf from the Influenza WG, and Tamara Pilishvili from the Pneumococcal WG. The DFOs make it possible for the WGs to accomplish what they do, and they are outstanding in their dedication, professionalism, and intelligence. It was a great pleasure to be able to work with those colleagues as well. Dr. Duchin also thanked everyone who participated in the WGs on which he served for their contributions, particularly some who were not present who joined them for the Febrile Seizure WG. He said it was a great honor to be an ACIP member during the time that Dr. Pickering characterized as transformative, making explicit the evidence base on which ACIP makes its recommendations. That is outstanding and is moving ACIP in a very good direction. He was also very impressed by the increasing sophistication and capacity of the vaccine safety program. It has been outstanding to have the contributions of the Immunization Safety Office (ISO), particularly with respect to issues pertaining to febrile seizures and other ongoing monitoring. He stressed that it had been a pleasure, and that he looked forward to continuing to contribute to the extent possible in the future.



Dr. Renée Jenkins

Dr. Renée Jenkins is Professor and Chair Emeritus in the Department of Pediatrics and Child Health at Howard University College of Medicine in Washington, DC. She served as the Chair of the Childhood Schedule Harmonization Work Group and as a member of the HPV Work Group. She has also represented ACIP at National Vaccine Advisory Committee (NVAC) meetings. Looking at her resume, Dr. Jenkins has served on nearly every committee of the American Academy of Pediatrics (AAP) and the Society for Adolescent Health and Medicine (SAHM). Some of her publications include “Adolescent Hypertension” in 1975 and “Health Disparities across the Lifespan: Where are the Children?” in 2009. Dr. Jenkins has done virtually everything, including serving as the first African American President of SAHM in 1989, serving as the first African American President of the AAP in 2007, and being elected to the Institute of Medicine. ACIP stands in great honor of having Dr. Jenkins on the committee for the last four years.

Dr. Jenkins said that it had been an awesome experience and responsibility in that when decisions are made at ACIP, they hold. That is a heavy weight to bring to the table, but it also reflects a sense of how important it is to get it done right. Many people contribute to that, of whom they are appreciative. She said she came along during a time when adolescents were given one vaccine, tetanus-diphtheria (Td), to now which is so complicated. During her experience with the AAP, she and Dr. Schuchat became more connected by incredible challenges such as the Jenny McCarthy movement. She had Dr. Bocchini on speed dial because so many questions needed to be answered. Dr. Jenkins said that while this has been quite a transition for her, she learned a lot and appreciated all of the people who contribute. She gave a “shout out” to Dr. Cody Meissner, who was her ACIP buddy who oriented her. Another issue that is evolving that she will be interested in following is cost, and how ACIP does now have to figure out how to address that. Resources are not endless, so consideration must be given to how to best use them. At one point, it was just the science, safety, and such issues. But now, cost is also part of the equation. She congratulated Dr. Temte for being such a fearless leader, and said she would miss him and would see him in Wisconsin.

Dr. Temte then shared an image of the agenda from the first ACIP meeting convened 50 years ago on May 25, 1964, noting that the start time was 9:30 am. One of the agenda items was the simplification of the vaccine schedule, and another was the following statement pertaining to the formation of WGs:

It was felt by the Committee that as part of the modus operandi of its functioning that it would be desirable from time to time to call upon appropriate technical consultants or, as need be, to convene special subcommittees or panels to consider specific, complex problems regarding immunization practice.

In terms of the simplification of the schedule, in 1964 there were seven vaccines in use (polio, smallpox, measles, diphtheria, tetanus, pertussis, and influenza). Going back 77 years, in particular with a nod to the March of Dimes, Dr. Temte shared a link to a YouTube video showing Franklin Delano Roosevelt (FDR) going to the All Star game in 1937 and reflecting the logistics needed to get someone with polio from the vehicle to the stands. The link for the video is <http://youtube/CvKDwBMEycw>. This counters the myth that FDR tried to avoid being seen in public with his polio, and it also underscores the important need across the world to eliminate polio. Also shown in the video are Lou Gehrig, Jimmie Foxx, Hank Greenberg, and Dizzy Dean. Dr. Temte concluded with a passage from Dr. William Carlos Williams, who was a family practitioner in New Jersey who dealt primarily with very poor immigrant families. He was posthumously awarded the Pulitzer Prize in May 1963 for his writing, and was one of the first American physician authors who was both a poet and an essayist. The following is an excerpt from his first published piece, which deals with an infant with meningitis:

The baby is in a smother of sheets and crumpled blankets, its head on a pillow. The child's left eye closed, its right partly opened. It emits a soft whining cry continuously at every breath. It can't be more than a few weeks old.

Do you think it is unconscious, doctor?

Yes.

Will it live?

It is the mother. A grit tender-eyed blonde. Great full breasts. A soft gentle-minded woman of no mean beauty. A blue cotton house wrapper, shoulder to ankle.

If it lives it will be an idiot perhaps. Or it will be paralysed—or both. It is better for it to die.

There it goes now! The whining has stopped. The lips are blue. The mouth puckers as for some diabolic kiss. It twitches, twitches faster and faster, up and down. The body slowly grows rigid and begins to fold itself like a flower folding again. The left eye opens slowly, the eyeball is turned so the pupil is lost in the angle of the nose. The right eye remains open and fixed staring forward. Meningitis. Acute. The arms are slowly raised more and more from the sides as if in the deliberate attitude before a mad dance, hands clenched, wrists flexed. The arms now lie upon each other crossed at the wrists. The knees are drawn up as if the child were squatting. The body holds this posture, the child's belly rumbling with a huge contortion. Breath has stopped. The body is stiff, blue. Slowly it relaxes, the whimpering cry begins again. The left eye falls closed.

It began with that eye. It was a lovely baby. Normal in every way. Breast fed. I have not taken it anywhere. It is only six weeks old. How can he get it?

The pointed beard approaches. It is infection, is it not, doctor?

Yes.

But I took him nowhere. How could he get it?

He must have gotten it from someone who carries it, maybe from one of you.

Will he die?

Yes. I think so.

Oh, I pray God to take him.

Have you any other children?

One girl five, and this boy.

Well, one must wait.

Again the night. The beard has followed me to the door. He closes the door carefully. We are alone in the night.

It is an infection?

Yes.

My wife is Catholic—not I. She had him for baptism. They pour water from a can on his head, so. It runs down in front of him, there where they baptize all kinds of babies, into his eye perhaps. It is a funny thing.

William Carlos Williams – Danse Pseudomacabre, 1920
The Little Review VII. 1 46-49.

Dr. Temte pointed out that the striking thing about this writing from 1920 is that it was so matter of fact. Infants and young people dying of meningitis was so commonplace. This is horrific and something rarely seen anymore due to the benefit of all of the things that Ciro de Quadros talked about (e.g., sanitation, education, good medical care, and especially vaccines).

Dr. Pickering said he thought that for many of those in the room who lived through an era before vaccines were available, this was a very sad memory. Times are better now that most of these diseases can be prevented.

He noted that at nearly every meeting, delegations from the World Health Organization (WHO) Pan-American Health Organization (PAHO) are in attendance. During this meeting, he welcomed the following delegates from Mexico's Ministry of Health:

- Dr. Jose de Jesus Mendez, Infant Health Subdirector for Mexico's National Center for Child and Adolescent Health
- Dr. Emilia Cain, Medical Supervisor, Mexico's National Center for Child and Adolescent Health
- Dr. Paulina Saldana, Medical Supervisor, Mexico's National Center for Child and Adolescent Health
- Dr. Armando Gonzalez, Division Director of Prevention and Disease Detection for the Mexican Institute of Social Security

Dr. Pickering also welcomed Marla Dalton, Executive Director of the National Foundation for Infectious Diseases (NFID).

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. Stephanie Thomas, 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, October 29-30, 2014. The registration deadline for U.S. citizens is Monday, October 13, and for non-U.S. citizens is Monday, October 6. Registration is not required for webcast viewing. Stephanie Thomas can assist anyone who experiences difficulties with this process.

Dr. Pickering offered the following notes regarding liaison representatives:

- David Johnson joined this meeting as liaison representative for Pharmaceutical Research and Manufacturers of America (PhRMA) in place of Damian Braga
- Margot Savoy served as liaison representative during this meeting for the American Academy of Family Physicians (AAFP) in place of Jamie Loehr

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 Stephanie Thomas 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.

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

- CDC has developed vaccine schedule apps for the child, adolescent, catch-up, and adult schedules-with a contraindications and precautions table.
- Version 1.1 of the app is available in the app store for iPhone and iPad, and there is an Android version in the works.
- This is the 50-year anniversary of ACIP, which held its first meeting in May of 1964. More information about this will be provided during the October meeting.
- Safety issues will continue to be presented at every ACIP meeting. A separate vaccine safety presentation was planned for the first afternoon of this 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. It is important to note that at each meeting, ACIP members state any conflicts of interest.

Applications for ACIP membership are due no later than November 14, 2014 for the 4-year term beginning July 2015. 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 submitted 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 February 2014 ACIP meeting follows:

ACIP Recommendations Published Since February 2014		
Title	Publication Date	MMWR Reference
▪ 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(RR01):1-14
▪ Use of MenACWY-CRM Vaccine in Children Aged 2 Through 23 Months at Increased Risk for Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices	6/20/2014	2014;63(24):527-530

<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/index.html

Immunization Schedules (2014):

<http://www.cdc.gov/vaccines/schedules/index.html>

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

You Are the Key to HPV Cancer Prevention:

<http://www.cdc.gov/vaccines/youarethekey>

Vaccines for Preteens and Teens:

<http://www.cdc.gov/vaccines/who/teens/index.html>

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:

- Coyne-Beasley: Research support is allocated to the University of North Carolina (UNC) by Merck Pharmaceuticals for clinical trials.
- Bennett, Bocchini, Campos-Outcalt, Coyne-Beasley, Duchin, Harriman, Harrison, Karron, Jenkins, Kempe, Pellegrini, Reingold, Rubin, Temte, and Vazquez: No conflicts.

General Recommendations

Introduction

Jeffrey Duchin, MD Chair, General Recommendations Work Group

Dr. Duchin reminded everyone that the General Recommendations document is published in the *Morbidity and Mortality Weekly Report (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 topics addressed during this session included:

- Altered Immunocompetence
- Vaccination Programs

The updating process has basically been completed, with only a small amount of information that needs to be revised before the updated recommendations can be published.

Dr. Duchin thanked Dr. Rubin and colleagues at the IDSA, because much of what was done was integrating the IDSA's new guidelines for vaccination in persons with altered immunocompetence with the existing ACIP recommendations on vaccination of persons with altered immunocompetence. This is an increasingly complex area, so the collaboration with IDSA is very much appreciated.

Vaccination In Persons with Altered Immunocompetence & Vaccination Programs

Dr. Andrew Kroger CDC/NCIRD

Dr. Kroger provided an update on the proposed changes to the *Altered Immunocompetence* section of the General Recommendations. He noted that all ACIP members should have four documents, including a clean copy and a version with tracked changes for each section.

In terms of background, the following reflects the various components that are currently included in this section:

- ❑ General Principles:
 - Defines “altered immunocompetence”
 - Refers to a table that describes broad categories of altered immunocompetence
 - Includes a statement that says that when there is deliberation to occur, providers are always welcomed and encouraged to refer to another treating provider who may be an expert in infectious disease or immunology
 - Altered Immunocompetence as an Indication to Receive a Vaccine: Describes situations in which a vaccine may be recommended outside of a routine age group, because altered immunocompetence is part of the patient’s profile
- ❑ Vaccination of Contacts of Persons with Altered Immunocompetence: Emphasizes the need to provide community immunity
- ❑ Vaccination with Inactivated Vaccines: Highlights, by way of general principles, that the concern is primarily with efficacy issues
- ❑ Vaccination with Live Attenuated Viral and Bacterial Vaccines: Highlights, by way of general principles, that the concern is primarily with efficacy and safety issues
- ❑ Recipients of Hematopoietic Cell Transplants (HCT)
- ❑ Conditions or Drugs that Might Cause Immunodeficiencies: Highlights topics like asplenia for which it is difficult to apply general principles, such as withholding all live vaccines in all cases

As noted by Dr. Duchin, IDSA published clinical practice guidelines in 2013 for vaccination of immunocompromised hosts. As far back as November 2011, CDC was involved with cross-walking topics in the draft of this document with vaccine-specific and general recommendations ACIP guidance. The IDSA document was published December 4, 2013. The authors include Dr. Lorry Rubin, who is a former member of the General Recommendations WG and current ACIP member, Dr. Harry Keyserling, who is a former member of the General Recommendations WG and a current member while these deliberations were ongoing. This is a very important source document for changes to the General Recommendations. There will be some differences between the two groups, which are primarily at the level of vaccine-specific recommendations and are not a part of the General Recommendations WG process. The primary differences are as follows:

- ❑ IDSA: Recommendation for Gardasil[®] (HPV) for immunocompromised persons compared to ACIP recommendations
- ❑ ACIP: No preference for Gardasil[®] or Cervarix[®] in immunocompromised females
- ❑ IDSA: Recommendation for varicella vaccine for immunocompromised persons (within certain parameters) compared to ACIP recommendations....
- ❑ ACIP: Consideration for varicella vaccine for immunocompromised persons (within certain parameters)

In terms of what has changed in the General Recommendations document, there was information in the 2011 version that needed to be updated. Also, there is important resource information in the IDSA document as well as other source materials. For example, most of the primary source materials for changes to altered immunocompetence as an indication to receive a vaccine do not come from IDSA. These come from the vaccine-specific ACIP statements. This section addresses recommendations for use of pneumococcal, meningococcal, and HiB vaccines in patients who have conditions such as asplenia, anatomic barrier defects, cerebrospinal fluid (CSF) leaks, and Cochlear implants (CI). The WG has tried to harmonize the language in the General Recommendations document with the new information in the vaccine-specific documents for these vaccines.

IDSA information is added into the sections on inactivated vaccines and vaccination with live attenuated viral and bacterial vaccines, so Dr. Kroger focused on these two sections. In terms of the background principles, the general statement is made that inactivated vaccines are safe in patients with altered immunocompetence, but that there are efficacy issues with both live and inactivated vaccines with certain diseases. Some specific diseases are listed in the IDSA document that the WG would like to incorporate into the General Recommendations. This is in the section where inactivated vaccine efficacy issues are discussed (Page 4, Line 26). Information is included from the IDSA document about B-lymphocyte deficiency and receipt of immunoglobulin therapy, with a recommendation to withhold both inactivated and by extension live vaccines. This is an efficacy issue. Patients receiving immunoglobulin therapy are thought to have reduced response even to inactivated vaccines. This is new to the General Recommendations. Likewise, cancer therapy and receipt of anti-B lymphocyte therapy (e.g., rituximab) will be addressed here. From the IDSA, the WG hopes to incorporate a recommendation to delay inactivated vaccines 6 months as opposed to 3 months. Again, this would be an efficacy issue.

Safety and efficacy apply to the section on vaccination with live viral and bacterial vaccines. Clarification is included in this section about specific diseases (Page 5, Line 4). This will have relevance to the categories that were split out in the table as well. For instance, Chronic Granulomatous Disease (CGD) is described as a condition for which live bacterial vaccines should be withheld. However, with other phagocyte deficiency diseases such as Leukocyte Adhesion Deficiency (LAD) and Chediak-Higashi Syndrome (CHS), a recommendation is made to withhold both live bacterial and live viral vaccines. The 2011 General Recommendations are simplified in that they only recommend to withhold live bacterial vaccines, so this is new information from IDSA. The WG does not want to get into the specifics in the print of the General Recommendations document, but this has to do with the risk of these particular types of infections. With CGD and the lack of oxidative bursts associated with intercellular killing, patients have increased risk of bacterial infections. However, with LAD and CHS, there are adherence issues with the defects in natural killer cells that generate a risk for viruses and bacteria. A recommendation is included to withhold live bacterial vaccines with conditions such as defects of interferon-gamma/interleukin-12 axis, as well as a recommendation to withhold live bacterial and live viral vaccines with conditions such as defects of interferon-alpha or interferon-gamma. Again, that is a risk issue for those two conditions.

Table 13 currently appears as follows; however, it will be updated to include the information just provided:

TABLE 13. Vaccination of persons with primary and secondary immunodeficiencies

Primary	Specific immunodeficiency	Contraindicated vaccines*	Risk-specific recommended vaccines*	Effectiveness and comments
B-lymphocyte (humoral)	Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)	OPV†Smallpox LAIV BCG Ty21a (live typhoid) Yellow fever	Consider varicella vaccination in isolated humoral immunodeficiency	The effectiveness of any vaccine is uncertain if it depends only on the humoral response (e.g., PPSV or MPSV4). IGIV interferes with the immune response to measles vaccine and possibly varicella vaccine.
	Less severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiency)	OPV† BCG Yellow fever Other live vaccines appear to be safe.	Pneumococcal Hib	All vaccines likely effective; immune response might be attenuated.
T-lymphocyte (cell-mediated and humoral)	Complete defects (e.g., severe combined immunodeficiency [SCID] disease, complete DiGeorge syndrome)	All live vaccines§,¶,**	Pneumococcal	Vaccines might be ineffective.
	Partial defects (e.g., most patients with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia)	All live vaccines§,¶,**	Pneumococcal Meningococcal Hib (if not administered in infancy)	Effectiveness of any vaccine depends on degree of immune suppression.
	Interferon-gamma/Interleukin 12 axis deficiencies	All live bacterial vaccines (All live vaccines contraindicated in Interferon-gamma or interferon-alpha deficiencies)		
Complement	Persistent complement, properdin, or factor B deficiency	None	Pneumococcal Meningococcal Hib	All routine vaccines likely effective.
Phagocytic function	Chronic granulomatous disease	Live bacterial vaccines§		
	Leukocyte adhesion defect, and myeloperoxidase deficiency.	Live viral and bacterial vaccines§¶	Pneumococcal	All inactivated vaccines safe and likely effective. Live viral vaccines likely safe and

For HCT patients, the 2011 General Recommendations document refers to the source Tomblyn M, Chiller T, Eisele H, et. Al. *Biol Blood Marrow Transplant* 15:1143-1238;2009. When this was discussed in February 2009 for the last iteration of the General Recommendations, there was a recommendation to specifically reference this document, which was followed. The document was readily available for those using CDC's website, and the WG tried to incorporate as much as possible in the document. IDSA now publishes recommendations for HCT in Rubin, LG, Levin MJ, Ljungman P., et. al. 2013 IDSA Clinical Practice Guidelines for Vaccination of the Immunocompromised Host. *Clin. Infect. Dis.* 2014; 58: e-44-100. HCT is a special category of altered immunocompetence because the patient is not only immunodeficient as a result of either underlying disease or treatment, but also is considered to be immunoablated (e.g., their entire immune history is completely removed). This raises concerns not only about which vaccines to give and contraindications or precautions, but also about revaccinating patients who have had vaccines administered prior to HCT.

The IDSA document is remarkably similar to the 2009 document. They are basically identical for pneumococcal conjugate vaccine (PCV) vaccines for which a specific series is recommended post-HCT. Zoster and rotavirus vaccine are not recommended post-HCT, so that remains the same. The IDSA document is remarkably flexible with respect to different strategies for these patients. Often, multiple options are presented, specifically with the use of pertussis-containing vaccines. This is a unique issue with respect to HCT, because in this circumstance, patients who receive pertussis-containing vaccines will have waning of immunity anyway, so these two issues have to be reconciled. That is to say, the schedule for post-HCT should take into account that routine scheduling of pertussis vaccine already accounts for lack of residual immunity. The IDSA document does a good job of providing multiple options for patients with respect to use of pertussis-containing vaccines post-HCT. There are some changes from the 2009 document. HPV vaccine is recommended post-HCT in the IDSA document. Varicella vaccine is recommended in the IDSA document as long as the patient is immunocompetent, does not have graft versus host disease, and is 24 months post-HCT. That would be a new addition to the General Recommendations.

In terms of conditions or drugs that might cause immunodeficiency, IDSA classifies its categories somewhat differently than ACIP traditionally has done. It defines different levels of immunosuppression as high- or mid-level. In IDSA, high-level includes the following:

- Three-months withholding of live vaccines following completion of cancer chemotherapy
- Two-month withholding of live vaccines following completion of solid organ transplant rejection therapy
- Daily corticosteroid therapy with dose 20 mg or higher prednisone equivalent (or 2 mg/kg or greater) for 14 days or more
- Receiving immune modulators such as tumor necrosis factor (TNF)-alpha inhibitors or anti-B cell agents (rituximab)

IDSA low-level immunosuppression includes the following, which ACIP previously considered not immunosuppressed at all for the purposes of some drugs:

- Alternate dose corticosteroid therapy
- Methotrexate, azathioprine or 6-mercaptopurine in doses as stated in ACIP Zoster Vaccine-specific statement

IDSA defines the interval following the use of a medication in terms of low-dose (1 month interval), high-dose (3 month interval unless otherwise stated), solid organ transplant anti-rejection (2 month interval), and anti-B lymphocyte (6 month interval) for administration of both live and inactivated vaccines. There is a bidirectional nature to this recommendation in terms of what to do if the vaccine is given first. The IDSA document has made some changes here as well. The document recommends withholding live vaccines unless 4 weeks before the beginning of therapy, and a full recommendation to withhold 2 weeks before beginning of therapy. The provider would use this recommendation to determine the threshold by which they would need to wait if the vaccine is given first before starting therapy. For inactivated vaccines, IDSA recommends withholding 2 weeks before beginning of therapy.

The 2011 General Recommendations divides the discussion into the following categories:

- Vaccination of Children and Adolescents
- Adult Vaccination
- Evidence-Based Interventions to Increase Vaccination Coverage
- Other General Programmatic Issues

Changes by the WG have been to include the adult vaccination standards, which are discussed in the introduction to the entire *Vaccination Program* section. Clear language has been included to discuss the Affordable Care Act (ACA) that states, "Effective for all health-plans drafted or updated after September 2010, the ACA requires plans to cover ACIP recommended vaccines without deductibles or copayments when delivered by an in-network provider." There is a discussion of barriers to vaccination in the General Recommendations adult component of this section, which is where this language was inserted. ACA applies to childhood and adult vaccination, though it could be argued that the impact may be greater with adult compared to childhood vaccinations. The 2011 General Recommendations included information on cost-effectiveness, which the WG decided to remove. One reason was because it caused an imbalance in the document. While there was cost-effectiveness information in the adult section, there was really no cost-effectiveness or cost-savings data described in the child section. When this section was first built in the General Recommendations, ACIP-specific documents were incorporated about adult immunization and VFC. To balance this, the cost-effectiveness discussion was removed. Cost-effectiveness is best discussed in vaccine-specific statements rather than the General Recommendations.

The last change by the WG is the Strategies Table, which was updated based on the Task Force for Community Preventive Services (Task Force) with current updates from The Community Guide.org/vaccine/index.html. The Task Force has removed the word "strongly" and now states "recommended." They have made a change to certain recommendations as well. For instance, "patient or family incentives or sanctions" previously was listed as having "insufficient evidence." In the interim, the Task Force has divided that out as "patient or family incentives" are recommended and "sanctions" are not recommended. This appears in Table 15 as follows:

TABLE 15. Recommendations regarding interventions to improve coverage of vaccines recommended for routine use among children, adolescents, and adults	
Intervention	Recommendation
Increase community demand for vaccination	
Client reminder or recall systems	Recommended
Requirements for entry to schools, child-care facilities, and colleges	Recommended
Community education alone	Insufficient evidence
Community-based interventions implemented in combination	Recommended
Clinic-based education	Insufficient evidence
Patient or family incentives	Recommended
Patient or family monetary sanctions	Insufficient evidence
Client-held medical records	Insufficient evidence
Enhance access to vaccination services	
Reducing out-of-pocket costs	Recommended
Enhancing access through the U.S. Department of Agriculture's Women, Infants, and Children program	Recommended
Home visits, outreach, and case management targeted to particularly hard to reach populations to increase vaccination rates	Recommended
Enhancing access at schools	Recommended
Expanding access in health care settings	Recommended as part of multicomponent interventions only
Enhancing access at organized child care centers	Recommended

In conclusion, Dr. Kroger indicated that the next steps would be to invite discussion during this session, and an anticipated vote on the entire updated General Recommendations document during the October 2014 ACIP meeting. All of the important sections have been discussed by ACIP, with the exception of the introductory paragraph and the vaccine information sources. He will update those two sections. Areas that need some editing include vaccination of the hospitalized patient and all of the interventions such as anesthesia or surgery that may occur, alternate routes and whether doses are counted when given at alternate routes, and febrile seizures with respect to simultaneous vaccination.

Dr. Kroger expressed gratitude to outgoing Chair, Dr. Duchin. The WG went through a great deal of very complicated subject material over the last four years, which Dr. Duchin's meticulous but easy going style made very pleasurable.

Discussion Points

Dr. Riley (ACOG) is involved with high-risk obstetrics, and is commonly asked about women who are on rituximab. They have not been delaying their vaccination because there may be only six months of pregnancy. If there is a suggestion, it should be incorporated someplace because the natural reflex is going to be not to give it. She was concerned that inactivated influenza vaccine and tetanus and reduced diphtheria toxoids (Tdap) that should be given might be delayed because of the six-month concern, which will miss the ability to protect the infant.

Dr. Kroger responded that this is being discussed by CDC, less so the issue of vaccination of the pregnant woman herself, although that is an important topic, but the WG is also discussing the issue of whether immunodeficiency can be transferred to the infant. That has relevance with rotavirus vaccine, which is given in early infancy. He did not know how much movement there would be on those recommendations. It might be in the rotavirus vaccine-specific statement as opposed to the General Recommendations, but perhaps they can get it into the General Recommendations as well. The issue of vaccinating the pregnant woman herself, there is a general recommendation regarding live vaccination during pregnancy. Live vaccines generally are contraindicated in pregnancy, so the pregnancy itself might contraindicate the use of these medications as well if they are defined as immunosuppressive. This may need to be discussed further during review of the *Special Situations* section of the General Recommendations, which includes a discussion of pregnancy.

Dr. Rubin noted that in studies conducted in which people are vaccinated who have received rituximab, since it is essentially a B lymphocyte poison, they just do not make antibody. In terms of relying on humoral immunity, the likelihood of significant effectiveness is extremely low.

Dr. Riley (ACOG) inquired as to whether his suggestion would be not to bother in those patients.

Dr. Rubin replied that his personal suggestion would be that there is very little risk, but the likelihood of a positive effect is virtually zero so he would not give it.

Dr. Harrison inquired as to whether ACIP was going to attempt to harmonize with IDSA or remain divergent.

Dr. Kroger responded that the goal was to harmonize the General Recommendations with IDSA, but this does involve a degree of “cherry picking” from the IDSA document. That is what the WG attempted to do in the draft as opposed to not putting content in the draft and just including a citation. There will be ongoing attempts through discussion with vaccine subject matter experts (SMEs) on specific issues that may appear in vaccine-specific statements that may not harmonize precisely with what is in IDSA’s document. That is outside of the purview of the General Recommendations WG. The work is ongoing. The recommendations for use of zoster vaccine are not harmonized with ACIP specific recommendations, but the vaccine SMEs are aware of these issues.

Child/Adolescent Immunization

Introduction

Renée Jenkins, MD
Chair, Child/Adolescent Immunization Work Group

Dr. Jenkins indicated that this session would include a review of the status of the childhood/adolescent immunization schedule; a review of a provider interview project to assess the usability of the catch-up schedule; and a presentation of the draft supplementary table (job aid) for diphtheria, tetanus, and pertussis (DTaP) vaccine for ACIP review. She indicated that Dr. Kroger would present on behalf of Dr. Strikas, CDC Work Group Lead, who was unable to attend due to a scheduling conflict.

Healthcare Provider Review of 2014 Catch-Up Schedule and Supplementary Tables

Dr. Andrew Kroger
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Kroger indicated that CDC has the following two schedules currently being used for childhood immunizations:

- A schedule of recommended vaccines for children ages birth through 18 years
- A catch-up schedule for when vaccines have been missed or children are behind in the schedule

There has been an ongoing effort since 1964 to clarify the schedule as it has become increasingly complicated, and even more so recently. As follows is Figure 2, the 2014 childhood/adolescent immunization catchup schedule. There is abundant, dense text for some of the vaccines, particularly Hib and pneumococcal conjugate, and to a lesser extent DTaP/Tdap:

FIGURE 2. Catch-up immunization schedule for persons aged 4 months through 18 years who start late or who are more than 1 month behind — United States, 2014.
 The figure below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the sections appropriate for the child's age. Always use this table in conjunction with Figure 1 and first footnotes that follow.

Vaccine	Minimum Age (y)	Persons aged 4 months through 6 years			
		Dose 1 to dose 2	Minimum Interval Between Doses	Dose 3 to dose 4	Dose 4 to dose 5
Hepatitis A ¹	Birth	4 weeks	8 weeks and at least 16 weeks after first dose, minimum age for this dose 16 weeks		
Rotavirus ²	8 weeks	4 weeks	4 weeks ³		
Diphtheria, tetanus, & acellular pertussis ⁴	8 weeks	4 weeks	4 weeks	6 months	6 months ⁵
Hemophilus influenzae type a ⁶	8 weeks	4 weeks if first dose administered at younger than age 12 months 8 weeks (or first dose) if first dose administered at age 12 through 14 months 12 weeks (or first dose) if first dose administered at age 15 months or older	4 weeks ⁷ if current age is younger than 12 months and first dose administered at 7 months or older 8 weeks (or first dose) if current age is younger than 12 months and first dose administered at 7 months or older 12 weeks (or first dose) if current age is younger than 12 months and first dose administered at 12 months or older 16 weeks (or first dose) if current age is younger than 12 months and first dose administered at 12 months or older	6 months (or first dose) 12 months (or first dose) if current age is 12 months or older 18 months (or first dose) if current age is 18 months or older 24 months (or first dose) if current age is 24 months or older	6 months (or first dose) 12 months (or first dose) if current age is 12 months or older 18 months (or first dose) if current age is 18 months or older 24 months (or first dose) if current age is 24 months or older
Pneumococcal ⁸	8 weeks	4 weeks (or first dose) if first dose administered at age 12 months or older No further doses needed for healthy children if first dose administered at age 12 months or older	8 weeks (or first dose) if current age is younger than 12 months 12 weeks (or first dose) if current age is 12 months or older No further doses needed for healthy children if pneumococcal conjugate administered at age 12 months or older	6 months (or first dose) 12 months (or first dose) if current age is 12 months or older 18 months (or first dose) if current age is 18 months or older 24 months (or first dose) if current age is 24 months or older	6 months (or first dose) 12 months (or first dose) if current age is 12 months or older 18 months (or first dose) if current age is 18 months or older 24 months (or first dose) if current age is 24 months or older
Inactivated poliovirus ⁹	8 weeks	4 weeks ¹⁰	4 weeks ¹¹	6 months ¹² minimum age 4 years for first dose	
Meningococcal ¹³	8 weeks	8 weeks ¹⁴	See footnote 13	See footnote 13	
Meningococcal polysaccharide ¹⁵	12 months	4 weeks			
Varicella ¹⁶	12 months	3 months			
Hepatitis A ¹	12 months	6 months			
Persons aged 7 through 18 years					
Hepatitis A ¹	7 years ¹⁷	4 weeks	4 weeks (or first dose) if current age is younger than age 12 months or older 8 weeks (or first dose) if current age is 12 months or older and then no further doses needed for catch-up	6 months (or first dose) if current age is 12 months or older 12 months (or first dose) if current age is 12 months or older	6 months (or first dose) if current age is 12 months or older 12 months (or first dose) if current age is 12 months or older
Hepatitis B ¹⁸	12 months	6 months	6 months (and at least 16 weeks after first dose)		
Inactivated poliovirus ⁹	8 weeks	4 weeks	4 weeks ¹⁹		
Meningococcal ¹³	8 weeks	8 weeks ¹⁴			
Meningococcal polysaccharide ¹⁵	12 months	4 weeks			
Varicella ¹⁶	12 months	3 months if person is younger than age 13 years 4 weeks if person is age 13 years or older			

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

In an effort to improve childhood and adolescent immunization schedules, CDC and partner organizations have developed job aids to be used with the current catch-up schedule. In addition to testing the job aids, CDC wanted to learn from practicing providers their current usage of the catch-up schedule, ease of use, and how it might be improved so that a catch-up schedule can be more user friendly.

CDC created job aids for two vaccines:

- Haemophilus influenzae* type b (Hib)
- Diphtheria, tetanus, and acellular pertussis (DTaP); tetanus, diphtheria, and acellular pertussis (Tdap); tetanus and diphtheria (Td)

Two job aids were borrowed from the Immunization Action Coalition (IAC):

- Pneumococcal conjugate (PCV13: <http://www.immunize.org/catg.d/p2016.pdf>)
- Meningococcal conjugate (MCV: <http://www.immunize.org/catg.d/p2018.pdf>)

The job aids were tested in variable formats with healthcare providers. Formats were sometimes shown in algorithm forms as opposed to table form, and the table was broken up in different ways as well. Eight groups of healthcare providers were interviewed, including the following:

- Family Practitioners
- Pediatricians
- Public Health Nurses
- Nurse Practitioners
- Nurses in Private Settings
- Physician Assistants
- Medical Assistants
- Immunization Information System or Registry Staff

These target audiences were chosen because of their role in vaccinating children. Physician participants were identified who are board-certified in either pediatrics or family practice. All participants had to report spending at least 50% of their time in direct patient contact; deciding what childhood or adolescent immunizations they will recommend for at least five patients per week; and that they work primarily in a private practice or a public health clinic that provides immunizations to children. These qualifications did not apply to participants who worked at state registries.

CDC contacted several professional organizations in mid-February to recruit potential participants, including the following:

- American Academy of Pediatrics (AAP)
- American Association of Family Practitioners (AAFP)
- American Nurses Association (ANA)
- American Association of Physician Assistants (AAPA)
- National Association of Pediatric Nurse Practitioners (NAPNAP)

State health departments and state immunization registries were also contacted. The original goal was to contact 10 to 15 people from each of 8 providers groups, anticipating an approximately 46% response rate to result in 48 records. Contact information was received for 55 individuals, all of whom were contacted. The following table reflects the make-up of practices contacted and interviewed:

Type of Practice	Contacted	Scheduled	Interviewed	Target	% Completed
Family Practice Physicians	11	7	7	10	70
Public Health Nurses	9	4	4	5	80
Private Setting Nurses	6	3	1	5	20
Registry	3	2	2	3	66
Pediatricians	9	6	6	10	60
Nurse Practitioners	7	5	5	5	100
Physicians Assistants	4	1	1	5	20
Medical Assistants	6	4	4	5	80
Totals	55	32	30	48	62

The Survey Monkey internet-based survey tool was used to create a questionnaire for this project and to collect data. Survey Monkey collected demographic information, information about how the participants were using the current catch up schedule, and their initial impressions of the job aids. Respondents' answers from Survey Monkey were reviewed on the day of the phone interview, and they were then asked about three case studies of children with lapsed vaccinations. The case studies were for the pneumococcal, Hib, and meningococcal job aids. Participants were asked to review the case study, and answer using the catch up schedule and then the job aid. The interviews were conducted from March 20, 2014 through May 1, 2014. Over 50% of the target number was reached for 6 of the 8 groups, and 30 people were interviewed. By this point, there was enough similarity of responses to analyze the results.

The following example is one of the 4 pages of the DTaP job aid, which was one of the products given to the respondents:

Job Aid Example - DTaP

If Current Age	AND # of previous Doses of DTaP at DT	AND	AND	THEN ¹	Next Dose Due ²
4 months through 11 months of age	1	Unknown or 0	→	Give Dose 1 (DTaP) today	Give Dose 2 (DTaP) at least 4 weeks after Dose 1
		It has been at least 4 weeks since the previous/first dose	→	Give Dose 2 (DTaP) today	Give Dose 3 (DTaP) at least 4 weeks after Dose 2
		It has not been at least 4 weeks since the previous/first dose	→	No dose today	Give Dose 2 (DTaP) at least 4 weeks after Dose 1
	2	It has been at least 4 weeks since the previous dose	→	Give Dose 3 (DTaP) today	Give Dose 4 (DTaP) at least 6 calendar months after Dose 3 and at least age 15 months
		It has not been at least 4 weeks since the previous dose	→	No dose today	Give Dose 3 (DTaP) at least 4 weeks after Dose 2
		Unknown or 0	→	Give Dose 1 (DTaP) today	Give Dose 2 (DTaP) at least 4 weeks after Dose 1
1 through 3 years of age	1	It has been at least 4 weeks since previous/first dose	→	Give Dose 2 (DTaP) today	Give Dose 3 (DTaP) at least 4 weeks after Dose 2
		It has not been 4 weeks since previous/first dose	→	No dose today	Give Dose 2 (DTaP) at least 4 weeks after Dose 1
		It has been at least 4 weeks since the previous dose	→	Give Dose 3 (DTaP) today	Give Dose 4 (DTaP) at least 6 calendar months after Dose 3
	2	It has not been at least 4 weeks since the previous dose	→	No dose today	Give Dose 3 (DTaP) at least 4 weeks after Dose 2
		It has been at least 6 calendar months since the previous dose	→	If 12-14 months of age, no dose today	Give Dose 4 (DTaP) at 15 - 18 months of age
		It has not been 6 calendar months since the previous dose	→	If 15 months of age or older, give Dose 4 (DTaP) today	Give Dose 5 (DTaP) at least 6 months after Dose 4 and at 4 through 5 years of age
3	It has not been 6 calendar months since the previous dose	→	No dose today	Give Dose 4 (DTaP) at least 6 months after dose 3	

The job aid table is intended for instantaneous use by providers when they see a patient to make a decision about what immunizations are needed. The last column provides information about when the next dose is due, and is important for discussions with patients. This is a prospective tool. It is not meant to be used to validate doses that have already been given, but instead is to support use of the childhood schedule moving forward. This is an easier way to see the information.

This is the IAC pneumococcal job aid, which is useful and was included in the interview and focus group:

Pneumococcal Job Aid Example

Recommendations for Pneumococcal Vaccine Use in Children and Teens

Table 1. Recommended Schedules for Administering Pneumococcal Conjugate Vaccine (PCV)

Child's age now	Vaccination history of PCV7 and/or PCV13	Recommended PCV13 Schedule (For minimum interval guidance for catch-up vaccination, see *)
2 through 6 months	0 doses	3 doses, 8 weeks* apart; 4th dose at age 12-15 months
	1 dose	2 doses, 8 weeks* apart; 4th dose at age 12-15 months
	2 doses	1 dose, at least 8 weeks* after the most recent dose; 4th dose at age 12-15 months
7 through 11 months	0 doses	2 doses, 8 weeks apart**; 3rd dose at age 12-15 months
	1 or 2 doses before age 7 months	1 dose at age 7-11 months; 2nd dose at age 12-15 months, at least 8 weeks after the most recent dose
12 through 23 months	0 doses	2 doses, at least 8 weeks apart
	1 dose before age 12 months	2 doses, at least 8 weeks apart
	1 dose at or after age 12 months	1 dose, at least 8 weeks after the most recent dose
	2 or 3 doses before age 12 months	1 dose, at least 8 weeks after the most recent dose
24 through 59 months (healthy)	Unvaccinated or any incomplete schedule	1 PCV13 dose, at least 8 weeks after the most recent PCV7 dose
	4 doses of PCV7 or other age-appropriate complete PCV7 schedule	1 dose, at least 8 weeks after the most recent dose
24 through 71 months (with risk factor described in Table 3 below)	Unvaccinated or any incomplete schedule of less than 3 doses	2 doses, one at least 8 weeks after the most recent dose and another dose at least 8 weeks later
	Any incomplete schedule of 3 doses	1 PCV13 dose, at least 8 weeks after the most recent PCV7 dose
	4 doses of PCV7 or other age-appropriate complete PCV7 schedule	1 PCV13 dose, at least 8 weeks after the most recent PCV7 dose
6 through 18 years with immunocompromising condition, functional or anatomic asplenia (see specific conditions in Table 3 below), cochlear implant, heart, or cochlear implant	No history of prior PCV13	1 dose of PCV13

* Minimum interval between doses: For children younger than age 12 months, 4 weeks; for children age 12 months and older, 8 weeks.

<http://www.immunize.org/catg.d/p2016.pdf>

The IAC combines catchup vaccination with high risk recommendations, which is quite an effort and accomplishment. However, the Child/Adolescent Immunization WG's goal is to focus on the healthy child for CDC's tools.

In terms of the survey results, participants felt that the current catch-up schedule has very useful information but that it is difficult to read or understand. Specifically, the footnotes were brought up often as too dense, confusing, and that people can either miss them or not reference them. For the Hib job aid, a table and an algorithm were given to participants. Two-thirds of participants preferred tables over algorithms. Two participants had no preference. The preference was evenly split for the DTaP tables, but there was a slight preference for Version 2 that is a single table. Some participants felt that Version 1 was easier to read and provides a lot of information, but there was a slight preference to have a separate table for the tetanus toxoid-containing vaccines.

The meningococcal and pneumococcal job aids created by the IAC were provided to participants. Each table was on only one page. Participants liked these, and thought the tables were clear and easy to read. There were some comments about highlighting or bolding certain sections or moving footnotes directly into the table.

Overall people liked the job aids and think that they would be a helpful resource. Participants were very appreciative that CDC is creating something to help them with reading the current catch up schedule. The best summary of what the job aids should do came from a participant who said, "It should be clear, concise, and correct."

Regarding next steps, the job aids will be refined as necessary by CDC staff to appear the same as the DTaP example shown earlier. ACIP members were asked to review the DTaP format and offer any input in the next several weeks. The job aids will be CDC documents, and will be clearly noted as adjuncts to the published Recommended Immunization Schedule for persons 0 through 18 years of age to assist with schedule interpretation.

Discussion Points

Dr. Temte commented that 90% of the questions he gets in his clinic deal with just this question, particularly from medical assistants. He thinks having a flow-through table will be very beneficial as compared to the current tool, and he thanked the WG for this effort.

Dr. Harriman inquired as to whether there was a goal to work with manufacturers of electronic medical records (EMRs) to have these programmed in, which would be optimal.

Dr. Kroger replied that there has been an ongoing project with the registry branch of his division to ensure that the information in the CDC childhood schedule and the General Recommendations are incorporated into EMRs. The childhood schedule has the tool for moving forward for someone with a lagged schedule. The General Recommendations has the table that is useful for back-validating, which is known as evaluation in the registry and forecasting for forward thinking. CDC is working with the registry group to ensure that ACIP recommendations are programmed in. The registry group has stated repeatedly that they want to program in what ACIP recommends. The job aids will be harmonized with the childhood schedule, so it will not matter whether the job aid or the schedule is used to interact with the registry.

Beyond the registry, Dr. Harriman said she was thinking of EMR systems such that reminders and pop-ups would be programmed in.

Dr. Kroger said he thought there was a process to harmonize the way the registry functions with medical records as part of Meaningful Use as well. That is an ongoing concern and consideration.

Dr. Schuchat added that there is ongoing work with EMR vendors. The ideal circumstance is bidirectional information flow between the EMR and registries so that in a single application, a practitioner opens the EMR, it queries the registry for all relevant doses, and indicates what needs to be done at that point. This is a major priority for CDC in the Office of the National Coordinator.

Dr. Groom (IHS) said she was happy to see the job aids, but requested to follow-up with Dr. Kroger, because she was still seeing a contradiction in the catch-up schedule about whether one of the children in the case IHS presented to him would need the booster dose of Hib. As she read through the current language and tried to unpack it, she could come to two different conclusions.

Dr. Kroger acknowledged that SME follow-up is needed on that point, and indicated that the issue was one of beginning vaccination at 7 months or older and getting three doses in, and whether the dose at 12 months or older was needed.

Yellow Fever Vaccine

Introduction

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Dr. Bocchini reminded everyone that this WG has been tasked with evaluating the World Health Organization (WHO) decision for continuation of a booster dose for Yellow Fever (YF) vaccine. The Japanese Encephalitis (JE) Work Group became the JE and YF Vaccines Work Group. The membership of the WG was modified to add the expertise needed to evaluate the question they were asked to solve. He indicated that during this session, Dr. Staples would provide the GRADE evaluation of the available evidence pertaining to the use of YF vaccine booster doses, as well as the WG conclusions and recommendations for consideration, which would lead to a vote. He then highlighted some of the key issues.

Since 1965, the International Health Regulations (IHR) allowed countries to require a YF vaccine dose within past 10 years for entry. In April 2013, the WHO Strategic Advisory Group of Experts (SAGE) concluded single dose of YF vaccine is sufficient to confer sustained immunity and lifelong protection. Therefore, booster doses were no longer considered to be needed. However, SAGE did identify that there are specific risk groups who might benefit from a second dose or booster dose in its recommendations. YF vaccine is the only vaccine covered by IHR. IHR does stipulate that YF vaccine provides protection against infection for 10 years. Requiring proof of vaccination (i.e., certificates) from travelers is at the discretion of each country; therefore, the certificate of vaccination provided at the time of vaccination is valid for 10 years. In May 2014, the WHO World Health Assembly (WHA) adopted an amendment to the IHR that extends YF vaccine protection to the life of the person vaccinated. Therefore, they will no longer recommend booster doses, and the change to the IHR will be official in June 2016.

ACIP recommendations for YF vaccine were last updated in 2009 and were published in 2010. Currently, YF vaccination is recommended for the following:

- Persons aged ≥ 9 months traveling to or living in areas at risk for YF virus transmission in South America or Africa
- Laboratory workers exposed to virulent virus strains in their routine work
- Per IHR, YF vaccine may be required by a country for entry at intervals of 10 years

Also in the ACIP recommendations are the following statements:

- Because of risk of serious adverse events (SAEs), health-care providers should vaccinate only persons who are at risk for exposure to YF virus or require proof of vaccination for country entry.
- IHRs require revaccination at intervals of 10 years to boost antibody titer. Evidence from multiple studies demonstrates that YF vaccine immunity persists for many decades and might provide life-long protection.

In essence, ACIP has followed IHR recommendations, but has not specifically made recommendations about use of the vaccine.

Live attenuated YF vaccine was developed initially in the 1930s. The only YF vaccine available in the United States (US) is the 17D-204 strain vaccine (YF-VAX[®]) manufactured by Sanofi Pasteur. Over 540 million doses of YF vaccine have been administered worldwide. No human studies have been conducted to determine the efficacy or identify a correlate of protection for YF vaccine. One study established a minimal level of neutralizing antibodies needed to protect monkeys against virulent YF virus as \log_{10} neutralization index (LNI) ≥ 0.7 . This is not used for diagnostic evaluation of antibody response in humans given the vaccine. Humans are typically tested with a plaque reduction neutralization test (PRNT), but no correlate has been determined for this more commonly used test of protection. It is also not known whether the lack of detectable antibody in previously immunized person indicates susceptibility to YF after exposure.

As noted, the JE Vaccine WG was reformed to include YF vaccine in October 2013. The WG has met 12 times to discuss YF vaccine booster doses. During these teleconference, the WG has reviewed the duration of immunity following YF vaccine and the safety of YF vaccine booster doses. The WG completed the GRADE analysis, reviewed the epidemiology of YF vaccine in travelers, and developed proposed recommendations. There have been two previous presentations to ACIP on this topic, including one in October 2013 focused on the WG charge and plans and one in February 2014 focused on YF and YF vaccine background information.

The WG has 21 members who attended calls regularly and includes subject matter experts in YF and other live viral vaccines, travel medicine physicians, and representatives from several liaison groups as well as the Food and Drug Administration (FDA), National Institutes of Health (NIH), Department of Defense (DoD), and CDC.

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

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The WG used GRADE to review data related to YF vaccine booster doses. The nine steps of GRADE are as follows:

- Develop policy question
- Identified and ranked importance of outcomes
- Searched and reviewed of published and unpublished data
- Summarized evidence for critical outcomes
- Evaluated quality of evidence for outcomes
- Assessed values related to options and outcomes
- Reviewed health economic data
- Considerations for formulating recommendations
- ACIP recommendations and GRADE category

During her presentation, Dr. Staples went through each of these steps as they relate to the WG considerations for YF vaccine booster doses. The first step was to develop a policy question. The primary policy question developed by the WG was as follows:

“Should booster doses of YF vaccine every 10 years continue to be recommended for healthy travelers and laboratory workers?”

This included healthy travelers and laboratory workers of the population. The intervention was to remove the current recommendation for booster doses versus the current option, which is to continue the current recommendation for booster doses of YF vaccine.

Next, the WG identified and ranked the importance of outcomes related to this policy question. Four benefits were assessed by the WG, including vaccine efficacy, vaccine effectiveness as measured by vaccine failures, seroprotection, and seropositivity. Although efficacy and seroprotection were considered critical, there are no data available for these areas. Given this, seropositivity, which was originally assessed by the WG to be important, was changed to critical. Vaccine effectiveness and seropositivity were considered critical by the WG and were included in the evidence profile. Five harms were assessed by the WG, including SAEs, two known YF vaccine-associated SAEs (viscerotropic disease and neurologic disease), anaphylaxis, and systemic adverse events. SAEs, viscerotropic disease, and neurologic disease were considered critical by the WG and were included in the evidence profile.

The WG next searched and reviewed published and unpublished data. To do this, the WG performed a systematic search and review of published literature. The WG identified 32 studies that reported primary data relevant to critical outcomes. In addition, the WG reviewed unpublished data from three sources as follows:

- ❑ Data from Brazil Ministry of Health (MOH) on duration of immunity and vaccine failures
- ❑ Vaccine Adverse Event Reporting System (VAERS) reports for YF vaccine administered from January 2007 through December 2013
- ❑ CDC Arboviral Diseases Laboratory data on antibody titers in vaccine recipients ≥ 10 years post-vaccination

Of the studies, five included data on vaccine effectiveness as measured by vaccine failures reported following YF vaccination from 1940 through 2013. The non-endemic population included travelers, laboratory workers, and military personnel from areas without YF virus transmission. The endemic population included persons who live in areas at risk for YF virus transmission. Few vaccine failures have been documented following YF vaccination over the last 70+ years. All but two cases where the data are known occurred in persons who reported receiving YF vaccine within the last 10 years. There was one vaccine failure noted 20 years and one at 27 years post-vaccination. To summarize the vaccine effectiveness data, 18 vaccine failures have been noted among over 540 million doses of YF vaccine delivered. There are limited data on the majority of cases that support the diagnosis of YF. Of the vaccine failures, 16 (89%) occurred in persons receiving a YF vaccine dose in last 10 years. Two vaccine failures occurred ≥ 10 years from last YF vaccine dose (20 and 27 years).

Seven studies contained seropositivity data 10 or more years following YF vaccination. Among those, two primary assays were noted. The mouse protection study which are no longer being used, and the more modern assay, the PRNT. For the PRNT, different cutoffs were used for virus inhibition, and different titers were used to define seropositivity. These seven studies contained data starting at 10 years post-vaccination and ranged from 77% to 100% of the subjects being seropositive. Six more studies contained seropositivity data up to 69 years post-YF vaccination. The range for those that were seropositive among these studies was 75% to 97%.

To summarize, there have been 13 observational studies with immunogenicity data for 1,137 persons vaccinated 10 or more years previously. There were 1,002 (88%) persons who were seropositive 10 or more years post-vaccination. However, when study size differences and variability between the studies were accounted for in a meta-analysis, the estimated seropositivity is 92% with a 95% confidence interval of 85% to 96%. The proportion decreases to 80% (131/164) by 20 years post-vaccination, but there are only 164 persons for whom there are data. The estimated seropositivity from the meta-analysis is also 80%, with a 95% confidence interval of 74% to 86%.

For all harms, studies were included that had denominator data or more specifically, the number of adverse events for the total number of doses distributed or administered. There were 9 studies with data on SAEs, which included data from 1990 through 2013. All of these studies were observational. To summarize the SAEs, there were 9 observational studies from manufacturers and national surveillance data that accounted for 333 million doses of vaccine administered. However, it is unknown how many of these doses were administered as primary versus booster doses, so rates could not be determined. There were 1,255 subjects who reported an SAE following YF vaccination. For 84% (1,054) of the subjects experiencing an SAE following YF vaccine, the vast majority, the dose type was unknown. Of the subjects experiencing an SAE following YF vaccine for whom the dose type was known, 7% (14/201) received a YF booster dose.

In terms of viscerotropic disease data, a number of cases could have been included in the SAE table. The studies include data from 1990 through 2010 and range from studies that have 42,000 up to 276 million doses administered. One viscerotropic disease case was noted following a booster dose of YF vaccine. To summarize, there were 8 observational studies from manufacturers and national surveillance data that included 437 million doses of vaccine administered. Again, it is unknown how many of those doses were administered as primary versus booster doses. Overall, 72 subjects reported viscerotropic disease following YF vaccination. The vaccination type was unknown for 57% (41) of subjects. For 3% (1/31) of subjects whose vaccination type was known, SAEs occurred following the booster dose.

Similar to the viscerotropic disease cases, the neurologic disease cases may have been included on the SAE table. The studies pertaining to neurologic disease included data from 1990 through 2010, and 3 neurologic disease cases were reported following booster doses of the vaccine. To summarize, there were 8 observational studies from manufacturers and national surveillance data that accounted for 462 million doses of vaccine administered. However, the number of doses administered as booster doses is unknown other than for one study. There were 218 subjects who reported neurologic disease following YF vaccination. For 50% (108) of these subjects, the vaccine type was unknown. For 3% (3/110) of subjects for whom the dose type was known, neurologic disease was reported following the YF booster dose.

Regarding evaluation of the quality of evidence for the outcomes, the following evidence types are used for GRADE:

- ❑ 1 = Randomized control trials (RCTs) or overwhelming evidence from observational studies
- ❑ 2 = RCTs with important limitations or exceptionally strong evidence from observational studies
- ❑ 3 = Observational studies or RCTs with notable limitations
- ❑ 4 = Clinical experience, observational studies with important limitations, or RCTs with several major limitations

For vaccine effectiveness, there were 5 observational studies that had a risk of bias as there was incomplete case capture and no comparison group. These were also further downgraded due to the indirectness as the majority of data were from endemic areas, and it is unknown how many persons at risk for YF would not have received a booster dose of the vaccine. The final evidence type is 4 for vaccine effectiveness. For seropositivity, there were 13 observational studies. They had the same limitations, with the risk of bias coming from those who might have been tested for their long-term seropositivity, indirectness due to differences in the population, the fact that no vaccine efficacy or seroprotection data are available, and different assays and different cutoffs were used to assess seropositivity. The final evidence type for seropositivity is 4. There were 8 to 9 observational studies related to the harms (SAEs, viscerotropic disease, neurologic disease). All harms were downgraded due to indirectness, as it was unknown for all but one study the number of doses that were administered as booster doses versus primary doses. Thus, the rate of SAEs could not be calculated. The evidence type was 4 for any SAE, viscerotropic disease, and neurologic disease. The overall quality of evidence for critical outcomes used to assess YF vaccine booster dose was Type 4—the lowest evidence type.

Before moving into the value assessment, Dr. Staples discussed an additional policy question considered by the WG. While the primary policy question focused on healthy travelers and laboratory workers, the additional policy question was created for special populations whose initial immune response to YF vaccine may be suboptimal. The question was:

“Should booster doses of YF vaccine every 10 years continue to be recommended for travelers and laboratory workers who had a precaution to vaccination that might have negatively impacted their immune response to their primary dose of YF vaccine (e.g., pregnancy, asymptomatic HIV infection, or age 6-8 months)?”

There were very limited data related to the special populations whose immune response to YF vaccine may be suboptimal. Therefore, the WG decided not to perform GRADE. However, the immunogenicity data were reviewed for pregnant women, HIV-infected persons, and young children for whom Dr. Staples presented data.

Regarding the immunogenicity of YF vaccine in pregnant women, the two studies that have been published on cohorts of pregnant women show that the proportion of pregnant women who develop antibody titers after YF vaccination is variable. One study found that 39% (40/101) of pregnant women vaccinated during their third trimester seroconverted compared to 92% of the general population. In the second study, 98% (425/433) of pregnant women vaccinated primarily during their first trimester developed YF-virus specific antibodies.

Two studies have been published with immunogenicity data for YF vaccine in HIV-infected persons that had a comparator group and were beyond the first one to two months post-vaccination. In the first study performed retrospectively among HIV-infected travelers, 83% (65/78) of HIV-infected persons had YF virus-specific antibodies one year post YF vaccination compared to 97% (64/66) of uninfected controls. This difference was significant ($p=0.01$). The second study found that only 17% (3/18) of HIV-infected children in an endemic area of Africa had YF virus-specific antibodies 10 months post vaccination compared to 74% (42/57) age and nutritionally matched children.

There were 9 studies with seroconversion rates following the primary dose of YF vaccine in children from endemic areas aged 6 through 36 months. The studies included those that have been published since 1980 and thus would use vaccine formulations that are currently in use today. Some of the studies were RCTs and others were observational. All but one of the studies was designed to assess the potential immune response when YF vaccine was co-administered with another vaccine. Again, the assays used were variable between the studies and each study had at least 100 children and up to 900 children in one of them. The seroconversion rates ranged from 78% to 96%. To summarize, there were 9 studies that included data on children 6 through 36 months of age in endemic areas. From these studies, 98% (2,433/2,754) of children seroconverted one to two months post-YF vaccination. There were very limited long-term immunogenicity data available for children beyond the first one to two months post-vaccination to know if their antibody decay rates would be different than adults.

Regarding the assessed values related to the options and outcomes, from 1970 through 2013, there have been 10 YF cases reported in travelers from the US (3) and Europe (7). Of the 10 cases, 9 were in unvaccinated travelers of whom 8 (89%) died. One traveler reported receiving YF vaccine 5 years before traveling to West Africa where she developed YF. She survived. YF vaccine has been available since the late 1930s. It is currently unknown how many cases of disease have been prevented due to vaccination. Overall, vaccination coverage rates reported from airport or clinic surveys for persons traveling to YF endemic areas is high at 91% to 93%.

The risk of YF disease and death in an unvaccinated traveler for a 2-week stay in West Africa is estimated to be about 50 disease cases and 10 deaths per 100,000 population. In South America, the risk is estimated to be 5 disease cases and 1 death per 100,000 population. The risk of YF varies based on location, duration, season, and activities. The WG agreed that the risk of YF will be lower in persons receiving at least one dose of YF vaccine 10 or more years previously, but it is not quantifiable given the lack of available data.

The WG discussed some additional considerations regarding disease risk in the US population. Overall, the WG considered persons who might be at higher risk of exposure to YF virus based on a number of factors, including: 1) location, with the YF disease risk in West Africa estimated to be 10 times higher than South America; 2) duration of travel, with longer travel (e.g., months to years) likely to increase risk of disease; and 3) the type of exposure, such as a more consistent exposure to virulent virus among laboratory workers. For each of these, there are minimal to no data to support these considerations of increased disease risk.

In the end, the values considered by the WG during the GRADE process were that YF is a severe disease with substantial mortality. There is no specific treatment for the disease. A safe and effective vaccine is available to prevent the disease. Furthermore, there is a low probability of SAEs with revaccination. The vaccine prevents importation and spread of YF virus. Finally, the vaccine is expensive.

In terms of the review of the health economic data, there are no data on the cost-effectiveness of vaccinating travelers with either primary or booster doses of YF vaccine. Providing YF vaccines to all travelers going to endemic areas would not be cost-effective, given the large number of travelers to endemic areas (~3 million/year). The risk of YF disease for vaccinated travelers is less than 5 to 50 cases per 100,000 population. The cost of YF vaccine varies from \$150 to \$350. Travel vaccines are usually paid for by travelers. These vaccines are not covered by most private insurance and are not included in the Vaccine for Children (VFC) program. Given this information, the WG decided not to perform cost-effectiveness study of YF vaccine booster doses.

Three potential recommendations were considered by the WG to begin with, including the following:

- A booster doses of YF vaccine every 10 years is recommended for travelers and laboratory workers.
- A single dose of YF vaccine is sufficient to confer sustained life-long protective immunity against YF disease, and a booster dose is not necessary [WHO SAGE recommendation].
- Booster doses are no longer recommended for most travelers or laboratory workers. However, booster doses are recommended for certain persons at risk for exposure to YF virus.

When formulating the recommendations to present to ACIP, the WG considered that there have been very few vaccine failures noted following YF vaccination. Most (92%) vaccine recipients are seropositive 10 or more years post-vaccination. SAEs are uncommon following booster doses of YF vaccine. High value is placed on preventing a serious disease with no treatment and poor outcome. Finally, the current statement in the ACIP recommendations regarding booster doses will soon be antiquated as IHR will remove the language of YF booster doses in June 2016. As a reminder, the language currently used in the ACIP recommendations that has been in place since 1969 states, "IHRs require revaccination at intervals of 10 years to boost antibody titers."

Based on the GRADE process, review of additional data, and SME, the WG reached the following conclusions. A single dose of YF vaccine provides long-lasting protection in most travelers. The WG proposes to no longer recommend a booster dose of YF vaccine for most travelers. Based on limited data, the WG would recommend YF vaccine booster doses for certain persons, including those who are at increased risk of exposure to YF virus and those whose immune response to their previous dose might have been compromised due to an existing condition at time of vaccination.

The WG proposed the following wording and recommendation categories for ACIP's consideration:

Option for ACIP Consideration (1 of 4)

“Booster doses are no longer recommended for most travelers or laboratory workers (Recommendation category A).”

Option for ACIP Consideration (2 of 4)

“However, based on limited data, a YF vaccine booster dose is recommended for certain persons either at increased risk of exposure to YF virus or whose immune response to their previous dose might have been compromised due to an existing condition at the time of vaccination (Recommendation category A).”

OR

“However, based on limited data, a YF vaccine booster dose may be considered for certain persons either at increased risk of exposure to YF virus or whose immune response to their previous dose might have been compromised due to an existing condition at the time of vaccination (Recommendation category B).”

Option for ACIP Consideration (3 of 4)

Booster doses for:

“Travelers who received their last dose of YF vaccine ≥ 10 years previously and plan to stay in an endemic area for a prolonged period (e.g., months or longer) or plan to travel to a highly endemic area (e.g., rural West Africa)” *Alternative: remove examples in parenthesis as they are based on limited data*

“Laboratory workers who routinely handle infectious YF virus and who have no detectable YF virus-specific neutralizing antibody titers or who received their last dose of YF vaccine ≥ 10 years previously and for whom YF virus-specific neutralizing antibody titers are unavailable.”

Option for ACIP Consideration (4 of 4)

Booster doses for:

“Persons who received their last dose of YF vaccine ≥ 10 years previously and who had, at the time of their last vaccination, a condition that might have compromised their immune response to that dose (e.g., age < 1 year, pregnancy, or HIV infection).”

“Persons who had an intervening condition, since their last dose of YF vaccine, that might have a substantial impact on their memory immune response (e.g., bone marrow transplantation).”

Based on the review of data and gaps that exist, the WG had the following recommendations for areas of further study:

- Assess neutralizing antibody levels ≥ 10 years post-initial vaccination in travelers
- Evaluate amnestic immune response to re-vaccination in persons without detectable antibodies
- Determine seroprotective level of antibodies using a PRNT by correlating it to LNI ≥ 0.7

- Establish role of vaccine-induced cell-mediated immunity in long-term protection against YF
- Assess neutralizing antibody levels among persons with suboptimal immune response to YF vaccine

Dr. Staples invited questions and discussion, as well as a vote on no longer recommending a booster dose for most travelers and a vote on whether to recommend or consider YF vaccine booster doses in certain persons. She noted that a VFC vote would not be necessary.

Discussion Points

Dr. Temte pointed out that this was an example of a category A or strong recommendation based on level 4 data and evidence, which is perfectly acceptable. The nice thing is that this lays out all of the evidence in a transparent manner for everyone to see.

Dr. Harrison inquired as to whether there was anything to be learned from the vaccine failures themselves in terms of whether there was something different about them immunologically or otherwise.

Dr. Staples responded that the vast majority of the vaccine failure data came from endemic areas, and some of the data are from the 1940s for military personnel. So, the non-endemic data are for people who were stationed in Africa during World War II. The data on those cases are old case reports. Very few recent vaccine failures have been documented. The most recent ones were documented in Brazil. Testing has been performed on those cases, but actually understanding what it was about those original persons is not clear. As a reminder, in clinical trials, when normal healthy adults or children are given the vaccine, in general there is a good seroconversion rate of greater than 99%. But, a small proportion of persons might not respond to the initial dose. There is nothing in common from the few vaccine failures noted that could denote who might be at risk.

Regarding the lumping together of all persons 10 or greater years post-vaccination, Dr. Duchin thought it was likely that immunity probably wanes with duration from vaccination. Those vaccinated at 11 years would be more likely to retain some endurance evidence of protection versus those vaccinated 30, 40, or 50 years ago. He wondered whether any of the data presented in slides 11 or 12 could be further analyzed to assess whether the seropositivity rates are lower the further out from vaccination. It appeared that some of the studies that assessed years post-vaccination, the greater number of years post-vaccination have slightly lower rates of seropositivity. He wondered whether someone who was vaccinated in their teens or early 20s who wanted to return to an endemic area at age 50, 60, or 70 should be subject to the same recommendations as someone who was vaccinated 11 years ago.

Dr. Staples replied that the WG discussed this. She tried to present the meta-analysis for 10 years or more versus 20 years or more, and there is at least a decrease though it is not significantly different between those two groups. The problem, going further out, is there are insufficient data. Minimal numbers of subjects have been followed throughout that period. There are current plans to conduct a study working with the military to assess people who may have been vaccinated at longer terms. But even then, the numbers would probably limit the WG from making firm conclusions. The WG discussed this option and did not feel that there were enough data to firmly establish a 20-year cutoff, and this might further complicate the already complicated proposed recommendations in terms of subcategories to consider a booster dose.

Dr. Plotkin (Vaccine Consultant) pointed out that revaccination of populations subject to endemic yellow fever is a major public health issue so he could understand why they would not recommend boosters. Here, the focus is essentially on US travelers who will want the maximum protection possible. Another point relates to the correlate of protection. He did not agree that there is no correlate of protection. Studies have been conducted in monkeys and other animals suggesting that a neutralizing titer of 1:40 is equivalent to protection, which means that titers lower than that may not protect. Assessing the geometric mean titers (GMTs) of a population is fine, but it is also important to assess those who fall below the GMT. There are studies showing falling titers with duration from the initial vaccination, which also has to be taken into account. In relation to Dr. Duchin's question, there is waning of antibody with time. Regardless of the study, there are data showing that antibody falls such that some percentage is below the likely protective titer long after vaccination. The issue with children is also important, because children do not respond to yellow fever vaccine as do older individuals. If he were writing the recommendation, he would recommend one booster dose for children at 10 years. He emphasized that he was not saying everyone needs to be vaccinated every 10 years, but he thinks there is a need in certain populations such as children for a booster dose. In Brazil where mass vaccination is used against yellow fever, 2% of individuals who have had yellow fever have been vaccinated. So, there are primary as well as secondary failures and these often occur in children. In relation to laboratory workers, the vaccine is expensive. However, if he were a laboratory worker, he would certainly want to at least have a high neutralizing titer. If not, he would definitely want to be boosted. There are data regarding the anamnestic responses to YF and, indeed, those who have low titers do respond. Though Dr. Plotkin noted that while it was difficult to speak to specifics without having the papers in front of him, he thought this recommendation went too far for travelers. He believes that travelers going to a YF endemic area should have at least one booster after 10 years.

Referring to slide 46 pertaining to booster doses, Dr. Orenstein (NVAC) thought the implication was that someone vaccinate at age less than one year, during pregnancy, or who had HIV infection, that individual would have to wait at least 10 years to have another dose. Slide 27 showed that only 39% of women in the first trimester seroconverted, and only 17% of HIV-infected children seroconverted at 10 months. It seemed to him that the 10-year timeframe is not appropriate, and that if someone is making another trip, they should be vaccinated regardless of the interval. The way it reads is that the interval should be 10 years before giving another dose.

Dr. Staples replied that the phrasing was discussed extensively in the WG regarding the same principle that, in fact, some of these population may have more rapid waning immunity and may be thought to require boosting sooner. It would be easy to boost them before their next travel, but what about an HIV-infected person who travels three or four times a year on a regular basis to an endemic area? Are they going to be boosted every time they travel? The WG did not feel that they had enough evidence to determine when they should be boosted, but they did favor including 10 years. However, she agreed that it would probably be wise to boost them before they travel again.

Dr. Bocchini added that while that was discussed in detail, there has never been a recommendation to administer this vaccine earlier due to a low seroconversion rate. Therefore, the WG tried to maintain the primary recommendation for booster doses in no less than 10 years. However, the WG also raised the issue that this needs to be studied and is one of the questions that is unanswered because there are no data.

Dr. Schmader (AGS) pointed out that another factor to consider with regard to adverse events is age, given that it is well known that older adults are at increased risk for SAEs from YF vaccines. He wondered whether the WG included this in their considerations.

Dr. Staples replied that the risk of SAEs with older age has been shown in a recently published study to be relative to the primary dose, because the low level of viral replication occurs after the primary dose. The study showed older adults' levels of viremia were higher in comparison to younger adults, and it took them longer to develop antibodies. In the current ACIP recommendation, age greater than 60 years is a precaution to the primary dose of vaccination. In terms of the booster dose, ideally there should be some sort of anamnestic response. In general, most people who receive a booster dose do not have actively replicating virus and the risk of SAEs due to YF vaccines is thought to be negligible. However, in general, a number of studies have shown that older persons are at risk for SAEs following any vaccination as they get older.

Dr. Temte said he was curious to know whether within the "Baby Boom" cohort more first-time vaccinees were being observed in individuals 60 years of age and older receiving YF vaccine due to retirement and international travel.

Dr. Schmader (AGS) responded that this is occurring. Many people are aging well and successfully into their 60s, 70s, and 80s who are traveling around the world. Therefore, this is a very important issue.

Dr. Fryhofer (AMA/ACP) inquired as to whether there is a list of countries that currently require the vaccination, which could help practitioners determine who would need a booster dose if they plan to enter a particular country.

Dr. Staples responded that this information is readily available on the CDC Traveler's Health website. People in the travel health group are devoted to contacting every country to check regulations every other year, and as regulations change. That is also published in the "Yellow Book," which is the travel health recommendation book. She recommends going on line, because if there are updates between when the book is published every two years, the information about which country requires proof of YF vaccination can be found on the CDC site. Additional language will be incorporated regarding which countries decide to administer booster doses or not. Some feedback has been received that some countries may continue to require booster doses, and that information will be available in real-time on the CDC website.

Dr. Fryhofer (AMA/ACP) said she understood to always check the website when she has a patient who will be traveling. She wondered whether any specific updating had been done yet to show which countries require just one dose, a dose every 10 years, et cetera based on the new international policy.

Dr. Staples indicated that the WGA met in May to propose that the change be made to the IHR. It will not go into effect until 2016. While WHO SAGE removed booster dose requirements, IHR are still in place, so countries can still allow a booster dose every 10 years. CDC will be incorporating this information as they learn which countries plan to still require it or not. This is a process that will have to be live, and on which CDC will have to continue to work.

Regarding the suggested booster dose for travelers who would be traveling for longer periods and in more highly endemic areas, Dr. Moore (AIM) said she would like to see more operational specificity. She agreed with the idea of leaving out particular locations, but if that were to be approved, she thinks more specific language will be essential for travel clinics to really understand what is meant by “highly endemic” in terms of rates. Rates and demographics may change as there are newly endemic areas.

Dr. Staples replied that a lot of these data already exist. The current ACIP recommendations have a section that notes when rates would be highest in Africa and South America, as well as the rates in those countries.

Dr. Englund (PIDS) expressed concern about including the age of less than one year. Incredible data are available to show that children less than two or three years of age do not respond well.

Dr. Karron wondered if any data were available on duration of protection after a single booster dose.

Dr. Staples responded that there are limited data pertaining to duration of protection in persons who receive vaccine booster doses, and most of the data are short-term to assess their response. There is little to draw from, given that the published literature includes less than 10 people.

Dr. Bennett said she continued to be concerned about the people who did not respond when they received their first dose. She requested further information about this, and why a booster would not be considered for them at potentially less than 10 years.

Dr. Bocchini replied that the WG discussed this, but felt that there were no data or studies to support moving forward. Some of the data are very limited in terms of number of people studied, so the WG felt that further study would be needed before decisions could be made about an earlier dose or second dose. There has been some discussion about having a two-dose series for younger children, rather than calling it a booster dose, but there are really no data upon which to base that recommendation.

Dr. Staples added that the Brazil Ministry of Health is proposing to conduct a study to assess a two-dose series, but the study has not yet been conducted.

Dr. Harrison said he was struggling because he was getting the sense that if the data were being reviewed routinely, ACIP would not be making this change, except for the change recommended by WHO.

Dr. Staples said the first recommendation published in 1969 used IHR requirements of 10 years to note that the booster doses should be given. ACIP has never recommended booster doses of YF vaccine. Beginning in April 2016, IHR will no longer require booster doses every 10 years, so ACIP will have to deal with some wording or recommendation. Many WG members did not feel that the data were strong enough to firmly state that booster doses need to be given every 10 years for everybody.

Dr. Kempe noted that the issue of whether patients are in an endemic area appeared to be crucial. She inquired as to where the studies were conducted that showed longer duration and how relevant they are to the US population.

Dr. Staples responded that the meta-analysis was done on the 13 observational studies to assess the 10-year cut, and it was also broken out to assess differences between endemic and non-endemic populations. Essentially, endemic and non-endemic were identical in terms of the proportion who were seropositive at 10 years.

Dr. Reingold said that as an “elderly” member of the ACIP who has now had his fifth YF vaccine, he supports the recommendations of the WG.

Dr. Temte asked Dr. Reingold whether he was involved in the SAGE discussions.

Dr. Reingold indicated that he was present for the SAGE discussions, but was not a member of SAGE at that time.

Dr. Staples added that she was on the SAGE committee that made these recommendations, and there were heated discussions pertaining to endemic versus non-endemic populations. There are many other considerations at the WHO level that are not taken into account at a US traveler level about the cost, coverage, and availability of the vaccine. It is important to point out that while SAGE used basically the same data, they had a slightly different policy question, which was: Is there evidence that a booster dose is required in immunocompetent individuals to ensure long-term protection? Based on the same data, SAGE reached the conclusion that there are not enough data to support requiring a booster dose.

Dr. Moore (AIM) said what struck her was the very definitive slide 10 that basically said that 18 vaccine failures occurred over 540 million doses and only 2 of those occurred beyond 10 years at 20 or more years after the last dose. On its face, that seems quite striking. But, the additional conversation suggests that perhaps that is an absence of all of the information rather than evidence of very strong protection.

Dr. Staples responded that the lack of vaccine failures was one of the considerations that SAGE took highly as one of the reasons to move forward with their recommendations. That needs to be caveated by pointing out that a lot of YF disease is occurring in areas where there may not be good surveillance to detect YF vaccine failure cases that occur. Another issue pertains to knowing vaccination status for some people. The other problem is that since 1965, WHO has recommended booster doses under IHR, so it is uncertain how many people have not received booster doses. This makes it difficult to put the 540 million doses into context in terms of how many are primary versus how many people have received routine booster doses. Few people have probably received booster doses in endemic areas in Africa, given that there have been large preventive campaigns. Booster doses are administered to the populations of South America and Brazil every 10 years. They are delivering 13 million doses of the 30 million that they have over a certain time period as booster doses. It depends on information, location, and the certainty behind it. Unfortunately, there is a lot of uncertainty.

With the thought of the vote looming over them, Dr. Jenkins questioned timing. There have been a number of responses that there are no data. She inquired as to whether there was anticipation that in another year, there would be better data.

Dr. Staples responded that there is unlikely to be sufficient data provided in the next few years. Small studies are planned that CDC is conducting to try to answer these questions, but nothing is going to be Earth-shattering or change. This vaccine has been available since the 1930s, and the data have not existed up to this point. There is not enough impetus to study this. Brazil is conducting the most research, and CDC has had conversations with the Brazil Ministry of Health about what they are planning to do. It is unclear whether the planned studies will provide enough certainty to make firmer recommendations. In general, the WG felt that this would not be the case.

Dr. Temte said he thought they had a situation in which the WG correctly identified the low quality evidence with which to work, and is to be commended for setting up a number of potential areas to be investigated as time goes on should someone be willing to fund such studies. Until then, he thought they were stuck with what is available in terms of making a recommendation. He inquired as to whether they needed to vote on two separate recommendations, or if it would be a package vote.

Dr. Staples responded that they were thinking that the vote should be a package deal.

Dr. Reingold made a motion to accept the recommendation as proposed.

Dr. Rubin said he remained unclear about the recommendation.

Dr. Staples indicated that this would be an option for consideration in terms of whether ACIP wanted to state that booster doses are recommended or considered for certain persons, and agreeing with the statement of removing parentheses or not.

Dr. Coyne-Beasley requested further clarification regarding whether they would not be voting for recommendation 1 of 4 if they were interested in recommendations 2 and 3. The first slide states “most” travelers, and it was not clear to her whether 2 of 4 was to explain which travelers would need it.

Dr. Staples responded that 1 of 4 would be the first statement written to indicate that booster doses are no longer recommended. That would be followed up with one of the statements on recommendation 2 of 4. That would be followed by recommendation 3 of 4 stating the specific persons for whom it is recommended.

Dr. Temte inquired as to whether there was a preference for “is recommended” versus “may be considered.”

Dr. Bocchini said the WG leaned more toward “is recommended” versus “may be considered” because it was a category A recommendation and provided additional guidance for travel medicine clinics.

It seemed to Dr. Bennett that the first statement and the statement on 3 or 4 may be somewhat contradictory in terms of the broadness of the first statement compared to specificity of the second. The first recommends for persons “whose immune response to their previous dose might have been compromised due to their existing condition at the time of vaccination” and the next states “≥10 years.”

Dr. Harriman agreed that the first statement was very broad, so perhaps it would be preferable to state, “these are the people for whom revaccination is recommended” rather than say “most people.”

Dr. Harrison wondered whether this could be a feedback providing session and that a more definitive recommendation could be brought back to the committee during the next ACIP meeting.

Dr. Bocchini replied that this would be up to ACIP. If they had additional feedback they would like to provide the WG and postpone the vote, that would be acceptable. But if there was general agreement that most travelers do not need a booster dose, these could all be linked together to solve the problem.

Dr. Temte indicated that one option would be to condense the recommendation and bring it back later in the day or during the next morning.

Dr. Staples shared the following example that was put forth for a more condensed version of the recommendation:

A single dose of YF vaccine may provide long-lasting protection and booster doses are not routinely recommended for all travelers or laboratory workers.

However, a YF vaccine booster dose is recommended for certain persons at risk for exposure to YF virus, particularly those with long stays or travel to highly endemic areas, and persons that were pregnant, age <1 year, or had HIV infection at the time of their initial vaccination.

Dr. Kempe indicated that one of her concerns was addressed with the condensed version; however, she requested further discussion regarding the age of <1 year for children.

Dr. Staples replied that in general, there are not enough data to make a more definitive statement. The data usually encompass a period up to 3 years of age. While this could be changed, there are sparse data upon which to base any other recommendation. Currently, age 6 to 8 months is a precaution to vaccination due to the potential for increased adverse events and potentially no seroconverting or having a good immune response.

Dr. Karron inquired as to whether there were any data in children under 5 years of age to show that both their initial response and duration of protection are comparable to older children and adults.

Dr. Staples indicated that there are no data on the duration of protection.

Given the dearth of data, Dr. Kempe thought they would have to rely on expert opinion in order to make a recommendation. She thought expert opinion would probably state that <1 year is not the right cutoff.

Referring to Dr. Englund’s comment and slide 29, “Seroconversion rates following primary dose of YF vaccine in children aged 6 through 36 months,” Dr. Pickering said he assumed that YF was given with measles vaccine which was a precedent. The seroconversion rates for YF seemed higher than what would be expected for measles vaccine at 6 through 9 months of age.

Indeed, when the measles vaccine is given at less than a year, it is not counted toward the two-dose measles vaccine schedule because of the potential lack of response. He wondered whether there was any correlation that could be made, whether measles vaccine titers are also available for that group to make some comparisons, and whether the measles vaccine was a consideration in using 6 months, 9 months, or 1 year.

Dr. Staples indicated that while she did not have the data in front of her to know what the measles responses rates were, she can look at those individual studies.

Ms. Pellegrini noted that one of the other issues raised was the length of duration not only for children receiving the vaccine, but also for people who receive it later in life. For example, someone who receives the vaccine in his or her 20s and then travels at age 70. She recognized the serious lack of data, but wondered whether they wanted to include anything about extreme amounts of time since initial vaccines.

Dr. Temte pointed out that one of the realities in clinical practice is that patients do not ask him for this vaccine because of their perceived risk. They ask for the vaccine because they are going to be traveling to a country that requires it. Once that requirement goes away, he believes they will observe a great decline in anyone requesting revaccination. As noted, there is a severe dearth of data, and the evidence is basically in the realm of expert opinion for the entire recommendation. With absolutely no evidence, he wondered how much more work would need to be done to get the recommendation to a level at which ACIP would be comfortable.

Acknowledging the complete lack of evidence, Dr. Karron suggested that the age be <5 years rather than <1 year.

Dr. Netoskie (AHIP) asked whether there was any evidence or information that would be helpful regarding the minimal interval from the first vaccine.

Dr. Staples replied that the only data available about the immune response regarded giving the vaccine sooner. The scenario presented in the very small study that was conducted had to do with administering vaccine to someone who loses their card in terms of what time of response is observed and whether any harm is being done. That study had less than 20 subjects total. All of those who received the vaccine at an interval less than 10 years already had antibodies. When they were given the dose and were all boosted, their antibody titers did not go as high as a primary vaccine recipient. Their kinetics were such that they returned to the state of where they were prior to receiving the vaccine in a short time period, versus a sharp immune peak and much more of a decay rate with the primary dose.

Dr. Neuzil (IDSA) indicated that this was discussed at SAGE, and there is at least one good study that evaluates MMR and YF vaccine. MMR does affect the response to YF vaccine if given concomitantly and not 30 days apart. That may be worth discussing in terms of age selection, and whether this was influenced in any way by the concomitant administration with a measles-containing vaccine.

Dr. Staples replied that the WG is aware of the concomitant administration and was not specifically dealing with interference from live viral vaccine administered at the same visit. In that study, the seroconversion rates with the separation of vaccine were lower than what would be anticipated. A study is planned in Argentina to reproduce those data to try to understand whether there is truly interference occurring when MMR is added in combination with YF

vaccine. Previous studies have shown that when YF and measles vaccines are given together they do not cause a problem in terms of immune response.

Dr. Kempe said she felt that the age cutoff for children remained unclear, and she wondered whether they should seek further input from other groups such as the Red Book committee and Pediatric Infectious Diseases Society (PIDS) rather than making a hasty decision.

Dr. Temte requested Dr. Bocchini's thought on that. Regardless, Dr. Temte felt that an age cutoff would be fairly arbitrary. Given that a recommendation will be made based on expert opinion, having a full level of expert opinion may be beneficial.

Dr. Bocchini indicated that the WG had representation from COID. However, he thought it would be very reasonable to seek additional feedback from representative organizations about an age cutoff and provide them with the data that the WG has before making a final decision.

Dr. Temte asked whether the decision was to table the vote until the next ACIP meeting, understanding that three of the ACIP members are rotating off. On the plus side, two of the new members were present during this meeting and heard the GRADE discussion.

Dr. Bocchini suggested that another possibility if everything else in the recommendation was acceptable would be to accept these recommendations except for the age cutoff for children, and have that come back to the committee after receipt of input from other organizations.

Dr. Bennett said her concern about that was that there were two sets of wording that were quite different. She thought the committee would probably want an opportunity to weigh in on the wording.

Dr. Harrison commented that it is difficult to bring highly complex issues to the full committee for the first time and expect a vote. He thought in the future, highly complex issues should be vetted for feedback.

Dr. Jenkins inquired as to what the issue was regarding seniors who travel, and whether there was enough evidence to be concerned about that at this point.

Dr. Staples replied that the concern with older individuals is the risk of adverse events that occur with the primary dose of vaccine. Given the considerations about booster doses, that should not apply.

Dr. Temte asked whether there was consensus to ask for thoughtful revision taking into account the comments during this discussion period, with the recommendation to be presented for a vote during the October 2014 meeting.

Dr. Bocchini said the WG would appreciate very specific comments related to options presented for category A versus category B and other options provided for ACIP's consideration.

Dr. Temte said he did not believe there would be a need for representation of the GRADE evaluation, and indicated that efforts will be made to directly inform the third new committee member. He thanked Dr. Staples for her patience with the deliberations, emphasizing that this is what ACIP is meant to be doing in terms of making complex decisions.

Influenza

Introduction

Ruth Karron, MD Chair, Influenza Work Group

Dr. Karron reminded everyone that the Influenza WG's primary activity has been to review the relative efficacy and safety of live attenuated influenza vaccine (LAIV) and inactivated influenza vaccine (IIV) for use in children. There has been additional consideration of the language for use of LAIV and IIV when both are available. The WG has also reviewed data on children with high-risk conditions, including children with a history of asthma or wheezing and other high-risk conditions. In addition, the WG has discussed the dose algorithm for children aged 6 months through 8 years, particularly for this year when there is not a strain change. The WG has also finalized the draft 2014-2015 ACIP Influenza Statement.

Novel Influenza Vaccines Work Group

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

Dr. Campos-Outcalt reported that the Novel Influenza Vaccines WG had been meeting regularly for a couple of months, and that the limited charge of this WG is to develop recommendations for use of influenza A (H5N1) vaccine during an inter-pandemic period. There are currently four H5N1 vaccines in the national stockpile; however, only two of those have been licensed for general use and only one will be available for inter-pandemic use (e.g., the GSK vaccine):

Virus	Clade	FDA Licensure
A/Vietnam/1203/2004	1	Yes (Sanofi)
A/Indonesia/5/2005	2.1.3.2	Yes (GSK)
A/bar-headed goose/Qinghai/1A/2005	2.2	No
A/Anhui/1/2005	2.3.4	No

Use of vaccine in the national stockpile is limited to a pandemic, and inter-pandemic use is not possible. The GSK vaccine, Q-Pan, will be produced in a small volume of approximately 100,000 doses and will be stored in part at the National Institutes of Health (NIH) and in part at the manufacturer's facility. These doses will be available to high-risk investigators and other high-risk groups. The WG will focus on making recommendations for this vaccine's use in a very limited group of people, and will be working to identify the target audience. The WG plans to conduct a GRADE analysis on the evidence for use of the Q-Pan vaccine, and to identify high-risk groups during inter-pandemic period. The WG planned to present recommendations to the full ACIP committee in October 2015. However, given the yellow fever discussion, it is more likely that language will be presented for discussion in October 2015 and a vote will be planned for February 2015.

Influenza Vaccine Safety Update

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

During this session, Dr. Cano presented the end-of-season influenza vaccine safety update for the 2013-2014 season. As a reminder, the strengths of VAERS are 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. Another limitation of VAERS is illustrated by the following graphic:

Limitations of VAERS data

	Adverse event	No adverse event
Individual vaccinated	Vaccinated with adverse event and reported to VAERS	Vaccinated no adverse event
Individual not vaccinated	Not vaccinated with adverse event	Not vaccinated no adverse event

VAERS only contains partial data in pink cell (incomplete population data)

- Not able to calculate rates of occurrence of adverse events
- Not able to determine increased risk
- Not able to calculate vaccination coverage

Of the total population, only individuals who were vaccinated and had adverse events that were reported to VAERS are included and are shown in the pink cell. VAERS data do not include those in the white cells, which include those who were vaccinated but who had no adverse event or who had not reported to VAERS. Given this limitation, VAERS is not able to calculate rates of occurrence of adverse events, determine increased risk, or calculate vaccination coverage.

The following table summarizes the licensed influenza vaccines that became available during the current season. There was a complete switch to quadrivalent LAIV this season, so comparison between trivalent and quadrivalent forms will be between seasons. For IIV, both trivalent and quadrivalent vaccines are available and comparison can also be made within the current season. The second column shows the abbreviations that Dr. Cano referred to during this presentation. The last column shows the recommended age groups for the vaccines listed:

Vaccine	Abbreviation	Brand name (Manufacturer)	Year licensed	Recommended age group
Quadrivalent inactivated influenza vaccine	IIV4	Fluarix [®] Quadrivalent (GlaxoSmithKline)	2012	≥3 yrs
		Fluzone [®] Quadrivalent (Sanofi Pasteur)	2012	≥6 mos
		Flulaval [®] Quadrivalent (GlaxoSmithKline)	2013	≥3 yrs
Cell culture-based trivalent inactivated influenza vaccine	ccIIV3	Flucelvax [®] (Novartis)	2012	≥18 yrs
Recombinant trivalent inactivated influenza vaccine	RIV3	FluBlok [®] (Protein Sciences)	2013	18-49 yrs
Quadrivalent live attenuated influenza vaccine	LAIV4	FluMist [®] Quadrivalent (MedImmune)	2013	2-49 yrs

VAERS surveillance includes US reports after IIV and LAIV received by VAERS for those vaccinated between 7/1/2013 and 5/2/2014. Signs and symptoms or diagnoses are coded into the VAERS database using the international Medical Dictionary for Regulatory Activities (MedDRA) terms. MedDRA terms are not mutually exclusive, and a report may have several different MedDRA. Medical records were reviewed for all serious reports after the newly licensed influenza vaccines listed in the above table and Fluzone Intradermal[®]. Pregnancy reports were also reviewed for spontaneous abortion, stillbirths, congenital anomalies, serious reports; as well as all reports of anaphylaxis with history of egg allergy. The Food and Drug Administration (FDA) conducted empirical Bayesian data mining to detect disproportional reporting in the VAERS database.

Between 7/1/2013 and 5/2/2014, there were 493 US reports to VAERS following IIV4 and approximately 7000 reports for IIV3. Most of the reports were classified as non-serious. It is important to look at the percentages rather than the actual numbers when comparing the results. Guillain-Barré Syndrome (GBS) was comparable for IIV3 and IIV4, and anaphylaxis was higher for IIV4 compared to IIV3 for the previous and current seasons. However, there was no disproportional reporting in data mining for GBS or anaphylaxis for the last season and the current season.

In a comparison for LAIV4 from this season to LAIV3 from last season, there were 486 total reports for LAIV3 compared to 657 for LAIV4. The percentages of serious reports and anaphylaxis were higher for LAIV3. GBS was comparable for both LAIV3 and LAIV4. There was no disproportionate reporting in data mining for GBS and anaphylaxis.

To summarize results for Fluzone Intradermal[®] (IIV3-ID) reports in VAERS from 7/1/2013 through 5/2/2014, there were 243 reports with 3% classified as serious. Of these, 20% were in males. The median age was 44 years, with a median onset interval of one day. The top five MedDRA terms included injection site erythema 62 (26), injection site swelling 55 (23), injection site pain 40 (16), erythema 39 (16), and injection site pruritus 34 (14). There were no new data mining findings for IIV3-ID this season.

In terms of the results for Flucelvax[®] reports in VAERS from 7/1/2013 through 5/2/2014, there were a total of 167 reports of which 3% were serious and 46% were in males. The median age was 36 years, with a median onset interval on the day of vaccination. The most common MedDRA term was drug administered to patient of inappropriate age 49 (31). The recommended age is 18 or older. However, 37% of the reports were in those less than 18 years of age. Other common adverse events included pain in extremity 18 (11), injection site pain 13 (8), rash 13 (8), and nausea 11 (7).

There were 20 FluBlok[®] reports in VAERS between 7/1/2013 and 5/2/2014, all of which were in females. None of the reports was considered to be serious. The most common MedDRA terms included pruritus 6 (35), dyspnoea 3 (18), headache 3 (18), erythema 3 (18), and rash 3 (18). The median age was 47, with a median onset interval on the day of injection.

There were 61 pregnancy reports in VAERS following IIV3 or IIV4 vaccination for the time period 7/1/2013 through 5/2/2014. The median age was 30 years, with a median gestational age at vaccination of 18 weeks. The pregnancy-specific outcomes included spontaneous abortions (5), stillbirth (1), fetal death, pre-term delivery (1), cleft lip and palate (1), Trisomy 18 (1), and increased fetal movement (1). Of the reports, 31 (~51%) were non-specific and 19 had no adverse events. There were 22 reports without any adverse events after LAIV4 and 1 serious report, which was a case of pulmonary hypertension in an infant whose mother received LAIV4.

There was one anaphylaxis report in VAERS following influenza vaccination in a person with a history of egg allergy. A 4-year-old male developed diffuse hives, watery eyes, sneezing, and vomiting within 15 minutes after IIV3. He had allergy testing after the reaction, which showed a positive skin prick test for commercial egg extract and gelatin and a positive serum test for egg white and bovine gelatin. His past medical history included perioral rash after ingestion of meringue icing, which has egg whites; and increased salivation, abdominal pain, and weakness after ingestion of gummy candies and marshmallows, which have gelatin. This case was reported in the literature and the authors concluded that the reaction was most likely related to gelatin rather than egg protein in the vaccine.

With regard to the findings from Vaccine Safety Datalink (VSD) surveillance for 2013-2014 influenza season, this is the sixth season that real-time Rapid Cycle Analyses (RCA) have been conducted within the VSD. The RCA for specific age groups is performed for the pre-specified outcomes using International Classification of Diseases (ICD)-9 codes as shown on the following table:

Pre specified outcomes*	IIV	LAIV
Anaphylaxis	≥6 months	2-49 years
Acute disseminated encephalomyelitis	≥6 months	2-49 years
Encephalitis	≥6 months	2-49 years
Transverse myelitis	≥6 months	2-49 years
Guillain-Barré syndrome	≥6 months	2-49 years
Bell's palsy	≥6 months [†]	2-49 years

With the exception of anaphylaxis, the outcomes are neurologic adverse events. For the 2013-2014 influenza vaccine, RCA used automated data from approximately 9.3 million patient records. As of April 11, 2014, approximately 3,811,478 doses of IIV3 (dose 1) and 218,875 doses of LAIV4 (dose 1) were administered. This total does not include Fluzone[®] high dose and interdermal, but does include cell culture-based and recombinant IIV3. There has been very limited uptake of IIV4 and cell culture-based and recombinant IIV3. There have been no signals in the VSD RCAs during the 2013-2014 influenza season for any pre-specified outcomes.

In summary, no new safety concerns were detected for IIV or LAIV during the 2013-2014 influenza season. Surveillance for the 2014-2015 influenza season will include enhanced safety monitoring for the following:

- Quadrivalent IIV and LAIV vaccines
- Cell culture-based IIV
- Recombinant IIV
- Pregnancy reports
- Reports of anaphylaxis in persons with history of egg allergy after IIV and LAIV
- Reports with history of asthma/wheezing after LAIV4

Assessing Fever Rates in Children Following LAIV and IIV

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Dr. Stockwell reported on a study conducted to assess fever rates in children ages 24 through 59 months of age after receiving LAIV or IIV during the 2013-2014 influenza season. The study was conducted by Columbia University's Clinical Immunization Safety Assessment Center (CISA) investigators through a contract from CDC.

LAIV is potentially more effective than IIV in children. Therefore, characterizing fever rates after LAIV and IIV with or without simultaneous vaccination may help inform national policies for pediatric influenza vaccination. That includes evaluation of quadrivalent influenza vaccines as they are introduced. One previous study in children suggested higher fever rates in the day 0-10 after LAIV versus IIV, particularly on day 2 when fever rates were 5.4% versus 2.0% [Belshe *et al* N Engl J Med. 2007]. Therefore, the risk interval for fever LAIV was thought to be from the day 0-2 period. In contrast, the at risk interval for IIV in a previous study was shown to be vaccination day or the day after vaccination, or the day 0-1 period [Rowhani-Rahbar *et al* Vaccine. 2012].

Text messaging can be used for public health surveillance and prevention efforts, such as reminder recalls for vaccination. Dr. Stockwell and colleagues successfully used text messaging to assess rates of fever after simultaneous vaccination with IIV3 and 13-valent pneumococcal conjugate vaccine (PCV-13) [Stockwell, Broder *et al* JAMA Pediatr. 2014] and decided to employ this method in this study as well. The primary objective of this study was to assess the rates of fever in children 24 through 59 months of age receiving LAIV compared to those receiving IIV. The primary hypothesis was that fever rates in risk window day 0-2 post-vaccination would be higher in those receiving LAIV versus IIV, with the day 0-2 being defined as the vaccination day and the first 2 days post-vaccination. That risk window was selected based on the two previous studies mentioned. The secondary hypothesis was that fever rates

in the non-risk window of days 3-10 post-vaccination would not be significantly different in those receiving LAIV versus IIV.

There were a number of secondary objectives in the Fever LAIV/IIV Study, which were to:

- Assess whether fever rates in the day 0-2 post-vaccination are higher in those children receiving IIV4 versus IIV3
- Characterize the clinical importance of the reported fevers with respect to height of the fever, occurrences of medically attended fever, and associated medically attended health outcomes
- Explore whether fever rates after vaccination are different in children who receive LAIV simultaneously with other childhood vaccines versus LAIV alone

The Fever LAIV/IIV Study was an observational prospective cohort study that was conducted between September 13, 2013 and April 13, 2014. Patients were recruited from Columbia University Medical Center (CUMC) / New York-Presbyterian Hospital clinical sites at the time of vaccination. Vaccination decisions were made solely by the healthcare provider caring for particular patients. The investigators did not randomize patients to which vaccine to receive, and receipt of other vaccines was not an exclusion criterion. The study was approved by the CUMC Institutional Review Board (IRB), and the CDC relied on the determination by the CUMC IRB. Families who were recruited were consented and completed an intake form, enrolled via text message, and were trained in the use of temporal artery scanner thermometer.

The eligibility and exclusion criteria for participants to be enrolled in the Fever LAIV/IIV Study included the following:

Eligibility Criteria

- Age 24 through 59 months
- Had a visit at a study site anytime during the study period
- Received a first dose of LAIV or IIV in the season
- Parent had a cell phone with text messaging capabilities
- Parent spoke English or Spanish, which are the primary languages at the clinical sites

Exclusion Criteria

- Had a chronic medical condition considered a contraindication or precaution to LAIV (except for asthma/wheezing history)
- Were currently on oral or other systemic steroids or used in past month
- Were currently on inhaled steroids or used in the past 2 weeks
- Had the presence of fever $\geq 100.4^{\circ}\text{F}$ at time of vaccination
- Had administration of any antipyretic in the 6-hour period prior to vaccination
- Stated intent, at time of vaccination, to use prophylactic antipyretics before the development of a fever
- Parent spoke only a language other than English or Spanish
- Parent was unable to read text messages
- The child was receiving the second dose of influenza vaccine in the current season

Parents were sent a text message on Day 0, the day of enrollment, and subsequently for the next 10 days at 8:00 pm. The information collected included the following:

- Temperature range, actual temperature, time taken
- Antipyretic medicine given, name and time
- Care sought (i.e., clinic and emergency department)

The following is the first text message that was sent:

FeverFLU. Reply 1-5. Child's highest temperature since last text?

1 = 95.0 to 100.3

2 = 100.4 to 102.2

3 = 102.3 to 104.0

4 = above 104

5 = Did not take temp today

Text responses were reviewed each morning to identify non-responders, initiate phone contact, troubleshoot problems, and collect unreported temperatures. Families also used a paper diary and were asked to send these back at the end of 10 days. A chart abstraction was conducted for medically attended visits during the Day 0-10 period post-vaccination for any ambulatory care, emergency department (ED), or hospital visits to the NYP/CUMC system. The following were abstracted:

- Chief complaint, final diagnosis
- Review of symptoms
- Documented temperatures
- Verify other vaccines (single and combination) given at time of enrollment using New York-Presbyterian Hospital's electronic health record, which includes an immunization registry (EzVac)

In terms of analyses and case definitions, Day 0 was defined as the time period immediately after vaccination to the response to the text sent at 8:00 pm on vaccination day. Days 1-10 were defined as being from response to the text sent at 8:00 pm the night before to the response to the text sent that night at 8:00 pm. Fever was defined as any temperature of $\geq 100.4^{\circ}\text{F}$ and moderate temperature of $\geq 102.2^{\circ}\text{F}$. The two time periods of Days 0-2 and Days 3-10 were assessed.

There were 991 patients approached of whom 642 patients were eligible, 102 patients refused, 5 patients had inadequate information, and 535 (83.1%) patients were enrolled and analyzed. Of the 535 patients enrolled, 309 (57.8%) received IIV and 226 (42.2%) received LAIV4. Of those who received IIV, 211 (68.3%) received IIV3 and 98 (31.7%) received IIV4. All LAIV was LAIV4. Of the children who received IIV3, almost two-thirds were 2 to 3 years old. Of those who received IIV4, about 60% were 4 to 5 years old. The quadrivalent product was not available for children under 3 years of age at the study sites. IIV4 was evenly divided between the three age groups.

Information received came primarily from the text messages. There was a good response rate, particularly during the Day 0-2 period. In terms of assessing the fever rates during the risk window of Days 0-2 for temperatures of $\geq 100.4^{\circ}\text{F}$, of the children who received IIV, 5.8% had a fever at 0-2 days post-vaccination compared to 3.8% of those receiving LAIV. That is a non-significant difference. Breaking down those receiving IIV3 versus IIV4, 5.2% of those receiving IIV3 and 7.1% receiving IIV4 had a fever. Again, that was a non-significant difference. Of note, 4 of the 22 had a temperature of $T \geq 102.2^{\circ}\text{F}$ and none of those were in the LAIV group. Looking at the rates during the non-risk window of Days 3-10 and a temperature of $\geq 100.4^{\circ}\text{F}$, 9.9% of children who received IIV compared to 10.4% of children receiving LAIV had a fever and that was non-significant. Further breaking down those receiving IIV3, 11.8% had a fever compared to 6.3% receiving IIV4 and 10.3% receiving LAIV4 and that was non-significant. Of note, only 10 of 33 fevers included temperatures $\geq 102.2^{\circ}\text{F}$ and 6 of those were in the LAIV4 group. With regard to co-administered vaccines in all of the groups, the majority of children received influenza vaccine alone. Of those who received co-administered vaccines, 82.6% received DTaP-IPV and/or Hep A.

A regression model was conducted assessing the risk window of Day 0-2 with a temperature of $\geq 100.4^{\circ}\text{F}$. The log binomial regression was adjusted first *a priori* for Hepatitis A vaccine and Kinrix® (DTaP-IPV) since those are the most commonly co-administered inactivated vaccines. Concurrent PCV13 vaccination was also adjusted for, given the historical association with fever following PCV13 and influenza vaccine co-administration. Also adjusted for were age group (12-23, 24-35, 36-48 months) and previous receipt of influenza vaccination. Other variables were considered but were not included based on a non-significant p-value >0.1 for the bivariate association with a temperature $\geq 100.4^{\circ}\text{F}$. These included ethnicity, gender, enrollment month, and high risk for influenza. Looking at the risk window of Day 0-2 with a temperature of $\geq 100.4^{\circ}\text{F}$, the adjusted relative risk of LAIV versus IIV was 0.60 and that was non-significant.

Sensitivity analyses were also conducted for the risk window of Day 0-2 with a temperature of $\geq 100.4^{\circ}\text{F}$, assessing just those children who received influenza vaccine alone. Those children who received any antipyretic medicine within 8 hours before the temperature that was taken for the report were removed. Only the data reported via text message were assessed, and the analyses were limited to children ≥ 3 year of age. The adjusted relative risk remained the same in all of these analyses at 0.60.

In the medical record review assessing all participants (n=535) from day 0-10, no febrile seizures or hospitalizations were documented. There were 9 ED visits and 17 ambulatory care visits. Assessing participants with fever in the Day 0-2 (n=22), 1 child who received IIV4 had an ED ambulatory care visit and 1 child who received IIV3 had an ED visit.

In summary, there was no significant difference in fever rates of $\geq 100.4^{\circ}\text{F}$ on vaccination day or in first 2 days post-vaccination with LAIV4 (3.8%) versus IIV3 or IIV4 (5.8%). That non-significance continued even after adjusting in the regression models. There were few fevers $\geq 102.2^{\circ}\text{F}$ in any study group, with 4 being in the IIV group and none in the LAIV4 group. There were also no significant differences in fever rates in the 3-10 days post-vaccination after LAIV4 versus IIV, and there were no hospitalizations or febrile seizures in the 0-10 days post-vaccination with any influenza vaccine. Data analyses are ongoing.

Discussion Points

Dr. Harrison requested that Dr. Stockwell comment on the statistical power of the study to find differences.

Dr. Stockwell replied that the study was powered to find about a two-fold difference between the studies. They would not have been powered to find a 2% difference considering that the rates are so small.

Dr. Kempe noted that the analyses were broken down by high fever for the first two days, but not for Days 3-10 for which it appeared to be a third versus a half. The issue regards whether there is enough statistical power.

Dr. Stockwell responded that LAIV groups would have been 6 out of 14 versus 4 out of 19 for Days 3-10. In terms of fever $\geq 102.2^{\circ}\text{F}$, there were not enough cells to assess this. Therefore, the raw crude data were reported for fevers of $\geq 102.2^{\circ}\text{F}$ rather than showing that statistical change for the moderate.

Dr. Rubin requested clarification from Dr. Cano regarding the cell culture-based vaccine in terms of whether those under 18 years of age were reported because they were given vaccine at an incorrect age rather than because they had an excess of adverse events.

Dr. Cano responded that they did have some adverse events. When the demographics were reviewed on the VAERS form, they were less than 18 years of age.

Dr. Moro added that those who received Flucelvax® but should not have were 11 to 18 years of age. The majority of them did not have an adverse event. Those who did have an adverse event mainly experienced local injection sites reactions. The reason for reporting was because the vaccine was administered at an incorrect age.

LAIV and IIV Vaccine Safety

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Dr. Grohskopf reported on LAIV and IIV vaccine safety in children with high-risk conditions that confer higher risk of poor outcomes or severe disease from influenza. As a reminder, there were a number of presentations during the February 2014 ACIP meeting related to GRADE analyses of LAIV and IIV for healthy children (e.g., children who do not have chronic medical conditions that confer a higher risk for severe outcomes due to influenza infection). Data were presented on several age groups, though the focus was primarily on children 2 through 8 years of age. The rationale for the selected age group was that LAIV is not licensed for children under 2 years of age, and 8 years is the upper limit of the age range for consideration of whether 1 versus 2 doses are needed. That was selected for programmatic consistency and simplicity of the recommendations to be formulated. During the discussion period after the GRADE assessment that was presented for healthy children during the February 2014 ACIP meeting, questions were raised regarding the use of LAIV for children with chronic medical conditions.

When the WG initially planned its work, they decided to tackle the literature on healthy children first. However, since the questions were raised, a review was done for high-risk children.

In terms of background, ACIP currently does not recommend the use of LAIV for children with asthma or other chronic medical conditions conferring high-risk of complications or severe illness due to influenza. The 2013-2014 package insert for LAIV, FluMist[®] quadrivalent licensed a couple of years ago and on the market for the first time during the 2013-2014 season, includes the following bullets in the Warnings and Precautions section that state the following:

- ❑ “Children younger than 5 years of age with recurrent wheezing and persons of any age with asthma may be at increased risk of wheezing following administration of FluMist[®] Quadrivalent. FluMist[®] Quadrivalent has not been studied in persons with severe asthma or active wheezing.”
- ❑ “The safety of FluMist[®] Quadrivalent in individuals with underlying medical conditions that may predispose them to complications following wild-type influenza infection has not been established”

In a review of comparative studies, similar to the review conducted for healthy children, the WG sought to evaluate studies that compared the two vaccines—not one or the other versus placebo, but studies that had an LAIV arm and an IIV arm. They may or may not have had placebo in addition. The following were considered for the comparative studies of LAIV and IIV:

Author	Season	Population	Design	Outcomes
Ashkenazi et al. PIDJ, 2006	2002-2003	6-71 months 2 RTIs in previous 12 mos.	Open-label, randomized	Medically documented wheezing Any Wheezing
Fleming et al. PIDJ, 2006	2002-2003	6-17 years clinical diagnosis of asthma plus ≥1 prescription for asthma medication within the past 12 months	Open-label, randomized	Medically attended wheezing Asthma exacerbation Asthma symptoms
Belshe et al. NEJM, 2007	2004-2005	6-59 months included children with mild or moderate asthma or wheezing history more than 42 days before enrollment.	Double-blind, placebo controlled	Medically significant Wheezing Any wheeze Hospitalization

The Ashkenazi and Belshe studies did not have an inclusion criterion that the child had to have asthma or wheezing, but there were children who had an asthma or wheezing history or asthma diagnosis in both of those studies. The Fleming study was specifically of children with an asthma diagnosis that included older children 6 through 17 years of age. Given the focus on the younger age group, data were not presented for the Fleming trial. However, the WG will likely return to this later.

The Ashkenazi and Belshe studies compared LAIV and IIV. Ashkenazi was an open label study and Belshe was a placebo-controlled blinded study that had placebo for LAIV and IIV. Belshe was a somewhat larger study than Ashkenazi. The data for these two studies subsetted out for the children who were between 24 and 59 months of age, and who had a history of asthma and/or wheezing. This was nicely broken down in a paper by Ambrose et al in 2012, which is where the data presented during this session was obtained.

The primary efficacy endpoint for the GRADE evaluation was laboratory-confirmed influenza, which was a critical outcome. This was not downgraded for any of the parameters (e.g., risk of bias, inconsistency, indirectness, or imprecision). There was a relative risk of 0.53, which was significant with a 95% confidence interval of 0.38-0.73, and an estimated risk difference of 47 fewer cases/1000 with LAIV. The 0.53 risk ratio corresponds nicely with the one obtained last February when these data were presented for the entire group of children, not just those with asthma and wheezing, which was 0.47. The overall evidence quality was high.

The definitions for the wheezing outcomes differed somewhat between Belshe and Ashkenazi, and for reasons of being consistent, Belshe was used for the evaluation of wheezing outcomes. For the Belshe paper, medically significant and medically attended wheezing outcomes were both reported and both were similar. For protocol-defined "medically significant wheezing" in children aged 24 through 59 months with a follow-up period of 42 days (6 weeks after vaccination), the WG downgraded on the basis of imprecision on the basis of the confidence interval including 1 and also being fairly wide. The risk ratio was 0.69, with a confidence interval that was not significant at the 95% level. The overall evidence quality assigned was 2, or moderate, due to downgrading for imprecision.

The protocol-defined "medically significant wheezing" in children aged 24 through 59 months with a follow-up period of 42 days, children with asthma and/or wheezing were included but there was a further subdivision of children who had no wheezing in the last 12 months. Of course, the N was smaller so the confidence interval was wider and again included 1. Therefore, the WG downgraded this for imprecision and assigned an overall evidence quality of 2, or moderate. For the children who wheezed in the last 12 months, there was an insignificant risk ratio and confidence interval. The WG downgraded for imprecision and assigned this an overall evidence quality 2, or moderate. For children who had an asthma diagnosis, the subset was only 120 to 130 children per arm. This is the one instance where the point estimate is on the other side of 1, but it is still fairly wide at 0.29-1.88. Because of that downgrade, this was estimated as 2, or moderate quality evidence.

An effort also was made to find studies involving head-to-head comparisons of the two vaccines for children with other chronic medical conditions, but few were found. However, this is preliminary and the WG will continue to search for these studies. The following four studies have been located thus far:

HR Condition	Study	Seasons	Subjects	N	Outcomes
Cancer	Carr 2011	2008-09 1 season	Children 2–21Y	28 LAIV / 27 TIV	SAFETY (SAEs): (a) 11Y old LAIV required hospitalization for fever, cough, rhinorrhea, myalgia, mild hypertension and positive Flu A test (b) 2Y old TIV developed afebrile seizure-like activity within 30 minute of TIV injection.
Cystic fibrosis	Gruber 1994	1989-1992 3 seasons	Children 6M–23Y	44 LAIV / 42 TIV subject years	SAFETY: fever = no difference EFFICACY: LCI = 6 LAIV and 3 TIV
	King 1987	1984-85 1 season	Children & young adults	27 LAIV, then MIV 1 week later	SAFETY: Reactions such as fever at Day 3 and Day 6 post-vaccination. Results not analyzed statistically.
HIV	Levin 2008	2004-05 1 season	Children 5–17Y	122 LAIV / 121 TIV	SAFETY: SAEs based on dairy cards, phone calls & scheduled study visits on different days for each arm. “Pulmonary signs” included asthma & wheezing ≤28 days = no difference between arms.

These are studies with small numbers of subjects, and at this point, the WG did not feel that there was sufficient evidence to move forward on children with high-risk medical conditions or asthma.

Dr. Grohskopf pointed out that there were some limitations to the evidence profiles she presented. The studies were not powered to detect differences in wheezing/asthma outcomes among the subgroup of children with a history of these conditions, and the confidence intervals were wide. The data do not clearly indicate the degree of asthma or wheezing severity for which LAIV benefits would outweigh risks. This becomes important when trying to formulate a recommendation, because it is important to clearly indicate the context in which the vaccine should be used. The data presented had a relatively long follow-up time of 42 days, and there are no data on earlier outcomes. At this point, there are few comparative data for other chronic medical conditions. No significant language changes were proposed for the upcoming season for high-risk medical conditions.

In terms of the evidence profile for healthy children 2 through 8 years of age, the outcomes considered are shown in the following table:

Outcomes			
Benefits	Value	Include?	Data?
Lab-confirmed influenza	Critical	Yes	Yes
Influenza-associated mortality	Critical	Yes	No
Influenza-associated hospitalization	Critical	Yes	Yes
MAARI	Critical	Yes	Yes
ILI	Important	Yes	Yes
Influenza-associated acute otitis media	Important	Yes	Yes
Harms	Value	Include?	Data?
Medically-attended wheezing	Critical	Yes	Yes
Medically-significant wheezing	Critical	Yes	Yes
Immediate hypersensitivity/anaphylaxis	Critical	Yes	No
Febrile seizure ²	Critical	Yes	No
Guillain-Barre syndrome	Critical	Yes	No
Respiratory symptoms	Important	No	--
Other neurologic outcomes	Important	No	--
Fever	Important	Yes	Yes
Any related SAE ³	--	Yes	Yes

Due to an inability to find any evidence from the studies on influenza-associated mortality, this was not included in the results. Though considered to be critical, it was not possible to assess immediate hypersensitivity/anaphylaxis, febrile seizure, and GBS given that these are sufficiently rare outcomes. Though considered to be important, an evidence profile was not included for respiratory symptoms or other neurologic outcomes because these were not defined specifically enough to make them feasible to assess. Because there were a couple of serious outcomes that were rated critical that could not be assessed, any related SAE was included. However, a value was not included for this because of the disparate types of events that occurred. Given that the evidence profiles for healthy children were presented during the February 2014 meeting, Dr. Grohskopf reviewed only those that had a significant result or were critical safety outcomes.

For laboratory-confirmed influenza, data were assessed from Ashkenazi and Belshe. The Ashkenazi was open-label, while the Belshe study was blinded. Data from both studies were restricted to children aged ≥ 24 months, so children 6 through 23 months of age are not included. The evidence profile for laboratory-confirmed influenza was not downgraded for any serious concerns. The risk ratio was 0.47 with a confidence interval of 0.38 – 0.58. The overall evidence quality assigned was 1, or high. The risk difference was estimated to be 46 fewer cases/1000.

The other outcome that showed a significant difference in favor of LAIV was influenza-associated otitis media, and this was not downgraded. The same two studies were used for this profile, Ashkenazi and Belshe. The risk ratio was 0.47 with a confidence interval of 0.30 – 0.73. This was rated overall as a 1, or high quality evidence. The other critical outcomes (medically-attended acute respiratory illness, hospitalization, and ILI) did not show significant differences.

For medically significant wheezing, only the Belshe study was included in order to keep the definitions of the wheezing outcomes consistent. This assessment included children 24 through 49 months of age, with a follow-up time of 42 days. Although there was a slightly larger group of children for this profile, the confidence interval was fairly wide and the evidence was downgraded for imprecision. The overall quality of evidence was 2, or moderate. Children in the Belshe study could have been vaccine-naïve or not, so data were reported after dose 1 for both previously vaccinated children and vaccine-naïve children. The overall quality of evidence for vaccine-naïve children also was rated as 2, or moderate.

In summary of the outcomes for which there was information, there was a significant difference for laboratory-confirmed influenza and otitis media in favor of LAIV and there was no difference for the other outcomes. The lowest quality of evidence for the critical outcomes was hospitalization with an evidence quality of 3. The WG elected to count the lowest quality as MARRI rather than hospitalization, because the hospitalization data was not influenza-associated hospitalizations, so it was downgraded for indirectness. Because there is another critical outcome, laboratory-confirmed influenza, for which there is a specific outcome, hospitalization was not used as the lowest evidence quality. The overall quality of evidence for the benefits outcomes was 2, or moderate. All of the harms had a moderate quality of evidence.

Given that Medimmune presented on supply issues during the February 2014 ACIP meeting, Dr. Grohskopf did not address this. Another issue pertains to cost. A formal cost-effectiveness analysis has not been conducted on the relative cost of LAIV and IIV. It is likely that this would be a very complex undertaking at this point due to the very large number of products and presentations available. It will probably take a couple of years to conduct this type of analysis when there is a better sense of what is being used, and what the ratio is of IIV3 to IIV4 use is and whether it reaches some type of equilibrium. The WG decided that they did not feel it was necessary to have a formal cost-effectiveness analysis to move forward. The comparative prices per dose are from the VFC tables and are as follows:

Vaccine product	Price/dose
LAIV	LAIV4: \$22.70
IIV (with indication for ≤8 years)	IIV3: \$7.65 –\$14.81
	IIV4: \$14.90 – \$21.09

A 2008 cost-effectiveness model estimated a cost savings of \$45.80 per child with LAIV as compared with IIV, but it is unclear what the applicability of this particular model would be given the current range of products, including quadrivalents which were not in use in 2008 [Luce BR et al, Vaccine (2008),;26:2841-2848].

In summary of considerations for formulating recommendations, the overall evidence type was 2 or moderate for efficacy and safety. Evidence is lacking for some critical outcomes, such as influenza-related mortality, febrile seizure, GBS, and immediate hypersensitivity. The studies might not be powered to detect some rare but serious events. In terms of the balance between benefits and harms, benefits appear to outweigh harms, there is modestly better efficacy of LAIV at an estimated 47 fewer cases of lab-confirmed influenza per 1000, and no significant differences were observed in the rates of wheezing and fever. The Influenza WG placed a high value on the prevention of lab-confirmed influenza. There is uncertainty at present regarding the relative cost-benefit given the currently available range of vaccines.

There are some limitations. All of the published studies used trivalent vaccines instead of quadrivalent vaccines, which were not yet available. All LAIV is now quadrivalent, but there is still a mixture of IIV3 and IIV4. The quadrivalent vaccines were licensed on the basis of being immunogenically non-inferior. There is no reason to expect that efficacy would be any less from a safety standpoint, given that across the board the safety profiles seem similar. However, it is possible that there could be rare but SAEs that could be identified over the years of post-marketing for which there would not have been adequate power to determine in the pre-marketing period. It is unclear whether the greater relative efficacy of LAIV is sustained with repeated vaccination over sequential years or with increasing age. Studies in adults generally have noted similar efficacy between the two vaccines, or slightly greater efficacy of IIV. It does seem that there is a point at which something changes, but exactly where that is remains unclear.

Proposed Recommendations

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Dr. Grohskopf reviewed the proposed recommendations for the 2014-2015 season. The *MMWR* will be in the Policy Note format again for 2014-2015. The core recommendations have not changed. Annual influenza vaccination is recommended for all persons aged 6 months and older. New and/or revised information includes the following:

- Influenza vaccine virus composition for 2014-2015
- A minor change to the egg allergy language
- A minor change in the pediatric dosing algorithm
- New recommendations regarding the use of LAIV and IIV for young children where either is available and appropriate

Given the information just presented and that has been discussed within the WG over the last several months, the following new language is proposed for the use of LAIV and IIV for health children aged 2 through 8 years:

Use of LAIV and IIV for Healthy Children Aged 2 through 8 Years

- All individuals ≥ 6 months of age should receive influenza vaccine. Influenza vaccination should not be delayed to procure a specific vaccine preparation if an appropriate one is already available.
- When both LAIV and IIV are available, LAIV should be used for healthy children aged 2 through 8 years who have no contraindications or precautions (Category A).
- If LAIV it is not immediately available, IIV should be used. Vaccination should not be delayed in order to procure LAIV.

Discussion Points

Dr. Reingold requested that Dr. Grohskopf explain the difference between the first and third bullets for this recommendation.

Dr. Grohskopf replied that there is not a lot of difference, but the WG felt that it was important to emphasize this point.

Dr. Bocchini inquired as to how this would impact the second dose if the first dose is one vaccine and that same vaccine is not available in a timely fashion for the second dose, and whether a separate statement should be made about this.

Dr. Grohskopf indicated that this could be clarified in the recommendations if necessary, but the WG was not proposing a change in the current recommendation that each dose can be either. It is not necessary to have both LAIV or both IIV. It could be one or the other.

Dr. Brady (AAP) reported that one of COID's concerns is the fact that providers already placed their orders in February for the doses. If the preferential language "should be used" is included in the recommendation, there could be issues related to how families might respond if pediatricians run out of the vaccine that should be used. The other situation is that a much larger proportion of infants is being vaccinated, and the additional children who need multiple doses in the older age group may be problematic in that LAIV may not necessarily be a more effective vaccine in that age group. The draft recommendations being sent to the AAP board will state that LAIV "should be considered" rather than "should be used" for healthy children to make it less preferential.

Dr. Hahn (CSTE) commented that the second bullet could simply state, "When LAIV is available, it should be used . . ." because as written it sounded as though it was saying, "do not use LAIV unless you have both on hand."

Dr. Englund (PIDS) pointed out that the first bullet might be applicable this year and next year, given that some trivalent vaccines are still available. There has been confusion over the past year about withholding trivalent until quadrivalent is available. It is about more than just LAIV and IIV, so she liked the first bullet and thought it would be helpful.

Ms. Pellegrini raised the issue of families who would be sensitive to the price point. While the ACA language requiring insurance coverage of these vaccines is very helpful, a significant number of families are still not covered by those protections for one reason or another. While she did not have a specific proposal, she wanted to make sure they were thinking about the strength of this recommendation in terms of guiding families toward LAIV when for some of them the approximately \$10 price difference may play a role in their decision.

Dr. Bennett thought all of those families would be covered by the VFC.

Ms. Pellegrini clarified that she was thinking about families with private coverage who are not covered by ACA protection.

Dr. Duchin noted that ACIP has tried to emphasize that both of these vaccines are excellent and effective, and that when possible, LAIV is preferential. However, not receiving LAIV is not a major disadvantage.

Dr. Grohskopf indicated that there was some additional language related to LAIV regarding some conditions for which ACIP has recommended LAIV not be used to clarify that per the package insert, those are precautions. The additional language is as follows:

Persons Who Should Not Receive LAIV

- ❑ LAIV Should not be administered to:
 - Those aged <2 years or >49 years;
 - Those with contraindications as per the package insert:
 - Children aged 2 through 17 years who are receiving aspirin
 - Persons who have had severe allergic reactions to the vaccine or its components;
 - Pregnant women;
 - Immunosuppressed persons;
 - Persons with egg allergy;

- Children aged 2-through 4 years who have had a wheezing episode noted in the medical record within the past 12 months, or for whom parents report that a health-care provider stated that they wheezing or asthma within the last 12 months; and
 - Persons who have taken influenza antiviral medications within the previous 48 hours.
- Other chronic medical conditions conferring higher risk of complications due to influenza are precautions to use of LAIV
- Per package insert, safety has not been established

Vaccine Strain Selection for 2014-2015

The FDA Vaccine and Related Biologic Products Advisory Committee (VRBPAC) convened on February 28, 2014 at which time they recommended the same composition for the 2014-2015 season as for the 2013-2014 Northern Hemisphere vaccine, 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.
- A B/Brisbane/60/2008-like virus for quadrivalent vaccines in addition to the first three

Strain selection information was presented primarily for information, given that this is what the composition of the vaccine will be for the 2014-2015 influenza season.

The next two topics have relatively minor changes. One of these pertains to the algorithm for determining the number of doses for children 6 months through 8 years of age. According to a couple of studies, children in this age range seem to need two doses of vaccine instead of one the first time they are vaccinated in order to achieve an optimal immune response. This was a relatively uncomplicated situation until the 2009 pandemic during which the doses received of the 2009 H1N1 antigen had to be counted. For 2012-2013, the approach was the same and consisted of two approaches, both of which were acceptable. There was a simplified approach which considered only doses since July 2010, and a more complicated approach that was good for those in settings with good registry data that considered all vaccination history, including the pre-pandemic period. For 2014-2015, the WG proposes to keep both the simplified and complicated approaches, but with the additional information that children in this age group who received at least one dose of the 2013-2014 seasonal vaccine need only one dose in 2014-2015. This is being done because the vaccine viruses will remain unchanged for the 2014-2015 season, and it is analogous to a change that was made for 2011-2012, which was the last time that the strains were unchanged from the previous seasons. These are as follows:

Determining Doses for Children Aged 6 Months through 8 Years

- Children age 6 months through 8 years receiving vaccine for the first time require 2 doses
- Need to consider doses of pandemic 2009 H1N1
- For 2012-13 and 2013-14 two accepted approaches
 - Simplified approach considering only doses since July 2010
 - Second approach considering all vaccination history
- For 2014-15, both approaches retained, with additional information that children in this age group who received at least 1 dose of 2013-14 seasonal vaccine need only one dose in 2014-15
 - Vaccine viruses unchanged this season

- Analogous to 2011-12 recommendations (strains also unchanged)

Discussion Points

Dr. Groom (IHS) commented that for those trying to program this into their EHRs and registries, to have this decision come in June is very challenging. They definitely want to incorporate it because it will dramatically reduce the number of children who need two doses, but she suggested in the future including something in the recommendation so that if there is not a strain change, it can be assumed that only one dose for these children would be needed. Then moving forward, everyone could anticipate this a lot sooner.

Dr. Grohskopf replied that while she appreciate this, unfortunately VRBPAC and WHO meetings tend to occur in February, it is sometimes difficult to know what will occur with the strains. This may or may not be an issue going forward, because one thing that is under discussion is that this will become less of an issue the further out from the pandemic year. At some point, the WG is likely to discuss returning to the simplest approach that was last applicable in 2009, which was two doses should be administered the first time. This required only a sentence rather than an algorithm. The WG had some discussion regarding the change and the difficulties that poses to programming.

Referring to Slide 6, it seemed to Dr. Gorman (NIH) that changes had been made to the list that the FDA lists as precautions or warnings to contraindications. He said he would like for those to be separated out.

Dr. Grohskopf replied that an effort was made in the 2013-2014 statement to make a distinction between those conditions that are package insert specified contraindications, of which there are only two, and those conditions for which ACIP recommends against use of LAIV. There has long been a dichotomy of those conditions. For example, probably the largest one is against use in persons who have chronic medical conditions conferring a higher risk of complications from influenza. An attempt was made to make that same distinction in the proposed recommendation by reflecting the age indication in the first bullet, while the second bullet reflects the pathogen groups that are package insert-defined contraindications. The remaining bullets under the first main bullet should not be administered to those with conditions for which ACIP does not recommend use.

Dr. Gorman (NIH) recommended that the language state “persons who the ACIP does not recommend receive LAIV” as opposed to “should not.”

Dr. Middleman (SAHM) thought that the bullet regarding 2 through 4 year olds who have had a wheezing episode made it seem like adolescents who have a diagnosis of asthma are included in that. It implies that vaccine could be administered to those who are 5 years of age and older who do have asthma or who have had wheezing.

Dr. Grohskopf indicated that there was an additional bullet that should have been included, and that the draft guidance provided to ACIP members included a bullet on persons of any age with asthma.

Ms. Stinchfield (NAPNAP) pointed out that the Vaccine Information Statements (VIS) are sometimes the only documents that clinicians look at. Now that this is separated out into precautions, she wanted to ensure that the VIS writers carried that over and not overstate it there.

Dr. Moore (AIM) asked what the intent of the WG was related to the use of LAIV when there is a precaution and it is truly not a contraindication, in terms of whether they were saying that if there is a precaution for LAIV and IIV is on hand, LAIV should not be used. However, if only LAIV is on hand, it should be used.

Dr. Grohskopf clarified that any preferential language pertained strictly to healthy children and not those with chronic medical conditions. Regarding the action step for precautions or conditions that would be deemed a precaution that are not listed under the “should not be administered to” section, precautions are situations that generally require clinical judgment and for which the benefits and harms have to be weighed. It is difficult to make a statement about the relative benefits and harms in this particular case simply because there are insufficient data for a lot of groups. At this point, it is difficult to have a recommendation in a document that is intended to cover every possible scenario in the absence of those data. By the definition of “precaution,” that would involve clinical judgment.

Dr. Kimberlin (AAP) inquired as to whether the language “should be used for healthy children” would go into the immunization schedule footnote as such. The AAP Board of Directors approves language of “should be considered” and ACIP states “should be used,” there will be a divergence of schedules after many years of trying to harmonize them.

Dr. Schuchat emphasized that this would be reflected in the schedule.

Dr. Brady (AAP) entered a plea for the language approved by AAP and ACIP to be identical, given the number of years it has taken to be harmonious.

Ms. Pellegrini inquired as to whether the AAP recommendation was based on the fact that ACIP was out of sync with pediatricians’ ordering schedules for vaccine, such that the AAP and ACIP language would be out of sync only for one year.

Dr. Kimberlin (AAP) responded that this was part of the discussion, and that they would potentially be discordant for only one year if there were no additional information to suggest that there may be a need to reconsider that.

Dr. Schuchat reminded everyone that ACIP moved away from using the term “should be considered” based on the AAP’s strong recommendation that this be done.

Dr. Brady (AAP) responded that that was based on whether a vaccine was permissive. The recommendation under consideration was based on not placing someone in a situation in which families might think that the practitioner was not doing what was best for their child.

Dr. Harrison said his greatest concern was that for a clinician trying to figure out what to do, it was not clear what “should be considered” meant.

Dr. Temte pointed out that in February practices have already ordered influenza vaccine for the upcoming season, in June practices have already ordered and the influenza vaccination season

is underway, and in October the vaccination season is well underway. There really is not a good time to make changes in influenza vaccine recommendations. As part of the discussion regarding recommendations and codifying language, ACIP tried to strongly move away from “should be considered,” which is confusing to clinicians.

Dr. Hosbach (Sanofi Pasteur) said that from the manufacturer perspective, a mid-season recommendation such as this is disruptive. Not only have clinicians ordered, but when this recommendation is published, they could cancel their orders. Manufacturers are already well into and nearly finished with the major manufacturing process. It is not without precedent that ACIP has given forewarning that something is coming in an outgoing year. This is disruptive to a number of stakeholders, including EHR systems. This will complicate things for manufacturers, and will have a financial impact for manufacturers and perhaps health care practitioners.

Ms. Stinchfield (NAPNAP) said she was experiencing déjà vu from the conversation when universal influenza vaccine was recommended for everyone 6 months of age and older, and she thought it was this same time of year. At that time, the term “as feasible” was added. Regarding Dr. Hosbach’s comments, if vaccine rates were in the 80% to 90% she would worry about the disruption. However, the US has a long way to go to vaccinate people who are eligible and for whom IIV is available. Therefore, she did not see a need to hold.

Dr. Temte added that in his own state, especially for children 5 through 17 years of age, uptake is about 30% to 32%.

Dr. Decker (Sanofi Pasteur) stressed that the AAP participants noted that the studies comparing LAIV and TIV were sufficiently old, and practice has changed sufficiently since then. Therefore, it is not entirely clear that whether the benefit observed in those studies still pertains. In that regard, the manufacturer of LAIV has an obligation to the FDA obligation to conduct an efficacy trial in the group for whom the proposed recommendation is being made (2 through 8 years of age). He inquired as to when the results of that study would be available.

Dr. Grohskopf replied that she did not know when the results would be available.

Dr. Friedland (GSK) indicated that GSK certainly supports the use of evidenced-based recommendations. He thought the language providers would like to see would be for clarity and understanding of the recommendation, so he thought there would be value in the language to say that when IIV vaccines are used, they are safe and effective in this patient population. The proposed language did not necessarily state that.

Dr. Duchin noted that the annotated text describes both vaccines as safe, effective, and desirable. He reminded everyone that the issue of timing had been discussed during a number of ACIP meetings, and the WG attempted to signal its intent about this during multiple meetings. This meeting marked at least the third one during which this was discussed and an indication was given that the WG was moving in this direction.

Dr. Grohskopf indicated that there was a minor change to the recommendation for vaccination of persons with severe egg allergy. Since 2011-2012, there has been a dichotomy between what to do with persons who have mild allergy defined as hives in response to egg exposure versus severe allergy defined as any symptoms other than hives following egg exposure. For

the most recent round of the recommendations discussed a year ago, recombinant influenza vaccine (RIV) came into existence. The language as it currently reads is as follows:

Vaccination of Persons with Severe Egg Allergy

- ❑ Persons with symptoms other than hives are recommended to
 - Receive recombinant influenza vaccine (RIV3) if age 18 through 49 years, or
 - Be referred to a “physician with expertise in the management of allergic conditions.”
- ❑ Joint Task Force on Practice Parameters (ACAAI/AAAAI), 2013:
 - Cites 2012 review of 4,172 patients, including 513 with history of severe allergic reaction—no occurrences of anaphylaxis; some milder reactions
 - Recommends that “special precautions regarding medical setting and waiting periods after administration of IIV to egg-allergic recipients beyond those recommended for any vaccine are not warranted”
- ❑ However,
 - Occasional cases of anaphylaxis possibly due to egg in VAERs
 - Concern that not all settings may have required equipment and personnel
- ❑ New language seeks to
 - Clarify that referral is not strictly necessary, assuming that the person who is going to be administering it is a physician with expertise in allergic conditions
 - Maintains 30 minute wait period: reiterates need for resuscitative resources

Vaccination of Persons with Severe Egg Allergy

Proposed change from:

“Persons who report having had reactions to egg involving such symptoms as angioedema, respiratory distress, lightheadedness, or recurrent emesis; or who required epinephrine or another emergency medical intervention, particularly those that occurred immediately or within a short time (minutes to hours) after egg exposure...may receive RIV3, if aged 18 through 49 years and there are no other contraindications. If RIV3 is not available or the recipient is not within the indicated age range, **such persons should be referred to a physician with expertise in the management of allergic conditions for further risk assessment before receipt of vaccine**”.

To:

“...may receive RIV3, if aged 18 through 49 years, and there are no other contraindications. If RIV3 is not available or the recipient is not within the indicated age range, **IIV should be administered a physician with experience in the recognition and management of severe allergic conditions**.”

Discussion Points

Dr. Jenkins noted that the change should read, “administered by a physician . . .”

Referring to the slide regarding LAIV, Dr. Rubin suggested changing the first phrase to say “When feasible, LAIV should be used . . .” to address some of the concerns with price, availability, et cetera.

Dr. Kempe agreed that this wording would be helpful in light of the fact that people might find themselves in a bind for the next year or so.

Instead of including this in the final recommendations, Dr. Duchin suggested annotating the guidance with that type of information as is frequently done when a recommendation is published. This type of statement would put it into some context that would explain the timing, ordering issues, and the fact that this might be challenging the first year, but people should not feel bad about that.

Dr. Bennett clarified that the objection to the first bullet stating “When both LAIV and IIV are available” was that it implied that practitioners must have both in the office.

Dr. Karron thought the phrasing suggested for that was “when LAIV is available,” which she agreed with because this made is much cleaner and simpler. However, it did not address the feasibility issue. She agreed with Dr. Duchin that perhaps this could be annotated rather than being included in the primary language.

Ms. Pellegrini emphasized that there are multiple aspects to feasibility, and she wondered how strong this preferential recommendation would be in terms of whether it was limited to a small universe of feasibility issues, or if it was broad enough to include family preference, economic consideration, et cetera. That is, there is a large philosophical question.

Dr. Kempe agreed and said she could think of a lot of children who for some strange reason prefer the injection. As a physician, she is never going to say “no” because she wants them to receive the vaccine. It may help to word the recommendations in terms of the data. Both LAIV and IIV are efficacious and safe. Data suggest that LAIV may be more effective in healthy children; therefore, that should be a preference. Stick with the facts. “Should be used” is too encompassing and does not really incorporate what ACIP is trying to do, which is make recommendations based on what the evidence shows.

Dr. Karron commented that the additional language in the recommendations actually goes through the evidence and discusses the data. She thought it would be rather cumbersome to actually include that in the proposed recommendation. From the WG’s perspective, this has been a long time coming and there has been a lot of discussion. The WG specifically chose the language “should be used” after deliberation and review of the data.

Dr. Temte reminded everyone that that was based on moderate to high quality evidence.

Dr. Savoy (AAFP) inquired as to whether people would feel better if there were job aids similar to those shown earlier in the day that were more specific. If she just read the text as written, she would have assumed that if she had LAIV and IIV, she should give the live vaccine. However, if she did not have both she should give whichever one she had. A job aid could clarify this without having to change the actual recommendation.

Dr. Coyne-Beasley emphasized that the session was running about 25 minutes overtime, and she wanted to ensure that the Adult Immunization WG did not get bumped again.

Dr. Temte said to let the record show that during the last meeting, he promised Dr. Coyne-Beasley that would not happen and the Adult Immunization WG would have its time in the afternoon.

Dr. Brady (AAP) agreed that probably from the perspective of what he mentioned previously, if the second bullet was changed to “if LAIV was available” and did not include both. Then if a pediatrician did not have any LAIV, that would give them an easier out.

Dr. Bocchini agreed, but stressed that this would be a one year statement, so it would be suitable to make an interim change with the language mentioned and then change it again next year based on the fact that people would be ready to order in a different way.

Dr. Temte clarified that the proposed language for the use of LAIV and IIV for healthy children aged 2 through 8 years was suggested to read as follows:

- All individuals ≥ 6 months of age should receive influenza vaccine. Influenza vaccination should not be delayed to procure a specific vaccine preparation if an appropriate one is already available.
- When available, LAIV should be used for healthy children aged 2 through 8 years who have no contraindications or precautions (Category A).
- If LAIV is not immediately available, IIV should be used. Vaccination should not be delayed in order to procure LAIV.

Vote

Dr. Duchin made a motion to accept the recommendations as a package as proposed, with the clarifications and changes suggested. Dr. Harrison 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

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:

- 9-valent HPV vaccine clinical trial data
- Policy considerations and approach to GRADE for 9-valent vaccine
- 2-dose schedules for bivalent and quadrivalent HPV vaccines

The HPV vaccine WG is working to prepare for the expected licensure of the 9-valent HPV vaccine in late 2014, and is continuing to review the data on 2-dose schedules. In 2013, the WG heard a GSK presentation on the GSK 2-dose development program, and recently reviewed available data on 2-dose schedules.

The overall proposed timeline for consideration of the investigational 9-valent vaccine is reflected in the following table:

ACIP Date	Topic
October 2013	Overview of 9-valent vaccine clinical program
February 2014	Attribution of types in HPV-associated disease Clinical trial data
June 2014	Clinical trial data GRADE Policy Questions
October 2014	Health Economics GRADE Recommendation options and discussion
February 2015	Earliest potential vote

To review, during the October 2103 ACIP meeting HPV session, an update was presented on HPV vaccination coverage in the US; review of 9-valent HPV vaccine was begun, with a presentation from Merck on the clinical development program. 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.

9-Valent HPV Vaccine Clinical Trial Data

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

Dr. Luxembourg reminded everyone that last time, there was a presentation of the three pivotal studies in the program:

- Protocol 001: Efficacy study in young women
- Protocols 002 and 009: Immunobridging studies in adolescents

These studies have been completed and are continuing as longer-term effectiveness and immunogenicity studies.

The following Phase III studies are ongoing:

- Protocol 003: Immunobridging study in young men
- Protocol 010: Two-dose regimen

During this session, Dr. Luxembourg presented information on the following supportive studies that have been completed:

- Protocols 005 and 007: Concomitant use studies
- Protocol 006: Study in prior quadrivalent HPV vaccine recipients
- Integrated summary of safety for Protocols 001, 002, 005, 006, 007, and 009

To summarize the presentations during the February 2014 meeting on Protocols 001, 002, and 009, all efficacy and immunogenicity objectives were met. Non-inferiority was demonstrated with respect to the 4 original types in the quadrivalent vaccine. Approximately 97% protection was documented against HPV 31-, 33-, 45-, 52-, and 58-related disease. Non-inferior immunogenicity was demonstrated in boys and girls versus young women. The AE profile was similar to that of the quadrivalent HPV vaccine, except that there were more injection site AEs that were mostly mild to moderate in intensity.

The immunogenicity objective of Protocol 005 was to demonstrate that concomitant administration of 9vHPV vaccine with Menactra[®] and Adacel[®] does not interfere with the antibody response to any of the vaccine antigens. The safety objective was to evaluate the safety and tolerability of the 9vHPV vaccine when concomitantly administered with Menactra[®] and Adacel[®]. On Day 1 in the concomitant cohort, subjects received 9vHPV vaccine concomitantly with Menactra[®] and Adacel[®]. Subjects in the non-concomitant group received 9-valent alone. The non-concomitant group received Menactra[®] and Adacel[®] one month later. All subjects received a second and third dose of 9vHPV at Months 2 and 6, respectively.

With respect to the 9vHPV vaccine antigens, the non-inferiority criterion was met for all 9 HPV types (all $p < 0.001$). The seroconversion rates in the concomitant group were the same as in the non-concomitant group after vaccination with 9vHPV vaccine. Menactra[®] contains 4 *N. meningitidis* serogroups, and the non-inferiority criterion was met for all 4 of these serogroups. This means that there is no substantial difference between the concomitant and non-concomitant cohorts. In terms of the Adacel[®], the non-inferiority criterion was met for diphtheria, tetanus, and all 4 pertussis antigens.

To summarize the findings for Protocol 005, 9vHPV vaccine can be administered concomitantly with Menactra[®] and Adacel[®]. There is no interference with the antibody response to any of the vaccine antigens, and 9vHPV vaccine is generally well-tolerated.

Repevax[®] is used in Europe, so it is not directly relevant to the US. To be complete, Dr. Luxembourg summarized the findings for Protocol 007, indicating that concomitant administration of 9vHPV vaccine and Repevax[®] does not interfere with the antibody response to any of the vaccine antigens. Concomitant administration of 9vHPV vaccine with Repevax[®] is generally well-tolerated in young adolescents. These are very consistent with the findings of Protocol 005.

Protocol 006 was primarily a safety study to help healthcare professionals advise their patients about 9vHPV vaccination (e.g., individuals seeking follow-up vaccination or with unknown history of HPV vaccination). The safety objective of Protocol 006 was to evaluate the safety and tolerability of the 9vHPV vaccine in prior Gardasil[®] recipients. The immunogenicity objective of Protocol 006 was to demonstrate that the 9vHPV vaccine is immunogenic with respect to HPV 31, 33, 45, 52, 58 in prior Gardasil[®] recipients.

The study population was comprised of 900 girls and young women. There were approximately 180 subjects aged 12 through 15 years and approximately 720 subjects aged 16 through 26 years. All subjects were prior recipients of a 3-dose regimen of Gardasil[®]. Subjects were randomized 2:1 to 9vHPV vaccine or saline placebo in order to allow safety profile of the vaccine to be more completely defined. The key immunogenicity endpoints included anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 titers and seropositivity rates for Day 1, Month 2, and Month 7. The key safety endpoints included injection-site and systemic AEs Day 1 to 15 following any vaccination through Vaccination Report Card (VRC)-aided surveillance, and SAEs for Day 1 through Month 7. Subjects received 3 doses of Gardasil[®] before entering the study, and their doses had to be administered within a period of 12 months and documented by medical records. A time interval was requested of 12 months between the last dose of Gardasil[®] and the first dose of whatever they were receiving in the trial, so that the antibody response to Gardasil[®] had decreased for all subjects to a immunogenicity plateau and so that the study would contain a homogeneous population in terms of antibody titers.

In terms of the safety data for 9vHPV vaccine versus placebo, the vaccine appeared well-tolerated. There were very few discontinuations due to vaccine-related AEs and very few vaccine-related AEs as well. It was important to assess injection site AEs because the subjects in the 9vHPV vaccine cohort will have received 6 doses of HPV vaccine in their lifetimes. The frequency of injection site reactions was consistent with that observed in Protocol 001, with pain, swelling, and erythema were by far the most common. Injection site AEs were of mild to moderate intensity, so tolerability appears to be acceptable.

Regarding immunogenicity in prior Gardasil[®] recipients, a primary endpoint was to assess seroconversion rates. In the girls and young women subsets, seroconversion rates were high. This means the vaccine is very immunogenic in both populations. With respect to immunogenicity in prior Gardasil[®] recipients aged 12 to 15 years following Dose 1 and Dose 3, substantial GMTs were observed for types 6, 11, 16, and 18. . After 1 dose at Month 2, there was a substantial increase. After Month 3, there was not much of a change. This means that most of the increase occurs after the first dose. This is not a surprise, given that they were all prior Gardasil[®] recipients. It is a memory response. For the additional types, in general there was no or very little antibody at Day 1. There was a substantial increase following the first dose, with further increase after the third dose. With some of the types, there was more than a 3-fold difference. These results suggest that there is benefit in receiving more than one dose for the additional types. In young women 16 to 26 years of age, memory response for the original types and the new types was essentially the same. The girls and young women are analyzed separately because immunogenicity is age-dependent.

To summarize the key findings for Protocol 006, 9vHPV vaccine has an acceptable safety profile in prior Gardasil[®] recipients. Most injection-site reactions are of mild or moderate intensity. 9vHPV vaccine is highly immunogenic with respect to the new types in prior Gardasil[®] recipients. Of the subjects, greater than 98% became seropositive after 3 doses of 9vHPV vaccine. Important considerations for Protocol 006 are that the study investigated subjects who received 3 doses of Gardasil[®] followed with 3 doses of 9vHPV vaccine. The study did not investigate mixed regimens of the 2 vaccines. This was primarily a safety, placebo-controlled study. No subjects who were naïve to HPV vaccination were enrolled in this study.

An exploratory immunogenicity analysis was conducted which compared Protocol 006 to the other 9vHPV vaccine studies. The goal was to assess the immunogenicity of 9vHPV vaccine after qHPV vaccine versus 9vHPV vaccine alone. There are a number of caveats. Since no subjects received 9vHPV vaccine only in this study, this was a cross-study comparison. Studies of other vaccines have shown that previous antigenic encounter may result in a lower subsequent response to a related antigen. The explanation may be that memory response was favored over primary response. Protocol 006 may represent a similar situation. Because there is strong L1 homology among HPV types (example HPV 16 vs. HPV 31: 83% homology), the HPV antigens in Gardasil[®] and the additional antigens in 9vHPV vaccine are related antigens. This means that it cannot be said that subjects who were prior recipients of Gardasil[®], strictly speaking, are totally naïve to the additional types. It is of interest to assess what is occurring.

In the cross-study immunogenicity comparison of 9vHPV in prior Gardasil[®] recipients compared to subjects naïve to HPV vaccination, the two groups were not distinguishable in terms of seroconversion rates. In young women 16 through 26 years of age, the GMTs for types 6, 11, 16, 18 in subjects who received 9vHPV vaccine following 4-valent vaccine were higher than that observed in the combined studies where subjects received 9vHPV vaccine alone. This is consistent with memory response once again. Looking at the new types, the picture is reversed and immunogenicity is lower with respect to the new types. The GMTs in subjects who received 9vHPV vaccine following 4-valent vaccine are lower for the new types but still higher than with natural HPV infection. Looking at the GMTs in girls 12 through 15 years of age who received 9vHPV following 4-valent vaccine compared to women who received 9vHPV only, the difference was less in respect to the additional types. For some types, the GMTs are comparable, but for some the GMTs are slightly lower. For the original types, GMTs are higher.

The results of the cross-study immunogenicity comparison should be interpreted with caution, given that this was an exploratory analysis comparing across different studies. The findings were consistent with previous observations of lower response to antigenic variants following initial exposure to a given antigen. The practical consequences of these findings are likely limited for several reasons. Seroconversion rates are high in all subjects. The clinical significance of differences in GMTs between vaccination groups is unknown, given that there is no known threshold of antibody protection. In Protocol 001, lower Month 7 anti-HPV 31, 33, 45, 52, and 58 titers are not correlated with lower efficacy. The impact of “Original Antigenic Sin” is considered limited in the context of influenza vaccination. Revaccination is associated with reduced mortality risk compared with first time vaccination (Voordouw AC., *JAMA* 292:2089-95, 2004).

Turning to safety results, Dr. Luxembourg reminded everyone that in Protocol 001, the safety profile was generally comparable for the 9-valent and 4-valent vaccines, but there was a higher frequency of injection site AEs with the 9-valent vaccine. There were approximately 7000 subjects in each cohort in Protocol 001. With respect to the integrated safety data for all six studies (001, 002, 005, 006, 007, and 009), the integrated database includes over 13,000 subjects, and the safety profile is comparable to what has been observed so far in Protocol 001. The vaccine is well-tolerated and most of the AEs are injection site-related, and there are very few SAEs that are vaccine-related. Pain, swelling, and erythema are the most common injection site AEs and the numbers and frequency are consistent with what has been observed in Protocol 001. In the integrated database, most injection site reactions are mild to moderate in intensity. Systemic vaccine-related AEs with an incidence of more than 1% included headache, pyrexia, nausea, dizziness, and fatigue. These are everyday life events, and are common in any vaccine trial. There were 5 vaccine-related SAEs, 2 of which required hospitalization. All

were resolved, and there was nothing unusual that has not previously been observed in the 4-valent program.

To summarize the safety conclusions, 9vHPV vaccine was found to be generally well-tolerated in over 13,000 subjects. There were few discontinuations, few vaccine-related SAEs, and no vaccine-related deaths. The adverse experience profile is generally comparable to that of the 4-valent HPV vaccine. There were more 9vHPV vaccine injection-site AEs, but most were mild to moderate in intensity. The adverse experience profile is comparable across age groups, gender, race, ethnicity, and HPV status at baseline.

In terms of the overall summary, a non-inferior antibody response was demonstrated with respect to the original types compared to the 4-valent vaccine. Approximately 97% protection was demonstrated against HPV 31, 33, 45, 52, and 58-related disease. Non-inferior immunogenicity was demonstrated in boys and girls versus young women. 9vHPV vaccine is generally well-tolerated, and the AE profile is similar to that of the 4-valent vaccine. There were more injection-site AEs with the 9vHPV vaccine, but most were mild to moderate in intensity. 9vHPV vaccine can be co-administered with Menactra[®] and Adacel[®], is generally well-tolerated, and is highly immunogenic in prior 4-valent HPV vaccine recipients. As a reminder, the 9vHPV vaccine is still an investigational product under review by the FDA.

9-Valent HPV Vaccine: Overview of WG Considerations

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Dr. Dunne pointed out that this presentation would set the stage for a GRADE review of the evidence for 9-valent HPV vaccine in October 2014. In order to frame the policy questions, she reviewed the attribution of HPV types to cervical precancers and cancers. This was presented to ACIP in February 2014. She then discussed the 9-valent HPV vaccine policy questions for consideration; the available 9-valent HPV studies; the conclusions from the WG on critical outcomes to consider for GRADE; the population, intervention, comparison, and outcomes (PICO) for the primary policy questions; cost-effectiveness considerations; and next steps for GRADE.

With regard to HPV type attribution by cancer site in the US, most cancers are attributable to HPV16/18. The 5 additional types are associated with 14% to 18% of cervical, vulvar, and vaginal cancers, and 6% to 9% of anal, penile, and oropharyngeal cancers.

To provide an overview of attribution of the 9 HPV types to cervical intraepithelial neoplasia (CIN)2+ and HPV associated invasive cancers, about 50% of CIN2+ are attributable to HPV16/18 and about 25% to the 5 additional types in 9-valent HPV vaccine. Of invasive cancers, 62% are attributed to HPV16/18 and this is similar for males and females. Of cancers, 11% are attributed to the 5 additional types in the 9-valent HPV vaccine, and this is different for females and males with 14% in females and 5% in males.

To summarize the 9-valent HPV vaccine policy questions for GRADE, the primary questions are: 1) Should 9vHPV vaccine be recommended routinely for 11 or 12 year olds?; and 2) Should 9vHPV vaccine be recommended for females aged 13 through 26 years and males aged 13 through 21 years who have not initiated or completed the vaccine series? The ACIP HPV WG was strongly interested in considering these policy questions for males and females at the same time for programmatic reasons, although because the outcomes are different for males and females as well as the attributable fraction of 9 types to cancer, the PICO would be considered separately for males and females. The workgroup would like to consider a recommendation for adult males with available data in October 2014, even though there would likely not be an adult male indication for 9-valent HPV vaccine at the time of first licensure. The additional policy questions included: 1) Should girls/women who received 3 doses of quadrivalent HPV vaccine be revaccinated with 9vHPV vaccine?; and 2) Should 9vHPV vaccine be recommended for men who have sex with men (MSM) through age 26 years?

The available data for the initial filing of 9-valent HPV vaccine are shown in the following table:

9vHPV Studies for Initial Filing*			
Study	Population	N	Objective
<i>Pivotal efficacy study</i>			
001	16-26 yo women	14000	Dose-ranging, efficacy, immunogenicity, safety
<i>Immunobridging studies in adolescents</i>			
002	9-15 yo boys & girls and 16-26 yo women	2800	Adult-to-adolescent immunobridging
009	9-15 yo girls	600	HPV4-to-9vHPV immunobridging
<i>Concomitant use studies</i>			
005	11-15 yo boys & girls	1240	Concomitant use: Menactra, Adacel
007	11-15 yo boys & girls	1040	Concomitant use: Repevax
<i>Study in prior qHPV vaccine recipients</i>			
006	12-26 yo girls & women	900	Safety in prior HPV4 recipients

*Study 003 Immunogenicity study in 16-26 yo males expected October 2014, 1100 MSW and 300 MSM

Dr. Dunne highlighted some features of the data available for policy considerations. As a reminder, the main trial was a comparison of HPV4 and 9-valent HPV and there was no placebo arm. For adult females, there will be efficacy and immunogenicity data, and for adult males there will be immunogenicity data. The data on revaccination with 9vHPV are available for females only, and the immunization schedule in the trials was 0, 2, 6 months.

In order to address the critical outcomes to consider for GRADE, the ACIP HPV WG was surveyed in May 2014 on the key outcomes; 21 responses were received. This included outcomes in females and males, and benefits and harms. The Association of Immunization Managers (AIM) members were also surveyed, and 26 responses were received. AIM feedback was consistent with that of the ACIP HPV WG.

Critical outcomes for females included cervical cancer, cervical precancer, anal cancer, vaginal/vulvar cancer, CIN, definitive therapies and oropharyngeal cancer, as well as SAEs and anaphylaxis. As a reminder, for many of the outcomes there is no direct data from the clinical trials, so outcomes were listed for which there are direct data including cervical precancer, CIN, definitive therapies, SAE, and anaphylaxis. For some outcomes, there will not be direct data but there may be indirect data such as data on cervical precancer, vaginal/vulvar precancer, or immunogenicity. For males, the critical outcomes included anal cancer, oropharyngeal cancer,

SAEs, and anaphylaxis. There will be no direct data on these outcomes in males; however, there will be indirect immunogenicity data.

Regarding the PICO comparison and outcomes for the primary policy questions, for the question of routine vaccination at 11 or 12 years, the population is females immunized at age 11 or 12, the intervention is of 9vHPV and comparison of HPV4, and the critical outcomes were as highlighted earlier. The primary objective is an evaluation of HPV6, 11, 16, 18 equivalence, and evaluation of HPV 31, 33, 45, 52, 58 superiority. For males, the population is males immunized at 11 or 12, with the same intervention, comparison, and the critical outcomes highlighted earlier. The primary objective is the evaluation of HPV 6, 11, 16, and 18 equivalence. Superiority of 5 types of HPV outcomes will not be evaluated in males, given that the attribution of 5 types to males' critical outcomes such as anal and oropharyngeal cancers is limited.

The PICO for the question pertaining to older females and males includes the population of females immunized at ages 13 through 26 years; intervention of 9vHPV vaccine; comparison of HPV4; critical outcomes as highlighted earlier; and the objective of evaluation of HPV6, 11, 16, 18 equivalence and HPV 31, 33, 45, 52, 58 superiority. For males, the population includes males immunized at ages 13 through 21 years, intervention of 9vHPV vaccine, and HPV4 as the comparison. The objective for males is evaluation of HPV 6, 11, 16, 18 equivalence.

As highlighted earlier, the data available for the primary policy questions include efficacy and immunogenicity in adult females, immunogenicity in boys and girls, and immunogenicity in adult males. Data in adult males are expected to be available in October of 2014 for GRADE consideration, but will be pending FDA approval for an adult male indication at the time of primary licensure.

Cost-effectiveness is also considered for GRADE. For 9vHPV vaccine, cost-effectiveness data will be presented for males and females separately and combined in October 2014. Also, the cost-effectiveness of revaccination with 9vHPV after receipt of 3 doses of HPV 4 will be presented. A variety of CDC and external models will be presented that use US data.

In summary, the purpose of this presentation was to provide the foundation for the next presentation to ACIP on GRADE. Policy question and PICO have been developed, and tables of evidence will be developed on 9vHPV vaccine and presented to the ACIP HPV WG. Cost-effectiveness and GRADE data will be presented to ACIP during the October 2014 meeting in order to be prepared for possible recommendations in early 2015.

Discussion Points

Dr. Karron remembered that in a previous presentation, Dr. Dunne spoke about ethnic and racial disparities in terms of the 5-valent and she was not clear whether that was for carriage, CIN2+, or for cancer.

Dr. Dunne responded that during the February 2014 ACIP meeting data were presented by Dr. Hariri and Dr. Saraiya; there was discussion regarding attribution of 5 and 9 types to CIN2+ and cancers. There were race/ethnicity differences for the cervical precancers in particular. However, the largest percentage of precancers are due to HPV16/18 regardless of race. For the invasive cancers, the attributions of 16/18 are the same across race/ethnicity.

Dr. Karron inquired of Dr. Luxembourg as to when data would be available on the 2-dose regimen for the 9-valent vaccine.

Dr. Luxembourg responded that the study is ongoing and data are expected before the end of 2015.

While the change in antibody titer between Doses 1 and 3 was shown, Dr. Harrison wondered about the change between Doses 2 and 3.

Dr. Luxembourg responded that in Protocol 001, post-dose 2 and post-dose 3 antibody titers were analyzed. There is an increase, but it is relatively small at about 30% (Post-minutes note: The increase between post-dose 2 and post-dose 3 varies by HPV type, ranging from approximately 20% to 70%).

Dr. Vazquez inquired as to whether there was information on what occurs with one or two doses in the cross-study.

Dr. Luxembourg replied that this type of information is not available for the cross-study comparison. In Protocol 006, only post-dose 1 was studied. In Protocol 001, only post-dose 2 was studied.

Dr. Reingold requested that Dr. Dunne elaborate on the decision not to assess the critical outcome in males for HPV 31, 33, 45, 52, and 58.

Dr. Dunne replied that it would be possible to assess these outcomes, but the focus of the WG was that the attribution to these specific 5 types is less for males than for females. The attribution for penile is 9% and the overall attribution for males is 5%. Cost-effectiveness data have not yet been presented, but that will be presented in October 2014. This will provide additional information regarding the cost-effectiveness of 9-valent for males versus females.

Dr. Karron said she was aware that there is a formal study assessing two doses, but she wondered whether there are existing data for naïve individuals getting two doses of 9-valent vaccine. Perhaps they received three, but there are immunogenicity data after two doses. She wondered whether those data already existed, or if they did not exist and Merck anticipates getting these data with the upcoming study.

Dr. Luxembourg responded that the only data Merck has for two doses are in the context of Protocol 001 in young women 16 through 26 years of age. It is not completely relevant to what the ACIP would be interested in for two reasons. One is that it is not the group where a 2-dose regimen would be considered. The other is that the schedule is different from what will be considered, because the subjects received doses at Day 1, Month 2, and Month 6. Any 2-dose schedule would be with longer intervals. That is to say that Merck does not have relevant data at this time.

2-Dose HPV Vaccine Schedules: Review of Data / HPV Vaccine WG Plans

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Dr. Markowitz indicated that the purpose of this presentation was to inform and update the committee on the accumulating data on 2-dose HPV vaccination schedules. As background, there are two licensed HPV vaccines in the US, quadrivalent vaccine (Gardasil[®]) and bivalent vaccine (Cervarix[®]). Both are virus-like particle (VLP) vaccines using L1 surface protein. The vaccines contain different adjuvants. The licensed schedule for both is a 3-dose schedule with the second dose given 1 to 2 months after first, and the third dose 6 months after the first.

For licensure of the currently available HPV vaccines, large efficacy trials were performed in 16 through 26 year old females. The endpoints were precancer lesions. Bridging immunogenicity trials were conducted in 9 through 15 year olds—an age group in which efficacy trials are not possible. Licensure in this age group was based on the non-inferior antibody response in this age group compared with women in the efficacy trials. For both vaccines, over 99% of vaccinees developed antibody after vaccination, and the antibody titers in the younger age group were higher than those aged 16 through 26 years.

GMTs for HPV 6, 11, 16, and 18 one month after the third dose of quadrivalent vaccine, were highest in the youngest age group for all four types and decreased with increasing age at vaccination. [Giuliano, et al. JID 2007]. Similar findings by age were found for HPV 16 and 18 GMTs for the bivalent vaccine

The main basis of protection is thought to be neutralizing antibody, but the minimum protective antibody threshold is not known. The high efficacy found in vaccine trials has precluded identification of a protective titer, but vaccination induces antibody titers that are much higher than natural infection. In clinical trials of the quadrivalent HPV vaccine, some vaccinees lost detectable HPV 18 antibody, but there was no loss of protection against study endpoints.

There is global interest in simplified schedules for HPV vaccine. These would be more convenient for providers, parents, and vaccinees; and might facilitate implementation by reducing logistical challenges for vaccine delivery and decrease resource needs. The high efficacy found in the initial clinical trial prompted investigation of reduced dose schedules.

Before reviewing the data, Dr. Markowitz mentioned what is considered to be the immunologic basis of the HPV vaccination schedule. The 3-dose schedule (0, 1-2, 6 months) can be considered a “prime-prime-boost,” with the first two doses being priming doses and the third dose being the boost. Two-dose schedules that have been studied with at least 6 months between the doses can be considered a “prime boost” schedule without the second priming dose. Memory B cells require at least 4 to 6 months to mature and differentiate into high-affinity B cells. Six months between the first and last dose allows the last dose to efficiently reactivate memory B cells.

WHO's SAGE considered 2-dose schedules during their meeting in April 2014. At that time, they recommended a 2-dose HPV vaccination schedule for girls, if vaccination is initiated prior to 15 years of age. The minimal interval between 2 doses is 6 months, and the interval may be extended to 12 months if this facilitates administration. A 3-dose schedule remains necessary if immunization is initiated after the 15th birthday. A 3-dose schedule (i.e., at 0, 1-2, 6 months) remains recommended for immunocompromised individuals, including those known to be HIV-infected. SAGE reviewed a variety of data on 2-dose schedules for this decision, some of which Dr. Markowitz reviewed during this session. This included a systematic review of the literature and the European Medicines Agency (EMA) assessment report for Cervarix[®]. These are available on the WHO website:

http://www.who.int/immunization/sage/meetings/2014/april/report_summary_april_2014/en/

http://www.who.int/immunization/sage/meetings/2014/april/presentations_background_docs/en/

Manufacturers have submitted data for regulatory approval in a variety of countries. Bivalent vaccine has regulatory approval for use as a 2-dose schedule in Europe from the EU and 5 other countries, as well as countries in Africa, Latin America, and Asia. HPV4 also has regulatory approval for use as a 2-dose schedule by the EU and a variety of other countries.

Regarding the current status of regulatory issues in the US, for the bivalent vaccine, there has not been a submission to FDA and the manufacturer has no plans to submit. For the quadrivalent vaccine, Merck has no plans for submission to FDA as they are focusing on their 9-valent vaccine which is under consideration now as a 3-dose schedule. For the 9-valent vaccine, there are no data on 2 doses included in the BLA under consideration by FDA, but a 2-versus 3-dose trial has been initiated [Clinicaltrials.gov NCT01984697].

With that background in mind, Dr. Markowitz then reviewed the available data on 2-dose schedules. Most of the data are from immunogenicity studies. There are limited efficacy data from post-hoc analyses, and there are post-licensure effectiveness data which are challenging to interpret.

Regarding the immunogenicity studies comparing 2- versus 3-dose schedules, there are 3 studies of the bivalent vaccine and 2 studies of the quadrivalent vaccine. The Romanowski (Protocol 048) study was a GSK study that was also a dose ranging study. There are two publications from this study, with the most recent having data from a 48 month follow-up [Hum Vaccin 2011 and Hum Vaccin 2014]. The Puthanakit (Protocol 070) is considered by GSK to be their confirmatory study of 2 doses. These data were presented during two international meetings in the last 8 months, but have not been published [EUROGIN 2013; ESPID 2014]. The Lazcano-Ponce study was conducted by independent researchers in Mexico [Vaccine 2014]. There are two studies with a direct comparison of 2- and 3-dose schedules for the quadrivalent vaccine. Neither of these was industry sponsored. The Dobson study was conducted in Canada and is the only published study for quadrivalent vaccine [JAMA 2013]. The Sankaranarayanan is being conducted in India. This study was originally planned as an efficacy RTC of quadrivalent vaccine with over 20,000 girls 10 through 18 years of age who were randomized to receive 2 or 3 doses. The original design was going to evaluate CIN outcomes, but this study was not completed as planned due to the study being halted by the government. At the present time, data are only available on a subset for immunogenicity and for incident infection, and the randomized design has been compromised [EUROGIN 2013].

Four of the five studies (Romanowski, Puthanakit, Lazcano-Ponce, and Dobson) had a group which included the standard 3-dose schedule at age 15 through 26 years, the age group of the women in the efficacy trials. The main comparisons were between antibody response in this group, and the experimental 2-dose schedules in the young adolescents. Four studies (Romanowski, Lazcano-Ponce, Dobson, and Sankaranarayanan) also were designed to allow direct comparison of the 2- and the standard 3-dose schedules within the same age group. One study (Romanowski) of the bivalent vaccine compared two different intervals 2-dose schedules: a 0,6 months schedule and a 0,2 month schedule. This comparison was made in several age groups.

Four studies contributed to the analysis of girls who received 2 doses and the women who received 3 doses in the systematic review used for the SAGE review by D'Addario, et al . For HPV16 for all comparisons, there was no difference in seroconversion or seropositivity between the girls who received 2 doses and the women who received 3. For HPV 18 in the one study of quadrivalent vaccine, seropositivity was higher at 24 and 36 months in the girls who received 2 doses compared with the women who received 3 doses, but this was not statistically significant. The same four studies contributed to the analysis comparing GMCs in girls receiving 2 doses and women receiving 3 doses one month after their last dose—three of the bivalent and one of the quadrivalent vaccine. Studies were stratified by high and middle income countries. Results were considered separately for types 16 and 18. All trials met the criteria for non-inferiority. For most comparisons, data favored girls receiving the 2-dose schedules.

Two studies contributed to the analysis of differences in the proportions of girls of the same age seroconverting or seropositive who received 2 doses compared with those who received 3 doses. For HPV 16, for all comparisons there was no difference in seroconversion or seropositivity between the girls who received 2 doses or 3 doses. For HPV 18, in the Canada 1 study of quadrivalent vaccine (Dobson), seropositivity was higher at 24 and 36 months in the girls who received 3 doses compared to the girls who received 2 doses, but the lower confidence intervals include the non-inferiority margin.

In terms of the comparison of differences in GMC among girls of the same age group who received 2 or 3 doses at one month after the last dose, there are three studies—two of quadrivalent and one of bivalent. For HPV 16 in the bivalent trial, the GMC was lower after 2 doses compared with 3 doses, but not significantly. For the quadrivalent trial (Dobson), the estimates were not different between the two schedules one month after the last does. For HPV 18, both for the bivalent and quadrivalent vaccines, the GMCs after the 2-dose schedule were lower, but were non-inferior to 3 doses. For the limited data presented from the India trial, the 2-dose GMCs were non-inferior to the 3 doses GMC, and the data favored two doses.

All of the data for the comparison of 2 different interval 2-dose schedules were from one study of the bivalent vaccine. Intervals compared were a 0,6 months schedule compared with a 0,2 month schedule. The 0,6 month interval resulted in higher titers in all age groups for both HPV 16 and 18.

Dr. Markowitz then separately and in more detail reviewed the available data for the bivalent and quadrivalent vaccines, and focused on some data submitted for regulatory approval to the EMA and for other countries. For the bivalent vaccine, this included immunogenicity data and efficacy data. The main immunogenicity data came from 2 studies that were included in the meta-analysis mentioned earlier: Romanowski et al, Hum Vaccin 2011 and 2014; and

Puthanakit et al, EUROGIN 2013. The efficacy data were from two post-hoc analyses: Kreimer et al, JNCI 2011 and the unpublished post-hoc analysis of the GSK pivotal efficacy trial.

The bivalent HPV study in the SAGE review (Protocol 048) was a dose ranging trial as well as a 2- versus 3-dose trial. A 48-month follow-up was recently published that followed 2 groups who received the licensed formulation: 2 doses in 9 through 14 year olds and 3 doses in 15 through 26 year olds. All subjects remained seropositive for HPV 16 and 18 by ELISA at month 48, GMTs were non-inferior for the 2-dose group compared with the 3-dose group, and antibody kinetics were similar in both groups.

In Protocol 070, the GSK confirmatory trial of 2 versus 3 doses, 9 through 14 year old females were randomized to receive 2 doses at 0,6 months or 0,12 months. There was a concurrent group of 15 through 25 year olds who received 3 doses in the standard schedule. Data from the 0,12 month group were just presented in June 2014 and were not included in the SAGE review. In this trial, GMTs were non-inferior in the 2-dose group compared with the 15 through 25 year old women who received 3 doses. The longest follow-up to date is 6 months after the last dose. Data are only available for the 0,1, 6 month schedule and 0,6 month schedule groups. GMTs were slightly lower in the girls who received 2 doses, but non-inferiority criteria were met and titers were remained substantially higher than those after natural infection [Puthanakit, et al. ESPID 2014].

Efficacy data are available from two post-hoc analyses. It is important to note that these studies were not designed to evaluate the number of doses. Among women enrolled in the Costa Rica RCT, about 20% received less than 3 doses. In a post-hoc analysis, the endpoint was incident infection that lasted at least 10 months. The numbers are small, but it shows high efficacy among those who received 1, 2, or 3 doses, with an efficacy of 84% for those who received 2 doses; this was not different from the efficacy in those who received 3 doses [Kreimer A, et al. JNCI 2011].

In the second post-hoc analysis is from the pivotal RCT trial conducted by the manufacturer (Patricia Trial). In this large trial in 15-25 year old females, compliance with the 3 dose schedule was high and only 5% received 2 doses. Regarding the 2-dose and 3-dose efficacy against 6-month persistent HPV16/18 infection and incident infection, there was 100% efficacy against 6-month HPV16/18 persistent infection and 84.5% efficacy against 16/18 incident infection. Efficacy was 93.7 for 3 doses [GlaxoSmithKline. *GSKBio_WWMA_DoF068_1_2011*, Data on file. 2011; Assessment report, EMA/789820/2013].

The main data available on 2 doses for the quadrivalent vaccine are the immunogenicity data from a study conducted in Canada [Dobson, et al. JAMA 2013]. Some data available from a RCT of different 3-dose schedules of quadrivalent HPV vaccine also provide information on 2 doses [Neuzil, et al. JAMA 2011 and LaMontagne, et al. JID 2014].

In terms of the design of the quadrivalent 2- versus 3-dose study in the Dobson study, 9 through 13 year old females were randomized to receive 2 doses at 0,6 months or the standard 3 doses and there was a concurrent group of 16 through 26 year olds who received 3 doses by the standard schedule. The main analysis was comparing the 2-dose girls with the 3-dose women. For the 36-month results, non-inferiority criteria were met for all types and antibody response was generally higher in the 9 through 13 year olds who received 2 doses, with GMTs ratios greater than 1. In the comparison of the 2 and 3 dose schedules in 9 through 13 year olds, the GMT ratios were less than one, and non-inferiority was lost for HPV18 by 18 months and for

HPV 6 by 36 months. For the GMTs through 36 months for HPV 16 and 18 for the three groups in the 2- vs 3-dose trial, the antibodies followed the same kinetics for all schedules. Antibody reached a peak 1 month after the last dose and then declined between 7 and 18 months and reached plateau. Both 3- and 2-dose girls maintained at plateau levels higher than the young adult women. There are greater differences between groups for HPV 18 than HPV 16 [Dobson, et al, JAMA 2013].

The trial of quadrivalent vaccine was conducted in Vietnam, which evaluated different 3-dose schedules provides some data on response to 2 doses. As noted earlier, 11 through 13 year olds girls were randomized to the standard 0,2,6 month schedule or one of three experimental schedules: 0,3,9 month, 0,6,12 month and 0,12, 24 month schedules. The main end point was GMTs 1 month post dose 3. For the 0,3,9 and 0,6,12 schedules, non-inferiority criteria were met for all types. For the 0,12, 24 schedule, non-inferiority was not met for HPV 6 and 16. In a follow-up study, for GMTs 29 through 32 months post dose 3, non-inferiority criteria met were for all schedules [Neuzil, et al. JAMA 2011; LaMontagne, et al. JID 2013].

In the RTC in Vietnam, a serology sample was obtained pre- and post-dose three. The pre-dose 3 blood draw can be considered a post-dose 2. In terms of the GMTs after dose 2 in this study, there was a trend for higher antibody levels prior to dose 3 with increasing intervals between the first and second doses. Of note, because the schedules were different, the time between vaccination and blood draw after dose 2 also varied. For example, in the 0,2,6 month schedule, the time between vaccination and the post-dose 2 blood draw was 4 months while in the 0,6,12 month schedule it was 6 months [Neuzil, et al. JAMA 2011].

Data are now available from post-licensure monitoring studies; population impact on some early outcomes has been demonstrated in countries with high as well as moderate and low coverage (e.g., Australia, Denmark, Germany, New Zealand, Scotland, Sweden, UK, US). Four studies provide information on post-licensure effectiveness by number of doses, 3 of which are for HPV4 and 1 of which is for HPV2. Three were data linkage studies that use the registry data available in three countries and one was a serial cross-sectional study of prevalence. Two studies evaluated cervical abnormalities, one condyloma, and one type-specific prevalence. There are a variety of other ongoing studies, including one in the US looking at effectiveness against condyloma. There are a variety of challenges and limitation of these studies. First, there may be differences between 2- and 3-dose recipients. In these effectiveness studies early in the programs, outcomes being detected were in the catchup populations, not those who were vaccinated at the target age groups, so many people could have been infected before vaccination. Second, there are differences between 2- and 3-dose recipients. Third, the evaluations do not examine the 0,6 month 2-dose schedule. Instead, they examine persons who started the 0,2,6 month schedule but did not receive the third dose.

In regard to the Getlig data from Australia, the outcome was cervical abnormalities (CIN3/AIS or CIN2). As noted earlier, the hazard ratio (HR) for those who received 3 doses was 0.53, while for those who received 2 doses was 0.87 and that was not significantly different from the unvaccinated. For CIN2, the HR was 0.70 for 3 doses and 0.99 for those who received only 2 doses. The authors point out the main limitations of the study. While they controlled for differences between women who received 3 doses and those who received less than 3 doses, they note that women who had only 1 or 2 doses were younger age at first screening (indicating earlier sexual debut), older at vaccination, and had lower socioeconomic status (SES). The Crowe study from Australia had a difference study design, but also looked at cervical abnormalities. For the entire age range of 11 through 27 years, a difference was found between

2- and 3-dose recipients, with the adjusted odds ratio being 0.54 for 3 doses and 0.79 for 2 doses, which was significant. For the 15 through 18 year olds, the adjusted odds ratio was 0.43 for 3 doses and 0.77 for 2 doses. This study had some of the same limitation as the other study in Australia.

In the Herweijer quadrivalent HPV vaccine effectiveness study for prevention of condyloma in Sweden, an open cohort of females aged 10 through 24 was followed using population-based registers. This evaluation included over 1 million women and 20,000 cases of genital warts. Incidence was significantly reduced for 1, 2, and 3 dose vaccinees compared with those who were unvaccinated. The incidence ratio for 1, 2, and 3 dose vaccinees compared with the unvaccinated differed, with the incidence ratio being 0.18 for 3 doses and 0.29 for 2 doses. This study clearly demonstrated an impact from less than a complete 3 dose series; however, there were differences by number of doses. The authors point out that the main analysis was done with an interval of 3 months between vaccination and case counting. With a longer period between vaccination and case counting, more genital warts can be excluded that might be due to infection prior to vaccination. With a buffer period of 5 months or longer, a statistically significant difference in the risk of condyloma between 2 and 3 doses recipients was no longer observed.

The Kavanagh study in Scotland was a cross-sectional study of bivalent vaccine effectiveness in women aged 20 through 21 presenting for cervical cancer screening, which assessed HPV prevalence. Over 4700 specimens were tested between 2009 through 2012. Data were linked to immunization registries. The adjusted odds ratio differed for 2 and 3 doses: 0.43 for 3 doses and 0.68 for 2 doses.

In summary of the immunogenicity and effectiveness data, the GMTs for bivalent and quadrivalent vaccines were non-inferior after 2 doses given 6 months apart in young adolescent girls compared with 3 doses in a routine schedule in women 15 through 26 years of age. The GMTs were lower but non-inferior after 2 doses compared with 3 doses in adolescents of the same age group one month after the third dose. Some quadrivalent vaccines lost non-inferiority for two types at later time points. For both vaccines, GMTs are higher for 2 doses with longer intervals between doses in a 2-dose schedule. For efficacy, there were two small post-hoc analyses for the bivalent vaccine that found high efficacy. For the quadrivalent vaccine, more data may be available in the future from the study in India. For effectiveness, 4 post-licensure effectiveness evaluations assessed number of doses, 3 for the quadrivalent and 1 for the bivalent. These found lower effectiveness for 2 versus 3 doses. However, there are many limitations and challenges with post-licensure effectiveness evaluations at this point in the vaccination programs.

One of the main questions remaining is: Will there be differences in duration of protection for 2- and 3-dose schedules? Longer follow-up will be available from some studies. Some information is available from modeling studies that have assessed this issue [Jit et al. Vaccine 2014: 32]. Two studies suggest that if 2-dose schedules protect for at least 20 years, then the benefits of the 3rd dose are small. If 2 doses protect for 10 years, then the 3rd dose may prevent as many cancers as the first 2 doses. The WG intends to further evaluate this question for the US for later presentation to the full ACIP.

As mentioned earlier, SAGE has recommended a 2-dose schedule for HPV vaccination. However, before that time, several countries had changed to 2-dose schedules or to the so-called “extended 3-dose” schedules. The purpose of the extended 3-dose schedule is to allow implementation of the first 2 doses on a schedule that would essentially be the 2-dose schedule if it is decided later that the 3rd dose is not needed, (0, 6, 60 month schedule). The following are the countries with these extended schedules or with 2-dose schedules:

- ❑ Quebec, Canada
 - Implemented extended HPV4 3-dose schedule in 2008
 - Changed to HPV4 2-dose schedule in 2013
- ❑ British Columbia, Canada
 - Changed from HPV4 3-dose schedule to extended HPV4 3-dose schedule in 2010
- ❑ Mexico
 - Using extended 3-dose schedule (since national program 2012)
- ❑ Switzerland
 - Changed from 3-dose to 2-dose schedule for 11-14 year olds in 2012
- ❑ England
 - Will change from HPV4 3-dose to HPV4 2-dose schedule in fall of 2014

Just to review again the status of regulatory approval for 2 dose schedules in the US; for the bivalent vaccine, there has been no submission to FDA. For the quadrivalent vaccine, Merck has no plans for submission to FDA as they are focusing on their 9-valent vaccine, which is under consideration now as a 3-dose schedule. For the 9-valent vaccine, there are no data on 2 doses included in the BLA under consideration by FDA, but a 2 versus 3 dose trial has been initiated.

The 9-valent HPV vaccine 2- versus 3-dose trial is a Phase III immunogenicity study that started in December 2013. According to the website, the last visit for the last patient enrolled will be July 2015, and it is assumed that it would then take several months to analyze the data. There are 5 arms and a total of 1500 subjects to be enrolled. There are 3 experimental groups: 1) 2-dose groups at 0,6 in 9 through 14 year old girls; 2) 2-dose group at 0,6 months in 9 through 14 year old boys; and 3) 2-dose group at 0, 12 months in 9 through 14 year old boys and girls. There are 2 control groups: 1) 3-dose group in 9 through 14 year olds; and 2) 3-dose group in 15 through 26 year old women [Clinicaltrials.gov identifier NCT01984697].

The WG's plans are to review and consider 9vHPV as a 3-dose schedule, and to consider 2-dose schedules when data from 2- versus 3-dose trial of 9vHPV are available. However, the WG has had discussions about other options. The primary option is to consider a 2-dose schedule now for HPV2 and HPV4 in 9 through 14 year olds. For older individuals, a 3-dose schedule would be recommended. Because of the intersection of consideration of the 9-valent and 2-dose, the options are complicated. If a 2-dose schedule is recommended, the WG discussed the potential options when 9vHPV licensed. The options include waiting until there are data for a 2-dose schedule before considering recommendations for 9vHPV, recommending 9vHPV as a 3-dose schedule, or recommending the 9vHPV as 2-dose schedule with no data. Most of the WG members felt that the WG should continue to review and consider the 9-valent vaccine as a 3-dose schedule, and to consider 2-dose schedules when data from the 2 versus 3 dose trial are available.

To end this presentation, Dr. Markowitz reviewed data on coverage for the US from the NIS-Teen. Based on national vaccination coverage data among adolescents from 2006 through 2012, as of 2012, 85% of adolescents had received a Tdap vaccine and 74% had received the meningococcal conjugate vaccine. In contrast, only 54% of girls had received 1 or more doses of HPV and only 33% of girls had received all 3 doses of the HPV series. For the past 3 years, there has been very little increase in HPV vaccine for girls. Between 2011 and 2012, no change in coverage was observed. Among adolescent boys, 21% received 1 or more doses of HPV and 7% received all 3 doses of the HPV series. This increase reflects the routine recommendation for male vaccination made in 2011. 2012 was the first year of data since the routine recommendation. One of the reasons for the interest in 2-dose schedules is because of the potential to facilitate implementation by simplifying the schedules, although there are no data to demonstrate that simplifying the schedules themselves would increase vaccine initiation.

Coverage for at least one dose, at least 2 doses, and at least 3 doses all follow the same trajectory with drop-off similar between dose 1 and 2 and 2 and 3. Of persons who started the vaccination series, 67% completed all 3 doses based on NIS-Teen 2012. Overall, 33% received all 3 doses, about 10% received only 1 dose, and about 10% received only 2 doses [MMWR. 2013;62;685-93].

In terms of the estimated timeline for future plans, in October 2014 there will be a GRADE presentation and discussion of the recommendation options and economic analysis presentation. If data are available from the immunogenicity trial in males 15 through 26 years of age, those data will be reviewed during the ACIP meeting. Based on timeline for FDA review, the estimated earliest possible vote on the 9vHPV vaccine would be February 2015. Data from the 9vHPV 2-dose trial may be available by the October 2015 meeting.

Dr. Markowitz particularly expressed appreciation for Dr. Eileen Dunne, who will be moving to Thailand.

Discussion Points

Dr. Harriman inquired as to whether any of the countries that have switched to the 2-dose schedule signaled what they might do with the 9-valent vaccine.

Dr. Markowitz indicated that she has had some informal discussions with people about that, and believes that everyone is grappling with the same issues.

Dr. Duchin asked why a 2-dose regulatory approval was sought in so many other countries and not the US.

Dr. Markowitz called upon the manufacturers to address this inquiry.

Dr. Feinberg (Merck) indicated that in developing their products and contributing the evidence base that informs policy decisions, Merck engaged with policy-makers and regulators throughout the world. The level of interest for the 2-dose regimen has varied from country-to-country. In Europe, there was significant interest in this, so Merck provided the data that were used by regulators and policy-makers to lead to that discussion. That being said, as seen in the presentations by Dr. Markowitz and others, the manufacturers have been involved in generating data that are relevant to the deliberations that ACIP will be carrying out. There has been a

focus on the development of the 9-valent vaccine, which is a very complicated program in and of itself, and in wanting to make sure that the transition from the quadrivalent to the 9-valent vaccine is smooth and effective from a medical and public health perspective. Thus, Merck felt that its efforts were best focused on delivering the 9-valent vaccine with the strongest dataset to support it. In the meantime, they are generating data on 2 doses of the 9-valent vaccine. Generating data on the 2 doses of the quadrivalent vaccine beyond what is already available did not seem like the best investment of resources and time.

Dr. Friedland (GSK) indicated that GSK has submitted and has had approved 2-dose Cervarix[®] in over 71 countries. It is recommended as part of the immunization recommendations in a number of countries to use the 2-dose schedule in their programs. In the US, the story with Cervarix[®] is slightly different. Because of the low uptake of the use of Cervarix[®] in the US, GSK is devoting its efforts to the 2-dose Cervarix[®] program in other countries around the world, particularly in developing countries where there is a greater opportunity for the use of the product, particularly around helping with adherence to and compliance with the schedule.

Dr. Karron wondered what 2-dose schedule Merck is studying for the 9-valent vaccine.

Dr. Markowitz responded that Merck is studying the 0,6 and 0,12 month schedules.

Ms. Pellegrini pointed out that attention had been devoted to the 3-dose versus 2-dose schedules. She encouraged the WG and ACIP to pay equal attention to the intervals. The current interval of 0, 2, 6 is incredibly challenging for families. If a change could be made to a 0, 12, 24 schedule that aligns with an annual well teen visit, she believes uptake would increase dramatically.

In terms of targeting previously fully immunized individuals with 3 doses of HPV4, Dr. Temte asked whether there were considerations for revaccination. He was thinking about the switch over from PCV7 to PCV13 when there was an algorithm in which not everyone would receive the full complement.

Dr. Markowitz said that for PCV13, the consideration was giving a single dose to people who had previously been vaccinated with PCV7 the WG will be considering data that are available regarding revaccination.

Dr. Schuchat pointed out that the timeline for the WG presenting data to the full committee referred to the 9-valent vaccine. She thought it would be helpful to hear committee input regarding what else they would like to consider regarding changing the intervals or a 2-dose schedule in advance of other formulations potentially being available. If heading toward a fewer-dose schedule, changing the interval sooner would be better.

Dr. Kempe thought the data were strong to support a 0,6 or 0,12 interval. She wondered whether they would be willing to do this without those data when the 9-valent vaccine is approved. It seemed as if the 9-valent vaccine were approved, they would recommend changing the intervals. Yet, everyone recognized the problem with having to make rapid adjustments in primary care. She said she would like to hear from the other committee members whether there would be any chance of what essentially would be an off-label recommendation for that interval.

Dr. Temte reflected on Ms. Pellegrini's comments that in a primary care setting, the US is doing atrociously in terms of increasing HPV coverage over the past 8 years. Part of the problem arises from dealing with adolescents in primary care, given that adolescents do not present for follow-up in 1 to 2 months. As the parent of a 2-dose son who was immunized on a 0, 12 interval, he said he was guilty as charged and could attest to how difficult it is to get a teen in. The realities of medical practices are incredibly important in terms of implementing a very good vaccine.

Reflecting on the discussion of changing from 4 doses to 3 for pneumococcal conjugate vaccine and the standard of evidence the committee seemed to want, Dr. Reingold said he was dubious. It was not clear to him that there would be any more convincing evidence to support changing from a 2-dose to 3-dose schedule for HPV than there were for changing from a 4-dose to 3-dose schedule for pneumococcal conjugate vaccine. Based on the pneumococcal conjugate vaccine discussion, he was not convinced that the committee was ready to do that.

Dr. Bennett said she thought the HPV data were better than the pneumococcal conjugate data, because there are actually comparative trials for HPV.

Dr. Reingold agreed that this was true for immunogenicity. However, in terms of the data for the clinical outcomes, the relative risks for the 2-dose schedule are not very impressive and they certainly do not look comparable to the 3-dose schedule.

Dr. Bennett stressed that those were all 0,2 and did not compare 0,6 or 0,12 so there really are no data on that.

Dr. Markowitz said she wanted to show the effectiveness data because she thought there was a feeling that there would be a lot of effectiveness data to possibly inform the 2-dose schedule. But, the effectiveness data are difficult to interpret at this point post-licensure not only because of the different intervals between doses, but also because of the catch-up population being evaluated in these studies and the differences between 2- and 3-dose vaccinees. It is interesting to see the data, but she was not sure how informative it would be for ACIP's deliberations.

Dr. Temte indicated that he has a screening test in his clinical practice for cervical cancer, but does not have one for invasive pneumococcal disease.

Dr. Bocchini pointed out that the opportunity for considering a 2-dose schedule would be very different if they were not also faced with the 9-valent vaccine that may be licensed within the next 6 months. That would create a situation in which ACIP would be making multiple changes in vaccine recommendations within a very short period of time, which could make it very difficult for primary care practitioners to follow the recommendations or trust them as they evolve.

Dr. Schuchat requested a reminder about what type of application is expected for males for the 9-valent vaccine in terms of age groups, et cetera. There was some discussion regarding off-label intervals and so forth.

Dr. Markowitz indicated that the first licensure expected at the end of 2014 will be for females 9 through 26 years of age and males 9 through 15 years of age. The data on 15 through 26 year olds will be available for the October 2014 ACIP meeting, even though they will not yet have been submitted to the FDA. The feeling of the WG is that it would be very difficult

programmatically to have the quadrivalent vaccine recommended for the older males, but the 9-valent vaccine recommended for females 9 through 26 and males 9 through 15 years of age. Therefore, the proposal is to move forward with the recommendation for the full age group of females and males, even though technically this would be off-label for the 15 through 26 year old males.

Dr. Pickering inquired as to what type of data would be available from Merck at the end of 2015. He also wondered whether the antibody levels and kinetics of the 5 strains in the new vaccine are similar to 16/18.

Dr. Luxembourg responded that the available data would be immunobridging data comparing the immunogenicity data at the peak, which means 1 month after the last dose. The kinetics of between the additional and original types are similar based on the 3-dose immunobridging studies.

Vaccine Safety

Introduction

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Dr. Shimabukuro reintroduced the topic of the febrile seizure (FS) signal in 2010-2011 following trivalent inactivated influenza vaccine (TIV) and 13-valent pneumococcal conjugate vaccine as a lead-in to the two main presentations for this session. As a reminder, “A FS is a seizure accompanied by fever ... without central nervous system infection, that occurs in infants and children 6 through 60 months of age”^{*} Febrile seizures are fairly common during childhood; about 2% to 5% of young children will have at least one febrile seizure.^{*} FSs can happen with any condition that causes a fever, including typical childhood illnesses, many of which can be prevented by vaccination. Rarely, FSs can occur after vaccination. Nearly all children who have a FS recover quickly and are healthy afterward with no lasting effects. However, FSs often result in a visit to an emergency room and can be very frightening for parents and caregivers [^{*} Subcommittee on Febrile Seizures; American Academy of Pediatrics. Neurodiagnostic evaluation of the child with a simple febrile seizure. Pediatrics. 2011;127(2):389-94].

The post-licensure vaccine safety monitoring infrastructures are shown in the following table:

System	Collaboration	Description
Vaccine Adverse Event Reporting System (VAERS)	CDC and FDA	US frontline spontaneous reporting system to detect potential vaccine safety problems
Vaccine Safety Datalink (VSD)	CDC and health plans	Large linked database system used for active surveillance and research
Clinical Immunization Safety Assessment (CISA) Project	CDC and academic centers	Expert collaboration which conducts individual clinical vaccine safety assessments and clinical research
Post-Licensure Rapid Immunization Safety Monitoring (PRISM)	FDA and health plans	Large linked database system used for active surveillance and research

Definition of a signal in pharmacovigilance is, “Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information” [Safety of Medicines - A Guide to Detecting and Reporting Adverse Drug Reactions - Why Health Professionals Need to Take Action. Geneva, WHO, 2002 (<http://apps.who.int/medicinedocs/en/d/Jh2992e/2.html>)].

To recap background and key events, 2010-2011 there was a VAERS data mining signal for Fluzone[®] and febrile seizures. The clinical relevant age group was children 6 through 23 months of age.* It is important to note that Fluzone[®] is the only TIV that is approved for use in children 6 through 23 months of age. At the same time, a signal was detected through VSD RCA for TIV in children 6 through 59 months of age.** As a reminder, RCA is weekly near real-time surveillance conducted during the influenza season and for other vaccines in the VSD. At the same time, surveillance was being conducted for PCV13, so it was possible to conduct an epidemiological study to assess TIV and PCV13 FSs. The key finding from that study was that the attributable risk (AR) for concomitant TIV+PCV13 peaked at 16 months, with 45 additional FSs per 100,000 children vaccinated. In the following season, 2011-2012, the TIV formulation did not change. The VSD RCA signal for TIV persisted. During that season, a CISA TIV-PCV13 fever study was conducted.*** The key finding from that study was that children 6 through 23 months of age who received TIV and PCV13 together at the same visit were about 3 times as likely to have a fever on days 0-1 compared with children who received TIV or PCV13 without the other product. In 2012-2013, there was a change in the TIV formulation and the 2013-2014 TIV was also a different formulation from 2010-2011. No VSD RCA signal was detected for TIV [*Leroy et al. Vaccine. 2012;30(11):2020-3; **Tse et al. Vaccine. 2012 Mar 2;30(11):2024-31; ***Stockwell et al. JAMA Pediatr. 2014;168(3):211-9].

There was a signal for FSs following CSL TIV in Australia during the 2010 Southern Hemisphere influenza season, which precedes and informs the US influenza season. Because of the finding in Australia, CDC and FDA conducted enhanced monitoring for FSs following TIV in 2010-2011 [<http://www.tga.gov.au/pdf/alerts-medicine-seasonal-flu-100702.pdf>; ** Vaccine Safety Datalink; ***Clinical Immunization Safety Assessment Project]. CDC routinely conducts monitoring for FSs every year during the influenza season, but because of what had been observed in Australia that season, every seizure report that came into VAERS was reviewed and 0-1 day and 0-7 day risk intervals were assessed in the VSD RCA. In terms of AR estimates for FSs following the first TIV, a small increased risk was observed for FSs peaking around 16 months of age. However, when TIV and PCV13 were administered together, a noticeable large peak of FSs occurred at 16 months of age with an AR of 45 additional FSs per 100,000 children vaccinated with TIV+PCV13 together [Adapted from Tse et al. Signal identification and evaluation for risk of FSs in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011. Vaccine. 2012;30(11):2024-31. *Vaccines may have been received concomitantly with non-TIV, non-PCV13 vaccines].

CDC, FDA, and ACIP reviewed the data during the 2010-2011 season. After evaluating all the information, CDC determined that no changes in the childhood immunization schedule were necessary and posted this information on the CDC website. Language was also added to the inactivated influenza Vaccine Information Statement (VIS) for the next season to include the following:

Moderate problems following inactivated flu vaccine:

- Young children who get inactivated flu vaccine and pneumococcal vaccine (PCV13) at the same time may be at increased risk for seizures caused by fever. Ask your doctor for more information. Tell your doctor if a child who is getting flu vaccine has ever had a seizure.

*<http://www.cdc.gov/vaccines/hcp/vis/vis-statements/flu.html>

Additional questions following the 2010-2011 FS signal included the following:

- Did other vaccines besides TIV and PCV13 play any role?
- Was there something unusual about the 2010-11 influenza vaccine that resulted in the increased risk for FSs in young children?
- What do the data prior to the 2010-11 influenza season show?

Seizures Following Administration of Multiple Vaccines: A VSD Study

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Dr. Duffy reminded everyone that AAP defines FSs as, “seizures that occur in febrile children between the ages of 6 and 60 months who do not have an intracranial infection, metabolic disturbance, or history of afebrile seizures.” Prior to the 2010-2011 influenza season, other vaccines had been associated with an increased risk of FS, which are shown in the following table:

Vaccine	Post vaccination risk interval, days
Diphtheria-Tetanus-whole cell Pertussis (DTP)	0 – 3
Measles-Mumps-Rubella (MMR)	6 – 11
Measles-Mumps-Rubella-Varicella (MMRV)	7 – 10
Inactivated Influenza (TIV) 2010-2011 season formulation	0 – 1
Pneumococcal conjugate vaccine-13 valent (PCV13)	0 – 1

As reflected in the above table, the risk interval associated with each vaccine differed. A transient risk occurs over a several day period post-vaccination. Given that MMR and MMRV are live vaccines, the risk interval is related to the incubation period of the live virus. In 2010-2011, the new finding for TIV and PCV13 were signaled.

A study was conducted in response to the 2010-2011 findings. The interest in PCV13 in 2010 was due to the fact that the vaccine was new in that year. Subsequent to then, the VSD PCV13 RCA for 2010-2011 did not find an increased risk of FS when comparing PCV13 to PCV7. The objective of Dr. Duffy's current study is to assess whether vaccines other than PCV13 given concomitantly with TIV affect the risk of FS following receipt of TIV. This is a VSD study. The VSD is a collaboration between CDC and several integrated healthcare organizations, and has a combined annual population of over 9 million people (approximately 3% of the US population). For this study, 10 VSD sites geographically dispersed across the US contributed data: Group Health Cooperative, Kaiser Permanente Northwest, Kaiser Permanente Northern California, Kaiser Permanente Southern California, Kaiser Permanente Hawaii, Kaiser Permanente Colorado, Health Partners, Marshfield Clinic, Harvard Pilgrim, and Kaiser Permanente Georgia. These tend to represent more closed-model health plans that have good data capture and well-defined populations.

Case-finding included searching for any medical visits with an ICD-9 diagnosis code of 780.3x (convulsion) occurring in the emergency department (ED) or inpatient settings. The first occurrence of the code had to be within 42 days to find incident events and exclude any follow-up. Medical records were abstracted to confirm the diagnosis and the time of onset in relation to vaccination. The study period included July 1, 2006 to July 1, 2011. The study focused on the 6- through 23-month age group, because they are at highest risk for FS at baseline and this is the age during which vaccines are recommended in the schedule. The FS case definition for this study was, "Clinician diagnosis of seizure; and fever measured or reported; and exclusion of patients with intracranial infection, metabolic disturbance, or history of afebrile seizures. A Self-Controlled Risk Interval (SCRI) method was used for the analysis, and a Conditional Poisson Regression Model was used to model the incidence rate ratio (IRR). Only cases that occurred post-vaccination were used. The risk interval was Days 0-1 and the comparison interval was Days 14-20, with the thought being that Days 0-1 are the biologically plausible risk period for FSs following inactivated vaccines and the 14- to 20-day period represents a baseline risk in which vaccination plays no role in the incidence of FS. Attributable Risk (AR) was determined by multiplying the relative risk (RR) by the background incidence rate in the VSD population per person day, and taking into account a 2-day risk interval.

In terms of the background rate of seizures in the VSD population regardless of vaccination, the peak incidence is at about 16 months of age. At the peak incidence, there are almost 5 seizures per 100,000 persons per day. Also of interest in this study is vaccine combinations. The number of unique vaccine combinations received by children in practice in the VSD is large, with over 2,000 different combinations when unique products and formulations are considered. The percentage of vaccines given alone to children at 6 to 23 months is very low for most vaccines as expected, because vaccines are often co-administered. One exception to this is the inactivated influenza vaccine, which is given by itself in the VSD population about 50% of the time. This has been fairly consistent over the years examined.

The SCRI analysis of TIV by influenza season using non-chart-confirmed data offers an initial sense of whether there were differences in influenza vaccine across seasons. For years prior to 2010-2011 when just influenza vaccine doses given alone were stratified, there was no indication of increased risk of FS. This appeared to be different in the 2010-2011 season, and higher RRs were observed for those who received TIV simultaneously with another vaccine.

Regarding the chart-confirmed analysis, case-finding began with over 1.9 million vaccination visits within the study period for children in the target age group. Among these, 596 children were identified who had a medical visit for a convulsion during the pre-specified post-vaccination intervals. A random sample was selected of 468 charts, of which 428 charts were available for review. In reviewing the charts, 18 of the cases did not represent a new seizure event. In 14 cases, the clinician was not sure whether there was a seizure. Of the events, 21 were non-febrile seizures. In 27 cases, the fever status was not documented so those cases had to be excluded. Several cases had to be excluded for reasons related to timing of vaccination. For example, 2 people were vaccinated after they had a seizure, and 11 people had a time of onset that differed from what was recorded in the administrative data.

Ultimately, 333 chart-confirmed FSs were included in the study (103 in the risk group and 230 in the comparison group). More seizures occurred in the 12- through 23-month age group compared to the 6- through 11-month age group as would be expected from the baseline rates. There were no significant differences by sex, race, or ethnicity although this is a diverse population. Further assessing these patients and their medical histories, for about half of the patients this event represented their first seizure in their lifetime. This means that half had a previous history of seizure. No differences were observed between the groups in family history of FS, premature birth, neonatal intensive care unit (NICU) admission, or developmental delay. Children who had their seizure in the risk interval were slightly more likely to have received an antipyretic in the 7 days before their seizure, but were not more likely to have received antibiotics in the previous 7 days. Some children had a possible non-vaccine cause of fever documented at the time of their evaluation. The most common of these other causes included otitis media, upper respiratory infection, or viral syndrome. Of children in the risk interval, 37% had some other cause documented compared to 77% of children in the comparison group. As expected, this suggests that some of these seizures were influenced by the recent vaccination. Only 10% of children in the comparison group and 13% in the risk group were admitted for their seizure. There was no significant difference. The following chart shows the vaccine exposures these patients had in descending order of frequency:

Vaccine	Risk %	Comparison %	SCRI bivariate IRR (95% CI)
PCV7	51	30	2.7 (1.9 - 3.8)
Hib	46	25	2.9 (1.9 - 4.2)
TIV	43	37	1.8 (1.3 - 2.6)
HepA	43	45	1.5 (1.0 - 2.1)
DTaP	39	27	2.2 (1.5 - 3.3)
MMR	24	22	1.8 (1.1 - 2.8)
Var	24	22	1.7 (1.1 - 2.8)
DTaP-IPV-HepB	21	8	4.1 (2.2 - 7.5)
PCV13	17	10	2.6 (1.4 - 4.8)
RV5	13	5	3.8 (1.7 - 8.3)
MMRV	12	8	2.2 (1.1 - 4.6)
DTaP-IPV-Hib	5	5	1.5 (0.5 - 4.1)
HepB	4	3	2.0 (0.6 - 6.8)
MIV	3	8	0.6 (0.2 - 1.9)
IPV	1	0.5	3.5 (0.2 - 55)
PPV23	1	0	Undefined

PCV7, Hib, TIV, HepA, and DTaP were the most common vaccines. The crude RR shown in the far right column did not take into account any confounding or interaction between different vaccines. This just illustrates that if any vaccine is assessed without taking into account confounding of other vaccines, there will not be a true estimate of the risk.

Looking at the issue of combinations of different vaccinations received on the same day, there were 129 unique vaccine combinations received among the 333 cases. Among these combinations, only 21 were received by four or more patients. This is to say that risk for each combination cannot be assessed separately, so these are examined through regression modeling. First, the two time periods were examined separately: 2006-2007 through 2009-2010 influenza seasons and the 2010-2011 influenza season to determine whether there were differences. Based on those results, it seemed valid to pool all of the study time together. The approach was then to perform multivariate modeling to identify vaccines associated with an increased risk of FS, while accounting for confounding and effect modification between multiple vaccines received on the same day. The process was to begin by considering all of the vaccines shown on the above table, and conduct a manual backward elimination process to look for those that had some effect on FS using TIV as the main effect of interest. The vaccines retained in the final multivariate model included TIV, PCV7 or 13, and DTaP-containing vaccines considered as a group. Once these vaccines were identified using that process, separate models were also examined for each strata defined by the mutually exclusive combinations of these three vaccines.

In the assessment of TIV when given without the other two vaccines, there was no suggestion of an increased risk of FS. When PCV7 was given without the other vaccines, the RR was 2, which was borderline significant. This is consistent with previous findings. When DTaP was given without the other two vaccines, there was not a suggestion of increased RR. When PCV was given at the same time as DTaP, the risk was similar to when PCV was given alone. When TIV was given with DTaP, there was an increased RR of FS of 3.5, which was statistically significant. When TIV was given on the same day as PCV7, similar results were observed. The highest RR, 6.6 (2.8 – 15) occurred on days when children received all three vaccines together. The same approach was used to assess the 2010-2011 influenza season, the difference being that the sample size was smaller and none of the RRs were statistically significant when restricted to the single influenza season. However, a similar pattern is observed.

The investigators believed that comparing the results for the two time periods offered the best estimate of risk for the different vaccine combinations. The RRs were then extrapolated into attributable risks. The differences between the AR estimates for each age group reflected the difference in background incidence of FS in the population rather than a difference in RR due to vaccination. The highest estimate of AR was for the combination of the three vaccines given at 15 months of age, which results in an estimate of 38 FS cases per 100,000 children vaccinated with that combination of vaccines compared to the background rate.

In conclusion, the concomitant administration of TIV + PCV and TIV + DTaP-containing vaccines had higher risks of FS than when the vaccines were given independently. The concomitant administration of TIV + PCV + DTaP-containing vaccines had the highest RR. These increased risks with concomitant vaccination were observed in all influenza seasons studied, not just during the 2010-2011 season.

Febrile Seizures After TIV: PRISM System, 2010-2011 Influenza Season

**Alison Tse Kawai, ScD
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On Behalf of the Mini-Sentinel PRISM Team**

Dr. Kawai noted that for the 2010-2011 influenza season, VSD investigators found a 2.4-fold increased risk of FSs following TIV when adjusting for concomitant PCV13 [Tse et al., 2011]. Similarly, VSD investigators found a 2.5-fold increased risk of FSs following PCV13 when adjusting for concomitant TIV. Furthermore, risk difference calculations suggested a greater risk of FS with same day TIV and PCV13 vaccination when compared to separate day vaccination. However, a formal test of significance was not available at that time. Also relevant were the VAERS findings in which there was disproportional reporting of FS following 2010-2011 FluZone[®]. As a result of the VAERS findings, the FDA posted a notice on its website telling the public about the findings, and also stating that further investigation was underway. As part of that investigation, the FDA Center for Biologics Evaluation and Research (CBER) provided funding to conduct the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) study. The study questions for this assessment of children 6 through 59 months of age in the 2010-2011 influenza season included the following:

- 1) Was exposure to TIV or PCV13 associated with a greater risk for FS when compared to unexposed periods?
- 2) Assuming children received both TIV and PCV13, did administering them on the same day lead to a greater risk for FS when compared to separate days?

These questions were examined in the PRISM system, which is the vaccine safety component of the FDA-sponsored Mini-Sentinel Pilot Program developed to conduct active surveillance for medical product safety. PRISM Data Partners currently include five health insurers. For this study, data were included from three PRISM Data Partners participating at the time: Aetna, HealthCore, and Humana. Children 6 through 59 months of age who were vaccinated between July 1, 2010 through June 30, 2011 were included in the study. Information was also collected on DTaP-containing vaccines to adjust for the potential confounding influence on relative risk estimates for TIV or PCV13. A self-controlled risk interval study design was used. A 0-1 day risk interval was used, with 14-20 days used for the control interval. Exposures to TIV, PCV13, and DTaP or DTaP combination vaccines were identified in claims and immunization registry data. TIV, PCV13, and DTaP administration was validated in medical records if available. Cases were excluded if they were later determined to have LAIV or PCV7 exposures based on medical record review. Outcomes were identified in claims data using ICD-9 codes for seizures, simple FSs, complex FSs, or other seizures (780.3, 780.31, 780.32, or 780.39). Codes were included for inpatient and ED settings only. FS status was validated using medical record reviews. Each case was independently reviewed by two pediatrician adjudicators blinded to vaccination status, and FS were considered confirmed if there was a seizure and fever within 24 hours or a diagnosis of FS. Also excluded were those with conditions stated in AAP treatment guidelines for FS, as well as those with focal seizures unless they were associated with a diagnosis of complex FS.

Approximately 1.9 million children were identified as potentially eligible for this study. Of those, approximately 840,000 children received 1 of 3 vaccines of interest in the study. Of those, 252 were identified to have had a potential FS event in the risk or control interval according to electronic data. As mentioned earlier, medical record review was conducted of potential FS cases identified in electronic data. Of the 252, 86% had charts available to confirm FS status. Of those, 152 were confirmed for a positive predictive value (PPV) of 70%. Of the 64 not confirmed, 19 were excluded because seizures were ruled out, 7 were deemed possible seizures without sufficient documentation, 8 were seizures without sufficient documentation of fever, 22 were afebrile seizures, and 8 were excluded due to other reasons.

Medical record review was also conducted of vaccinations identified in claims or immunization registry data. For the vast majority of vaccinations identified in electronic data, medical records were available. Of the charts, 79% were available for TIV exposure, 91% were available for PCV13 exposure, and 91% were available for DTaP exposure. Vaccine confirmation rates were high when charts were available. TIV or influenza vaccine was chart-confirmed in 98% of cases. PCV13 or PCV was chart-confirmed in 94% of cases. DTaP was chart-confirmed in 100% of cases. Because the chart-confirmed rate of vaccination rates was so high, the analysis included vaccines identified in electronic data or in medical records. Following medical record review, 5 cases were excluded because medical records indicated that seizures occurred outside of the risk or control intervals following vaccination. A further 5 were excluded because LAIV or PCV7 was identified in the medical record.

In terms of the descriptive characteristics of the confirmed febrile seizure cases, the vast majority occurred before 2 years of age as expected. Most occurred in the ED setting without requiring hospitalization. About a third experienced more than one vaccine of interest on the index date of vaccination, demonstrating the high rate of concomitant vaccination in the study. Of note, the rate of concomitant vaccination is much lower than what was seen in the VSD.

Next, the first research question was analyzed: In the 2010-2011 influenza season, was exposure to TIV or PCV13 associated with a greater risk for FS, when compared to unexposed periods? This was done by calculating RR and AR estimates comparing exposed to unexposed periods. RR was estimated using a series of conditional Poisson models. The first models were bivariate or unadjusted models. Then adjustments were made for age and calendar time. The primary analytic model was adjusted for age, calendar time, and the three vaccines of interest. The shape of the age- and calendar time-based risk curves were determined prior to including them in the age and calendar time adjusted models. To do this, person time was included from the underlying PRISM cohort regardless of vaccination. Specifically, quadratic splines were used to adjust for age and calendar time.

In the unadjusted analysis, each of the IRRs were above 1.0. PCV13 was statistically significantly associated with risk of FSs. When further adjusted for age and calendar time, the results were similar and PCV13 was significantly associated with the risk for FSs. When further adjusted for concomitant vaccines, the IRRs for TIV and PCV13 attenuated slightly and PCV13 was no longer statistically significantly associated with risk of FSs. Furthermore, the IRR for DTaP attenuated greatly to 1.

Each of the ARs, regardless of vaccine type or age, was below 4 per 100,000 doses. The highest AR was seen for PCV13 followed by TIV. The AR for DTaP was negligible. The highest ARs were seen at 16 months of age, and the lowest AR were seen at 59 months of age. AR was also calculated based on the worst case scenario, which was done by calculating the ARs

that corresponded to the upper limit of the 95% confidence interval for the IRRs. Under these assumptions, the AR for TIV ranged from 0.93 to 7.1 per 100,000 doses. For PCV13, the AR ranged from 1.2 to 9.2 per 100,000 doses. These AR estimates for TIV and PCV13 based on the worst case scenario were quite modest in size considering that the baseline risk of FS is approximately 2700 per 100,000 children across a child's lifetime.

The second research question was then assessed: Assuming children received both TIV & PCV13 in the 2010-2011 influenza season, did administering them on the same day lead to a greater risk for FS when compared to separate days? This was done by calculating the difference in AR for same day vaccination versus that for separate day vaccination. Specifically, the ARs were translated from the IRR estimates from the self-controlled risk interval design data described earlier. The AR for same day vaccination was calculated based on the IRR estimates from the Conditional Poisson Model described earlier. The AR for separate day vaccination was calculated by summing the AR for TIV without concomitant PCV13 plus the attributable risk for PCV13 without concomitant TIV. An assessment was then made of whether the AR for same day vaccination was equal to the AR for separate day vaccination. To test whether there were meaningful differences between the ARs for same day and for separate day vaccination, the two ARs were then subtracted. Using Monte Carlo simulations, 95% CIs were constructed. No evidence was found to suggest that same day TIV and PCV13 was associated with an excess risk of FS when compared to separate day vaccination. In fact, the point estimate itself suggested 1.1 fewer FS per 100,000 children with same day TIV and PCV13 vaccination, when compared to separate day vaccination. However, it is important to note that the result was not statistically significant and the CI was quite wide.

The investigators also thought it was important to quantify any potential increase in risk following vaccination on the absolute scale. This was done by calculating AR by age in weeks since the baseline rate of FSs is known to vary dramatically by age. The AR was calculated as a function of the IRRs from the primary model, as well as the baseline rate of claims-identified seizures in PRISM population. The baseline rate was adjusted downward using the PPV of claims codes from this current evaluation. That quantity was then multiplied by 2, the length of the risk interval in days in order to get the AR per dose rather than per person day. The assumptions made when calculating AR were that the IRR was assumed to be constant across all ages, the baseline rate was based on quadratic spline for age, and the PPV was based on chart review of control interval cases.

Before making her conclusions, Dr. Kawai thought it would be important to lay the PRISM results in the context of the Tse et al., VSD review results from the 2010-2011 season. Of note, the IRR were statistically significant in the VSD study but were not in the PRISM study. However, the results between the two studies were considered to be consistent for two reasons. First, the IRRs were above 1.0 for both studies. Secondly, the CI overlapped widely. However, the CI in the PRISM study was much narrower and the point estimates lower. It is therefore thought that if present, any increased risk associated with TIV or PCV13 would likely be lower than previously thought. Next, same day versus separate day vaccination of TIV plus PCV13 was compared for the PRISM and VSD studies. For the PRISM study, the point estimate suggested that same day vaccination was associated with approximately 1.1 fewer FS per 100,000 children. However, the result was not statistically significant. The VSD study suggested that there were 7.3 excess cases per 100,000 children vaccinated with same day TIV + PCV13 vaccination. However, no statistical test was done.

The study had many strengths. The first strength was that a self-controlled risk interval design was used. A rigorous adjudication process of febrile seizure cases was implemented by 2 pediatricians blinded to vaccination status. Age, calendar time, and DTaP vaccine adjustments were also made in the analytic models. Perhaps the greatest strength was that there was 80% power to detect IRRs of a size of 2 or above. Like any other observational study, this study was subject to limitations including the inability to validate all vaccine exposures and the limited power to detect IRRs less than 2. However, vaccinations were confirmed in the vast majority of instances when medical records were available. Also, this was the largest study to date on the associations of TIV, PCV13, and risk of FSs in the 2010-11 influenza season in the United States.

In conclusion, in the 2010-2011 season, the IRR point estimates for TIV and PCV13 were above 1.0. However, TIV, DTaP, and PCV13 were not significantly associated with FS in the primary analytic models. The presence of increased risk cannot be ruled out for TIV or for PCV13. However, if they existed, the magnitude of IRRs is lower than originally thought and any potential increase on the absolute scale would be quite modest in size because the ARs based on the upper bound of the 95% CI for IRRs suggest this. Assuming children received both TIV and PCV13 in the 2010-2011 season, administering both vaccines on the same day was not significantly associated with risk of FS when compared to separate day vaccination.

Summary

Tom Shimabukuro, MD, MPH, MBA
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Dr. Shimabukuro thanked all of the CDC and FDA staff and staff at CDC's partner organizations who have been investigating who have investigated this issue over the past four years. Regarding whether the overall risk of FS increased with the 2010-2011 formulation of TIV, evidence from published studies includes the following:

- ❑ VAERS signal in 2010-11 for Fluzone®*
- ❑ VSD Rapid Cycle Analysis (RCA) signal in 2010-2011
 - Further analysis found a peak AR for concomitant TIV+PCV13 at 16 months of age with 45 additional FSs per 100,000 children vaccinated**
- ❑ Persistence of the VSD RCA signal for TIV during 2011-2012 (same TIV formulation as 2010-2011)
- ❑ CISA study that found a 3-fold higher rate of fever on days 0-1 when TIV and PCV13 were given together as opposed to separately (2011-2012 influenza season, adjusted for other concomitant vaccines including DTaP)***

The above studies could not adequately distinguish the independent risk of FS associated with TIV alone versus risk with concomitant vaccinations [*Leroy et al. *Vaccine*. 2012;30(11):2020-3; **Tse et al. *Vaccine*. 2012;30(11):2024-31; ***Stockwell et al. *JAMA Pediatr*. 2014;168(3):211-9].

In terms of the independent effect of TIV on risk of FSs, the PRISM analysis* found no statistically significant independent increased risk of FS associated with TIV during the 2010-2011 influenza season. The RR was 1.4 (95% CI 0.8, 2.4) in the adjusted analysis when TIV was adjusted for PCV13 and DTaP. The updated VSD analysis** found no statistically significant independent increased risk of FS associated with TIV during the 2010-2011 influenza

season, with a RR 1.2 (95% CI 0.2, 5.8) in the stratified analysis of TIV given without PCV13 or DTaP. The updated VSD analysis** found no independent increased risk of FS for TIV given without PCV13 or DTaP during the 2006 through 2009 influenza seasons. In terms of whether the risk of FS was greater when TIV was given with PCV and/or DTaP, the updated VSD analysis for the 2010-2011 season suggested that the RR increased about 3-fold when TIV was given with PCV and/or DTaP compared with unexposed periods.* Similar results were seen for the 2006-2009 influenza seasons. The PRISM analysis did not find any greater risk of FSs for same day versus separate day vaccination with TIV and PCV13 during the 2010-11 influenza season** [Duffy et al. Seizures Following Multiple Vaccines: A Vaccine Safety Datalink (VSD) study. June 2014 ACIP meeting; * Kawai. Assessment of FSs after Trivalent Influenza Vaccines during the 2010-2011 influenza season in the PRISM system. June 2014 ACIP meeting].

The weight of the evidence and the consistency of the findings from the VSD analysis over several seasons suggest that when TIV is given alone, risk of FS is not increased. When TIV is given with PCV and/or DTaP, however, risk of FS is increased. The highest risk is when TIV + PCV + DTaP are given together at 15 months of age. The AR was 38 additional febrile seizures per 100,000 children vaccinated with that combination, which is similar to FS risk seen with measles-mumps-rubella (MMR) vaccine* [Barlow et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. *N Engl J Med.* 2001;345(9):656-61].

In conclusion, simultaneous administration of TIV with PCV and/or DTaP vaccines appears to be associated with an increased risk for FS in young children. This increased risk is transient from the day of to the day after vaccination (days 0-1). Although frightening for parents and caregivers, FSs do not have lasting effects. Getting recommended childhood vaccines during a single healthcare visit has important benefits. On-time vaccinations keep children protected against many infectious diseases, and providing multiple vaccinations in a healthcare visit minimizes the number of healthcare visits that parents, caregivers, and children must make.

Discussion Points

Dr. Reingold found it interesting that the control interval chosen was after the risk interval rather than before. He wondered whether the same analyses had been done using the comparison interval before and after the risk interval, and if it made any difference.

Dr. Duffy indicated that the control interval was chosen specifically to exclude the risk period for MMR and MMRV vaccines. The goal was to replicate the original findings so that it would be closely comparable to the surveillance conducted in 2010-2011, which used the same risk intervals.

Dr. Reingold said he was not sure that was the answer to his question. He clarified that his question was, "If you choose the controlled interval before rather than after, does it make any difference?"

Dr. Duffy replied that they did not believe it should, but this has not been assessed.

Dr. Reingold said he was just curious because it seemed to him that if something touched off a seizure, perhaps during the several weeks after that, there would be a lower risk of seizure. The PRISM analysis showed that there is basically no greater risk of giving vaccines together on the same day with respect to the AR, which would be expected. But, this seemed to be at

odds with the conclusion that the RR of giving the vaccines together on the same day is increased. He wondered how the possibility could be excluded that each of the individual vaccines given separately has perhaps a 50% increase in RR, an RR of 1.5, which these studies do not have the power to exclude. In fact, the overall risk is no different giving them combined on the same day as opposed to giving them separately on individual days.

Dr. Kawai said she was not entirely sure she understood the question. In this study, the investigators did examine whether same day TIV + PCV13 was associated with a greater risk for FS and did not find any difference. For the RR estimates, they wanted to isolate the independent effect of each of the vaccines, which was why the joint effects of TIV + PCV13 were not presented in RR format.

Dr. Reingold referred to the slide that stated, "Simultaneous administration of TIV with PCV and/or DTaP vaccines appears to be associated with an increased risk for febrile seizures in young children." He emphasized that his point was that if giving one vaccine on one day has an RR of 1.5, which cannot be excluded with the CIs, then perhaps the risk of giving the vaccines individually on separate days, overall there is no greater RR than giving them all together on one day.

Dr. Duffy indicated that this was tested in the multivariate model. Using a multivariate model that included all three vaccines in the same model, tests were conducted for effect modification. In terms of the *P* results, the TIV/PCV interaction was 0.0494. The TIV/DTaP interaction was statistically significant at 0.0031, and the 3-way interaction was 0.0735, so it was tending toward significance but was not significant. He would argue that this suggests that there is a difference in RRs for the 2-way combinations at least, and a suggested interaction for the 3-way combinations that are different than giving them on separate days.

Regarding Dr. Reingold's question pertaining to why not a pre-control interval versus a post-post interval, Dr. Lee (MS/PRISM Team) said this had always traditionally been done because of the healthy vaccinee effect. One could argue that in this instance, it probably would have been okay because of the short time interval, and it probably would have made no difference either way. This was not done in this instance. In terms of the second question raised, both interpretations are correct but answer slightly different questions—one being the 2 vaccines and exposed period compared to an unexposed period. If two vaccines are given, then there is more risk of fever and potentially that puts the recipient at a higher risk of FSs. But regarding the assumption that children will receive vaccines and whether there is a greater risk for same day versus separate day, at least in the PRISM study, it is believed that there is no greater risk of giving them on the same day, assuming that children are going to be vaccinated anyway. The method was not available in the prior VSD study to be able to provide CIs. It looked elevated. It may have been that the CIs were wide in the first place, and the investigators could not say either way.

Dr. Gorman (NIH) inquired as to whether Dr. Kawai was talking about a Poisson distribution around the lambda as the model. He also said that in terms of quadratic smoothing or quadratic splining, his understanding was that Poisson is a logarithmic function and not a quadratic function. He asked whether that was just a terminology change in the 30 years since he looked this last, or if it is a difference in interpretation of how the math is done.

Dr. Kawai responded that she used a Conditioning Poisson Model, and that she used the quadratic spline for the age and calendar week effects, not the effects of vaccination.

Regarding Dr. Gorman's question about quadratic splining, Dr. Lee (MS/PRISM Team) said this was specifically used because there was so much time varying confounding by week of age that the investigators felt the need to adjust for that in the offset term.

Dr. Plotkin (Vaccine Consultant) asked about the recommendation concerning use of antipyretics for TIV.

Dr. Kimberlin (AAP) replied that the recent recommendation is that the AAP is not supportive of using prophylactic antipyretics, but is very comfortable with using antipyretics for children who have developed fever.

Dr. Plotkin (Vaccine Consultant) wondered whether there was any possibility of reexamining that in light of the data suggesting that TIV together with other vaccines increases the risk.

Dr. Kimberlin (AAP) said he thought that because of the concerns of the safety of the antipyretics in that age group, the risks of the antipyretics would have to be balanced with the risks of the FSs. His guess was that this would be a wash. Given the data suggesting that there is only a slight increase in the risk for an FS, a lot of children would be given antipyretics to prevent very few FSs. Also, there is not a lot of good data to suggest that using antipyretics prophylactically actually does reduce FSs. Therefore, he thought the AAP currently probably would stand on the recommendation that antipyretics should not be administered prophylactically but would have no problem with treating a fever.

Dr. Temte asked Dr. Broder whether she had a response.

Karen Broder (ISO) indicated that there is some pilot work underway with the CISA project through Duke University and CDC, which is exploring the effects of using prophylactic antipyretics versus placebo on immune responses after inactivated influenza vaccine. The work is just beginning, but over the next year or two these data might be informative—at least to speak to the issue of whether antipyretics blunt immune responses. That is the concern of previous literature.

Dr. Englund (PIDS) asked whether the investigators took rotavirus vaccination into account in their analyses. A recent paper in 2013 showed protective association of rotavirus vaccine and a decrease in FS. In other words, rotavirus is not very likely to cause a substantial amount of FS in children under 2 years of age and with the increasing use of rotavirus vaccine, the overall incidence of FS has gone down.

Dr. Duffy responded that the VSD study addressed the transient risk during the post-vaccination period and would not address the more cumulative effect over a child's lifetime in terms of how many febrile seizures they might have by being vaccinated versus unvaccinated with particular vaccines. Specifically regarding the 0-1 day risk interval post-vaccination, all other vaccines that the children in the VSD study received were assessed. No vaccines other than TIV, PCV, or DTaP seemed to have an independent effect once the effects of the others were controlled for. While they did not have data on monovalent rotavirus vaccine, there was no suggestion of an independent risk of FS with the pentavalent rotavirus vaccine in the 0-1 period.

Adult Immunization

Introduction

Dr. Tamera Coyne-Beasley, Chair Adult Immunization Work Group

Since the Adult Immunization WG was not able to provide this update during the February ACIP meeting, Dr. Coyne-Beasley highlighted the work done in advance of the publication of the adult schedule. She thanked all of the collaborating organizations and CDC staff for their help in publishing the yearly update and associated materials on the CDC website and elsewhere. The updated schedule is also published along with the updated adult immunization coverage data.

The ACIP recommendations were published in *Annals of Internal Medicine* on February 3, 2014 and were approved by the following:

- American College of Physicians
- American Academy of Family Physicians
- American College of Obstetricians and Gynecologists
- American College of Nurse Midwives

The recommendations also were published in the *MMWR* in an e-notice to readers on February 3, 2014 and a print version on February 6, 2014. The differences between the *Annals of Internal Medicine* and *MMWR* publications is that the *MMWR* publication highlighted the changes from the previous years and did not include figures in the contraindications tables. Since that time, there have been many communications documents and the CDC adult and adolescent immunization quiz was also updated in February 2014.

During this session, Dr. Walter Williams provided a summary of recently published non-influenza vaccine coverage among adults. Dr. Kris Sheedy provided an update describing the CDC adult immunization campaign, including materials developed to promote adoption of NVAC updated Adult Immunization Practice Standards. Dr. Coyne-Beasley provided an update on other key adult immunization activities to address lagging coverage in adults.

Update on Adult Immunization Coverage

Walter W. Williams, MD, MPH Medical Epidemiologist National Center for Immunization and Respiratory Diseases Centers for Disease Control and Prevention

In this presentation, Dr. Williams summarized the results from the 2012 NHIS on non-influenza adult vaccination coverage published in the *MMWR* on February 7, 2014. He described the data source, provided a top-level summary of the key coverage findings, and provided sources for additional information. The NHIS is an annual in-home survey about the health and health status of non-institutionalized civilians in the US using nationally representative samples. Questions about receipt of recommended vaccinations for adults are asked of one randomly selected adult within each family in the household. Weighted data were used to produce

national coverage estimates. The final sample adult component response rate for the 2012 NHIS was 61.2%. The sample size was 34,218.

This report does not include influenza vaccination, but does include pneumococcal vaccination (overall, including the 23-valent pneumococcal polysaccharide vaccine and the 13-valent pneumococcal conjugate vaccine); tetanus toxoid-containing vaccines (including Td or Tdap); hepatitis A; hepatitis B; herpes zoster (shingles); and HPV vaccines. Analyses were conducted to estimate Tdap vaccination of adults aged 65 years of age and older being collected in the NHIS for the first time starting in 2012. Comprehensive information on high-risk status for hepatitis A or B was not collected in the 2012 NHIS. Information was collected on travel status and chronic liver disease for high-risk for HepA, and diabetes mellitus for HepB. HCP were identified, including those who provided direct patient care.

Adults were considered to be at high risk for pneumococcal disease if they had been told by a doctor or other health care professional that they ever had diabetes mellitus; emphysema; coronary heart disease, angina, heart attack, or other heart condition; lymphoma, leukemia, or blood cancer. Adults were also considered to be at high risk for pneumococcal disease if during the preceding 12 months they had a cancer diagnosis (excluding non-melanoma skin cancer), asthma episode or attack, chronic bronchitis, weak or failing kidneys, or were current smokers.

As a reminder, there are two types of pneumococcal vaccine: 23-valent polysaccharide vaccine (PPSV-23) which has been recommended for many years for adults, and the 13-valent conjugate vaccine (PCV-13) which was recommended in June 2012 for adults with weakened immune systems and other specific groups. Estimates reflect overall pneumococcal vaccination coverage for PPSV-23 and PCV13 vaccine uptake. The 2012 NHIS did not estimate the proportion of pneumococcal vaccinations by type. Coverage among high-risk adults aged 19 through 64 years was 20.0%, and pneumococcal coverage among adults aged 65 years and older was 59.9%, similar to the estimates for 2011. Among adults aged 60 years and older, 20.1% reported receiving herpes zoster vaccination, a 4.4 percentage point increase from the estimate for 2011 (15.8%). That was primarily due to increases among non-Hispanic whites.

The proportion of adults who received a tetanus vaccination during the past 10 years was 64.2% for those aged 19 through 49 years, 63.5% for those aged 50 through 64 years, and 55.1% for those aged 65 years and older. Overall tetanus coverage did not increase from 2011. Reported Tdap coverage among persons aged 19 through 64 years was 15.6%, a 3.2 percentage point increase compared with the 2011 estimate. Again, that increase was due primarily to increases among non-Hispanic whites. Tdap vaccination coverage of adults aged 19 through 64 years among those with household contact with an infant aged less than 1 year was 25.9%, similar to the 2011 estimate. Tdap vaccination from 2005-2012 among HCP aged 19 through 64 years was 32.6%, a 5.8 percentage point increase over 2011. Of the respondents for Tdap vaccination, 34% were excluded from estimations of Tdap coverage, creating a potential for bias. Tdap coverage was estimated after excluding from the 34,218 respondents aged 19 years and over all those without a "yes" or "no" response for tetanus vaccination status in the past 10 years (5.4%); those without tetanus vaccination status during 2005–2012 (3.7%); and those who reported tetanus vaccination during 2005–2012 but were not told (20.4%) or did not know the vaccine type (4.3%). This yielded a sample of 22,653 respondents aged less than 19 years for whom Tdap vaccination status could be assessed. Sensitivity calculations were conducted to assess the magnitude of potential bias that might result from these exclusions. Depending on what proportion of excluded respondents actually received Tdap, actual Tdap coverage could fall within the range of 11.2% to 39.4% for adults 19

through 64 years and 6.0% to 31.0% for adults age 65 years of age and over. This sensitivity analysis assumed no errors in reporting when the responses were all “yes” or “no” combinations.

With regards to the proportion of tetanus vaccine that was Tdap among those who received a tetanus vaccination, among 13,145 respondents 19 years of age and over who received a tetanus vaccination during 2005–2012, 52.6% reported that they were not informed of the vaccination type and 11.1% could not recall what type of tetanus vaccination they had received. Of the remaining 36.3% of respondents who reported they knew what type of tetanus vaccine they received, 65.4% reported receiving Tdap. Among 1,501 health-care personnel 19 years of age and over who received a tetanus vaccination, 33.1% reported they were not informed of the vaccination type, and 9.3% could not recall what type of tetanus vaccination they had received. Of the remaining HCP (57.6%) who reported they knew what type of tetanus vaccine they received, 76.3% reported receiving Tdap. Vaccination of HCP for Tdap was statistically higher than that among non-HCP.

Hepatitis A coverage remained low among adults aged 19 through 49 years at 12.2%, and was similar to the estimate for 2011 (12.5%). HepA coverage was higher among those with travel outside the US to an endemic area (18.9%) compared with those without endemic area travel (8.6%). Vaccination coverage among adult travelers to highly endemic countries was similar to the estimate for 2011. Hepatitis B coverage among adults aged 19 through 49 years was 35.3%, similar to the estimate for 2011. Among persons with diabetes, coverage was 28.6% for adults aged 19 through 59 years and 15.1% for adults aged 60 and older, similar to the estimates for 2011, highlighting the need to increase awareness of the higher risk for acute HepB in this population and the need for vaccination.

Among women aged 19 through 26 years, 34.5% reported receiving at least one dose of HPV vaccine, an increase of 5.0 percentage points from the 29.5% reported for 2011. Again, this increase was due to increases primarily among non-Hispanic whites. Coverage among women aged 19 through 21 years was 44.3%, similar to the 2011 estimate. Coverage among women aged 22 through 26 years was 28.2%, a 6.7 percentage point increase compared with 2011. The increase among women aged 22 through 26 years indicated that some catch-up vaccination is occurring in this age group, primarily among white women. Data were not collected on age of HPV vaccination in 2012, so it was not possible to determine whether vaccination occurred as part of an adolescent program or when recipients were 19 years of age or older. Data on age of HPV vaccination was collected in the 2013 NHIS. Coverage among males has remained low since the ACIP recommendation to vaccinate males in October 2011. Receipt of at least one dose of HPV vaccine among males aged 19 through 26 years was 2.3%, similar to the estimate for 2011. Coverage was 2.4% for males aged 19 through 21 years and 2.2% for those aged 22 through 26 years.

To summarize, compared with estimates from the 2011 NHIS, modest statistically significant increases in 2012 were observed for three of the more recently recommended vaccinations for adults, HPV, herpes zoster, and Tdap. The increases ranged from 3 to 6 percentage points. The increases in HPV, Tdap, and zoster vaccination were due primarily to increases among non-Hispanic whites, indicating a widening gap in coverage compared with non-Hispanic blacks, Hispanics, and non-Hispanic Asians. The differences seen in HPV vaccination coverage of non-Hispanic white and Hispanic women is not observed in data from the NIS among teens. This is being assessed in greater detail by comparing cohorts reporting vaccination in NHIS versus NIS. There are similar overall results when comparing HPV coverage among persons

who are 17 years old in NIS teen data and 18 years olds in NHIS data, except that there were substantial differences for Hispanics that may actually indicate a large bias in the NHIS self-reported data for HPV vaccination among Hispanic women.

For the vaccination groups for which the results were reported by race/ethnicity, the vaccination coverage among non-Hispanic whites and the difference in coverage for non-Hispanic blacks, Hispanics, and non-Hispanic Asians compared to whites, there were statistically significant disparities for 31 of the 42 comparisons by vaccine and age/target groups. These disparities ranged from -2 percentage points for Hispanics versus whites for HepA in 19 through 49 year old adults, to -27 percentage points for Asians versus whites for HPV in 19 through 26 year old women. There was only one instance with higher coverage than whites, with Asians having HepA coverage seven percentage points higher than whites aged 19 through 49 years.

To summarize the racial/ethnic disparities, compared with 2011, racial/ethnic differences persisted for all six vaccines and widened for Tdap, herpes zoster, and HPV. Non-Hispanic blacks, Hispanics, and Non-Hispanic Asians generally had lower vaccination coverage than non-Hispanic whites for all vaccines routinely recommended for adults with several exceptions. For PPSV/PCV13 among those 19 through 64 years of age, blacks had coverage similar to whites. For Tdap among those 19 years of age and older, Asians had coverage similar to whites. For Tdap among those 65 years of age and older, blacks had coverage similar to whites. For HepA, blacks had coverage similar to and Asians had coverage higher than whites. For HepB, Asians had coverage similar to whites. Among HCP, non-Hispanic black and Hispanic HCP had lower coverage for Tdap, but coverage similar to whites for HepB.

The findings in this report are subject to at least five limitations. First, the NHIS sample excludes persons in the military and those residing in institutions, so the results apply only to the civilian, non-institutionalized population. Second, the response rate was low at 61.2%. A low response rate can result in sampling bias if the nonresponse is unequal among the participants regarding vaccination. Third, the determination of vaccination status and identification of high-risk conditions in NHIS were not validated by medical records. Self-report of vaccination is subject to recall bias and overestimation of rates. However, adult self-reported vaccination status has been shown to be sensitive for pneumococcal, tetanus, hepatitis A, hepatitis B, HPV and herpes zoster vaccination and specific for vaccination with all these vaccines, except for tetanus vaccination [Rolnick et al. Self-report compared to electronic medical record across eight adult vaccines. *Vaccine* 2013;31:3928-3935]. It is important to note that the accuracy of recall by young adults of vaccinations routinely recommended during adolescence has not been studied. Fourth, the Tdap estimate is subject to considerable uncertainty since many respondents were excluded from estimations of Tdap coverage. Finally, age at vaccination was not known for vaccines adults reported having “ever” received, so it is not clear for younger adults whether vaccination occurred as an adult aged 19 or older or was given as part of a child or adolescent vaccination program.

In conclusion, vaccination coverage estimates for the three vaccines in this report that are included in *Healthy People 2020* (pneumococcal, herpes zoster, and hepB for HCP) are well below the respective target levels of 90% for persons aged ≥ 65 years and 60% for persons aged 18 through 64 years at high risk (pneumococcal vaccine), 30% (herpes zoster), and 90% (hepatitis vaccine for HCP). Despite some improvements in vaccination, coverage remains low for most vaccines routinely recommended for adults and racial and ethnic disparities remain. Much remains to be done to increase utilization.

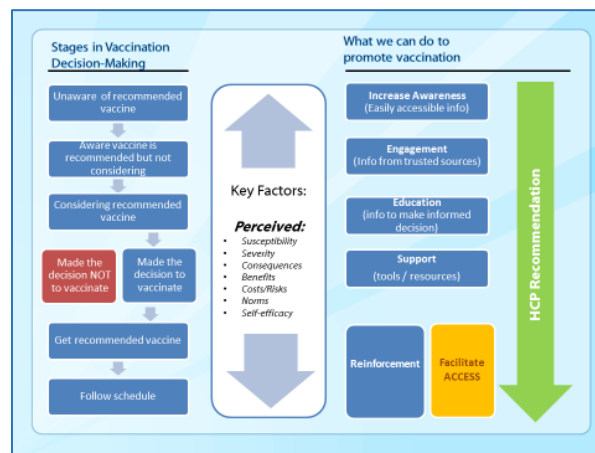
Update on CDC's Adult Immunization Communication Activities

Kristine Sheedy, PhD
Associate Director for Communication Science
Office of the Director
National Center for Immunization and Respiratory Disease
Centers for Disease Control and Prevention

Dr. Sheedy presented an update on CDC's communication activities related to adult immunization. In the fall of 2012, CDC launched a 2-year adult immunization communication program. The broad goal was to develop a brand as well as messages and materials that could help raise awareness and promote immunization according to the recommended schedule by targeting adults and the physicians and other healthcare professionals who serve them.

Knowing that making changes in social norms and behaviors related to adult immunization requires a long-term effort well beyond the 2-year project timeline, CDC set out to lay a strong foundation for this in future work through formative communication research. The research included a national survey, which Dr. Sheedy shared with ACIP in 2013; focus groups with adults; and a review of available published and gray literature related to adult immunization communication. In addition, 28 in-depth interviews were conducted with physicians and nurse practitioners and nurse practitioners. The topics discussed with them included vaccine administration, knowledge of immunization schedules, attitudes regarding VPDs, vaccine recommendations and conversations, and resources and support needed. Summaries of this research are available for those who are interested in more details.

Based on CDC's research, best practices, and a number of helpful behavioral change models and theories, the following framework was developed for how communication efforts can encourage adults to get vaccinated:



The bottom line is that behavior change is complicated. On the left side of the framework are the different states that people may go through in terms of vaccine decision-making. On the right side are the various strategies that can be helpful in moving people through those changes. In the middle are some of the key factors that mediate those. It is known that it is important for all of these to be delivered by the most trusted sources (e.g., doctors and other health care professionals), which is the green arrow going through all of the stages.

There are some key drivers in CDC's framework and approach to communicating with adults about immunization. These include stressing the relevance and importance of timely vaccination by highlighting susceptibility and explaining the severity and potential costs of getting vaccine-preventable diseases. However, this information has to be balanced with empowering messages that present vaccination as a doable step that can be taken to protect themselves and their loved ones. It is also necessary to provide plain language information that can help adults make informed decisions, and provide support in getting vaccinated. The information should be tailored as much as possible. For CDC's communication to the public, adults are encouraged to talk with their HCPs about vaccines that are right for them.

Key principles of CDC's communication with HCPs include reminding them why vaccination is an important preventive measure, and their role in making sure their patients are protected. The recently updated NVAC standards provide guidelines that call on all HCPs to take certain steps, including sharing a strong recommendation. It is important to share what has been learned from consumer research regarding what can make recommendations compelling, and how to best address patients' questions and concerns.

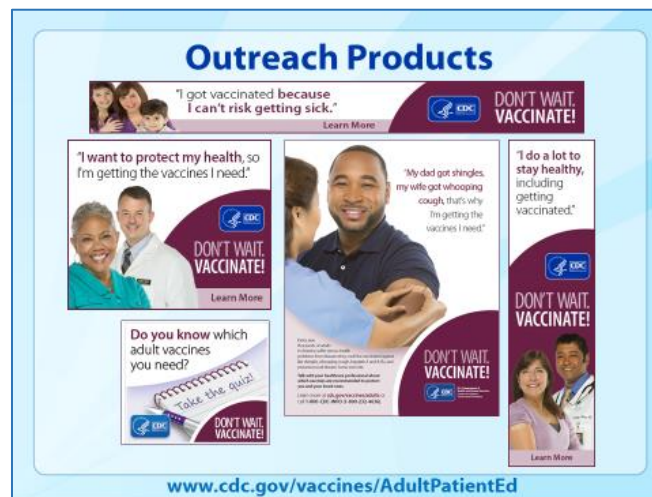
In CDC's most recent research with HCPs, not all physicians responded positively to information about the standards, in some cases feeling that it is not realistic to ask them to assess vaccination status and discuss needed vaccines at every visit. For instance, when they are dealing with a patient who has an acute issue.

A critical piece of CDC's focus was the conversation between providers and their patients. For some patients, a clear and strong recommendation that a vaccine is needed may be sufficient. Others may want additional information. CDC summarized the five main best practices the agency identified for strengthening vaccination recommendations into an approach called SHARE, which includes the following:

- **Share** the reasons why the recommended vaccines are right for the patient given age, health status, lifestyle, job, or other risk factors.
- **Highlight** your own experiences with vaccination to reinforce benefits and strengthen confidence.
- **Address** patient questions and any concerns about vaccines, including side effects, safety, and vaccine effectiveness, in plain and understandable language.
- **Remind** patients that many vaccine-preventable diseases are common in the U.S. and can be serious for them.
- **Explain** the potential costs of getting VPDs, including serious health effects, time lost (such as missing work or family obligations), and financial costs.

While there is no magic message or script that can work across all adult vaccines and for all patients, CDC believes that these are important communication strategies that providers should keep in mind when helping patients make the decision to get recommended vaccines.

CDC has developed a variety of communication resources that can be used with a broad general audience of adults, as well as those with chronic conditions. These include outreach products (e.g., posters, flyers, web buttons, banners, et cetera), materials that can be used for patient education such as fact sheets, and tools to assist adults such as the online vaccine quiz and the revamped adult immunization website. The following are a few samples of CDC's media and outreach products:



Communication products, resources, and tools have also been developed to encourage and support HCPs in improving adult immunization practices, who are critical in getting adults vaccinated. CDC launched its vaccine schedule app in May 2014. In its first 20 days of being available, it was downloaded 3600 times. That includes the adult immunization schedule. Materials for HCPs includes a series of fact sheets on improving adult immunization practice, including vaccine assessment, recommendations, administration, referral, and documentation. Each sheet covers one of the steps and provides tips, resources, and tools to aid in implementation:



The second sheet in the series includes the SHARE approach, as well as some tips on how to address common questions.

CDC continues to look for opportunities to get the word out broadly about adult immunization, and had the opportunity to do that in February 2014 with the release of the 2014 adult immunization schedule and the NHIS 2012 adult vaccination coverage data. Some of the activities included the following:

- Coverage in national media of adult vaccination coverage rates
- Social Media: CDC, Dr. Frieden, and Dr. Besser (ABC news) tweet about adult vaccination
- Radio Media Tour with CDC and ACP vaccination experts reaching an estimated 35,876,886 listeners from live and taped interviews, and a :60 packaged news segment
- Distribution of a matte article for placement in print and electronic media

The next major outreach effort will be during National Immunization Awareness Month in August 2014. CDC looks forward to working with partners to try to get the word out about adult immunization during that month.

The next steps for CDC are to continue to share key research findings with partners and health communication professionals; continue to test and develop patient education materials and other HCP resources, including Spanish language; and continue to disseminate messages, products, and resources through engagement of partners and media. Of course, with influenza season approaching, CDC will look for opportunities to promote adult immunizations and for encouraging people to get their annual influenza vaccinations. As always, CDC asks its partners to use the agency's products in a number of ways, and to feel free to offer input and feedback.

Key Adult Immunization Activities to Address Lagging Coverage In Adults

Dr. Tamera Coyne-Beasley, Chair Adult Immunization Work Group

Dr. Coyne-Beasley presented information about some of the key activities that are underway to address lagging coverage in adults. She highlighted one of the primary activities, the National Adult and Influenza Immunization Summit (NAIIS) (aka the Summit). This summit is a partnership of 300 organizations with goals to convene adult and influenza immunization key stakeholders, identify actions that can be taken by members to improve the uptake of ACIP adult-recommended vaccines, and improve uptake of adult immunizations recommended by ACIP and influenza vaccine among all ages. A meeting was last convened in May 2014 in Atlanta, Georgia. However, the Summit work groups meet year-round. There are five work groups that are dedicated to issues related to providers, patient education, access and collaboration, quality, and decision-makers.

Highlights of the May 2014 NAIIS meeting included the following:

- Presentations by Dr. Howard Koh, Dr. Tom Frieden, and Dr. Anne Schuchat, with Dr. Koh noting the forthcoming National Adult Immunization Plan
- Preliminary data from the University of Colorado that pointed out limited knowledge among providers regarding issues of billing and payment for adult immunizations (e.g., which are covered by Medicare B versus by D)
- Limited use of immunization information systems by adult medical providers
- Additional evidence confirming willingness of patients to be vaccinated if strongly recommended by their providers

- Presentations and discussions of challenges of developing quality measures for adult immunizations
- Many examples of success in raising coverage where practice standards for adult immunizations were applied
- Influenza vaccine dose projection from manufacturers of 157 million doses for 2014-2015 season

Presentations from the May 2014 NAIS can be found at www.izsummitpartners.org

In terms of future key activities, the NAIS members are committed to exploring a CPT code for vaccine counseling; promoting implementation of the updated standards of practice for adult immunizations; increasing awareness of adult immunizations through National Immunization Awareness Month; identifying and disseminating provider business tools to reduce practice costs as barrier for providers; continuing evaluation of adult immunization quality measures; and addressing barriers related to in-network provider status requirements for patients and providers.

Discussion Points

Dr. Duchin indicated that at the local public health level, he deals with HCPs who have immunization issues and finds that one barrier is the perception of the time investment that is needed by providers to engage in the activities they are being asked to do with respect to counseling and explaining the risks, benefits, and burden of disease. He inquired as to whether CDC has assessed how much time it takes a provider to implement recommendations in the practice setting. It is important for practitioners to have a realistic expectation of how much time this will take. Increasingly, patients are being managed by medical teams as opposed to individual providers. Those teams have specialists who deal with specific aspects of a patient's health. He wondered whether CDC had explored the potential to have immunization be a part of the team medicine approach and how that might work.

Dr. Coyne-Beasley indicated that she is a member of the Provider WG where many of these issues are being discussed. The amount of time it takes is one of the primary reasons the WG is looking into the development of a CPT code so that not only can the amount of time it takes be evaluated, but also so that physicians can be reimbursed for that time. Management by medical teams is also being discussed and considered by the Provider WG.

Dr. Bennett emphasized how discouraging adult immunization uptake is. A lot of work has been done to look granularly at what it takes to immunize adults in practices. John Fontanesi at UC San Diego used to study this in great detail, and there is a lot of interesting information from his work. The point about medical teams is a critical one. Years ago it was established in her own community that using extenders of professionals was the best approach and was the most cost-effective and most efficient. Much of this can be automated to a large extent, so it is important to look for solutions that make this part of the way providers do business (e.g., through automation, use of extended teams, and standing orders).

Dr. Kempe indicated that based on national surveys of family medicine and internal medicine providers, one of the biggest time issues is figuring out what people need and not having the information to do that. Having spent her career in implementation of delivery in pediatric practices, she thought they could learn a lot from each other. Since a major part of pediatrics is delivering immunizations, she expressed her hope that they could learn lessons from one another. She put in a major plug for systems changes, because behavior change is very difficult. The “low hanging fruit” really is much easier. The majority of adults as parents of children are not vaccine-hesitant or resistant. They simply do not know they need vaccines, and are vaccines are not routinely mentioned. Immunization registries, which now exist in every state, can immediately start having adult records and many states already do. This can provide a forecasting function at the point of care, and automatically generate reminder/recalls for entire populations. The efficiency is huge. Getting from 20% to 60% could be pretty quick if systems like this were implemented.

Dr. Temte noted that he went through his recertification process in 2014 for AAFP. Maintenance and certification are required every 7 to 10 years, and part of that is a quality improvement project. He selected immunization for his quality project. This gets somebody in the habit of doing an assessment of reminder/recall. AAFP has approximately 9000 family doctors every year who have to be recertified. CDC could partner with professional societies in terms of creating a “low hanging fruit” that would be easy to do.

Ms. Hayes (ACNM) indicated that ANA was recently funded through CDC and ASTHO to work on a communications project, with which they had a lot of fun. One of the things that they developed was super women that have amazing graphics, with shields with bacteria and viruses coming at them. This is all downloadable for free from <http://www.midwife.org/Immunization-Resources-for-Midwives> because it was funded by CDC, for which she expressed gratitude. The posters are giant and gorgeous and are available at midwife.org for shipping costs only.

Dr. Riley (ACOG) indicated that ACOG has known for a long time that getting obstetricians and gynecologists on board with immunization campaigns has been difficult, and that it is the business aspect of starting an immunization program within an office that is a stumbling block. ACOG teamed up with AAP and there is a webinar on Wednesday July 30, 2014 from 12:00 PM to 1:00 PM titled “The Immunization Business and Clinical Strategies for OBGYN Practices.” Basically it is obstetricians and gynecologists learning from what pediatricians have been doing for years, and doing very well. She referred everyone to the ACOG website immunizationforwomen.org for more information. The intended audience is OB/GYNs, but it could be any practitioner.

Dr. Even (ACHA) indicated that ACHA has adopted the idea that an institution is a really good way to get college students up to date on their immunizations. ACHA has a document that includes all of the recommended adult immunization for college students, which is kept up to date based on ACIP recommendations. As a practitioner and a director of a health center, her challenge has been not the interest by providers but the complexity. This is where a registry would be helpful. If they get an immunization in their electronic record, it will get dumped it into the state registry in Missouri. Students come to them from all over the country and fax and send documentation records, and only a few immunizations are required, so they pay attention to those. They are trying to increase the familiarity of the nurses and providers to ask whether students have had their Tdap. Their providers are interested in trying to move this forward.

Dr. Jenkins inquired as to whether there was any analysis by income level. It seemed to her that if there were disparities by ethnicity, it may be linked to disparities by income. The issue of practices that serve low-income populations is another challenge for the business model. Pediatricians report that setting up to administer immunizations is incredibly expensive in terms of the equipment and type of monitoring to manage immunizations. She wondered whether anything was known about the income differentials and whether the Provider WG is assessing practices that may need some incentives in order to be able to set up for immunizations.

Dr. Williams replied that for this particular report, they basically assessed the covariates that he referenced at the beginning of his presentation: age, high risk status, and vaccination target group criteria. They have performed specific analyses on individual vaccines that included assessment of other demographics and access to care characteristics such as education, whether a person had a regular doctor, and whether they had health insurance and types of insurance. Where those types of analyses have been done, consistently a risk is seen for lower vaccination uptake among those with lower education, no regular doctor, no health insurance, and who make less money.

Dr. Coyne-Beasley added that the Provider WG has talked about immunization registries. It is known that adults completely underutilize immunization registries. A larger issue is that it is assumed that everyone will have an electronic health record. But looking at the diversity of providers and who they serve and the resources that people have within their offices, there is a wide range. To try to meet that need, it is important to the Provider WG to have a diversity of providers as members of the work groups to help them figure out needs. She said she also appreciated the conversation about teams, because that is how vaccination programs can be done most efficiently and successfully in offices. They did not mean to imply at all that the work is going to be easy. Getting a diversity of opinions from practices with a wide variety of resources will be important in trying to combat this issue. Immunization registries are very important and so are electronic health records and accessing them. There are practices without internet access.

Dr. Kohn (Merck) said he did not see any data in the presentations about the rates of immunization among HCPs. He wondered if it was realistic to expect that providers would carry the desired messages if they were not getting vaccinated themselves. It is known that even in the setting of the H1N1 pandemic this was really a challenge. He wondered if anyone had any thoughts about that and the types of activities they might engage in that area to improve adult immunization rates.

Dr. Williams replied that at least two data points were provided for HCP in the presentation on coverage, one for Tdap and one for HepB vaccination. The experience has been that when HCPs themselves serve as models as well as offering some recommendations in their practices for their clients, vaccination levels in those types of practices are much higher than when that circumstance is not the case.

Dr. Fryhofer (AMA/ACP) said that the internists do have a quality improvement project for which MOC credits are available. ACP also has an ACPConnect. What they are trying to do is find joy in quality improvement so they can also share in the joy of knowing their patients are vaccinated.

Dr. Bob Hopkins (Emergent BioSolutions) said he had always wondered whether it is possible to implement a personal vaccine record or personal medical record specific to vaccines in order to empower patients that could be started from birth. Skirt the HCP all together and go right to the mom, and then carry that forward through teen years, college, and further.

Dr. Coyne-Beasley responded that she saw this approach more in terms of pediatrics than adults. This happens quite frequently in non-industrialized countries. She does a lot of mission work, and one of the things that is interesting to her is that often-time there are no electronic medical records or immunization registries. But somehow built into some of the cultures and countries where she has worked that are non-industrialized, people carry a health record around with them in the way that people in the US carry around a purse or wallet. Some communities have high population-based immunization data for some of their communities, but do not have some of the advances the US has. She does believe there are opportunities to empower families, patients, and adults to keep their own records. This was done a lot in pediatrics many years ago where everyone had their AAP guide. That is a great alternative in addition to trying to do some of the automation.

Dr. Sheedy said she thought the comment about an app was also worth thinking about. They might be hard-pressed to get adults to download an app that was only about immunization, but if it was wrapped up in the different things they need at the different stages of their lives and immunization was a part of that, they might be more likely to put that on their iPads or iPhones.

Dr. Gellin (NVPO) noted that Dr. Koh has spoken many times at the summit as making adult immunizations is a priority for him. He asked for the development of an adult immunization strategic plan, which is in development. Also, HHS has been working with the National Quality Forum to develop performance measures. Those are out in drafts and comments are being taken. A webinar is also schedule. All of these are related to improving the systems for adult immunizations.

Dr. William Schaffner (NFID) read the following comment into the record on behalf of the Gerontological Society of America (GSA):

The Gerontological Society of America (GSA) is pleased to present this statement on behalf of this initiative, the National Adult Vaccination Program (NAVVP), which is a multi-stakeholder industry-supported collaboration to improve adult vaccinations aligned with recommendations of the CDC's Advisory Committee on Immunization Practices. The members of the Gerontological Society of America include researchers, practitioners, educators, economists, health policy experts, and others interested in expanding scientific knowledge across the lifespan, making it a natural home for the NAVVP. The NAVVP promotes that immunizations continue to be one of the greatest public health success stories. Additionally, NAVVP along with this committee, clearly recognizes that vaccine-preventable diseases disproportionately affect older adults. With this in mind, on behalf of GSA's NAVVP, we look forward to joining with the ACIP as you continue to consider the need for strong vaccine recommendations that include the unique challenges of older adults and the need to protect them from preventable diseases through vaccines. Thank you.

Day 1: Public Comment

No public comments were offered during this session.

Typhoid Vaccines

Brendan R. Jackson, MD, MPH
Medical Epidemiologist
Enteric Diseases Epidemiology Branch
National Center for Emerging and Zoonotic Infectious Diseases
Division of Foodborne, Waterborne, and Environmental Diseases

Dr. Jackson indicated that the most recent ACIP recommendations for typhoid immunizations were issued about 20 years ago in 1994. Because some of the information in this document is now out of date, CDC proposes to update it with new information about typhoid epidemiology, vaccine safety, and vaccine availability.

Because typhoid fever is uncommon in the US, Dr. Jackson provided some brief background information. The disease is caused by *Salmonella enterica* serotype Typhi. Contrary to most other *Salmonella* serotypes, humans are the only reservoir. Infection is usually acquired from food or water contaminated with human feces. The incubation period is relatively long, ranging from about 6 to 30 days. The disease usually has an insidious onset with gradually increasing fever, malaise, headache, and anorexia. Typhoid fever can be severe and deadly, particularly if untreated. For example, a US study from the 1940s reported a case fatality rate of over 10%. Life-threatening complications include septic shock and intestinal hemorrhage and perforation. The disease can now be treated with one of several antimicrobial agents, including the following: fluoroquinolone, beta-lactam, azithromycin, chloramphenicol, or trimethoprim-sulfamethoxazole. However, antibiotic resistance is common and increasing in many parts of the world, placing greater importance on prevention tools like vaccines.

Although typhoid fever is uncommon in the US, it remains a major problem on a global scale. In the US, about 400 cases are reported annually compared with an estimated worldwide burden of over 20 million cases per year. Of the US cases, 90% are associated with foreign travel and 75% of these cases are associated with travel to South Asia.

The following table shows the three typhoid fever vaccines included in the 1994 ACIP statement:

Vaccine	Vaccine Type	Mode of Administration	No. of Doses
Ty21a vaccine	Live, attenuated	Oral	4
Vi capsular polysaccharide vaccine	Subunit	Parenteral	1
Heat-phenol-inactivated vaccine	Inactivated whole-cell	Parenteral	2

Currently, the oral Ty21a vaccine and the parenteral Vi capsular polysaccharide vaccine are still marketed in the US. The heat-phenol-inactivated vaccine, which was associated with high rates of fever and other systemic reactions, was discontinued in 2000. The two available vaccines have been estimated to have similar efficacy of about 50%, though individual reports range from 45% to 80%.

Because immunization offers only partial protection against typhoid fever, travelers and other persons at risk should follow recommended food and water practices. Additionally, these vaccines offer little or no protection against paratyphoid fever, which is an increasingly common disease that causes symptoms similar to typhoid fever.

Regarding the choice of vaccine, the most recent ACIP recommendation states, "Either oral Ty21a or parenteral ViCPS is preferable" to the parenteral inactivated vaccine, because the now discontinued inactivated vaccine caused substantially more adverse reactions and was no more efficacious. Typhoid vaccine is indicated for travelers to endemic areas, household contacts of carriers, and laboratory workers who work frequently with *Salmonella* serotype Typhi cultures or specimens. Travelers and clinicians can now consult www.cdc.gov/travel to find the most updated recommendations for each country. As of 2011, CDC no longer recommends typhoid immunization for travelers to 26 countries, including Eastern Europe.

In summary, CDC proposes no substantial changes to the existing typhoid recommendations. For this reason, there are no plans to convene a WG. However, ACIP will be asked to vote during a future meeting on the new ACIP document with updated information on typhoid fever epidemiology, vaccine safety studies, and vaccine availability.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Schuchat reported that the International Health Regulations (IHR) and World Health Assembly (WHA) have updated guidance on polio vaccination given the state of the world's polio eradication efforts. An *MMWR* was expected to be published soon to clarify what this means for Americans traveling or living abroad regarding their need to have documentation for a recent polio vaccination. The next National Immunization Conference will be held on September 29-30, 2014 at the Crowne Plaza Ravinia in Atlanta. This will be the first National Immunization Conference in three years. Between now and the next ACIP meeting, there will be several reports on immunization coverage that CDC hopes partners will promote and highlight. Teen immunization coverage will be reported in the July 25, 2014 *MMWR*, and HPV coverage will be reported in that same issue as a stand-alone report. Toddler coverage will be reported in an August *MMWR*, and kindergarten coverage and exemptions in a September *MMWR*. Given the key priority areas for the nation's immunization in terms of modernizing the immunization information systems in light of changing health IT and addressing lagging HPV vaccine coverage in teens, a number of FOAs were due to be published over the next several weeks.

Centers for Medicare and Medicaid Services (CMS)

Ms. Hance reported that CMS has updated regulations to ensure consistency between immunization quality measures and regulations.

Department of Defense (DoD)

Dr. Geibe reported that there have been no known cases of Japanese encephalitis (JE) in the armed services in more than two decades, but the DoD continues to reinforce recommendations for use of the vaccine in high risk settings, the need for careful screening, and assessment of risk conditions. Additional implementation guidance should be coming out to educate the DoD community. The DoD is also working to inform its providers and beneficiaries about potential changes to polio immunization recommendations for certain countries. So far, there has been no problem with personnel in regard to this issue. With respect to adenovirus, live oral vaccine has been used since October 2011, which continues to be a very successful vaccine with probably over 100,000 lost training days saved and far fewer hospitalizations. Though there have been challenges, DoD also continues to work on the area of HPV vaccine.

Department of Veterans Affairs (DVA)

Dr. Kinsinger reported that DVA is continuing a number of information technology projects to update its electronic medical record (EMR) to ensure inter-operability with the DoD and with other agencies and providers. DVA participated in the Adult Immunization Summit in May and presented work that it is doing, in conjunction with the Indian Health Service, to determine the proportion of veterans receiving care within the Veterans Health Administration (VHA) who have received a set of recommended vaccinations, measured as a composite score. DVA is also working with a private retail pharmacy to record influenza immunizations in its EMR given at the pharmacy's locations to veterans who receive care in VHA facilities. A pilot program done this past influenza season in Florida will be expanded to the entire VHA system.

Health Resources and Services Administration (HRSA)

Dr. Houston indicated that the Notice of Proposed Rulemaking to amend the Vaccine Injury Table to add intussusception as an adverse event associated with rotavirus vaccine in some circumstances was published in July 2013. The second public hearing was held on April 28, 2014, and the Final Rule is in the process of being developed. On March 31, 2014, HRSA published a Notice of Proposed Rulemaking proposing a Pandemic Influenza Countermeasures Injury Table for certain covered countermeasures identified by the Secretary in several Public Readiness Emergency Preparedness Act Declarations. The public comment period ended in May, and the final rule is in the process of being developed. The Advisory Commission on Childhood Vaccines (ACCV) made several recommendations to amend the Vaccine Injury Table during several meetings. The last meeting was held on June 5, 2014. Those recommendations are being considered. Increasing numbers of petitions are being filed with the national Vaccine Injury Compensation Program (VICP) each year. In FY 2012, 400 petitions were filed. In FY 2013, there were 501 petitions filed. It is projected that this year, 550 petitions will be filed with the program.

Indian Health Services (IHS)

Ms. Groom shared information about the IHS's adult immunization activities. The IHS electronic medical record system includes health reminders. Adult vaccine coverage is monitored on a quarterly basis. Tdap coverage for adults 19 years of age and older is 70%, zoster vaccine coverage for adults 60 and older is 39%, and pneumococcal polysaccharide vaccine coverage for adults 65 and older is 75%. This is attributed to the fact that reminders are in place. IHS is exploring implementation of a composite immunization measure as a performance measure. Rather than monitoring individual vaccines, consideration is being given to bundling age-appropriate vaccinations (Tdap, zoster, and pneumococcal polysaccharide) and implementing this across the agency this year. Also of interest to IHS is the concept of bundling vaccines with other preventive care measures (e.g., colorectal cancer screening, pap smears, et cetera) and bundling these measures as a preventive health measure. Along those lines, IHS is exploring conducting some FLU-FIT projects and is looking at an initiative Kaiser tried last year with FIT kits as a model. This involves bundling influenza vaccination with the provision of colorectal cancer screening FIT kits.

National Institutes of Health (NIH)

Dr. Gorman highlighted four NIAID programs and presented an update on one set of clinical trials. At a White House event on December 2, 2013, to mark the 25th annual World AIDS Day, President Obama announced that NIH plans to redirect AIDS research funds to expand support for research directed toward a cure of HIV. NIH plans to invest an additional \$100 million over the next three fiscal years to this increasingly promising area of HIV/AIDS research. Dr. Fauci noted that at this meeting that "our growing understanding of the cellular hiding spaces or reservoirs of HIV the development of new strategies to minimize or deplete these reservoirs, and encouraging reports of a small number of patients who have little or no evidence of virus despite having halted antiretroviral therapy, all suggest that the time is ripe to pursue HIV cure research with vigor."

NIAID's Concept Acceleration Program (CAP) is a team of individuals charged with identifying promising early findings and facilitating their translation into products suitable for advanced development. These individuals seek active engagement with entrepreneurs and scientists to nurture early programs and accelerate their progression to the clinic. These individuals offer strategic advice to help shepherd candidate products through the research and development process, including formulation and formation of product development teams with a broad base of experience. This team also can explain and facilitate access to NIH-provided core research services.

The NIAID Centers of Excellence for Influenza Research and Surveillance (CEIRS) has recently been re-funded. CEIRS continues and expands the institute's animal influenza surveillance program internationally and domestically, and focuses on several high priority areas in influenza research. The future direction of the CEIRS program includes continued surveillance research, determining mechanisms underlying transmission from animals to humans, and determining mechanisms for the duration of immunity. The CEIRS sites are as follows:

Emory University
Emory-UGA Center of Excellence for Influenza Research and Surveillance (CEIRS)
Principal Investigator: Dr. Walter Orenstein
Co-principal Investigator: Dr. Richard Compans

Icahn School of Medicine at Mount Sinai
Center for Research on Influenza Pathogenesis (CRIP)
Principal Investigator: Dr. Adolfo Garcia-Sastre

Johns Hopkins University
Principal Investigator: Dr. Richard Rothman
Co-principal Investigator: Dr. Andrew Pekosz

St. Jude Children's Research Hospital
St. Jude Center of Excellence for Influenza Research and Surveillance (CEIRS)
Principal Investigator: Dr. Richard Webby
Co-principal Investigator: Dr. Stacey Schultz-Cherry

University of Rochester
New York Influenza Center of Excellence (NYICE)
Principal Investigator: Dr. John Treanor
Co-principal Investigator: Dr. David Topham

Despite the success of vaccine therapy, people do still become sick and are treated with antibiotics. Antimicrobial resistance is an increasingly troublesome problem that NIAID is addressing with the Antimicrobial Resistance Leadership Group (ARLG), which was launched in 2013. The ARLG has developed a process for identifying the pressing clinical questions in antimicrobial resistance. The studies conducted by the ARLG may include clinical testing of new drugs to treat multi-drug resistant gram-negative bacteria, evaluating diagnostics devices in clinical settings, evaluating the effectiveness of new antibacterial stewardship programs, and optimizing treatment regimes to reduce the emergence of resistance. The ARLG is drawing on the creativity of the global research community by inviting concept submissions identify and address antimicrobial resistance priorities. At this time, the ARLG is conducting three studies, is in the start-up phase for six more, and is planning three more studies at this time.

In response to the outbreak of H7N9 last year, NIAID conducted two clinical trials that enrolled healthy adults 19 through 60 years of age to evaluate an investigational H7N9 vaccine developed by Sanofi Pasteur. The candidate vaccine was made from inactivated H7N9 isolated in China. Two adjuvants, MF59 and AS03, are being tested with the investigational vaccine because previous research involving other H7 influenza viruses have suggested that two doses of vaccine without an adjuvant may not produce an immune response adequate to provide effective protection. In pandemic situations, adjuvants can be used as part of a dose-sparing strategy that will allow the production of more doses of vaccine from the available supply of viral antigen thereby allowing a greater number of people to be vaccinated more quickly. The two clinical trials have completed enrollment of approximately 1700 human volunteers. The data gathered from those trials is being analyzed and the manuscripts are being prepared.

National Vaccine Advisory Committee (NVAC)

Dr. Orenstein reported that the NVAC last met on June 10-11, 2014. They heard presentations from ASTHO and AIM regarding challenges they were facing in supporting and improving upon the infrastructure for immunization programs. NVAC also heard about a potential \$50 million cut in the President's budget submission for FY 2015 compared to 2014 in the immunization funding line and passed a resolution asking for the rationale behind that budget cut, given the

challenges being faced with infrastructure. NVAC has three major working groups: Maternal Immunization Working Group, Vaccine Confidence Working Group, and HPV Working Group. The Maternal Immunization Working Group initially focused on how to improve compliance with current ACIP recommendations. That report was finalized and focuses on recommendations in five main areas:

- 1) Enhancing communication to address safety and effectiveness
- 2) Maximizing obstetric provider recommendation and administration
- 3) Focusing on efforts to improve financing for immunization services during pregnancy
- 4) Supporting efforts to increase the use of electronic health records for immunization for obstetrical providers
- 5) Overcoming issues with regard to vaccine liability laws that are barriers to vaccination of pregnant women

The report includes a sentence that specifically states that the ACIP could consider developing a separate statement that consolidates all of the information for pregnant women into a single document, with updating as new information becomes available, to make it easier for obstetric providers to access all of the information in one resource.

The HPV Working Group endorsed the report from the President's Cancer Panel to improve immunization. NVAC will continue to monitor the status of implementation of the recommendations of that report. The HPV Working Group continues to work on addressing issues with regard to vaccine confidence or hesitancy. NVAC expects to receive a set of recommendations during its September 2014 meeting to be finalized.

During the June 2014 meeting, NVAC also heard about the status vaccine innovation and research, specifically with regard to influenza. Over time, NVAC will deal more with the issue of incentivizing innovation and research to develop and improve vaccines.

National Vaccine Program Office (NVPO)

Dr. Gellin reported that NVPO supported the AHRQ to conduct a review of vaccine safety. Part of that report was scheduled to be published in *Pediatrics* the week following the June ACIP meeting, and other parts will be published online. NVPO hoped to have the IOM return to present an update on their SMART Vaccines tool (Strategic Multi-Attribute Ranking Tool for Vaccines). While IOM was unable to attend this ACIP meeting, hopefully they will be able to present during a future meeting.

Discussion Points

Dr. Fryhofer (AMA) reported that in November 2014, two reports of interest to ACIP will be presented to the AMA House of Delegates, one of which concerns immunization exemptions. This is a joint effort by AMA's Council on Science and Public Health and Ethics Committee. The other is a joint council report on pharmacist administration of immunizations. Organizations with policies on these topics that they would like to share to be included in the discussion as these reports are written were invited to email Dr. Fryhofer or contact Barry Dickinson, the Secretary for the AMA Council on Science and Public Health.

Dr. Plotkin (Vaccine Consultant) reported that he recently attended a meeting sponsored by NIH on the immunologic problems of vaccine development, such as waning immunity and how to address that problem. He expressed his hope that NIH would continue to fund additional research on this issue. The meeting addressed a large variety of problems, and was quite useful. Also, an article was recently published in *Nature Immunology* by Wayne Koff, Ian Gust from Australia, and Dr. Plotkin that discusses a human vaccines project focused on the immunologic problems of developing new vaccines. The idea is to create a project much like the genetics projects to advance vaccine research.

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, indicating that the primary focus of this session would be to review current data on efficacy, effectiveness, immunogenicity, and cost-effectiveness of pneumococcal vaccines. First, she offered a brief update on the work related to the 3-dose infant schedule.

As a reminder, in February 2014 the WG presented a very laborious GRADE review, which essentially indicated that there were high quality evidence and Category A recommendations for both 3+0 and 2+1 versus no vaccine. However, there was limited evidence comparing 3-dose schedules to a 4-dose schedule. Although there is evidence from other countries using a 3-dose schedule, it is not possible to compare the two schedules directly. Observance of direct effect and indirect impact of PCV13 continues in the US, which informs the WG's deliberations about how to move forward. The WG has been working with AAP and AAFP. Some potential projects include the following:

- Careful consideration of implementation issues and potential impact on non-adherence
- Survey of pediatricians and family practitioners to understand issues around hesitancy and refusals as they relate to PCV13
- Survey or focus groups of parents related to potential policy change
- Define groups to be excluded from potential policy change

The WG is still in the decision making process on these, with some having moved forward and others waiting to do so. ACIP will be updated during a future meeting on the WG's deliberations related to a 3-dose schedule.

Given the focus of this session on routine adult immunization with 13-valent pneumococcal conjugate vaccine (PCV13), Dr. Bennett offered a recap of the background regarding this issue. This vaccine was licensed for use in adults over the age of 50 in 2011. It was approved under an Accelerated Approval Pathway essentially based on non-inferior immunogenicity compared to PPSV23. The indications on the license included prevention of pneumonia and invasive disease in adults 50 years of age and older to prevent disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. One condition of

approval was an RCT PCV13 against pneumococcal pneumonia among adults over the age of 65. This trial, conducted in the Netherlands, is known as the Community-Acquired Pneumonia Immunization Trial in Adults ≥ 65 years old in the Netherlands (CAlPiTA).

The reason that the WG did not go forward with a recommendation in 2012 was two-fold. The GRADE review and immunogenicity results from the Phase III trials were presented to ACIP, and the cost-effectiveness and public health impact of different adult pneumococcal vaccination strategies were discussed at that time as well. The decision was made to defer a recommendation until more data were available, the most important of which were from CAlPiTA. The second most important data regard the indirect effects of PCV13 use in children. The WG has been presenting those data to ACIP over the last couple of years. ACIP recommended a dose of PCV13 for adults with immunocompromising conditions in addition to PPSV23. Those recommendations have been in effect and vaccination is moving forward.

Dr. Bennett concluded that the objective for this session was to review the information that was now available, and to present specific policy options for ACIP's input. However, the committee would not be asked to vote during this meeting due to the many complications related to making a recommendation for this vaccine, including the impact of the indirect effects on the older population and implementation issues that must be addressed.

PCV13 Efficacy Among Adults: Results of CAlPiTA Study

Dr. Rosalind Hollingsworth
Global Medical Lead for Prevnar 13[®]
Pfizer

Dr. Hollingsworth emphasized that pneumococcal pneumonia remains a significant public health problem for adults aged 65 years and older, as well as individuals younger than 65 years of age with underlying medical conditions that significantly increase their risk of pneumococcal disease. Given this unmet medical need, CAlPiTA, one of the largest vaccine efficacy studies ever conducted in the adult population, had a key focus to demonstrate and confirm the efficacy of Prevnar 13[®] for the prevention of vaccine-type community-acquired pneumonia (CAP) in adults aged 65 years and older irrespective of whether that pneumonia was considered to be invasive or non-invasive.

Indeed, the study met its primary and both secondary objectives, and with a safety profile that was consistent with that observed in previous studies of Prevnar 13[®] in the adult population. Dr. Hollingsworth presented an overview of CAlPiTA, the regulatory foundation underpinning the rationale and the need for the CAlPiTA study, an overview of the study design and results, and a short overview of the public health impact of Prevnar 13[®] serotypes of CAP among adults in the US.

Despite current vaccination strategies in children and adults in the US, hospitalizations due to all cause pneumonia by 2009 in adults aged 65 years and older still remained in excess of 1200 cases/100,000 population annually. It was this clear clinical need plus the uncertainty surrounding the effectiveness of pneumococcal polysaccharide vaccines for the prevention particularly of non-bacteremic CAP that supported the approval of Prevnar 13[®] for US adults aged 50 years and older via the FDA's accelerated approval pathway. The key focus of CAlPiTA was to confirm the efficacy under these regulations of Prevnar 13[®] to prevent a first episode of confirmed vaccine-type CAP in adults aged 65 years and older.

CAPiTA was a double-blind, randomized, placebo-controlled trial conducted in the Netherlands that included 84,496 adults aged 65 years and older who were randomized between September 2008 and January 2009 to receive a single dose of either Prevnar 13[®] or placebo. This study population was followed until a pre-specified number of vaccine-type CAP cases had accrued. This occurred in August 2013.

Adults had to be 65 years and older at time of study entry, male or female, ambulatory, living in the community, and registered with a general practitioner (GP) who was referring subjects into the study. Subjects could not have received any prior pneumococcal vaccine, and they had to be considered immunocompetent at the time that they were vaccinated. The typical contraindications to immunization applied. However, subjects could have underlying medical conditions that are typically associated with an increased risk of pneumococcal infection (e.g., chronic disease of the lungs, heart, liver, and kidneys), concomitant conditions (diabetes mellitus), and/or a current or past history of smoking.

The study included one primary efficacy objective and two secondary objectives. The primary objective was to demonstrate the efficacy of Prevnar 13[®] in the prevention of a first episode of vaccine-type CAP, including invasive and non-invasive cases. The secondary objectives were to confirm efficacy against a first-episode of vaccine-type non-bacteremic pneumonia (NBP), non-invasive pneumococcal CAP, or a first-episode of vaccine-type invasive pneumococcal disease (IPD) with or without pneumonia.

Detection of vaccine serotypes within the CAPiTA study was improved through Pfizer's development of a serotype-specific urinary antigen detection (SSUAD) assay. Before development of this assay, there was no effective or efficient way of detecting vaccine serotypes within cases of non-bacteremic, non-invasive pneumonia. To facilitate the successful conclusion of this study, a way to improve the identification of cases was needed. Simply, microspheres are coated with highly specific monoclonal antibodies that are able to bind to the vaccine serotype pneumococcal polysaccharides that are excreted in the urine of adults with X-ray confirmed pneumonia. This assay has been fully validated, and the results of that validation have been published [Pride MW, et al. *Clin. Vaccine Immunol.* 2012; 19(8): 1131-1141]. This allows for the detection of any one of the Prevnar 13[®] serotypes with 97% sensitivity and 100% specificity among this patient population.

There was a standardized approach for identifying study subjects presenting with a clinical suspicion of CAP at the emergency department (ED) of any of the 59 sentinel hospital sites located across the Netherlands that were responsible for capturing cases and suspected cases of CAP and invasive pneumococcal disease among the patient population. There was a good geographical spread of these locations to ensure capture of as many cases as possible. When study subjects presented at one of these sentinel sites, their diagnostic work-up included a chest X-ray, blood culture and urine sample for BinaxNOW[®] testing according to standard care practice, plus a protocol defined collection of urine for SSUAD testing. The definition of CAP was based on protocol defined clinical criteria, as well as X-ray findings that were consistent with pneumonia. This was adjudicated in every case by an independent adjudication committee who had to confirm that each X-ray, if it was truly a vaccine-type CAP case, was consistent with the appearance of CAP.

To be counted as a case of confirmed vaccine-type pneumococcal CAP, the individual had to exhibit two or more pre-specified clinical findings that are consistent with CAP. Their chest X-ray appearance also had to be consistent with CAP, and a culture was required of a vaccine-type CAP of pneumococcus from any sterile site and/or a positive result from an SSUAD test for one of the vaccine types. For the secondary endpoint of confirmed non-bacteremic, non-invasive vaccine type CAP, the investigators wanted to be truly certain that these were absolutely non-invasive cases of vaccine-type pneumococcal CAP. There had to be X-ray consistency, clinical signs and symptoms that were consistent with CAP, and identification of a vaccine type through the SSUAD. For this endpoint, all individuals had to have had blood taken for culture. The results of that culture had to be negative and if any other culture results were available for any other sterile sites, those also had to be negative. In terms of vaccine-type IPD, this simply required isolation of a vaccine-type pneumococcus from any normally sterile site, and included pneumonia and non-pneumonia cases.

In terms of the baseline characteristics of the subject population at the time they presented for vaccination, the mean age was 72.8 years and was well-balanced between the two groups. Approximately 55% of the population was male and again was well-balanced. Other characteristics were also well-balanced between the two groups. At the time individuals presented for vaccination, they were asked about their medical history specifically for the underlying conditions of asthma, diabetes mellitus with insulin use, diabetes mellitus without insulin use, heart disease, liver disease, lung disease, and splenectomy. Approximately 40% of the immunocompetent subjects eligible for study inclusion had at least one co-morbidity that might be expected to increase their risk of pneumococcal disease. Overall, 12% of each study vaccine group were current smokers. In terms of how this compares with the US population, data from the National Health Interview Survey (NHIS), 37% of adults aged 65 years and older were considered immunocompetent and reported at least one chronic medical condition that would be considered to increase their risk of pneumococcal disease [Weycker et al. *Vaccine* 2012. 30: 5437–44; National Health and Interview Survey. 2006 and 2011].

In terms of efficacy, as noted earlier, the study did meet the primary and both secondary endpoints. The results were highly statistically significant, with a confidence interval that was well above zero as pre-specified within the protocol. For the primary endpoint, there were 49 confirmed first episodes of vaccine-type CAP among recipients of Prevnar 13[®] compared to 90 in the placebo group for a point estimate of vaccine efficacy of 45.56%. For the secondary endpoint of non-bacteremic, non-invasive vaccine-type pneumococcal CAP, there were 33 cases among the Prevnar 13[®] recipients compared to 60 cases among the placebo group for 45% vaccine efficacy. As expected from the pediatric experience, there was higher vaccine efficacy for IPD compared to non-invasive disease, with a point estimate of vaccine efficacy of 75%.

A post-hoc analysis was conducted to stratify by age. It is important to note that this study was not powered to detect serotype specific vaccine efficacy. For those less than 75 years of age and those greater 75 to less than 85 years, the efficacy numbers were largely consistent with that observed in the overall study population for each endpoint. There were relatively small numbers of subjects for those aged 85 years and older of about 1500 subjects in each group. This accounted for only 3.5% of the overall study population. Thus, there were insufficient numbers in the oldest age group to be able to draw any conclusions about vaccine efficacy.

A post-hoc analysis was also conducted to assess serotype specific efficacy. Again, the study was not powered to look on an individual basis. However, this is of key interest. Despite the use of Prevnar[®] in the Netherlands from 2006 and the replacement of that vaccine with a 10-valent pneumococcal conjugate vaccine in 2011 under a 3+1 schedule and a 95% vaccine uptake, for the primary endpoint, episodes due to all 13 vaccine serotypes were observed. For the first episode of vaccine-type CAP, the majority of events which contributed to the overall analysis were observed from serotypes 1, 3, 7F, and 19A. Of these, serotype 7F was the only serotype under this post-hoc analysis to demonstrate statistically significant efficacy of approximately 77%. A consistent finding was observed for both secondary endpoints as well.

Another potential benefit based on conjugate vaccines' mechanism of action is the durability of protection that one might expect, which was also assessed in an ad-hoc manner. The mean duration of follow-up of the study population was 3.97 years. There was a clear separation of the Prevnar 13[®] group from the placebo group, which was sustained throughout the duration of follow-up of the study, with no suggestion at the end of the follow-up period that efficacy may be beginning to wane. Also reassuring with regard to duration of protection were the results of the pre-specified interim analysis, to which the investigators did not have access until the date the study was completed and the data were unblinded. In September 2011, an interim analysis was conducted. Although at that time vaccine efficacy did not reach statistical significance, it was reported at 49%. This again supported the idea of durability of protection across the duration of the study. Results were similar for both secondary endpoints.

Regarding safety, within the study design there was an immunogenicity subset. While the immunogenicity data were not yet available, this study subset also reported local and systemic reactions through 7 days after vaccination via an e-diary. There were approximately 2000 subjects in total in this subset. In terms of local reactions, as would be expected comparing Prevnar 13[®] to placebo, there was a statistically significant difference among individuals reporting any local reaction. However, reassuringly, there was no difference between the groups in the frequency or prevalence of reports of severe local reactions. This pattern of local reactions is entirely consistent with that observed in the regulatory trials that supported licensure of this product for adults. Similarly for systemic events, differences were observed between the Prevnar 13[®] and placebo groups in terms of the events reported in the 7-days following vaccination. Again, this is a very consistent profile with that which was observed in earlier studies of Prevnar 13[®] in the adult population.

SAEs were reported for all study subjects through 28 days following vaccination. The two groups were well-balanced in terms of the number of reports of SAEs. Information on mortality was collected for all study subjects throughout the case accrual period. There were 3006 deaths reported among individuals receiving Prevnar 13[®] versus 3005 in the placebo arm. None of these deaths or the SAEs were considered by the principal investigator to be related to the vaccine. In terms of deaths specifically due to all-cause CAP or IPD, among recipients of Prevnar 13[®] there were 62 deaths due to CAP of any cause versus 70 in the placebo group. For IPD, there were 4 cases among Prevnar 13[®] recipients versus 5 in the placebo group.

With respect to how vaccine efficacy will translate into public health impact through use of this vaccine, a key component of the CAPiTA study was the development of the SSUAD. Although the SSUAD was developed for use in the CAPiTA study to help facilitate detection of vaccine-type CAP cases, it is now enjoying huge utility globally in terms of offering good epidemiological insight into the spectrum of the vaccine serotypes causing CAP among adults.

A number of studies have now been conducted in North America and have been compared to the CAPiTA study to answer questions regarding serotype distribution and how much of CAP is due to the serotypes included in the vaccine primarily in settings where pediatric conjugate vaccines are used. Studies 4007 and 1147 were both Pfizer sponsored studies. Pfizer made the SSUAD available to CDC to enable testing of the urine samples collected from the EPIC study. Dr. Shelly McNeil and colleagues from Canada conducted a study using their PCIRN Serious Outcome Surveillance (SOS) Network Study.

Studies 4007 and 1147 were conducted in the US to assess adults presenting to hospitals with X-ray confirmed CAP. Study 4007 was conducted between February 2010 and October 2011, which encompasses the time period when US infants made the switch from Prevnar[®] to Prevnar 13[®]. Because of the exciting data observed from that study, Pfizer decided to resurrect that in the follow-on 1147 study. Study 1147 began in October 2013. An interim analysis was undertaken that included all cases of pneumonia that had accrued by January 2014. Based on the SSUAD assay, study 4007 reported a Prevnar 13[®] serotype prevalence rate of 11%; whereas, study 1147 conducted three to four years later reported a Prevnar 13[®] serotype prevalence rate of 13.6%. These studies were conducted well after the introduction of Prevnar[®] into the infant schedule in the US, and straddle the switch from Prevnar[®] to Prevnar 13[®]. Also interesting in both of these cases is that the original Prevnar 7[®] serotypes accounted for 25%, while the additional six serotypes accounted for the remaining 75%. Serotype prevalence rates in the EPIC study were about 9%, while Canada reported 16% prevalence rates. Within CAPiTA, the first episode for CAP was 14.2%. Based on SSUAD and/or culture results these contemporary studies suggest that the 13 serotypes in Prevnar 13[®] are responsible for 10% or more of CAP in North American adults. This information can be applied to rates of hospitalization in the US to estimate the burden of vaccine-serotype CAP.

Referring back to the Griffin data published in the *New England Journal of Medicine (NEJM)* in 2013, all cause pneumonia hospitalizations 10 years after introduction of 7-valent pneumococcal conjugate vaccine in the US pediatric population were still in excess of 1000 case/100,000 in those over 65 years of age [Griffin MR, et al. *N Engl J Med.* 2013; 369: 155-16]. If a conservative 10% prevalence rate is applied to these numbers, hospitalizations due to Prevnar 13-type CAP range from 121 cases/100,000 among the youngest elderly to >400 cases/100,000 in those aged 85 years and older. By applying US population statistics, exactly how many cases that translates to can be determined. Thus, in 2009 there were approximately 29,000 hospitalizations due to the Prevnar 13[®] serotypes in CAP among those aged 65 to 74 years; 31,000 in those aged 75 to 84; and 25,500 in those over 85 years of age. Adding those together represents approximately 86,500 hospitalizations due to Prevnar 13[®] type CAP in this age group. Crudely applying the vaccine efficacy numbers from CAPiTA, there are potentially about 40,000 hospitalizations each year in the US among those aged 65 years and older.

In conclusion, pneumococcal pneumonia and vaccine-type pneumococcal pneumonia continue to place a significant burden on adults in the US aged 65 years and older, as well as younger adults with underlying medical conditions that increase their risk. CAPiTA was a significant study due to its size, its focus on the questions of interest pertaining to prevention of non-bacteremic pneumonia, and the technology that was developed to underpin and insure the success of this study. Prevnar 13[®] demonstrated clinically relevant efficacy within that study for the prevention of vaccine-type pneumococcal CAP, with a durability of protection of at least four years and with a safety profile that was consistent with that observed in previous studies of Prevnar 13[®] in adults.

Discussion Points

Dr. Vazquez inquired as to whether subjects who were bacteremic or had a positive sterile site culture correlated with the urine positive or negative tests.

Dr. Hollingsworth replied that because there was 97% sensitivity and 100% specificity within the validation study, there was good agreement between the blood culture results and the UAD results. The assay missed one case of serotype 3 and one case of 6A within the validation study, but it is always better to miss cases than to get false positives. Within CAPiTA itself, there were 29 bacteremic cases where that comparison could be made. Again, there was good correlation between the blood culture results and the serotypes in the urine.

Dr. Vazquez asked whether the sensitivity and specificity within the CAPiTA study were similar to the pre-study.

Dr. Hollingsworth responded that this has not been recalculated. The purpose of the validation study was to provide sensitivity and specificity. While this was not revalidated within the CAPiTA study itself, looking crudely at the numbers, the test performed as well in CAPiTA as it had done previously.

Dr. Harrison wondered whether there was any evidence for vaccine serotype replacement, and about vaccine efficacy by underlying medical conditions.

Dr. Hollingsworth indicated that they had vaccine serotype information for non-vaccine serotypes from the culture results. Small numbers of the other serotypes were identified through that route, so it is not really possible to determine from this study. Regarding underlying medical conditions, the investigators have not been able to assess efficacy by individual comorbid condition. One difficulty is that because most of the subjects within this study population are over 65, many had more than one underlying medical condition.

Dr. Schuchat inquired as to whether vaccine efficacy was assessed against CAP with a negative urine result.

Dr. Hollingsworth replied that Pfizer is conducting a considerable number of analyses, and that they had a raft of exploratory endpoints. All-cause pneumonia was assessed for a first episode of any pneumococcal CAP irrespective of whether it was a vaccine or non-vaccine serotype. Vaccine efficacy was 30% and reached statistical significance. Non-bacteremic, non-invasive pneumococcal CAP of any serotype was 24%, but did not reach statistical significance. First episodes of all-cause CAP had a 5% point estimate of efficacy, but did not reach statistical significance.

Dr. Kempe requested that Dr. Hollingsworth comment on the SSUAD assay and carriage of pneumococcus.

Dr. Hollingsworth indicated that the cutoffs were defined for the UAD assay, which is a positive or negative assay. The cutoffs for the UAD assay were determined for each individual serotype specifically. A group of 400 adult control urines were collected from individuals in the Netherlands and the US who were either considered completely healthy with no evidence of respiratory infection, or they were undergoing elective surgery with no evidence of respiratory infection, as well as from individuals with chronic obstructive pulmonary disease (COPD). It was

assumed within that control urine population that there would be about a 5% to 10% carriage rate within the healthy adults or those undergoing elective surgery, with potentially a higher carriage rate among those with COPD. Those urines were then run through the UAD assay and the signals that were generated were assessed. The cutoffs were set to be able to distinguish between the signals observed in healthy individuals versus those seen in individuals with X-ray confirmed pneumonia.

Dr. Reingold inquired as to whether Dr. Hollingsworth could say something about the efficacy by age in the younger versus older people, recognizing that the study was not powered for this. He also noted that 10% is certainly an underestimate of the burden of disease because all outpatient pneumonias were not included; however, it is not an underestimate of the proportion of cases that are attributable to vaccine types.

Dr. Hollingsworth indicated that age was assessed and that among those aged 75 years and under and between 75 and 85 years of age, the overall efficacy was consistent with the population overall. For the oldest age groups, there were very small numbers of subjects in totality and a relatively small number of cases, so conclusions really could not be drawn.

Dr. Pickering noted that the previous day, there was a presentation on vaccine safety among children who receive combinations of vaccines versus vaccines singly. He wondered whether the CAPiTA study included a subset of people who received both PCV13 and influenza vaccines and, if so, whether there were differences in adverse events among them compared to individuals who received pneumococcal or influenza vaccine alone.

Dr. Hollingsworth replied that at the beginning of the study, there was co-administration of Prevnar 13® with TIV, with approximately 30% of the study population receiving both vaccines together. However, those individuals could not be included in the immunogenicity subset, and that was the group in which local reactions and systemic events were measured. Unfortunately, they do not have that solicited information in terms of the adverse event reporting. She was not aware of whether the overall population had been assessed in terms of SAEs and whether there were any differences between those two groups.

Dr. Schmader (AGS) inquired as to why nursing home residents were excluded, and whether there were any plans to conduct follow-up in that sizeable population that develops pneumonia at a rapid rate.

Dr. Hollingsworth indicated that nursing homes were excluded because those were not considered to be true community-acquired pneumonia cases. Though there are no plans at present to conduct follow-up on that population, she said that they always welcome good ideas.

Dr. Weber (SHEA) asked what percentage of the bacteremic diseases was caused by a vaccine serotype.

Dr. Hollingsworth replied that she did not believe they had that information. The only serotype not seen in IPD was 23F. All other 12 serotypes were present within this study population. A similar observation was made for the primary endpoint in terms of 1, 3, 7, and 19A making the major contributions.

Dr. Schuchat inquired as to whether the efficacy against CAP had been assessed in those who received both Prevnar 13® and influenza vaccines versus those who received only Prevnar 13®.

She pointed out that 30% of 85,000 people was larger than most studies that have been conducted against influenza.

Dr. Hollingsworth responded that this had not been assessed. Given the small number of overall cases, and bearing in mind that only 30% of the study population received both vaccines together, it is not possible from the parent study to do this type of evaluation. The investigators were looking for a total number of cases overall of about 130. They ended up with 139, which was the major determinant.

Ms. Pellegrini agreed with Dr. Reingold's comment that it seemed surprising that such a small number of cases occurred in the oldest age group. She wondered whether that was because of the number recruited in the first place, and whether they were all in nursing homes. She also inquired as to whether there was something in the recruitment process or otherwise that resulted in the small numbers of subjects over 85 years of age.

Dr. Hollingsworth replied that there were only about 1500 subjects in each vaccine group over 85 years of age, and that the small numbers of subjects over 85 years of age probably just reflected the population demographics.

Potential Public Health Impact and Cost-Effectiveness of PCV13 Use in Adults

Dr. Charles Stoecker
Tulane University
School of Public Health and Tropical Medicine

Dr. Stoecker reported that a cost-effectiveness model was used to assess either adding PCV for older adults or removing the risk-based recommendation for the pneumococcal polysaccharide vaccine (PPSV). For this study, the following items were evaluated:

- Program cost/savings
- Changes in disease, medical costs, and nonmedical costs
 - Societal perspective
- Population
 - Adults age 50+ or age 65+ as appropriate for each strategy being analyzed
 - Immunocompromised persons were excluded, given that there is already a recommendation for this group

The primary strategies assessed included the following:

1. PCV13 at age 50, which exclude the risk-based recommendation for those aged 50 through 64
2. PCV13 at age 65
3. PCV13 and PPSV23 at 50
4. PCV13 and PPSV23 at 65, which preserves the risk-based recommendation
5. Adding PCV13 at 50, which preserves the risk-based recommendation
6. Adding PCV13 at 65, which preserves the risk-based recommendation
7. Replacing PPSV23 at 65 with PCV13 at 65, which preserves the risk-based recommendation and replaces the polysaccharide dose at 65 with the conjugate dose at 65

Each of these seven strategies was compared to the current strategy, which is PPSV23 for high risk individuals aged 50 through 64 and PPSV23 for everyone at 65. The assessment tracked current 50 or 65 year olds through life expectancy, or until age 100. All assessed were current disease rates and herd impacts from the child immunization program ahead 6 years. All outcomes and costs were discounted by 3%, and all costs were expressed in 2013 dollars.

A cohort model was utilized in which cost per quality adjusted life years (QALYs) gained and cost per life year gained were assessed. Two cohorts were used: 1) 50 year olds for strategies that changed vaccinations for 50 year olds, and 2) 65 year olds for strategies that did not deviate from current recommendations until age 65. Each recommendation was compared to the status quo, and the incremental cost-effectiveness ratio was calculated by dividing the changes in costs by the changes in QALYs. The health outcomes assessed included cases of IPD, cases of NBP, cases of outpatient NBP, deaths due to IPD, deaths due to NBP, QALYs, and life years.

Regarding the inputs into the model, disease burden due to IPD was divided into two risk groups: healthy and high risk 50 through 64 years of age and healthy and high risk 65 years of age plus. The IPD rate was lower in those 50 through 64 years of age and higher in those 65 years of age plus. The percent of cases resulting in fatality ranged from 6% to 15%. The distribution of IPD due to PCV13 serotypes ranged from 25% to 26%. The distribution of disease due to the serotypes in PCV23 that are not in PCV13 ranged from 38% to 48%, and for non-vaccine serotypes ranged from 25% to 40%. This was from 2013 ABCs data.

Inputs for the NBP disease burden included the ¹inpatient NBP rate per 100,000; ²the percent of NBP cases resulting in fatality; ³the outpatient NBP rate per 100,000; and ⁴the percent of PCV13 serotypes [¹Simonsen et al Lancet Respir Med 2014; ²Huang et al Vaccine 2011 (National Inpatient Survey 2004 data); ³Nelson et al Vaccine 2008; ⁴CAPiTA, EPIC study, Pfizer supported US study]. Vaccine effectiveness inputs included PCV vs VT IPD (75%) and PCV vs VT NBP (45%) from the CAPiTA study; PPSV vs VT IPD (74%) from Moberley [2008 Cochrane Review]; and PPSV vs VT NBP (0) from Fry et al. [2002 Vaccine].

Inputs for herd effects from PCV7 in children turned out to be very important in the model. Changes were included separately for 50 through 64 year olds and those 65+ for non-vaccine types, PCV7, and serotypes in PPSV23 not in PCV7. For 50 through 64 year olds, the percent changes increased 38.9% for non-vaccine types, decreased 78.6% for PCV7, and increased 77.9% for serotypes in PPSV23 not in PCV7. For those 65+, the percent changes increased 64.5% for non-vaccine types, decreased 86.6% for PCV7, and increased 17% for serotypes in PPSV23 not in PCV7. In the model, these changes were then projected forward on “PCV6” and “PPSV23 not in PCV13” types.

Inputs for vaccine coverage rates included 20% for high risk 50 through 64 year olds from NHIS 2012 (*MMWR* Feb 7, 2014); 37.1% for healthy 50 through 64 year olds adapted from office visit ratios (NHIS 2012); and 59.9% for those 65+ from NHIS 2012 (*MMWR* Feb 7, 2014). The coverage rate for healthy 50 through 64 year olds is found by averaging 1) the high risk 50 through 64 coverage rate (20%) and 2) the ratio of the percent of 45 through 64 year olds who had seen a doctor in the last year (84%) to the percent of 65 through 75 year olds who had seen a doctor in the last year (92.5%) and multiplying that by the coverage rate for 65+ (59.9%).

Separate cost inputs were used for 50 through 64 year olds and those 65+ to represent different insurance statuses. The costs for PCV13 and PPSV23 vaccines were taken from the July 2013 CDC price lists, while vaccine administration and travel time and costs were taken from Maciosek et al [2006 *Am J Prev Med*]. For PCV13 vaccine, \$128 was used for 50 through 64 year olds and \$85 was used for those 65+. For PPSV23 vaccine, \$63 was used for 50 through 64 year olds and \$23 was used for those 65+. For vaccine administration, \$17 was used for both groups. For travel and time costs, \$29 was used for both groups.

Disease costs were taken from MarketScan (2010) as follows:

Variable	Base
50-64, IPD	\$42,906
50-64, IPT NBP	\$37,336
50-64, OPT NBP	\$ 136
65+, IPD	\$28,949
65+, IPT NBP	\$24,888
65+, OPT NBP	\$ 271

Inputs for utility decrements came from Melagaro & Edmunds [2004 *Vaccine*]. A case of IPD will cost 0.008665 QALYs, 3.2 days of healthy life lost, and 21 days of implied average duration of illness. IPT NBP will cost 0.006 QALYs, 2.2 days of healthy life lost, and 15 days of implied average duration of illness. OPT NBP will cost 0.004 QALYs, 1.5 days of healthy life lost, and 15 days of implied average duration of illness. The utility decrements turned out to be somewhat important, so alternate larger utility decrements were also used. Using the alternative decrements, a case of IPD will cost .075 QALYs, 27.2 days of healthy life lost, and 181 days of implied average duration of illness [Sisk et al 2003 *Ann Intern Med*]. IPT NBP will cost .075 QALYs, 27.2 days of healthy life lost, and 181 days of implied average duration of illness [Smith et al 2012 *JAMA*]. OPT NBP will cost .050 QALYs, 18.1 days of healthy life lost, and 181 days of implied average duration of illness [taking the ratio of OPT to IPT in Melagaro and applying to Smith].

In terms of the waning profile for 50 year olds, the polysaccharide vaccine wanes to zero by about 15 years. The conjugate vaccine does not weight to zero. There is no waning until age 65, and then at age 65 a 10% decline in efficacy is observed every five years. If vaccination is started at age 65, waning is the same except for the no waning between the ages of 50 to 65 [PPSV duration adapted from Fry et al. *Vaccine* 2002; PCV duration adapted from CAPITA results].

Regarding the results, there were some dominated strategies that are generally the strategies that remove the risk-based polysaccharide recommendation. These included increases in IPD, decreases in NBP, and overall decrease in QALYs and Life Years, and increased cost. So, dominated strategies were worse for health and cost. Health improving strategies preserved the risk-based PPSV recommendation and resulted in increased QALYs, Life Years, and cost. The dominated strategies that remove the risk-based recommendations, which either decrease health or have very large increased cost include the following:

1. PCV13 at 50
2. PCV13 at 65
3. PCV13 and PPSV23 at 50
4. PCV13 and PPSV23 at 65

Instead, focus was placed on the health improving strategies, which include:

5. Adding PCV13 at 50
6. Adding PCV13 at 65
7. Replacing PPSV23 at 65 with PCV13 at 65

Adding PCV13 at 50 in this model decreased IPD cases by 227, adding it at 65 decreased cases by 226, and replacing PPSV23 at 65 with PCV13 at 65 increased cases by 1298. Each strategy decreased the number of NBP cases. The decrease here is smaller and is likely due to the lower coverage rates assumed for the age-based recommendations in the 50 year old age group. Approximately 5000 fewer cases of hospitalized NBP were observed with this strategy, and similarly for outpatient NBP. Declines in deaths were observed for IPD under the first two strategies, and an increase in deaths due to IPD in the third strategy. Declines in deaths due to NBP were observed for all three strategies. All three strategies resulted in an increase in QALYs. For the third strategy, the increase in IPD is more than outweighed by the decreases in NBP when QALYs are added up. Similarly, there were increases in Life Years due to each recommendation.

Comparing the costs among the three strategies to the current strategy, adding PCV13 at age 50 will increase total costs by \$687 million in this model. The total costs are divided separately into medical costs, with declines observed in medical costs for each of the three strategies. The declines in medical costs reflect the lower amounts of disease due to increased vaccination. Increases were observed in vaccine total costs, which included travel and time costs as well. The total cost was then divided by the QALYs gain. Adding PCV13 at age 50 costs about \$461,229 per QALY gained. Adding PCV14 at age 65 instead resulted in a much lower cost of \$62,065 per QALY gained. Replacing PPSV23 at 65 with PCV13 at 65 resulted in a cost of \$46,396 per QALY gained.

Due to some uncertainties, sensitivity analyses were done. Due to lack of certainty about the QALY numbers used, the alternate source of higher QALYs was used. It is possible that the vaccine price could change with a large increase in PCV orders, so an analysis was run that assumed that PCV13 fell as low as the public price for PPSV223 at \$23.31 in 2013 dollars. Also assessed was how herd effects from the childhood program might affect these strategies in six years, which was based on when the herd effects observed to date in the PCV7 program in children manifested to an equal amount in the additional types in PCV13. The sensitivity analysis focused on the two age 65 strategy changes.

In terms of the sensitivity analyses for the strategy of adding PCV13 to the existing recommendations, the base case cost-effectiveness ratio was \$62,000 per QALY. Using the higher decrements, a modest change was observed down to \$54,000 per QALY. If the low price was used, assuming the price of the conjugate is as low as the polysaccharide, cost was \$12,000 per QALY. When added together, a small change was observed. In 2019, after the herd effects from PCV13 use in children have been manifested in the six additional serotypes in

PCV13 by the same extent as herd effects have been seen in PCV7, there was an increase to \$272,000 per QALY in the model.

The same sensitivity analysis was done for the replacement strategy, which resulted in a base case cost of \$46,000 per QALY in the base case and \$36,000 per QALY for the higher QALY decrements. When the price was changed to be the lowest price seen for pneumococcal vaccines, this strategy would actually be cost saving. That is, health would improve and there would be less total costs—even after accounting for the cost of the vaccines themselves. Using the higher decrements, the results were cost saving. However, looking six years ahead to the 2019 cohort, the results were dominated in this model. This means an increase in costs and decrease in health as measured either by QALY or Life Years.

The following table puts these QALY decrements into context in terms of where they fit with other interventions:

Intervention	2013 Cost/QALY	Source
Childhood Hib	cost saving	Zhou et al 2002 Pediatrics
AHCP Smoking Cessation Guidelines	\$4,000	Cromwell et al 1997 JAMA
Sigmoidoscopy followed by colonoscopy if high-risk polyp diagnosed every 10 years	\$28,000	Frazier et al. 2000 JAMA
Herpes Zoster Vaccination at 60	\$80,000	Ortega-Sanchez, 2013 ACIP
Mammography Screening (biennially) for Women 50-74 years	\$87,000	Stout et al 2014 J Natl Cancer Inst
Mammography Screening for Women 40-49	\$202,000	Salzmann et al 1997 Arch Intern Med
Lyme Disease vaccine with attack rate of 0.5%	\$255,000	Shadick et al 2001 Arch Intern Med
Value of a Statistical Life Year	\$492,000	Aldy and Viscusi 2006 ReStat
Pap Smears for Low Risk Women	\$1,779,000	Eddy 1990 Arch Intern Med

Limitations of this study include uncertainty surrounding QALYs, uncertainty surrounding vaccine waning, and projection forward of full PCV7 herd effects on PCV6 types.

In summary, the cost per QALY is approximately \$50,000 to \$60,000 under base-case assumptions. PCV13 for adults is comparable to other interventions accepted as cost-effective when added at age 65 to the current PPSV23 schedule or replacing PPSV23 at age 65 years. Simplified strategies that consider only age-based recommendations, excluding the high risk polysaccharide recommendation, are generally dominated. Health benefits vary between PPSV23 and PCV. PCV13 strategies decrease NBP compared to PPSV23. There is more IPD when exchanging a PPSV23 dose for PCV13. After the herd effects from the child program are fully realized, PCV13 in adults is much less cost-effective. The estimates range from dominated to \$270,000 per QALY.

Discussion Points

Dr. Temte inquired as to whether any synergistic effects were observed with respect to co-administration of the two vaccines.

Dr. Stoecker replied that no synergistic effects were assumed.

Dr. Gorman (NIH) asked whether the vaccine uptake rate factored into the model, and if any sensitivity analyses had been done based on coverage.

Dr. Stoecker indicated that for the high-risk group, a coverage rate of about 20% was assumed. That was for those included in the risk-based recommendation. For healthy 50 through 64 year olds, a prediction had to be made since there is not an analogous pneumococcal vaccine in this age group. A 37.1% uptake was assumed for that group, and approximately 60% was used for those aged 65+. In terms of the multivariate sensitivity analysis, the most important factors were herd immunity from the child program and the QALYs.

Dr. Orenstein (NVAC) asked what the rationale was for why vaccine cost was different by age.

Dr. Stoecker responded that an effort was made to account for different insurance status by age. Those aged 65+ are on public insurance, so the insurer will pay a lower price for vaccine than a private insurer. Private insurance generally faces a higher price for vaccine.

Regarding the strategy that replaced the polysaccharide in those 65 years of age with the conjugate vaccine, Dr. Reingold wondered how sensitive that analysis was to assuming some efficacy against non-bacteremic pneumonia. Zero efficacy was assumed against non-bacteremic pneumonia, but whether there is efficacy is controversial. He wondered how sensitive those numbers were to assuming some level of efficacy against non-bacteremic pneumonia.

Dr. Stoecker indicated that sensitivity analyses have been conducted on that. While he did not recall the exact sensitivity, he emphasized that the three main drivers of the cost-effectiveness ratios included herd immunity, QALYs, and waning.

Dr. Kempe said she was trying to reconcile the information from Dr. Hollingsworth's presentation with the herd immunity data in which there was a 10% rate of PCV13 related CAP in a fully mature program where there was 95% coverage, and whether Dr. Stoecker's assumptions aligned with that.

Dr. Stoecker indicated that for the cost-effectiveness model, a 10% CAP attributed to PCV13 types was used as the base case. That is the current state of the world, and does not account for projected changes in herd immunity. To account for projected changes in herd immunity, it was assumed that the serotype distribution in NBP is the same as in IPD. The IPD changes from ABCs data were applied to what are thought to be the PCV6 types in the 10% of the CAP that is due to PCV13 types. The 10% was reduced to account for reduction in PCV6 types.

Considerations for PCV13 Use Among Adults and Policy Options

Dr. Tamara Pilishvili
Respiratory Diseases Branch
National Center for Immunization & Respiratory Diseases

Dr. Pilishvili recapped the evidence presented to ACIP over the past couple of years to prepare for a discussion regarding age-based recommendations for PCV13 among adults. The policy question under consideration is: Should PCV13 be administered routinely to all adults 65 years of age or older? The rationale for focusing the key question on adults 65 years or older is that current ACIP universal recommendations target this age group, and the CAPiTA trial evaluating the efficacy of PCV13 against pneumococcal pneumonia currently ongoing in Netherlands targets this age group. The WG considered alternative strategies using both PCV13 and PPSV23 in sequence together, as well as the age-based strategies that begin at the age of 50

as presented by Dr. Stoecker. However, economic analyses showed that the strategies that start at the age of 65 are cost-effective and resulted in increased health benefits for all outcomes.

In 2012, when PCV was licensed for use among adults, an extensive GRADE evaluation was conducted of the evidence. The WG concluded at that time that the evidence quality was low or Type 3, given that there were limited studies on efficacy against invasive disease. There was only one RCT in HIV+ adults conducted in Malawi. There were no data on efficacy against pneumonia. The WG concluded and ACIP agreed that there was uncertainty about the magnitude of expected health benefits and cost-effectiveness due to two key pieces of data missing at that time, including unknown efficacy against non-bacteremic pneumonia and uncertainty about the magnitude that PCV13 use in children will reduce the vaccine-preventable disease burden among adults. A decision was made to defer the age-based recommendation until these two pieces of critical data became available.

Efficacy data are now available from CAPiTA. The results of which show that the vaccine is 75% efficacious in preventing vaccine-type invasive disease and 45% efficacious in prevention non-bacteremic pneumonia in adults 65 years of age and older. Therefore, the WG wanted to estimate what impact might be expected among persons aged 65 and older in the US. The WG estimated how many persons aged 65 years and older would need to be vaccinated to prevent a single case of PCV13-type IPD or a single case of PCV13-type CAP. The most recent incidence data for IPD were used from ABCs for a baseline of 6.5 cases/100,000 of vaccine-type disease. Published sources of inpatient and outpatient data were used for incidence of CAP. The rates were obtained for all CAP and the 10% presented in an earlier presentation was applied as an estimate of the proportion of all-cause pneumonia that is caused by PCV13 serotypes. Next, the vaccine efficacy estimates from CAPiTA were applied to estimate the number needed to vaccinate (NNV). Over 20,000 adults 65 years of age and older need to be vaccinated to prevent a single case of IPD. Approximately 1600 inpatients and 1100 outpatients need to be vaccinated to prevent a single case of CAP. If the assumption is made that inpatient and outpatient cases are two independent events, it also can be estimated that 650 adults 65 years of age and older need to be vaccinated to prevent a single case of CAP.

The WG assessed the quality of the new evidence that was not included in the previous GRADE evaluation. For the critical outcome of IPD, evidence from CAPiTA was downgraded from Type 1 to Type 2 due to indirectness. The trial was placebo-controlled so the comparison was no vaccine; whereas, in the GRADE evaluation and in the US the standard of care is polysaccharide vaccine. The study showed that PPSV efficacy against IPD, depending on the study, ranges from 50% to 80%. Therefore, it can be assumed that efficacy against invasive disease would be overestimated if comparing efficacy to polysaccharide vaccine instead of placebo. Nevertheless, it is still a moderate quality of evidence—Type 2. Based on the CAPiTA study results, the quality of evidence is Type 1 for pneumonia.

The WG updated the quality of the overall evidence from the previous GRADE assessments, which included extensive review of immunogenicity studies because that was the bulk of evidence available. Immunogenicity data were used as a surrogate for clinical outcomes. However, evidence is now available for IPD and pneumonia. The overall quality of evidence was assessed based on critical outcomes only, so in this case those are IPD or pneumonia. The lowest quality of evidence of Type 2 contributes to the determination of the overall evidence type. The conclusion is that a moderate quality of evidence supports the use of PCV13 in adults.

The answers to 4 questions were considered to determine the recommendation category. The following table compares the conclusions reached pertaining to these questions in 2012 with the conclusions reached in 2014 once the CAPIA results became available:

	2012	2014	Comments
Is the evidence type/quality of evidence considered to be lower?	Y	N	Data on efficacy against critical outcomes available
Is there uncertainty about the balance of benefits versus harms and burdens?	Y	N	Short-term: No uncertainty about the balance Long-term: Indirect effects likely reduce net benefits
Is there high variability or uncertainty in relative importance assigned to outcomes?	N	N	General consensus reached on which outcomes are critical to prevent
Is there uncertainty about whether the net benefits are worth the costs?	Y	N	Short-term: No uncertainty Long-term: uncertainty about whether the net benefits are worth the costs due to continued herd effects

The evidence is now of higher quality at Type 2, which is a change from the 2012 assessment of the Type 3 quality of evidence. There is no uncertainty about the balance of benefits versus harms in the short-term; however, there is uncertainty about the magnitude of expected benefits in the long-term due to expected indirect effects. There is no uncertainty in the relative importance assigned to various health outcomes. There was no uncertainty about cost-effectiveness in the short-term; however, in the long-term there is uncertainty about whether the net benefits are worth the costs due to continued herd effects.

The WG updated ACIP on herd effects from pediatric PCV13 use continuously, leading up to this meeting. The most recent ABCs data show that indirect effects of PCV13 use in children on the IPD burden among adults 65 years of age and older continue to be observed. A significant reduction of 53% has been observed in overall IPD post-PCV13 introduction in children compared pre-PCV13 periods. These reductions are driven by PCV13 serotypes. Reductions have also continued to be observed in PCV7 serotypes. An additional 71% reduction in PCV7 serotype disease was observed post-PCV13 compared to the pre-PCV13 period.

In terms of indirect effects of pneumonia, the studies have documented reductions on non-bacteremic pneumonia following introduction of PCV7 in children. Several studies were conducted using administrative datasets to document the impact on all-cause pneumonia and non-bacteremic pneumonia. These data have been shared previously with ACIP. A recently conducted study also documented the indirect effects of PCV13 use on the non-bacteremic disease burden in adults. Using administrative dataset hospitalizations for pneumonia using International Classification of Diseases (ICD-9) codes, this study documented a 35% reduction in non-invasive pneumococcal or lobar pneumonia following introduction of PCV13 in children. Reductions were observed among other adult age groups as well [Simonsen et al Lancet Resp Med 2014].

To summarize what is known about the indirect effects of PCV13 use among children, PCV7 introduction led to near elimination of PCV7-type IPD among adults of all age groups. There is evidence of continued declines in PCV7-type IPD in adults due to herd effects. The indirect effects of the pediatric PCV13 program have further reduced the proportion of adult IPD and pneumonia caused by PCV13 types. Studies report reduction in non-bacteremic pneumonia in adults following PCV7 and PCV13 introduction in children. The key point is that the expected benefits of PCV13 use among adults will decline over time.

Similar to what was presented in Dr. Hollingsworth's presentation, but in a setting of herd effects rather than one snapshot of time and one year, the WG estimated the PCV13 type burden among adults 65 years of age and older. Extrapolating based on the PCV7 experience and the herd effect, the estimated number of cases was determined for 2015, which is the first year that PCV13 could potentially be introduced, and for 2019. Based on this, an estimated 2600 cases of IPD and nearly 140,000 cases of total CAP are observed in 2013 in the US due to PCV13 serotypes. In 2015, a 20% reduction was applied due to herd effects based on the post-PCV7 experience. The number of cases would be reduced slightly to 2000 for IPD and over 100,000 cases of total CAP. In 2019, again using the projected herd effects based on the PCV7 experience, an 86% reduction due to herd effects was applied. The number of cases of IPD would be greatly reduced to nearly 400 for IPD and close to 20,000 for total CAP.

Next, the potential direct effects of PCV13 introduction in 2014 in the US were applied. The efficacy estimates from CAPiTA for IPD and non-bacteremic pneumonia were applied to the projected cases expected in 2015 based on herd effects, incorporating the 20% reduction in vaccine type disease. Consideration was also given to what would be a reasonable coverage estimate for PCV in the first year after vaccine introduction. The PPSV coverage experience was largely used for this. For 2015, a 10% coverage estimate was used and was ranged from 5% to 30%. This suggested that approximately 160 IPD and 5000 total CAP cases would be preventable. For 2019, the disease burden was determined using the 80% reduction due to herd effects, and applying the direct effects from PCV13 use using a higher coverage rate of 30% and ranging it from 20% to 60%. Again, the PPSV experience was used to determine this. The largest annual increment that has been observed historically for the polysaccharide vaccine has been 3.5%. However, between 2001 and 2008 a 1% increase has been observed on average. Using a more liberal approach of 3.5%, coverage from 2015 to 2019 would be expected to increase 25% to 30%. As an upper limit, coverage closer to current polysaccharide coverage was used. Even if coverage tripled from 2015 to 2019, the number of cases preventable would be almost half of the number of cases from 2013 at 80 cases of IPD and 2600 cases of total CAP. Thus, herd effects alone are expected to reduce the disease burden and long-term limit the number of cases preventable through direct PCV use among adults.

To summarize the presented evidence, a moderate quality of evidence (Type 2) supports the use of PCV13 among adults. PCV13 is safe for use among adults, and is efficacious in preventing IPD and non-bacteremic pneumonia among adults 65 years of age and older. The vaccine preventable disease burden remains among adults 65 years or older. Adding a dose of PCV13 to existing recommendations for PPSV23 is a cost-effective strategy and prevents illness among adults 65 years of age and older. However, herd effects will continue to reduce PCV13-type disease burden and limit the utility of PCV13 use among adults in the long-term.

The two policy options under consideration by the WG are as follows:

- ❑ Add a dose of PCV13 at age ≥ 65 years to currently recommended PPSV23 regimen
 - PCV13 dose followed by a dose of PPSV23 at age ≥ 65 years
 - Risk-based recommendations for PCV13 and PPSV23 use remain unchanged
- ❑ Replace a dose of PPSV23 at age ≥ 65 years with a dose of PCV13
 - PCV13 at age ≥ 65 years
 - Risk-based recommendations for PCV13 and PPSV23 use remain unchanged

The first option would add an extra layer of complexity to the recommendations, and potentially would impact the uptake of the new recommendations. The second option does not add an extra layer of complexity because it assumes replacing a dose of PPSV with PCV. However, based on the assumptions of efficacy against IPD and the serotype coverage provided by the polysaccharide vaccine, the second option may lead to additional IPD cases. For both of these options, discussions are ongoing because appropriate intervals in a sequence of PCV followed by PPSV should be defined, and recommendations and appropriate intervals must be determined for adults who have previously received polysaccharide vaccine and/or the conjugate vaccine, which is currently recommended for adults with immunocompromising conditions. As shown in Dr. Stoecker's presentation, consideration was given to simplified strategies that include age-based recommendations with PCV and removing the PPSV, and keeping only age-based strategies and removing the risk-based strategies. However, all of the strategies that remove the polysaccharide vaccine have the potential to lead to additional cases of IPD even though some of the strategies were more cost-effective than others. Most of the age-based strategies were dominated; that is, they led to higher costs and worse health outcomes.

In terms of the desirable characteristics of pneumococcal vaccine for universal use among adults 65 years of age and older, prevention of IPD and pneumonia is critical. Data are now available showing that PCV13 leads to 75% efficacy against IPD and 45% efficacy against non-bacteremic pneumonia. Adequate coverage of disease-causing serotypes is needed. It is known that at least in the short-term, the strategies under consideration for PCV would result in adequate coverage. There is still vaccine-preventable disease burden remaining, and adequate coverage by PCV of disease-causing serotypes would be provided. However, in the long-term, the herd effects may change that balance and result in a smaller fraction of vaccine-preventable disease burden remaining. Given the level of complexity of the current recommendation for PCV and PPSV use, the potential new age-based recommendation could provide an opportunity to simplify the recommendations. Thus far, the policy options under consideration do not allow for that simplification. Therefore, some of the WG members have concern with respect to implementation issues related to those policy options. It would be beneficial to have a cost-effective option. At least short-term, some of the strategies are cost-effective. However, in a setting of fully realized herd effects, the same strategies are no longer cost-effective.

To summarize the WG's conclusions thus far, a recommendation for universal PCV13 use is warranted in the short-term. However, continued herd effects may limit the utility of a universal recommendation in the long-term. The policy options under consideration add complexity to the current PCV13/PPSV23 recommendations in terms of the appropriate sequence and intervals between PCV13 and PPSV23, and previous PCV13 and/or PPSV23 history. Policy language must be drafted to address concerns pertaining to the complexity of current pneumococcal recommendations, as well as the time-limited utility of universal PCV13 use. There is an

opportunity to prevent disease during the 2014-2015 respiratory season that is rapidly approaching. However, timely implementation may require a decision before the October 2014 ACIP meeting.

The Pneumococcal WG will continue refining the policy options, and requested input from ACIP on the following questions:

- What concerns do you have about the proposed policy options?
- How should the expected decline in the utility of the recommendation influence PCV13 recommendations?
- How feasible would it be to have a time-limited recommendation?

Discussion Points

Dr. Karron inquired as to whether there are any efficacy data on simultaneous or sequential administration of PPSV and PCV13, and in what order, that could be drawn upon.

Dr. Pilishvili replied that there are no clinical efficacy data on sequential administration of PCV13 and PPSV. The immunogenicity studies used for licensure of PCV13 for adults evaluated the sequence of PCV13 followed by PPSV, and the sequence of PCV13 alone among naïve adults and adults who previously received a polysaccharide vaccine at an interval of three to six years prior to enrollment in the study. Those data contributed to the recommendation for immunocompromised adults, and consideration was given to sequence. PCV13 given before PPSV seems to be the most optimal sequence. There are limited data validating what the optimal interval should be, so this was based on the evidence from the immunogenicity studies available that suggest that certain intervals are acceptable. The WG will have this discussion for immunocompetent adults going forward to deliberate what the appropriate intervals would be.

Dr. Karron asked whether there are creative ways to monitor the decline in utility by assessing CAP and IPD in the 50 to 65 year age group, or in unimmunized individuals over 65 years of age. She wondered whether something could be proposed going forward other than a time-limited recommendation in order to have some data.

Dr. Pilishvili thought these were good ideas. She pointed out that if an age-based recommendation for 65 and older was made, it would be very difficult to tease apart direct versus indirect effects in the future. For younger age groups, it might be easier since there is no age-based recommendation. But, there is a risk-based recommendation for immunocompromised adults, so there will still be a mixture of the direct and indirect effects.

Noting the age 60 platform for zoster vaccine and the age 65 platform for PPSV23, Dr. Moore (AIM) was curious as to whether the WG or others had considered the option of a recommendation at age 60 for PCV13 and at age 65 for PPSV23, given the known advantage of receiving the PCV13 first.

Dr. Pilishvili indicated that this exact strategy was not considered. The closest consideration to that was presented by Dr. Stoecker, which was the dose of PCV at age 50 and then at 65. Switching it to 50 could be explored.

Dr. Temte pointed out that in a very poor manner, clinicians attempt to provide zoster vaccine at age 60. There are natural points in time for vaccinating the elusive group of adult patients. Trying to get someone in for a PCV13 vaccine and follow it up with that in 8 weeks is very impractical in real life. But, having a platform as suggested would be worthwhile to consider.

Given that indirect effects are so vital in all of the models, Dr. Byington (COID) wondered what could be predicted about indirect effects should the schedule for children change.

Dr. Pilishvili pointed out that indirect effects were considered when evidence for reduced schedules for children was evaluated. The data available are from countries that have introduced reduced three-dose schedules from the beginning, and have observed a herd effect very similar to what the US data show.

Dr. Schuchat recognized that there has been a lot of uncertainty about the next few years in terms of the herd effect, and that an attempt was made to apply the trajectory observed following implementation of the 7-valent vaccine in 2000 to predict what would happen after 2010. When the 7-valent vaccine was introduced, increased coverage in young children took a while. However, when the 7-valent vaccine was replaced with the 13-valent vaccine, there was already pretty high coverage and the committee also recommended a fifth dose in older children. While catch-up was not perfect, many children under 5 years of age received 13-valent protection pretty quickly compared to the first 5 to 7 years of the 7-valent era. Coverage with four doses is just now reaching 80%.

Luis Jodar (Pfizer) emphasized that all of the studies conducted to measure the proportion of the 13 serotypes contributing to CAP were done in North America in a mature program. The proportion of the 7 serotypes included in the data presented was about 25%. This is 14 years after the introduction of PCV7, so he was not necessarily sure that what is being observed with IPD in the ABCs data could be extrapolated to what is being observed with CAP. This is important because there is persistent disease. He also cautioned about extrapolating the 6 additional serotypes with what has been observed with the 7 serotypes. For instance, serotypes 1 and 5 are covered for a very short time, so the impact from herd protection on those serotypes might not necessarily be extrapolable to what is observed with the 7 serotypes. For serotype 3, for instance, there is some evidence of direct protection as seen with CAPiTA and the case-control that Merck presented during the previous meeting. This impact is not being observed in coverage. Complementary to Dr. Karron's comments, there is a simple tool that can be used immediately for monitoring. The reason all of the models have used 10% is due to the ability to use the UAD tool measure the proportion of the 13 serotypes that contribute to CAP in the US. Continuous monitoring is being done in 10 sites. Pfizer offered the UAD assay to test this in the EPIC study, and can continue to monitor the proportion of the 13 serotypes and how that activity is reduced or not over time. From 2010 and 2011, 11% to 13.6% was observed, so it is important to be cautious. A reduction in CAP is being observed in ABCs, and UAD is a simple tool for monitoring over time. Pfizer will continue monitoring and will offer this assay to any investigator who would like to monitor as well.

Dr. Pilishvili recalled that Dr. Hollingsworth mentioned that 25% of serotypes are due to PCV7 serotypes for CAP, which she thought needed to be explained. It is 25% out of the 10% of all CAP that is due to PCV13 types, which translates to around 2% of all CAP that is due to those 7 serotypes. IPD data were assessed in a similar fashion looking at the percent distribution of PCV7 types out of PCV13 types, and the picture is similar. It is not actually different for IPD versus CAP; however, the percent distribution does not offer a full picture of the dynamic state

of serotype distribution and how disease rates are changing. PCV7 rates continue to decline through PCV13 even though the percent distribution has remained the same. The different herd effects observed depending on the serotypes in PCV13 were taken into account in all of the analyses during a snapshot of time post-PCV7, which was 2003 through 2009. This time period does not include the full post-PCV7 herd effects observed. After that period, a plateau was assumed for Dr. Stoecker's analysis as well as the projected 2019 data that Dr. Pilishvili showed, which assumes that perhaps some remaining disease will persist. In other words, a conservative approach was taken to account for post-PCV13 herd effects.

Dr. Paradiso (Paradiso Biologics Consulting) indicated that the observation is that about 3% of the community-acquired pneumonia is currently PCV7 types, which was observed in the study. The herd effect applied for 2019 assumes that there is an 86% reduction to 1.4% of the PCV13 types. That assumes that the PCV13 types will be reduced in 6 years to below the PCV7 types 14 years after introduction. He does not think that is occurring is really understood. CAP serotypes seem to be somewhat different, but it is important to be careful about the amount of indirect effect. He agreed with the committee comments that it will be somewhat difficult to dissect direct and indirect effects, but there are ways to do that since not all of the population, even over 65, are going to be vaccinated.

Dr. Grabenstein (Merck) indicated that Merck is the producer of the 23-valent vaccine. He acknowledged the many hours of the work group and Dr. Stoecker, because this is not an easy task. However, he thought the situation was brighter than that model showed fundamentally because the 23-valent vaccine has a greater efficacy against non-bacteremic pneumonia than was shown of zero percent. The reference provided for this comes from three old, small studies that largely relied on sputum analysis or pneumolysin assays. One drew blood in only 6 of the 200 cases. The urine antigen test did not exist then. It does now, so the assays that are available should be used for the 23-valent vaccine. The principle one to his mind is the Murayama study published in BMJ where 49 of the pneumonia cases were urine antigen positive. Only 3 of them were from blood culture diagnosis. This study's 64% efficacy is in stark contrast to zero percent efficacy. The last time that was part of the sensitivity analysis, and should at least be that way this time. There's also the Ochoa-Gondar observational study. Some of the slides shown looked at 13-type disease only as if that was all of the disease there is. However, there are 90 serotypes. The 23 non-13 serotypes now account for 30% to 40% of US adult IPD. Dr. Grabenstein said he was confident that ACIP would not leave American adults vulnerable to IPD and pneumonia from the 23 non-13 types, which the 23-valent vaccine can handle quite well. Therefore, he requested that the model be reassessed in terms of its assumptions. At least the cost per dose would have to be recalculated, because Medicare providers do not pay the CDC list price. He asked that the committee consider maximizing the number of serotypes that are targeted to protect American adults.

Public Comment Period

Robert Blancato

Executive Director

National Association of Nutrition and Aging Services Programs (NANASP)

We serve hundreds of thousands of seniors every day, providing nutrition and nutrition education. Our goal is to keep seniors independent. We're in the nutrition and the prevention business. We're here today to urge a broader use of pneumococcal vaccine in adults, especially older adults, and considering lowering the age of older adults to 60 to match the age

of eligibility in our programs, like the Older Americans Act (OAA), and to start raising awareness earlier. We know that pneumococcal kills 1 in every 4 to 5 people over 65 who contract it, or 90% of the deaths that occur from complications of influenza and pneumonia. In 2012, CDC indicated that only 20% of adults at high risk for pneumonia had received the vaccine. It has consequences, including more than 600,000 annual hospitalizations and a direct cost of \$14 billion a year. Our association adopted a resolution at our 2014 annual meeting calling for greater public and private efforts to raise awareness about immunizations for older adults 60 and older as a preventative health goal. Our program serves thousands of seniors, hundreds of thousands of seniors, every day. One case of flu at our centers can and does spread, and it could have been prevented. Let us and other national aging organizations work with this committee to increase awareness about immunizations for at-risk older adults. Thank you very much.

Virginia T. Ladd, RT
President and Executive Director
American Autoimmune Related Diseases Association, Inc. (AARDA)

Autoimmune diseases, according to NIH, affect up to 24 million Americans and that's looking at 26 of the more than 100 autoimmune diseases. Most autoimmune diseases, other than the endocrine ones like type 1 diabetes or thyroiditis, are treated with immunosuppressants. Those immunosuppressants include Prednisone, which has been a long stay treatment for multiple autoimmune diseases. In the last decade, the targeted immunosuppressants of biologics have also been added to that and have actually been very effective. But these therapies do suppress the immune system significantly. The autoimmune diseases are caused actually by dysregulation of the immune system, which has a hyper-response to yourself. The only treatment is to down-regulate that immune system for the disease. This makes the patient very vulnerable to infections and pneumonia particularly, which many are hospitalized as a result of that each year. Of the average person who would get an autoimmune disease, 75% are women and it usually occurs before the age of 50, so the childbearing years, so it's a younger population. We would like to suggest that you increase the numbers of people vaccinated to protect these people, even though I understand the recommendation for immunocompromised people is there. But, when you look at even the percentage of older folks who are not vaccinated and then you consider the numbers, I mean really millions of young people with autoimmune disease, you will see the percentage of them that will not be vaccinated. So, the herd effect is very important for this population and lowering the age will increase the herd effect faster than 2019. Thank you.

Frankie Milley
Founder/National Executive Director
Meningitis Angels

I'm the mother of an only child who died from meningococcal disease, and I'm also the Founder and National Director of Meningitis Angels. I usually don't do this, but I made a few points because I didn't want to forget anything. First of all, I want to thank the committee, the voting committee, the work groups, and everybody here who spends so many hours of their lives dedicated to making sure that we're all protected against vaccine-preventable diseases. Many of us owe you our lives and the lives of the children and our family members. Again, I want to speak to the infant pneumococcal vaccine. Again, as the committee moves forward, I'm kind of disappointed that you guys didn't just go ahead and vote and put this to bed. With that being said, as you move forward in still discussing this that you need to be reminded that in my world

of dealing with parents, which I deal with many every day on both sides of fence, some of them with their little space-cadet theories and that you guys all came from a space ship, but I just want you to know that I think we have several risks by deleting this dosage. The first one being that most parents, if you told them they need 4 doses of something, they may get 3. My fear is that if you say, "You need 3 doses of pneumococcal vaccine," they're only going to get 2 and we're going to see a big problem resurface. Another one is that you need to be reminded, I've spent years of my life working, volunteering, and making sure that requirements and rules are made and passed state-to-state requiring daycare entry, and middle school entry, and college entry laws regarding meningitis. My fear is that—and a lot of these laws and rules actually spell out indication and dosage recommendations. If we go back and change the dosage recommendations, then we're going to have to go back and adjust a lot of those rules and laws, and I'm going to tell you right now, we're going to lose them. We're going to lose those laws. We're going to lose those rules, because the anti-vaccine movement is strong. It's stronger than ever, and they're going to be fighting us on every turn. I have spent 13 years of my life. Ryan's 16th anniversary was Tuesday, okay, from his death. I have spent 13 or more of those years since his death fighting to make sure our kids are vaccinated. I'm afraid when you start talking about changing all of the rules, whether it's HPV, pneumococcal, meningococcal, we risk losing the laws that we already have in place in the requirements. Thirdly, I think we send mixed messages when we start changing dosages after we know they've worked, and they've been proven to work, and we're seeing declines in disease. I think we're sending mixed messages to those parents out there who are resistant or anti-vaccine to say—okay, they're going to start to get confused and they're going to say, "See, they're proving our point. We didn't need all of these to begin with." So, finally, as we say in Texas once more, "If it ain't broke, don't fix it." Some of these just aren't broke. You guys do a good job. I know at the end of the day when this is over with, you're going to vote to keep it. I just know you will, because I think it's the right thing to do. I want to say one last thing. Gregory, that was with me a few months ago in February with his parents, and his mother came up and spoke, Greg is in the hospital right now. He's having surgery to try to stop the seizures again, and also some reconstructive surgery on some of his bones and hip. You know, our kids that fight meningococcal and pneumococcal disease, they don't just come home from the hospital and it's over with. They either die or they come home from the hospital and they face lives full of surgery, and torment, and torture, and ridicule, and hurt, and disappointment. Don't start changing rules that you've already made and recommendations when they're for the right thing, and that's to save lives. Thanks again.

Open Discussion

Dr. Temte requested that the committee take a few minutes to provide feedback for Dr. Bennett and the WG. He recapped some of the suggestions, including adding PCV13 at age 65 and sequencing that with PPSV23; replacing the PPSV23 with 13; assessing alternative ages, for example, age 60 in conjunction with current recommendations for zoster vaccine at that age.

Dr. Schuchat said she was expecting the committee to discuss the idea of a vote before the October meeting and whether that should be planned for. Since this was a public meeting, she thought they should have this conversation.

As a new member, Dr. Reingold requested clarity about the advantage of potentially convening a meeting and making a decision prior to October and whether that was to try and influence immunization in advance of this year's influenza season.

Dr. Schuchat replied that if the committee deliberated on this and was ready to vote during the summer, clinicians and the public seeking vaccination this fall in conjunction with influenza vaccine would know what vaccine they ought to be seeking. Or, they at least would have heard ACIP's formal position on this. A significant amount of vaccination occurs in September, October, and onward.

Dr. Duchin noted that number of concerns expressed by pediatric colleagues about the short time interval between a new recommendation and the ability of providers to stock the recommended vaccine. He wondered how much of a concern would that be if ACIP were to make a recommendation in the late summer or early fall in an attempt to influence immunization practices that same fall.

Dr. Schaffner (NFID) said that while he did not have an answer to the conundrum, he wanted to discuss the issue of the difficulty of translating the best epidemiologic science into practical recommendations. The current pneumococcal recommendations are the single most complex set of recommendations of any vaccine for any age group, and they are directed toward the least effective immunizers—healthcare providers. Anecdotally, local attempts to translate the immunocompromised recommendations for pneumococcal vaccines into practical effect have run into serious difficulty. Approaching this philosophically, seeking perfection is often the great enemy of the current good. As noted, adult providers do not respond rapidly to new recommendations. He suggested clarifying and simplifying the whole array of pneumococcal vaccine recommendations moving forward in an attempt to make them work most effectively for the most people.

Ms. Pellegrini pointed out that in addition to the practical issues for providers, there are practical issues for insurance coverage. This has implications as well for the age selected. She requested clarification from the CMS representative regarding how quickly Medicare would cover a newly recommended age if it was 65 and older.

Dr. Hance (CMS) responded that Medicare currently covers PCV13. The issue is that there is currently one vaccine administered under Medicare. Often, Medicare does not follow the ACIP recommendations. It is a statutory requirement that Medicare provide the one pneumococcal vaccine. There are issues, and CMS is working with CDC on these.

Dr. Schuchat clarified that the polysaccharide and conjugate vaccines currently are included in Medicare Part B coverage. The issue is that one dose is permitted at age 65. For the Medicare population who are typically offered the pneumococcal vaccine, there would not be a delay in determining which one.

Dr. Temte emphasized that the issue pertained to whether both vaccines would be covered if the recommendation were to administer PCV13 followed by a PPVS23.

Dr. Hance (CMS) replied that this is being looked into.

Regarding a vote before October, Dr. Campos-Outcalt thought that while an email could be distributed to the members for a vote, convening a teleconference with discussion would be preferable.

Dr. Pickering indicated that the Federal Advisory Committee Act (FACA) rules and regulations require that all ACIP meetings are open to the public and transparent, so it would not be permissible to have a vote by email. A teleconference must be published in the *Federal Register* 15 working days before the call, and an effort would be made to use other means of notification as well, such as through the ACIP website. The public would be permitted to call in to make comments just as is done in open, in-person meetings. FACA is an advisory committee that advises Dr. Frieden, CDC's director. If Dr. Frieden wanted a meeting convened intermittently due to a public health emergency or public health need, that would be possible. Given that it did not seem that sufficient data have been distributed and digested to vote during this meeting, there would be a possibility of having a vote before the next meeting if considered necessary.

Susan Silverman (Pfizer) indicated that in the event that the committee should decide to make a decision before October, vaccine would be available for physicians who do not already stock it. Pfizer has a number of adult physicians who already stock PCV13. Claims databases show that 50% of all adult immunizations in the US occur between September and December. Dr. Schuchat was right in saying that if there is a possibility to have a discussion and vote before then, there would be an opportunity to address the majority of this year's respiratory season.

Dr. Schuchat said CDC appreciated how complex the information was, and did not expect the committee to vote during this meeting. However, the hope was that there would be enough input for the WG to continue to deliberate, and that a virtual meeting could be arranged following all FACA laws if the committee was ready for a vote before October. Regardless of how confusing it may be or how long it might take to achieve acceptable uptake, there will be a lot of CAP this winter. The vaccine is already licensed and covered by Medicare, so the question regarded whether consumers, clinicians, pharmacists, and public health know ACIP's plans.

Dr. Moore (AIM) pointed out that a recommendation for age 60 would shift some of the burden onto Affordable Care Act (ACA)-compliant private insurance programs. That would avoid many of the issues faced with Medicare. This would allow some of the age group to potentially take advantage of the vaccine with the zoster platform at age 60 when they are covered potentially by ACA-compliant insurance plans.

Dr. Duchin expressed confusion about the Medicare coverage situation. While Drs. Schuchat and Hance indicated that the vaccine is covered, it seemed that if 13-valent vaccine is used, 23-valent would not be covered.

Dr. Hance (CMS) indicated that Medicare currently pays for both. The issue is that a person is eligible for one vaccine. Potentially, if someone received 13-valent vaccine, they would no longer be eligible for the 23-valent. There may be situations for which it is covered, which they are working on now.

Dr. Duchin inquired as to the timeline for resolving this issue, given that knowing this would be important for the WG and ACIP.

Dr. Hance (CMS) said that she was not in a position to give a timeline as they just began to explore the options, and emphasized that Medicare coverage is based on a statutory provision and statutory requirement.

Dr. Kempe thought this was crucial information to know before voting, given that there could be a shift from the 23-valent to the 13-valent, which was not a desirable alternative.

Dr. Fryhofer (AMA/ACP) noted that while pneumococcal vaccination is very important and is lifesaving, as Dr. Schaffner also pointed out it is very confusing and dysfunctional to implement the appropriate vaccination program. Clarity is needed and this recommendation must be simplified as much as possible moving forward. However, if a recommendation is made for 65 year olds and above, without Medicare coverage, they would be stuck before they began. This is not a \$20 or \$23 vaccine. She requested that the manufacturers indicate the price they are charging practitioners. Patients and physicians cannot “eat this.” It has to be covered, or this could be a big barrier. Time is of the essence. There is a great vaccination opportunity by combining this with influenza vaccine, but it is not going to be successful in the 65 and older age group if Medicare does not buy in and provide coverage for patients.

Dr. Temte agreed that this is a very complicated issue, and that it would be difficult to reach a resolution during this meeting. He suggested devoting a 3- to 4-hour period in August to revisit the issues via a web or teleconference. There also needs to be a relatively formal GRADE presentation, parts of which have already been done, to inform the deliberations if a decision is going to be made.

Dr. Bennett summarized that she was hearing that people were interested in moving the timeline on this decision forward if possible and, therefore, having an additional meeting. She thought the WG needed to reconvene quickly to consider some of the issues that were raised during this meeting about feasibility, implementation, and simplification of the schedule to determine whether they could come forward with a strong recommendation by August.

Dr. Pickering emphasized that if a meeting were to be held, notification would be made via the *Federal Register*, the ACIP website, and through emails. CDC will do everything possible to ensure that the public is involved in this meeting.

Dr. Reingold inquired as to whether they would also have to deal with the question of what is recommended about use of the conjugate vaccine in people who already received a dose of the polysaccharide vaccine.

Dr. Bennett agreed that this is a problem and said she did not necessarily think there was a way to make this simple. Additional thought should be given to the possibility of simplification, but if there is no hope of simplification, then there is no point in holding back.

Dr. Schuchat suggested that the WG consider a narrow vote that could be implemented quickly, while addressing much of this later. While clinicians would appreciate everything being done at once, other issues could be addressed at a later stage.

Dr. Kempe agreed, but stressed that they need an answer about coverage because if this means one vaccine versus the other, that is a very different decision.

Dr. Duchin endorsed this, and thought it would be counterproductive for people to be disqualified from receiving a vaccine they need because they have already received a complimentary vaccine. That is intimately tied to whether the Medicare issue will be resolved, and he did not see the point in moving forward without knowing this.

It was Ms. Pellegrini's recollection that under the ACA requirement, private plans are not required to cover new vaccinations until the next year's plan. That could be at the end of the next vaccination season or after that.

Dr. Temte requested that Dr. Netoskie clarify, if a decision were made in August or October for someone under the age of 65, when would that be implemented under ACA for insurers.

Dr. Netoskie (AHIP) said it was his understanding that coverage could be deferred until the next planned year. However, many plans do implement this upon the recommendation by ACIP, so it will be somewhat variable in the marketplace.

Dr. Schuchat added that plans actually have until the next planned year coming up 12 months after publication in the *MMWR*, so it could be longer than 12 months after publication. That means it could be a couple of seasons.

Dr. Bennett expressed appreciation for the input from the committee, and indicated that the WG would get back to them very soon.

Dr. Temte concluded that the Secretariat would explore the possibility of a conference in August, as well as people's availability.

Measles Updates

Global Update

Mr. James L. Goodson
Global Immunization Division
Center for Global Health
Centers for Disease Control and Prevention GID

During this session, Mr. Goodson discussed the Global Vaccine Action Plan (GVAP), the Measles and Rubella Strategic Plan, measles and rubella targets that come from those two documents. He also discussed the Measles & Rubella Initiative vision and the global and regional progress toward measles elimination.

The GVAP is the key global document that currently provides the vision statement and serves as the guide for global immunization efforts worldwide. The GVAP was developed by a group of global partners through the Decade of Vaccines Project, which was largely funded by the Bill and Melinda Gates Foundation. The GVAP document was published by the World Health Organization (WHO) and approved by the World Health Assembly in 2012.

Another key document is the Global Measles and Rubella Strategic Plan, 2012-2020 developed by the Measles & Rubella Initiative. This initiative is a global partnership that was established in 2001 by five core partners: American Red Cross (ARC), CDC, United Nations Foundation (UNF), UNICEF, and WHO. The strategic plan took over 15 months to develop, with extensive consultation and consensus building. It was signed off by the Heads of Agency of the five core partners. The targets in the strategic plan are aligned with those in the GVAP, and the strategic

plan provides a common vision, which is to “Achieve and maintain a world without measles, rubella and congenital rubella syndrome.”

At global level, there are three targets to be achieved by 2015. These include: 1) measles-containing vaccination coverage (MCV1) of at least 90% at the national level and 80% in every district of the first dose; 2) reported incidence of measles of less than 5 cases/million population; and 3) measles mortality reduction of 95% compared with 2000 levels. The 2020 GVAP goal is measles and rubella elimination in five of the six WHO regions of the world. Since September 2013 when the Southeast Asia Region adopted an elimination goal for measles, all six regions of the world now have a set date for measles elimination: 2000 American Region (AMRO); 2012 Western Pacific Region (WPRO); 2015 European Region (EURO) and Eastern Mediterranean Region (EMRO); and 2020 African Region (AFRO) and Southeast Asian Region (SEARO). In addition, two of the six regions have established rubella elimination targets: 2010 AMRO; and 2015 EURO.

Regarding progress toward the global 2015 targets, this year marks the 40th anniversary of WHO EPI program, which was an offshoot of the smallpox eradication program. The EPI was established globally in 1974, so it is worth looking back at the impact of measles vaccination over time. Since 1980, MCV1 coverage has increased and a 94% reduction has been observed in reported measles cases globally from approximately 4 million cases in 1980 to little over 200,000 in 2012. Since 1985, there has been an impressive 90% reduction in estimated measles deaths worldwide. Progress for this indicator has been monitored since 2000. From 2000 to 2012, there was a 77% decrease in incidence, with a 78% decrease in deaths. Although short of the 2015 target of a 95% reduction, 13.8 million deaths have been averted through measles vaccination since 2000.

There has been great public health success in measles and rubella elimination in the Region of the Americas. Both of those endemic viruses have been eliminated in the Western Hemisphere. Today, the Region of the Americas continues to be the model for achieving measles and rubella elimination around the world. The vaccination strategies of routine immunizations combined with mass vaccination campaigns successfully stopped endemic measles virus transmission in 2002 and rubella in 2009.

In terms of the secular trend in coverage with the first dose of measles-containing vaccine or MCV1, MCV1 coverage has leveled off at 84% for the past four years globally. Three regions still have MCV1 coverage of less than 90%: AFR, SEA, and EMR. So, there is still work to be done. The AMR, EUR, and WPR have sustained MCV1 above 90% for at least the past eight years.

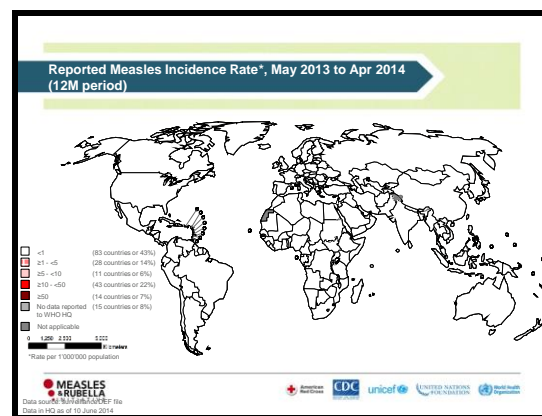
WHO recommends that all children receive two doses of measles vaccine. Global routine coverage of a second dose of measles-containing vaccination (MCV2) remains low at 56% in 2012. This was primarily due to a number of countries that have yet to introduce a routine second dose of measles-containing vaccines. The number of countries with MCV2 is increasing each year, with an additional planned for 2014. Each year, additional countries will be introducing a second dose. It is important to recognize that the routine second dose in many of these countries can provide an important opportunity for EPI vaccinations to extend beyond the first year of life. This can establish an important child health platform.

In addition to routine delivery of measles vaccinations, 33 countries implemented mass vaccination campaigns with measles vaccine or combined measles/rubella vaccine in 2013.

Through these campaigns, nearly 200 million children were vaccinated. Over three quarters of all campaigns provided other vaccines in addition to measles vaccine, which primarily included rubella and oral polio vaccine (OPV).

In addition to vaccinations, another critical component of elimination strategies is the implementation of case-based surveillance. The Global Measles and Rubella Laboratory Network (LabNet) was fully established in 2000, and has grown from 80 laboratories in 2001 to over 700 labs currently. The CDC laboratory in the Division of Viral Diseases (DVD) serves as a global specialized measles and rubella laboratory within the LabNet. The network has established standardized testing procedures and maintains a strong quality assurance program, annual proficiency testing (PT), and laboratory accreditation of LabNet laboratories. The LabNet also has established global measles virus reference strains and nomenclature, which are updated periodically and are published in the *MMWR*.

The global database for countries to submit virus genotypes and sequences allows for phylogenetic analyses to help track transmission of virus pathways. In terms of the global distribution of measles virus genotypes detected, during April 2013 through March 2014 of the 24 known measles virus genotypes historically, eight were detected and some have clearly been eliminated. In 2014 the Western Pacific Region experienced an increase in cases that was largely due to an increase in reported cases in China and a very large outbreak in the Philippines. For the 12-month period from May 2013 to April 2014, a number of countries experienced a high measles burden, including the Philippines. The countries experiencing a burden of 50 or more measles cases/million population, well above the incidence target, are shown in red in the following map:



Prior to 2013, the Philippines experienced two large measles outbreaks in 2010 and 2011, each reporting over 6,000 cases. The current outbreak appears to have started in October 2013, and it is much larger than previous outbreaks. It peaked in January 2014, with over 8000 reported cases in that month alone. Findings from the outbreak investigation, to which CDC contributed along with the Ministry of Health and WHO, assessed data through 2014. Based on this assessment, there were over 26,000 suspected measles cases, including 6000 that were laboratory-confirmed, and over 100 reported measles deaths. Of the confirmed cases, 42% were in the Metro Manila area. The majority of cases overall were among children less than 5 years of age who were unvaccinated or had an unknown vaccination status.

In conclusion, Dr. Goodson highlighted the importance and great appreciation of the US support to local efforts. This support is critical, not only for reducing morbidity and mortality globally, but also for lowering importation pressure in the US and thereby helping to maintain elimination in the Region of the Americas.

Domestic Measles Update

Gregory S. Wallace, MD, MS, MPH
Lead, Measles/Mumps/Rubella/Polio Team
Epidemiology Branch, Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Wallace reported that the outbreak in the Philippines has imported virus into several other countries, including the US. While most of the importations have been genotype B3, another genotype (D9) is circulating in a different region of the Philippines that has also been imported into the US. It is important to remember that from year-to-year, importations are influenced not only by what is occurring in neighbouring countries, but also by travel patterns. The US tends to be less sensitive to travel patterns to what may be occurring in Africa, but is very sensitive to what is occurring in Europe. Europe has been a dominant importation site in recent years, but this year has been very low. Nearly half of US importations this year have been from the Philippines.

In terms of the number of reported cases by month since the beginning of elimination in the US, for the period from 1997-2001, there was a range of cases over time that was relatively low. From the period right after the documentation of elimination, the range was even lower with no new cases after about June. In 2008, a couple of outbreaks attributed to a larger number of cases than observed in recent years. 2011 was influenced by a lot of transmission within Western Europe that led to more importations than usual. While 2012 was closer to a good or normal year, there were three independent outbreaks in 2013 that led to an increase in the relative number of cases. In 2014, increases began earlier than ever because the Philippines experienced an early outbreak and there were many US importations that led to outbreaks. One importation led to a very large outbreak that is still ongoing.

To summarize 2014, 514 cases had been reported from 20 states including 16 outbreaks as of June 20th. There have been 48 importations, of which 23 were from the Philippines reflecting their epidemiology and travel patterns between our two countries. It is important to note that the vast majority of cases of importations are US residents who travel abroad, so there is an opportunity even with what is occurring globally to have an intervention. There has been a lower than usual number of reported hospitalizations of 56 cases (11%). Some of that may have to do with the characteristics of the community suffering the large outbreak this year. Amongst the cases in US residents (N=506), 81% were unvaccinated, 12% had an unknown vaccination status (78% of those were adults), and 7% were vaccinated (including 5% with 2 or more doses). Among the unvaccinated, 87% were personal belief exempters, 3% were unvaccinated travellers ages 6 months through 2 years, and 5% were too young to be vaccinated.

The following table depicts the list of the US outbreaks of 20 or more linked cases since the documentation of elimination in the US:

**Measles Outbreaks with >20 Cases,
United States, 2001-2014***

Year	Outbreak Name	State	# of Cases	Import Status	Genotype	Setting	1st & last rash onsets	Duration	Median Age	Age Range
2014	Knox County	OH	340*	Imported (Philippines)	D9	Community	3/22/2014 –	13 weeks and counting	23 y (early) 13 y (late)	2 wks – 52 y
2013	Brooklyn	NYC	58	Imported (UK)	D8	Household/ community	3/13/2013 – 6/9/2013	13 weeks	10 y (early) 19 mos (late)	0 mos – 32 y
2005	Tippecanoe County	IN	34	Imported (Romania)	D4	Church/ household	5/16/2005 – 6/24/2005	6 weeks	12 y	9 mos – 49 y
2008	DuPage/Cook County	IL	30	Imported-virus	D4	Homeschool	5/17/2008 – 7/3/2008	7 weeks	10 y	8 mos – 43 y
2014	Manhattan	NYC	25	Imported-virus	B3	Community	2/11/2014 – 3/24/2014	6 weeks	22 y	3 mos – 63 y
2013	Stokes/Orange County	NC	23	Imported (India)	D8	Community	4/5/2013 – 5/7/2013	5 weeks	14 y	12 mos – 59 y
2014	KC Metro	MO/KS	22*	Imported-virus	B3	Community	5/5/2014 –	7 weeks and counting	5 y	2 wks – 37 y
2013	Tarrant/Denton County	TX	21	Imported (Indonesia)	D9	Church	7/21/2013 – 8/21/2013	5 weeks	11 y	4 mos – 44 y
2011	Hennepin County	MN	21	Imported (Kenya)	B3	Shelter	2/15/2011 – 4/24/2011	10 weeks	23 m	3 mos – 51 y
2008	Brooklyn/Kings County	NYC	21	Imported (Israel, Belgium)	D4	Community	2/17/2008 – 4/25/2008	10 weeks	15 m	5 mos – 11 y

*as of June 20, 2014

In terms of the features of the outbreaks, all have occurred in recent years, are larger than they were previously, and some begin in older age groups. It is not uncommon for an outbreak to begin in an older age group, but to impact younger age groups as households are exposed. Two outbreaks are currently ongoing, one in Ohio and another in Missouri and Kansas. In Ohio, the initial three cases had travelled to the Philippines to engage in relief work to help them rebuild following a hurricane. Then it reached US communities where the outbreak is predominately occurring in three counties that have very complex mixing patterns. CDC believes that transmission is beginning to slow down, but case ascertainment has been an issue. There has also been a significant amount of vaccination within the community.

To put this into perspective, prior to vaccination, the US had approximately 3 to 4 million estimated cases annually and approximately 500,000 reported cases; 48,000 hospitalizations; 4000 encephalitis cases; and 450 to 500 deaths. There was a quick drop in reported cases with vaccination programs. There were some challenges, many of which were attributable to one-dose outbreaks in school aged children. That led to a second dose recommendation just as the resurgence was occurring in 1989 through 1991, which primarily affected inner city children who lacked access to vaccines. This helped lead to the VFC program. The combination of the second dose recommendation and the VFC program removing barriers to vaccine quickly resulted in a large decrease in cases, along with the ability to declare elimination.

Prior to elimination, most US importations were from the Americas. In addition to our two-dose recommendation and the VFC program, the PAHO organization simultaneously committed to elimination. This significantly contributed to the reduction of importations into the US. Then importations came from other areas, and were influenced by the epidemiology and travel patterns. By the late 2000s, most cases were coming from Europe. This year, there was a shift to the WPRO region, which is dominated by the Philippines this year. There is less travel to China, but certainly what is occurring there is of concern.

Coming out of the resurgence in 1993, though a multi-state outbreak occurred, there began to be evidence of a lack of endemic transmission and very quickly a low number of cases. This was followed by an observation that was more concerning. In 2008, there was not an increase in the number of importations, but there were a couple of outbreaks that led to an increase in the number of reported cases. In 2011, there was an increase in importations and one relatively large outbreak. There were still a number of importations in 2013, with three individual outbreaks contributing to that transmission. In 2014, the pattern was similar to 2013. However, the Ohio outbreak contributed the most.

Most importations lead to no transmission, or transmission to one person. Often, these are household transmissions. However, some transmissions lead to 10 or more cases. This year, the majority of US cases are only one or two cases of linked transmission. However, some do include 10 or more transmissions, which is more than observed in the past. Whenever there is an increase in the number of cases in the US, the incidence rates increase in the youngest children. The children are the most vulnerable to complications, and some of them are too young for vaccination.

With regard to what is working in the US, national vaccine coverage remains high and the vaccine works. Public health departments continue to take a very aggressive stance in terms of every case and contact to interrupt transmission. If the first couple of cases had been identified in the Ohio outbreak, transmission would not be as high as it is now. There has also been improvement with the implementation of healthcare worker recommendations, and electronic health records for hospital staff to keep transmission from occurring in those settings.

There are a number of challenges. Heterogeneity is one issue. Outbreaks reveal groups of a high enough proportions of people who do not get vaccinated who are accumulating and aging over time. What occurs globally certainly influences what occurs in the US, and importations are going to continue. Most importations are via US residents who could have been vaccinated before leaving the country. Early diagnosis of initial cases is still a challenge and has consequences. It is important to think about measles when thinking about other rash illnesses in travellers. The initial Philippine importations into Ohio were first suspected to be dengue, which often occurs. Children were also worked up for Kawasaki's disease and who actually had measles. Implementing travel recommendations continues to pose challenges. The recommendation is for children to be vaccinated down to age 6 months before travelling, but there is still a lack of awareness. Adults who are now too old to have been recommended to receive two doses should be required to receive a second dose before traveling. This is a resource-intensive public health response. Every time there is a case, public health departments have to divert resources to try to stop transmission early, and there is also a concern of mission fatigue as this continues.

The key messages are that measles in the US is a global issue, with most importations coming from US travellers. There is an opportunity to intervene with US travellers. Measles is very contagious, so when it is transported to the US, it is going to impact those who are unvaccinated. It is important to keep measles in the differential diagnosis of febrile rash illnesses. Obtaining travel history, exposure to travellers, vaccine history, and viral specimens is important. Measles outbreaks have revealed that a huge variety of groups do not get vaccinated in the US. Each year, a different group is identified who may not have been considered in the past. The intervention for these groups must be tailored for the reasons that they may or may not be getting vaccinated.

Discussion Points

Dr. Temte inquired as to whether there are any efforts with highly mature registries to map out pockets of high risk across the country in an effort to preempt potential outbreaks.

Dr. Wallace responded that this is something CDC would like to do, and has made some attempt to implement such an effort. Some modeling work is being done to try to use those registries to assist health departments in understanding the potential consequences of what is

being observed in their registries. This could help them to leverage resources to try to intervene.

Dr. Fryhofer (AMA/ACP) noted that the adult schedule states that adults born before 1957 are generally considered immune to measles and mumps. All adults born in 1957 or later should have documented one or more doses of MMR vaccine. She requested clarity regarding whether Dr. Wallace was saying that more should be done with even adults born before 1957 before they travel.

Dr. Wallace clarified that the 1957 recommendation still holds, and that those born after 1957 and who have had only one dose should receive a second dose before traveling.

Dr. Reingold thought the regional elimination goals were heartening, but noted that a close look suggests that at least two of the regions will not meet their current goals in terms of measles elimination. There is clearly more work to be done, and there is certainly an ongoing risk to travelers. Given the data shown, he was curious as to what is being done to ensure that US travelers are actually immune before they leave the US and return.

Dr. Wallace replied that every opportunity is taken to reiterate the travel recommendations and reinforce that message. Even early in 2011 when an increase was observed in importations, many of the cases were in 6 through 15 month olds. Many times young families are bringing a child back from the country from which they immigrated, and that can be a source of importation. With the current situation, CDC is spending a lot of time conducting clinical provider- and physician-based webinars and discussions to keep this information before them.

Dr. Schuchat added that since April, CDC has been ramping up the outreach related to risk in travelers. The travel health site on the web, as well as their partners, did a lot more. In addition to risk in the Philippines, CDC did a lot in advance of the World Cup. While this may or may not have reached all travelers, there was a lot of media and clinician outreach to try to get to those travelers and their clinicians.

Dr. Wallace indicated that the Division of Quarantine and Migration (DQM) makes a lot of efforts related to travel alerts and educational efforts that appear at airports and so forth.

Dr. Seward (SME) added that CDC also works with AAP to target young children ages 6 through 11 months old and 12 through 15 months old, who are missed opportunities. However, many travelers are personal belief exempters. Many people who travel, including the two who came back from the Philippines into Ohio, had chosen not to be vaccinated after knowing the recommendations. CDC's effort is to communicate as much as possible, and to try to deal with other issues.

Dr. Hahn (CSTE) asked whether new pockets were being discovered. If so, it would be helpful to advertise this to states so that they can begin looking for these pockets to try to persuade at least some people to get vaccinated.

Dr. Seward (SME) indicated that CDC convened a nationwide conference call with CSTE the previous week to alert people, especially with regard to the outbreak among the Amish population in Ohio. That is a very large group in many states. CDC is doing everything they can within that population, which is highly at risk.

Dr. Zahn (NACCHO) indicated that in Orange County where he works in California, there have been 22 cases of measles since the beginning of the year. Of those, 5 were in healthcare workers. By and large they are immunized, they received two doses of documented measles vaccine, and they have serology documenting that they are immune. The issue is that they are considered immune and go about working. They probably have some immunity and have somewhat attenuated disease, so for the first few days when they have a runny nose and cough, they continue to work and see patients. In terms of mission fatigue, it takes a lot of work for all of these responses. A healthcare worker in an emergency department may, in the four days before the appearance of a rash, see over 1000 patients in close contact. Those are extremely difficult responses. One of the major emphases that NACCHO has been trying to get out to healthcare providers is that they should get immunized, and if they have been immunized, that they still need to practice infection control precautions because they cannot be 100% sure that they are immune.

Dr. Wallace added that this includes early recognition or at least suspicion so that the patient is isolated as soon as possible. It is not uncommon for a case to have been in a healthcare system for some time before they are recognized.

Dr. Zahn (NACCHO) noted that some providers insist that they are immune because they received their two doses, so they may not wear their N95 mask in a negative pressure room as a result because they think it is annoying.

Dr. Temte added that that is coupled with the fact that studies have shown that up to 70% plus of physicians present to work when they are sick and continue to work.

Related to a healthcare worker taking care of children, Ms. Stinchfield (NAPNAP) surveyed all of the children's hospitals across the country that are on their Infection Prevention Director's listserv about the question of wearing masks. Some people do not wear them because they are counting on their immunity, some people wear surgical masks, and some people wear N95 masks. Some states have very strict Occupational Safety and Health Administration (OSHA) laws, while others do not. This area would be helpful to clarify.

Dr. Wallace indicated that those recommendations are in the surveillance manual. When he recently spoke with several health departments, he also got a variety of responses with respect to compliance.

Dr. Seward (SME) added that those are the recommendations made by Healthcare Infection Control Practices Advisory Committee (HICPAC) and CDC for isolation guidance, and ACIP in the 2013 recommendations. A healthcare worker with evidence of immunity with two doses should be protected with an N95 or higher when entering a room. That message must be disseminated.

Dr. Kempe inquired as to whether more aggressive means of decreasing under-vaccination could be undertaken, such as decreasing personal exemptions or other implementing policy regulations like publishing the percentage of unvaccinated children in preschools, schools, et cetera.

Dr. Wallace reiterated the efforts being undertaken by PAHO in the Americas, the VFC program removing barriers, and the two-dose recommendation. Another important part of that was also school laws and having a second dose, school-based recommendation where people got

caught up before there was a lot of mixing. That was critical to what was done in the US, and what other nations have not been able to do because of their unwillingness to institute school-based laws. There has been a lot of battle back and forth every year in probably almost every state where the degree of ease to become a personal exempter goes back and forth. At least anecdotally, if the ability to opt out is made more strenuous, that helps and is definitely an area that is worth continued pursuit.

Mr. Goodson added that there seems to have been some momentum change in vaccine acceptance in the last couple of years, which is a positive sign. It is important to better understand the groups who are philosophical exempters, because there is quite a continuum. In some communities where there has been low vaccine coverage, once an outbreak occurs, they have accepted vaccine.

Dr. Pickering inquired as to whether the recommendations for traveling children down to 6 months of age to receive vaccine, and for those 4 to 6 years of age to receive their second dose if they have not had it, are being implementing in the communities where there are outbreaks.

Dr. Wallace replied that going down to 6 months of age has occurred in limited situations. This is a local decision, so if the epidemiology of the outbreak being experienced within the US indicates that, there are times when the first dose is administered early down to 6 months. In 2011 in Minnesota with the distribution that was happening in homeless shelters, that did occur. There is no contraindication to administering the second dose before 4 to 6 months of age. Again, when the epidemiology has pointed in that direction, it has been done. Sometimes it is a question of resources. The first prioritization is always to administer one dose in those who have had no doses. Certainly, getting the second dose early before 4 to 6 is completely acceptable even when there is not an outbreak. Going down to 6 months is reserved for when the epidemiology demands it.

Mr. Goodson added that globally, the WHO recommends that for a measles response, vaccination should begin at 6 months of age. The challenge is that the early doses should not count toward the two doses that all children need. Families need to be reminded when they receive a dose during an outbreak response that the child still needs to receive their two regularly scheduled doses. The reason for that is that vaccine effectiveness at 6 months of age is reduced down to 50% to 60%, so even though they are vaccinated, a large number of them may not be protected.

Meningococcal Vaccines

Introduction

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

Dr. Rubin indicated that this session would focus primarily on outbreaks of meningococcal disease and the potential use of serogroup B vaccines. At present, a meningococcal B vaccine (MenB) has not been licensed in the US. However, two investigational MenB vaccines are under development. Both vaccines have received a "Breakthrough Therapy" designation from

the FDA. Pfizer Vaccines has submitted a complete Biologic License Application (BLA) to the FDA, and Novartis Vaccines has submitted a rolling BLA to the FDA. The Novartis vaccine is licensed in Europe, Australia, and Canada.

In 2013, two universities experienced outbreaks of serogroup B meningococcal disease, with a combined 13 cases and one death reported. MenB vaccination campaigns were conducted at both universities in response to the outbreaks using an investigational MenB vaccine from Novartis Vaccines that was obtained through an expanded access Investigational New Drug (IND) application sponsored by CDC.

An ad hoc WG was developed that is comprised of ACIP Meningococcal Work Group members, ACIP members, state public health officials, college health professionals, and CDC. This WG's first meeting was convened January 30, 2014 with biweekly meetings. This WG has three objectives, which are to:

- Review available data on the recent epidemiology of meningococcal disease and outbreaks
- Develop guidance for use of MenB vaccines under a CDC-sponsored IND in an outbreak setting
- Update the current meningococcal outbreak guidelines once MenB vaccines are licensed in the US

Regarding additional Meningococcal WG activities, a Policy Note on the use of Menveo[®] in infants at increased risk for meningococcal disease was published on June 20, 2014. This publication summarizes the use of three meningococcal conjugate vaccines in children aged 2 through 23 months at increased risk. The WG is also discussing the approach to recommendations for use of serogroup B vaccines once they are licensed.

Epidemiology of Meningococcal Disease Outbreaks in the US

Sarah Meyer, MD, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

In this presentation, Dr. Meyer reviewed the epidemiology of meningococcal disease in the US, outbreaks of meningococcal disease, and results of the recent evaluation of clusters and outbreaks in organizational settings.

Since the early 2000s, rates of meningococcal disease due to all serogroups, including serogroup B, have declined to historic lows in the US. In addition, vaccination coverage of the adolescent MenACWY vaccine has increased in recent years since introduction in 2005. With this high vaccination coverage, serogroup B is now the predominant cause of meningococcal disease in the adolescent age group, as opposed to prior to vaccine introduction when serogroups C and Y were the most commonly reported.

Despite the higher rates of serogroup B disease in adolescents, it is important to note that the overall burden of disease is very low, with an average of 29 cases reported annually from 2010-2012 in 11 through 24 year olds. Outbreaks of meningococcal disease are rare in the US, historically causing only 2% to 3% of US cases. Reports of school- and organization-based clusters or outbreaks are uncommon in the published peer-review literature. From 1989-2004, during the pre-MenACWY vaccine era, 22 school-based outbreaks were reported in the US. Of

these, 7 were serogroup B outbreaks and 14 were serogroup C outbreaks. The majority of these outbreaks consisted of 2 or 3 cases. Little difference was seen between serogroup B and C outbreaks in terms of duration of the outbreak and interval between reported cases, with a median of 3 days between cases for serogroup B and 2 days for serogroup C.

Since 2009, 5 universities have reported serogroup B clusters or outbreaks, with 2 to 13 cases reported in each. With these most recent university outbreaks factored in, as well as a serogroup C outbreak in an elementary school in 2010, the size of outbreaks appears larger, with more outbreaks reporting greater numbers of cases. In addition, the median interval between cases is increased, creating a more indolent pattern for serogroup B outbreaks. However, it is unclear if these differences are real or if the differences are related to increased recognition of cluster-associated cases in the setting of historically low disease rates.

In summary, serogroup C meningococcal outbreaks are less frequently reported since high adolescent coverage with the MenACWY vaccine has been achieved in the US. The 3 most recent university-based serogroup B outbreaks were atypical compared to previous outbreaks, with a greater number of cases reported and longer intervals between cases.

In light of these recent serogroup B outbreaks, an evaluation was conducted to understand the current epidemiology of meningococcal clusters and outbreaks in the US. Prior to revising guidance for use of meningococcal vaccines in an outbreak setting, including use of an unlicensed serogroup B vaccine under a CDC-sponsored IND, it is important to understand the full breadth of epidemiologic features of meningococcal clusters. This includes identifying previously unreported clusters and understanding whether the recent serogroup B university outbreaks are representative of the current epidemiology of meningococcal disease outbreaks.

Although information on outbreak-associated cases is collected through the National Notifiable Diseases Surveillance System (NNDSS), reporting is likely incomplete. Complete and systematically collected data on clusters and outbreaks of meningococcal disease occurring in the US is important when evaluating outbreak guidelines. Thus, a retrospective review of meningococcal cases reported since January 1, 2009 was conducted by state health departments and CDC to identify clusters of meningococcal disease. An Epi-X announcement with a call for cases and clusters was published on January 24, 2014, followed by a standard questionnaire administered to each state.

For the purposes of this evaluation, a meningococcal cluster is defined as follows:

- 2 or more cases of the same serogroup in an organization in ≤ 3 months (not including secondary cases) **OR**
- An increase in disease rates of the same serogroup in a community or a specific population in a community (rate 2 times the rate during the same time period in prior years).

A meningococcal outbreak is defined as:

- 3 or more primary cases of the same serogroup in ≤ 3 months

Clusters and outbreaks are classified as:

- Organization-based **OR**
- Community-based

From January 1, 2009 to December 31, 2013, 3,745 cases of meningococcal disease were reported in the US through NNDSS. Eighteen states reported 71 clusters or outbreaks through the Epi-X announcement. Fifty-two clusters met the cluster definition with 207 cases, comprising 5.5% of all US cases. Among these, 22 clusters also met the outbreak definition with 146 cases or 3.9% of all US cases. All subsequent analyses represent primary cases from clusters meeting the cluster definition.

From 2009-2013, cluster-associated cases occurred throughout the year in each of the years of the evaluation. The distribution of clusters has been widespread, and the number of clusters per year has ranged from 6 to 17. The majority of clusters in the US are community-based clusters, with 37 reported from 2009-2013. Also reported were 14 organization-based clusters and 1 unknown cluster.

Given the need to develop interim guidance for the use of unlicensed serogroup B vaccines under a CDC-sponsored IND in organizational settings, Dr. Meyer focused the rest of the presentation on results from organization-based clusters.

In terms of serogroup distribution, approximately 60% of organization-based clusters are due to serogroup B, compared to approximately 35% of sporadic cases. The median population size of the cluster is over 14,000 persons. The median number of cases per cluster is 3. The median duration of the cluster is 48.5 days. The median age of cases in organization-based clusters is 19 years, compared to 35 years among sporadic cases reported to NNDSS. The case-fatality ratio in organization based-clusters is 17%.

Among the 14 organization-based clusters reported, 7 occurred in universities. The other organizations reported included a fraternity party associated with a university parents weekend in which parents of the students became ill, a long-term care facility, a correctional facility, a meditation center, a homeless shelter, an elementary school, and a hockey league affiliated with a university. Among the 7 non-university-based clusters, 2 were due to serogroup B. The number of cases per cluster ranged from 2 to 8 and the duration of the cluster from 2 to 245 days. Among the 7 university-based clusters, 5 were due to serogroup B. The number of cases per cluster ranged from 2 to 10. The median number of days between cases ranged from 3 to 75 days, for a total duration of the cluster of 25 to 616 days. The overall case-fatality ratio in organization-based clusters was 17%, but differed by serogroup. Serogroup B clusters had a case-fatality ratio of 6.1%. In serogroup C clusters, the case-fatality ratio was 42.9%.

In the setting of historically low cases of meningococcal disease, meningococcal clusters account for a greater proportion of cases than in years past, and are likely recognized and reported more readily. A substantial proportion of organization-based clusters are associated with universities and are due to serogroup B. The three recent serogroup B university-based clusters have appeared atypical compared to clusters in years past in terms of number of case and duration. However, the course of a cluster is unpredictable, and it is difficult to determine if and when additional cases will occur.

The comparison of current meningococcal cluster or outbreak epidemiology to historical data has limitations. Over time, there have been changes in the definitions, recognition, and reporting of meningococcal clusters. In addition, advances in molecular genotyping may alter the interpretation of which cases are associated with a particular cluster. Regardless, meningococcal disease clusters and outbreaks cause substantial concern necessitating a public health response.

In conclusion, serogroup B organization-based clusters are rare and heterogeneous, limiting the ability to make definitive interim vaccination recommendations based on data alone. Interim guidelines for use of serogroup B vaccines under a CDC-sponsored IND should provide concrete guidance, yet allow for the flexibility to evaluate each outbreak on a situational basis.

Interim Guidance: Use of Serogroup B Meningococcal Under a CDC-Sponsored IND

Jessica MacNeil, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

During this presentation, Ms. MacNeil reviewed interim guidance that has been developed for the use of the serogroup B meningococcal vaccine under CDC's sponsored expanded access IND application.

As noted, there is currently no vaccine for serogroup B meningococcal disease licensed in the US. Recent outbreaks on college campuses highlight the difficulty and challenges of controlling serogroup B meningococcal disease. Vaccination campaigns were conducted at two universities experiencing serogroup B outbreaks in 2013 using an investigational MenB vaccine developed by Novartis Vaccines under an expanded access IND sponsored by CDC.

The FDA's current regulations allow for the use of a drug or vaccine that is not approved for use in the US to treat serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. The mechanism allowing for this use is known as an expanded access IND.

In January 2014, an ad hoc Meningococcal WG was convened with the following terms of reference:

- Review available data on the recent epidemiology of meningococcal disease and outbreaks
- Develop guidance for use of MenB vaccines under a CDC-sponsored IND in an outbreak setting
- Update the current meningococcal disease outbreak guidelines once MenB vaccines are licensed in the United States

The first two of these objectives have been completed, with the outcomes presented during this session. Once a MenB vaccine is licensed in the US, the WG will complete the final objective.

During the development of the interim guidance, several key issues and challenges were discussed based on the experience with providing MenB vaccine under an IND mechanism at the two universities experiencing outbreaks in 2013. When providing a vaccine under an IND, there are additional steps to getting a vaccination campaign in place; therefore, there is a need

to consider options early in an outbreak. In addition, there was a need to reduce confusion about how to define populations within organizations. There was also recognition that waiting for additional cases to occur before acting is difficult for organizations, and that there needed to be clear steps for each case outlined in the document. Finally, there is no evidence that MenB vaccines eliminate carriage, so providing primary protection to vaccinees must be the goal of vaccination in this setting.

The current comprehensive meningococcal B guidelines are included as an appendix in the 2013 "Prevention and Control of Meningococcal Disease" *MMWR*. In these guidelines, vaccination of a population at risk should be considered when 2 to 3 cases of the same serogroup occur during a 3-month period with an attack rate of 10/100,000 in the affected community. This threshold is based on data from outbreaks of serogroup C prior to routine adolescent meningococcal vaccination. However, defining the denominator for calculating an attack rate in the affected community is often challenging for health departments and organizations. The population at risk can either be defined as organization-based when cases have a common affiliation but no close contact, or community-based when cases occur in the geographic area but no close contact or affiliation is identified.

The purpose of the interim guidance document is to identify serogroup B outbreaks early so that there is time to vaccinate in response to the outbreak if it is determined to be necessary. The current document provides guidance for use of MenB vaccine using an expanded access IND sponsored by CDC, but it does not provide definitive guidelines or recommendations. In this document, the WG tried to simplify the criteria for when vaccinations should be considered. Importantly, this guidance applies only to serogroup B outbreaks in organizational settings and does not apply to community outbreaks or outbreaks caused by other serogroups. This guidance is only intended to be in place until a licensed vaccine is available in the US, which may be as short as a year.

There are three key differences between the interim guidance and the comprehensive meningococcal outbreak guidelines that were published previously. In the interim guidance, recommendations for organizations are divided into two groups based on organizational size versus requiring calculation of an attack rate. The interim guidance also increases the timeframe during which cases may occur from 3 months to 6 months. In addition, the language around mass chemoprophylaxis has been revised to allow for some instances where it may be considered for use in conjunction with a vaccination campaign for outbreak response.

The objectives of the interim guidance document are to assist decision-makers with determining the need for vaccination with MenB vaccines; clarify the process for obtaining the vaccine; and improve the timeliness of implementation of vaccination campaigns. Clear definitions are provided in the guidance document for cases that should be included in outbreak case counts, what represents and organizational-based outbreak, and how to determine population size and the vaccination group.

Serogrouping of clinical specimens should be initiated within 24 hours of identification of *Neisseria meningitidis* from a normally sterile body site whenever possible. Laboratories that cannot initiate serogrouping within 72 hours should transfer the isolate or specimen to a laboratory that can perform this testing or to CDC within 24 hours. Genotyping data may provide supportive evidence for an outbreak among meningococcal cases. The data from isolates should be interpreted in the context of the epidemiology of the cases.

Decisions to vaccinate should be evaluated on a situational basis in consultation with the local and state health department and CDC, taking into account all circumstances specific to the organization and epidemiology of the outbreak. Factors to be taken into consideration include the following:

- Number of cases
- Population size of the organization
- Time interval between cases
- If strains causing cases are identical
- Feasibility and cost of mass vaccination campaign
- Vaccine availability
- If outbreak strain is likely to be covered by a MenB vaccine
- Public concern

The WG has divided its guidance by organizational size. For organizations with a population size of less than 5000, when one case of meningococcal disease occurs, routine public health practices should be followed, including serogrouping of the isolates, conducting a case investigation, and providing chemoprophylaxis to close contacts. The situation should be monitored closely and the isolates should be saved for future molecular genotyping. In organizations of this size, the trigger point is reached when 2 or more cases occur within 6 months. The recommendation is to complete all of the same public health response activities as following a single case. In addition, all isolates should be sent to CDC for molecular genotyping and additional testing. If all isolates are identified as serogroup B and are likely covered by a MenB vaccine, then a MenB vaccination campaign may be considered.

In organizations with more than 5,000 persons, the recommendations are similar after a single case. When two cases occur in 6 months and both are identified as serogroup B, the state health department should contact CDC to discuss the cases and should continue to monitor the situation closely. In organizations of this size, the trigger point is reached when 3 or more cases occur in 6 months. Isolates should be sent to CDC for molecular genotyping and additional testing. If all isolates are identified as serogroup B and are likely covered by a MenB vaccine, a vaccination campaign may be considered.

CDC will work with state and local health departments and organizations as just described to determine the need for MenB vaccine on a situational basis. Organizations that provide MenB vaccine via the FDA's expanded access IND sponsored by CDC are required to identify a local co-investigator on the IND, and are required to participate in safety follow-up activities required under the IND. To date, universities implementing MenB vaccination campaigns have been responsible for funding the cost of the vaccine and its administration. Vaccination under CDC's IND has been limited to persons affiliated with the two universities where outbreaks have occurred.

In developing the interim guidance, the WG also felt it was important to better understand the current recommendations and available data on the use of mass chemoprophylaxis for outbreak control. A review of the literature from 1971 through the present was completed, and 18 instances where mass chemoprophylaxis was used as an outbreak response were included. The WG conclusions from this review were that there is limited data available on the use of ciprofloxacin for mass chemoprophylaxis during outbreaks, but that overall, decreases in carriage were seen soon after chemoprophylaxis was administered. Carriage was not

eliminated and generally returned over time, and there was an unclear impact of mass chemoprophylaxis on prevention of additional cases.

The purpose of chemoprophylaxis is to eradicate nasopharyngeal carriage of *N. meningitidis* and thus prevent disease in close contacts of a patient with invasive meningococcal disease. Antimicrobial chemoprophylaxis of close contacts is important to prevent secondary cases. The guidance emphasizes that mass chemoprophylaxis is not recommended as a stand-alone measure to control outbreaks of meningococcal disease, and should only be considered as an interim measure to reduce carriage and transmission in the period before potential protection from vaccination can be achieved. Situations where mass chemoprophylaxis is likely to be successful include small or closed populations where high antibiotic coverage can be rapidly achieved, and where there is limited mixing with outside populations.

There are several challenges to successfully implementing mass chemoprophylaxis, including the following:

- Identifying a smaller logical “at risk” population
- Ensuring all persons in the target group receive treatment within a short time frame
- Potential for multiple sources of transmission within a population
- Prolonged risk for exposure in outbreak setting
- Cost of the drug and its administration
- Drug side effects and idiosyncratic reactions
- Interactions with frequently used medications such as anti-depressants
- Emergence of drug-resistant organisms

If mass chemoprophylaxis is undertaken, it should be administered to all targeted persons at the same time, ideally in less than 24 hours. In many outbreak settings, particularly when a small, closed at-risk population cannot be defined, the disadvantages of providing mass chemoprophylaxis outweigh the possible benefits to prevent future cases. If the decision to offer mass chemoprophylaxis prior to implementation of a vaccination campaign is made, communicating the need for vaccination for potential protection for the duration of the outbreak is critical. Additionally, use of mass chemoprophylaxis should not delay implementation of a vaccination campaign.

Other control measures, such as restricting travel to an area with an outbreak, closing schools or universities, or canceling sporting or social events or meetings are generally not recommended as part of outbreak control because these interventions are unlikely to alter the course of the outbreak. However, educating communities, physicians, and other health-care personnel about meningococcal disease to promote early case recognition and early care-seeking behaviors is an important part of managing suspected meningococcal disease outbreaks. These education efforts should be initiated as soon as an outbreak is suspected.

The plan was to publish the interim guidance document on the CDC website shortly after this meeting so that it will be available to interested health departments and organizations before the next school year. As mentioned previously, updates to CDC’s comprehensive meningococcal disease outbreak guidelines will be developed and shared with the ACIP once serogroup B meningococcal vaccines are licensed in the US. CDC will also work to identify opportunities to evaluate the impact of using MenB vaccines in outbreak response.

In summary, meningococcal disease is a rare but serious infection. Fortunately, outbreaks are rare, but they do occur and the timing of additional cases in an outbreak is not easy to predict. Serogroup B cases will continue to occur, especially in the adolescent age group, which means that it is difficult to differentiate between sporadic cases versus catching an outbreak in its early stages. Vaccination is now possible to control serogroup B outbreaks, but implementing a vaccination campaign under an IND is a complex process. Licensure of serogroup B vaccines in the US will be an important step to protect individuals during serogroup B meningococcal disease outbreaks.

Discussion Points

Dr. Temte asked Dr. Sun whether he could provide further information on licensing of the meningococcal B vaccine in the US.

Dr. Sun (FDA) replied that this information is now in the public domain. Both manufacturers, Novartis and Pfizer, have submitted licensing applications to the FDA. These applications are under review. Because both products were given breakthrough therapy status, the review process is more abbreviated. Data still have to be reviewed. Pending review and if all goes well, the timing for the regulatory decision will be toward then end of 2014 or early part of 2015.

In terms of revising the meningococcal outbreak guidelines in general, Dr. Duchin inquired as to whether the WG planned to align the current ACY recommendations similarly to what was done with meningococcal type B disease. He also asked what was known about the impact of the vaccine on carriage rates in the outbreak settings.

Ms. MacNeil responded that the main focus of the WG so far has been on developing the interim guidance, and they have not started working on the full revisions. The idea is to move more toward this model versus the calculation of an attack rate, but it will be necessary to wait to see what occurs after the MenB vaccine is licensed. There is not a lot of evidence to support that these vaccines will eliminate carriage or potentially prevent someone from acquiring carriage.

Dr. Warshawsky (NACI) inquired as to whether the purpose of genotyping was to tell if there was a match with the meningococcal strains covered by the vaccine, or to tell whether the strains match each other. She wondered whether the cutoff would still apply if there were two different strains circulating.

Ms. MacNeil replied that the molecular genotyping would be to determine whether the strains match each other. Additional testing is done to determine whether a vaccine would cover that strain. The WG tried to make the guidance relatively flexible in order to address each situation independently. Sometimes there are changes in the genotype during an outbreak, so they may not exactly match. The WG did not want to set up a situation in which nothing could be done because of the guidelines.

Dr. Cohn added that the genotyping from almost every outbreak in the last several years always matched, or they were very close and over the course there was a small change. To answer the question regarding if there is a small change and one is covered by the vaccine and one is not, the expectation is that most strains will be covered by these vaccines. But, that issue would have to be addressed if that occurred. People felt like, in the college community especially,

even if several cases did not match phenotypically, it would still be causing the same amount of concern in the community and the drive toward vaccination would still exist.

Dr. Schaffner (NFID) informed everyone of a new report from the NFID entitled, “Addressing the Challenges of Serogroup B Meningococcal Disease Outbreaks on Campuses.” The report was based on a roundtable that NFID held in April 2014 with CDC colleagues, external public health experts, and some college health officials. Some of the experts included Paul Offit, Carol Baker, and Jim Turner. Dr. Schaffner shared a few key points from the panel’s conclusions, which nicely complemented Ms. MacNeil’s presentation. First, despite its rarity, the severe nature of meningococcal disease makes advanced planning, particularly in the college setting, very advantageous if not imperative. The second is that increased efforts are needed to educate healthcare professionals and raise awareness about the early signs and symptoms of meningococcal disease so that cases can be identified promptly. Third, educational resources need to be readily available for the public when outbreaks do occur. Lastly, licensure of meningococcal serogroup B vaccines will have the single greatest impact on improving the timeliness of responses to these outbreaks. Copies of the report were made available on the information table outside of the meeting room, and are also available on the NFID website.

In terms of logistics, Dr. Zahn (NACCHO) inquired as to whether the IND has an expiration date.

Ms. MacNeil replied that there is not currently an expiration date on the IND. Each university had separate amendments done for the IND. Each university is considered as a separate group, and future outbreaks would have to be considered separately as well.

A representative from Novartis responded to the question regarding whether meningococcal B vaccine would prevent carriage, indicating that it is very difficult in a clinical trial before licensure and implementation of vaccination to determine whether a vaccine is going to prevent carriage. Nevertheless, Novartis conducted a study in the United Kingdom (UK) that is soon to be published that shows that there is an impact on *Neisseria meningitidis* carriage. Obviously, the numbers are low, but the impact on overall meningococcal carriage is there. There is also a published paper from a vaccine which has been used in Normandy where carriage was reported to be reduced by 60%. Hopefully, data will be published before ACIP has to make a decision.

Hepatitis Vaccines

Art Reingold, MD ACIP Hepatitis Work Group Chair

In years past, ACIP had a Hepatitis Vaccine WG, but it was not active last year. The decision was made earlier in 2014 to reconvene a WG on hepatitis A and B vaccines, two important early vaccines in the armamentarium. There are existing hepatitis A and B vaccine recommendations. The hepatitis A vaccine recommendations are from 2006, while the hepatitis B vaccine recommendations are from 2005 and 2006. The primary purpose of reconvening a WG is to oversee the updating of these two sets of recommendations, and to bring them to the ACIP for consideration. Additional updates and recommendations have been made for use of both vaccines in the interim.

The current recommendations and updates for hepatitis A vaccine include the following:

- ❑ ACIP Routine Recommendation for Hepatitis A Vaccine (2006). *MMWR* 2006 May 19;55(RR-7):1-23.
- ❑ Update: Prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the ACIP. *MMWR* 2007 Oct 19;56(41):1080-4.
- ❑ Updated recommendations from the ACIP for use of hepatitis A vaccine in close contacts of newly arriving international adoptees. *MMWR* 2009 Sep 18;58(36):1006-7.
- ❑ FDA Approval of an Alternate Dosing Schedule for Twinrix®. *MMWR* 2007 Oct 12;56(40):1057.

The primary goal of the WG with regard to hepatitis A will be to combine these various documents into a single up-to-date set of recommendations for the use of hepatitis A vaccine.

After a number of interesting challenges in trying to deal with hepatitis A outbreaks in hyperendemic areas, and interesting and innovative ways of implementing the vaccine, a decision was finally made in 2006 to recommend hepatitis A vaccine as a routine immunization for all children ages 12 through 23 months old.

Based on 2012 NIS data, children in the 19 through 35 month age group were at about 53% coverage with two doses. The 2020 target is 85% with two doses, so there certainly is room to improve coverage with hepatitis A vaccine. At the time the universal vaccination recommendation was made, there were no recommendations for catch-up in older children or in older individuals. Coverage among children 13 through 17 years of age is approximately 48% with two or more doses of hepatitis A vaccine. By 2018, this age group will begin to realize the effects of the vaccination of children 12 through 23 months of age when the first cohorts of children coming of age after the universal recommendation will begin to reach adolescence. Over the next several decades, if vaccination coverage increases, there will be a more fully vaccinated population. However, large numbers of children, adolescents and adults remain unvaccinated. So, catch-up vaccination is another area of interest.

The WG plans to consider a couple of issues. The current recommendation for post-exposure prophylaxis (PEP) for persons one through 40 years of age is to receive vaccination; however, for those over the age of 40 the emphasis is on the use of immunoglobulin. In large part because of the dearth of data regarding the effectiveness of vaccine for post-exposure prophylaxis in people over the age of 40 in terms of immunogenicity and other aspects of the response, the WG will consider whether any changes are needed with regard to the recommendation for PEP in older individuals.

Simultaneously, the WG expects to discuss whether any other risk groups might benefit from immunization. There have been foodborne outbreaks in which food handlers with hepatitis A are involved. These are very expensive outbreaks for local and state health officials. The turnover of food handlers is extraordinarily high, and many may not regularly access healthcare. The question of vaccination of food handlers is likely to raise a number of challenging issues for health departments. Nevertheless, the WG will be discussing whether any other risk groups might benefit from hepatitis A vaccination. The WG expects to bring any issues that might

require further discussion to the full committee, as well as a fully integrated and updated statement regarding the use of hepatitis A vaccine.

With regard to hepatitis B vaccine, the WG's mandate is to create a fully integrated current document describing the use of hepatitis B vaccine. The current recommendations and updates for hepatitis B vaccine include the following:

- ❑ ACIP Routine Recommendation for Hepatitis B Vaccine 2005 (Infants/Children). *MMWR* 2005 Dec 23;54(RR-16):1-31.
- ❑ ACIP Routine Recommendation for Hepatitis B Vaccine 2006 (Adult). *MMWR* 2006 Dec 8;55(RR-16):1-33.
- ❑ Use of hepatitis B vaccination for adults with diabetes mellitus: recommendations of the ACIP. *MMWR* 2011 Dec 23;60(50):1709-11.
- ❑ FDA Approval of an Alternate Dosing Schedule for Twinrix®. *MMWR* 2007 Oct 12;56(40):1057.

The specific timeframe for bringing the integrated current information to the full committee for discussion has not yet been determined.

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 and influenza vaccines. She indicated that supplies of Pentacel®, Daptacel®, and Adacel® vaccines have steadily increased during 2014. During the second quarter, the availability of additional supplies of these vaccines has allowed both the VFC and private providers to order these vaccines without restrictions. GSK continues to have sufficient supply of Pediarix®, Boostrix®, Infanrix®, and Kinrix® to cover the anticipated demand levels of its pertussis-containing vaccines, although presentation preference may be impacted on occasion.

Each year during the National Influenza Vaccine Summit, US-licensed influenza vaccine manufacturers provide projections of influenza vaccine production for the US market for the upcoming season. CDC reaches out for periodic follow-ups to confirm/adjust manufacturer projections. In May 2014, manufacturers projected an aggregate total of approximately 157 million doses of vaccine for the 2014-2015 season. In June 2014, follow-up queries resulted in a revised projection of 153-158 million doses of vaccine for the 2014-2015 season. Changes in these projections are due to adjustments made by manufacturers based on demand for vaccines during the pre-book process that was not yet completed when the information was shared in May. GSK's recently updated its projections from 35 million doses in May 2014 to 28-33 million doses in June 2014 following a Warning Letter from the FDA relating to an inspection at their FluLaval® influenza vaccine manufacturing facility in Canada. GSK's Fluarix®, manufactured at a different facility, is not impacted by the Warning Letter.

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

Day 2: Public Comment

Rich Greenaway **Immunization Coalition of DC**

I'm just really impressed with the presentation that we got this morning about PCV13, and I think that it is really important that the ACIP consider this for movement. I encourage the ACIP, in light of this new data and in context of the disease burden, to take the additional steps necessary and meet in August and do something so that we can help to prevent disease in the fall. You know, we can't just shelve the fact that we've got a vaccine. I mean, we can't forget about the fact that we've got a vaccine because it's inconvenient for us to follow through and get all of the players to work on it and basically, you know, pay for the vaccine. I like the idea of putting the 50-year old recommendation in play, because then we don't have to worry about people who are on public health plans. Their personal health plans will pick it up. So, I just encourage the ACIP to look at this and consider it in August.

Tama Lee **National Meningitis Association**

First of all, I'd like to congratulate the CDC for working so quickly to address the outbreaks at Princeton and UCSB in providing meningococcal B vaccination and symptoms education for the students and faculty at both campuses. As most of you know, NMA was founded by parents like me who have been devastated by the loss of a child due to meningococcal disease. I lost my son, Casey, in 2000. I've worked with NMA since it was founded in 2002. Since then, the immunization community has made great strides in meningococcal disease prevention. Teen vaccination rates are at a high, and disease incidence is at a historic low. But, we can't stop now. This disease is devastating and it still affects families all across America. Soon we'll have the ability to provide routine protection against serogroup B disease in adolescents. Just within this past year at NMA, we've heard from many families whose lives have been changed forever because of serogroup B disease. I'm here today on their behalf. We have all worked together over the years—advocates, policy makers, public health experts, healthcare professionals, and vaccine manufacturers. We cannot now pass up opportunities to provide better protection for our children. I hope this committee considers this as discussions surrounding meningococcal b vaccines continue. Thank you.

Kora Peters **Adult Industry**

Hello. I'm Kora Peters, and I'm here today representing the adult industry. I'm here today to tell you that, as you know, adult performers are at high risk for sexually transmitted diseases (STDs). I want to specifically talk about hepatitis A. Men who have sex with men (MSM) are considered a high risk group for hepatitis A, presumably because of sexual behaviors that put them at risk of infection. But female and male adult performers who are not MSM regularly

engage in the same high risk behaviors as MSM. Because of this, I believe ACIP should consider recommending that all adult performers be given occupational high risk status. Adult performers are not getting hepatitis A vaccinations, and I believe that if it were made a specific CDC recommendation that they would be more likely to protect themselves and each other by getting vaccinated. We don't know how common hepatitis A infection is among performers because the industry does not currently test for it, although they did add hepatitis B to the panel in August of last year. I know ACIP requires evidence before making any new recommendations, so I would like to request that the new Hepatitis Work Group take up this issue. The studies suggest that all adult performers are at increased risk for hepatitis A, which I believe they are, then ACIP should consider recommending the vaccination for them. I think that that would make what is a risky lifestyle choice a little safer. Thank you for your time.



Certification

Upon reviewing the foregoing version of the June 25-26, 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.

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