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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
February 20-21, 2013
Atlanta, Georgia

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), Kent "Oz" Nelson Auditorium
Atlanta, Georgia 30333
February 20-21, 2013

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
Wednesday, February 20, 2013			
8:00	**Welcome & Introductions**		Dr. Jonathan Temte (ACIP Chair) Dr. Larry Pickering (Executive Secretary, ACIP)
8:30	**Agency Updates** · CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NVPO, NIH		
8:45	**Pneumococcal Vaccines**		
	· Introduction		Dr. Nancy Bennett (ACIP, WG Chair)
	· Impact of PCV13 use in children	Information & Discussion	Dr. Matthew Moore (CDC/NCIRD/DBD)
	· PCV13 for children 6 through 18 years old with immunocompromising conditions: GRADE		Ms. Tamara Pilishvili (CDC/NCIRD/DBD)
	· PCV13 recommendations for children 6 through 18 years old with immunocompromising conditions	**Vote**	Ms. Tamara Pilishvili (CDC/NCIRD/DBD)
	· Vaccines for Children	**VFC Vote**	Dr. Jeanne Santoli (CDC/NCIRD)
10:00	***Break***		
10:30	**Haemophilus influenzae b (Hib) Vaccine**		
	· Introduction	Information, Discussion & **Vote**	Dr. Lorry Rubin (ACIP, WG Chair)
	· Updated Hib Vaccine Recommendations		Dr. Elizabeth Briere (CDC/NCIRD)
	· Vaccines for Children: Hib-MenCY	**VFC Vote**	Dr. Jeanne Santoli (CDC/NCIRD)
11:30	**Japanese Encephalitis**		
	· Introduction	Information & Discussion	Dr. Joseph Bocchini (ACIP, WG Chair)
	· Japanese encephalitis vaccine for U.S. travelers		Dr. Marc Fischer (CDC/NCEZID)
12:15	***Lunch***		
1:30	**Pertussis Vaccines**		
	· Introduction		Dr. Mark Sawyer (ACIP, WG Chair)
	· Update on immunization safety monitoring: Tdap administered to pregnant women	Information & Discussion	Dr. Frank Destefano (CDC/NCEZID)
	· Pertussis in the United States and Tdap revaccination		Dr. Thomas Clark (CDC/NCIRD)
3:15	***Break***		
3:30	**Smallpox Vaccine Work Group**	Information	Dr. Lee Harrison (ACIP, WG Chair)
3:35	**Vaccine Supply**	Information	Dr. Jeanne Santoli (CDC/NCIRD)
3:45	**General Recommendations**		
	· Introduction		Dr. Jeff Duchin (ACIP, WG Chair)
	· Timing and spacing of immunobiologics	Information & Discussion	
	· Contraindications and precautions		Dr. Andrew Kroger (CDC/NCIRD)
	· Special situations		
5:00	**Measles and Rubella Initiative**	Information	Dr. Lisa Cairns (CDC/CGH/GID)
5:30	**Global Polio Eradication Initiative**	Information	Dr. Robert Linkins (CDC/CGH/GID)
6:00	**Public Comment**		
6:15	**Adjourn**		

Thursday, February 21, 2013

8:00	**Unfinished Business**		Dr. Jonathan Temte (Chair, ACIP)
8:15	**IOM Immunization Schedule Report**	Information & Discussion	Dr. Ada Hinshaw* (Uniformed Services University of the Health Sciences, Bethesda, MD)
9:00	**Adult Immunization**		
	· Introduction		Dr. Tamara Coyne-Beasley (ACIP, WG Chair) Dr. Carolyn Bridges (CDC/NCIRD)
	· Updated adult immunization coverage	Information & Discussion	Dr. Walter Williams (CDC/NCIRD)
	· Provider survey results on adult immunization		Dr. Laura Hurley (University of Colorado)
	· Consumer awareness regarding adult immunization		Dr. Kris Sheedy (CDC/NCIRD)
	· Discussion		Dr. Tamara Coyne-Beasley (ACIP, WG Chair) Dr. Carolyn Bridges (CDC/NCIRD)
10:15	***Break***		
10:45	**Influenza**		
	· Introduction		Dr.Wendy Keitel (ACIP, WG Chair)
	· Epidemiology and surveillance update		Dr. Lyn Finelli (CDC/NCIRD)
	· Vaccine Supply	Information	Dr. Jeanne Santoli (CDC/NCIRD)
	· Vaccine effectiveness	&	Dr. Mark Thompson (CDC/NCIRD)
	· FluBlok	Discussion	Dr. Lisa Dunkle (Protein Sciences)
	· Upcoming topics		Dr. Lisa Grohskopf (CDC/NCIRD)
	· Proposed 2013-2014 recommendations	**Vote**	Dr. Lisa Grohskopf (CDC/NCIRD)
1:15	**Public Comment**		
1:30	**Adjourn**		

* Chair, Committee on the Assessment of Health Outcomes Related to the Recommended Childhood Immunization Schedule, Institute of Medicine

Acronyms

GRADE	Grading of Recommendations Assessment, Development and Evaluation
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCIRD	National Center for Immunization and Respiratory Diseases
TBD	To be determined
Tdap	Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
WG	Work Group

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core Surveillance
ACA	Affordable Care Act
ACHA	American College Health Association
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
ACIP	Advisory Committee on Immunization Practices
AE	Adverse Events
AFP	American Family Physicians
AFP	Acute Flaccid Paralysis
AHIP	America's Health Insurance Plans
AI/AN	American Indians/Alaska Natives
AIM	Association of Immunization Managers
AMA	American Medical Association
ANA	American Nurses Association
Anti-FIM	Anti-Fimbrial Agglutinogens
aP	Acellular Pertussis
APERT	Adult Pertussis Trial
APhA	American Pharmacists Association
BARDA	Biomedical Advanced Research and Development Authority
BEVS	Baculovirus Expression Vector System
BLA	Biologics License Application
BMBL	Biosafety in Microbiological and Biomedical Laboratories
CAPITA	Community Acquired Pneumonia Immunization Trial in Adults
CDC	Centers for Disease Control and Prevention
CISA	Clinical Immunization Safety Assessment
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic Obstructive Pulmonary Disease
CRS	Congenital Rubella Syndrome
DSMB	Data Safety Monitoring Board
DTaP	Diphtheria, Tetanus, and Pertussis
DVA	Department of Veterans Affairs
EHR	Electronic Health Record
EOC	Emergency Operations Center
EMA	European Medicines Agency
EMR	Electronic Medical Record
FDA	Food and Drug Administration
FM	Family Medicine Physicians
FMAP	Federal Medical Assistance Percentage
GBS	Guillain–Barré Syndrome
GIM	General Internists
GMCs	Geometric Mean Concentrations
GMFRs	Geometric Mean Fold Rises
GMTs	Geometric Mean Titers
GPEI	Global Polio Eradication Initiative
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
GVAP	Global Vaccine Action Plan
HA	Hemagglutinin
HP2020	Healthy People 2020
HHS	(Department of) Health and Human Services
Hib	*Haemophilus influenzae B*
HICPAC	Hospital Infection Control Practices Advisory Committee
hMPV	Human metapneumovirus
hPIV	Human Parainfluenza Virus
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
HSCT	Hematopoietic Stem Cell Transplant
IDSA	Infectious Disease Society of America
IgG	Immunoglobulin G
ILI	Influenza-Like Illness
ILINet	Influenza-Like Illness Surveillance Network
IMB	Independent Monitoring Board
IOM	Institute of Medicine
IPD	Invasive Pneumococcal Disease
IIS	Immunization Information System
IIV	Inactivated Influenza Vaccine
ISO	Immunization Safety Office
JE	Japanese Encephalitis
JE-MB	Inactivated Mouse Brain-Derived JE Vaccine
JE-VC	Vero Cell Culture-Derived JE Vaccine

LAIV	Live Attenuated Influenza Vaccine
MDG	Millennium Development Goal
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Measles, Mumps, Rubella
MMRV	Measles, Mumps, Rubella, Varicella
MMWR	*Morbidity and Mortality Weekly Report*
NACCHO	National Association of County and City Health Officials
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NAIS	National Adult Immunization Summit
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCHS	National Center for Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
NEJM	*New England Journal of Medicine*
NFID	National Foundation for Infectious Diseases
NHIS	National Health Interview Survey
NIH	National Institutes of Health
NIS	National Immunization Survey
NIS-Teen	National Immunization Survey-Teen
NIST	National Institute of Standards and Technology
NMA	National Medical Association
NNDSS	National Notifiable Diseases Surveillance System
NNV	Number Needed to Vaccinate
NREVSS	National Respiratory and Enteric Virus Surveillance System
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
OIG	Office of the Inspector General
OPA	Opsonophagocytic Assay
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PGO	Procurement and Grants Office
PIDS	Pediatric Infectious Diseases Society
PPSV23	Pneumococcal Polysaccharide Vaccine
PREA	Pediatric Research Equity Act
PRISM	Postlicensure Rapid Immunization Safety Monitoring System
PRNT	Plaque Reduction Neutralization Test
QALY	Quality-Adjusted Life Year
RCT	Randomized Controlled Trial
RCVs	Rubella-Containing Vaccines
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAEs	Serious Adverse Events
SAGE	Strategic Advisory Group of Experts (WHO)
SBRA	Summary Basis for Regulatory Action
SIAs	Supplementary Immunization Activities
SME	Subject Matter Expert
SNS	Strategic National Stockpile
SSD	Sickle Cell Disease
Td	Tetanus-Diphtheria
Tdap	Tetanus and Reduced Diphtheria Toxoids
TIV	Trivalent Inactivated Influenza Vaccines
UNICEF	United Nations Children's Fund
US	United States
US Flu VE	US Influenza Vaccine Effectiveness Network
USPSTF	US Preventive Services Task Force
VA	Department of Veterans Affairs
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Effectiveness
VFA	Vaccines for Adults
VFC	Vaccines for Children
VRBPAC	Vaccine and Related Biologic Products Advisory Committee (FDA)
VSD	Vaccine Safety Datalink
WHA	World Health Assembly
WHO	World Health Organization

Welcome and Introductions

Dr. Jonathan Temte
Chair, ACIP

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

Dr. Temte called the meeting to order, welcoming those present. He turned the floor over to Dr. Pickering for opening remarks.

Dr. Pickering welcomed everyone to the February 2013 Advisory Committee on Immunization Practices (ACIP) meeting. He indicated that the proceedings of this meeting would be accessible to people not in attendance via the World Wide Web, and he 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 ACIP meeting to assist with various meeting functions: Stephanie Thomas, Felicia Betancourt, Natalie Greene, Reed Walton, and Chris Caraway. Dr. Pickering emphasized that there would be a full agenda, and 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 one to 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 90 days following this meeting. Minutes of the October meeting are posted on the ACIP website. Members of the press interested in conducting interviews with ACIP members were instructed to contact Tom Skinner, who was in attendance, for assistance in arranging the interviews.

Dr. Pickering recognized a delegation of visitors organized by the Pan American Health Organization (PAHO) of the World Health Organization (WHO), including the Executive Secretary of the El Salvadorian Advisory Committee on Immunization Practices, accompanied by technical staff from the PAHO office in Washington, DC. The previous day, the PAHO group and CDC staff from the Global Immunization Division (GID) held a meeting to exchange experiences on the use of evidence for immunization decision making. Delegates from the El Salvadorian Advisory Committee on Immunization Practices learned about how the United States (US) ACIP draws upon evidence to formulate immunization policy and, in particular, how ACIP has incorporated Grading of Recommendation Assessment, Development and Evaluation (GRADE) to evaluate the quality of evidence. Drs. Jean Smith, Doug Campos-Outcalt, and Faruque Ahmed attended that meeting and presented discussions on the GRADE system. Following the overview of ACIP, the delegates shared their recent experiences of formalizing their committee through a ministerial charter. Members of the El Salvadorian committee are seeking to institutionalize evidence-based decision making for immunization in their country. Dr. Pickering expressed appreciation to PAHO and Sabin Vaccine Institute, which provide financial and logistical support for participation of National Immunization Committee members from Latin America in ACIP meetings.

Also in attendance were five junior and senior high school epidemiology students from the Walker School's public health program, which is a partnership between the Walker School and the David J. Sencer Museum at CDC. Their focus this semester is vaccine safety, and four of these five exceptional young women will be interning at CDC this summer. Dr. Pickering pointed out that one of the textbooks these students are studying was authored by Dr. Paul Offit, who was present and wished to meet with each of these students during the course of this meeting.

Dr. Pickering then offered the following liaison representative notes:

- The Pediatric Infectious Diseases Society (PIDS) is a new liaison organization. Dr. Janet Englund was the representative in attendance during this meeting. PIDS is actively involved in the training and education of pediatricians and other health care professionals in health care prevention through the use of immunization, research, and public health measures.

- The National Vaccine Advisory Committee (NVAC) liaison report would be presented by Dr. Gellin for Dr. Walk Orenstein.

- Dr. Mary Currier, State Health Officer for Mississippi State Department of Health, was in attendance for Dr. José Montero.

- Dr. Sandra Fryhofer is the new liaison for the American Medical Association (AMA).

To avoid disruptions during the meeting, Dr. Pickering instructed those present to silence all cell phones off. Given that the meeting could not begin unless a quorum of members was present, all appointed members were asked to return from breaks and lunch in a timely manner to participate in the meeting.

Dr. Pickering 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 the vote. 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.

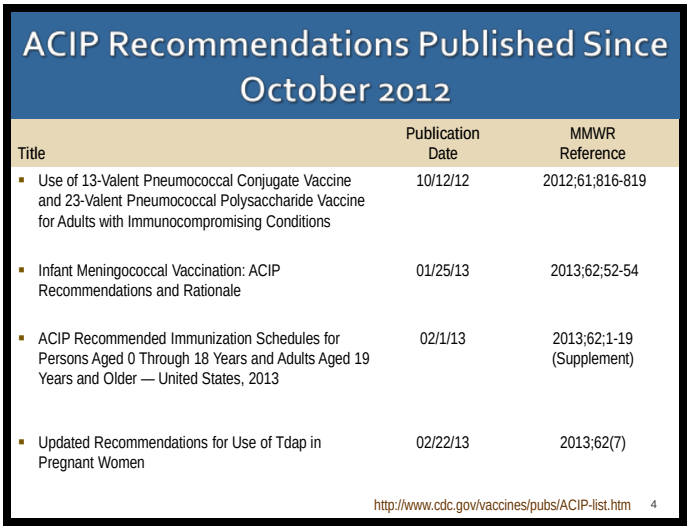
With regard to disclosure, to summarize conflict of interest provisions applicable to ACIP, as noted in the ACIP Policies and Procedures manual, Dr. Pickering indicated that members of the ACIP agree to forego participation in certain activities related to vaccines during their tenure on the committee.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

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

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

During every ACIP meeting, an update is provided with regard to the status of ACIP recommendations. Links to these recommendations and schedules can be found on the ACIP website. A listing of recommendations that have been published since the October 2012 ACIP meeting follows:



ACIP Recommendations Published Since October 2012

Title	Publication Date	MMWR Reference
Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine for Adults with Immunocompromising Conditions	10/12/12	2012;61;816-819
Infant Meningococcal Vaccination: ACIP Recommendations and Rationale	01/25/13	2013;62;52-54
ACIP Recommended Immunization Schedules for Persons Aged 0 Through 18 Years and Adults Aged 19 Years and Older — United States, 2013	02/1/13	2013;62;1-19 (Supplement)
Updated Recommendations for Use of Tdap in Pregnant Women	02/22/13	2013;62(7)

http://www.cdc.gov/vaccines/pubs/ACIP-list.htm 4

The following resource information was shared pertaining to ACIP:

Next ACIP meeting: Wednesday – Thursday, June 19-20, 2013.
Registration Deadline: Non-US Citizens and US Citizens June 3, 2013
Registration to watch the webcast is not required.

Vaccine Safety: www.cdc.gov/vaccinesafety/

Immunization Schedules (2012):
http://www.cdc.gov/vaccines/recs/schedules/default.htm

Childhood Vaccine Scheduler (interactive):
http://www2a.cdc.gov/nip/kidstuff/newscheduler_ie/

Adolescent vaccine scheduler (interactive):
http://www.cdc.gov/vaccines/recs/Scheduler/AdolescentScheduler.htm

Adult Vaccine Scheduler (interactive):
http://www.cdc.gov/vaccines/recs/Scheduler/AdultScheduler.htm

Vaccine Toolkit:
www.cdc.gov/vaccines/conversations

Vaccine Toolkit:
http://www.cdc.gov/vaccines/spec-grps/hcp/conversations.htm

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

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

Dr. Temte extended a personal welcome to Drs. Herbert Young and Bellinda Schoof from the Division of Scientific Activities at the American Academy of Family Physicians (AAFP).

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Wharton offered a brief update about what CDC has done since the Department of Health and Human Services (HHS) Office of the Inspector General released a report in June 2012 regarding the storage and handling of vaccines in the Vaccines for Children (VFC) Program. This report assessed vaccine storage and handling in provider offices in four states and one city, and identified a number of issues with storage and handling of vaccines. Since then, particularly the staff members of the Immunization Services Division, have focused an enormous amount of energy and effort on working with its immunization programs in states and cities to improve storage and handling practices. Among these efforts was a revision of the "Vaccines for Children Program Operations Guide" to strengthen program oversight guidance, which was updated and made available on the internet in November 2012. Updates were also made to "Vaccine Storage and Handling Guidelines," with interim guidelines released in November 2012. There is on-going work with the National Institute of Standards and Technology (NIST) to extend the science base for storage and handling practice, and regional trainings for the VFC's oversight staff are planned for the first half of 2013 that should help to inform everyone about the new guidelines. Dr. Wharton thanked all of the CDC and state program staff who have been working on this important, intense, and on-going effort to improve vaccine storage and handling. Although the focus of the report was on the VFC program, clearly the extent to which vaccine storage and handling can be improved for VFC will improve vaccine storage and handling in all vaccines in provider offices. CDC believes this is an opportunity for improvement, and a good deal of progress has been made.

Centers for Medicare and Medicaid Services (CMS)

Dr. Hance provided an update on two Affordable Care Act (ACA) provisions that went into effect on January 1, 2013 related to Medicaid and immunizations. The first was the primary care payment increase included in Section: 1202 of the ACA. A payment includes vaccine administration for children and adults in Medicaid when they are given vaccines by providers who qualify for the primary care payment increase. Also included in that Final Rule was an

update to the fee schedule for the VFC program, which is the first update made since the VFC program was implemented. The second provision is Section: 4106 of the ACA, which gives states that choose to cover, without cost sharing, all adult preventive services that are given an A or B recommendation by the US Preventive Services Task Force (USPSTF) or all ACIP recommendations, they are eligible for a 1% increase in the federal medical assistance percentage (FMAP) that they receive for those services.

Department of Defense (DoD)

Dr. Geibe commented on several immunizations administered by DoD. Influenza immunization service rates, including all Active Duty and Reservists in all of the services, were just over 95% as of February 19, 2013. Reservists typically reduce the numbers somewhat. While it is easy to achieve such high rates with mandatory immunizations, DoD likes to gloat a little about that. DoD began providing the Adenovirus Type 4 and Type 7 Vaccine on October 23, 2011. Over 250,000 Active Duty Service Members have been vaccinated as of February 16, 2013. Thus far, based on previous years and rates, it is estimated that over 50,000 lost training days; 15,000 cases of febrile respiratory illness; and over 1500 hospitalizations have been prevented using this vaccine. The services have not had any known cases of Japanese Encephalitis (JE) in Active Duty members in over two decades; however, DoD continues to reinforce ACIP recommendations for use of vaccines in high risk settings, need for careful screening, and assessment of local risk conditions. DoD acknowledges that there have been challenges in getting persons who started the 3-vaccine series of human papillomavirus (HPV) vaccine in their accession or basic training to complete that by their first permanent duty station. DoD is emphasizing and continuing to make the vaccine available to male and female service members at their first permanent duty station and medical departments that offer the vaccine to beneficiaries and Active Duty members per the current ACIP recommendations.

Department of Veteran's Affairs (DVA)

Dr. Kinsinger thanked Dr. Andrew Kroger for giving a very well-done and well-received presentation on a national call the previous week updating the VA field on the adult immunization schedule. Some of her colleagues in the DVA's Office of Public Health also recently convened a national call on the use of tetanus and reduced diphtheria toxoids (Tdap) in pregnant women. In terms of influenza, an early spike was observed in cases, but is currently declining. As of the previous week, DVA had administered over 1 million doses of vaccine to its patients.

Food and Drug Administration (FDA)

Dr. Sun noted that since the last ACIP meeting, FDA had two approvals of original Biologics License Applications (BLAs). These were for the cell-based influenza vaccines FLUCELVAX™ by Novartis and FluBlok® by Protein Sciences Corporation. There were also approvals for supplements to two existing vaccines. The first is FLUARIX® Quadrivalent, which is now the second quadrivalent influenza vaccine approved. In addition, the indication for Prevnar 13® was extended to 17 years of age. Also occurring at FDA is implementation of the Food and Drug Administration Safety Innovation Act (FDASIA) that was enacted by Congress on July 9. 2012. This is a wide-ranging law with 11 new titles. The titles most relevant to vaccines are Title V, which deals with pediatric drugs and devices in development, and Title IX, which deals with drug approval and patient access. New about FDASIA is the designation of a drug as breakthrough therapy, for which FDA is currently developing guidance.

Health Resources and Services Administration (HRSA)

No update presented.

Indian Health Services (IHS)

Dr. Temte called attention to a publication in the December 2012 issue of *Pediatrics* detailing the incredible effects of coverage in the American Indian / Alaska Native (AI/AN) population with parity with Caucasian children in the US. This is a very nice testament to what has been done through Indian Health Services.

Amy Groom reported that IHS is in its fifth year of monitoring its healthcare influenza vaccination, which was at 74% at the time of this meeting. This has been the percentage for the last four years, so IHS is not particularly pleased with its inability to make anything but incremental progress. Consideration is being given to how this can be improved for the next influenza season. IHS continues to monitor adult vaccine coverage on a quarterly basis, which was instituted in October 2012. In addition, IHS has been engaged in a significant amount of adult vaccine education with providers and community health representative, who are lay healthcare workers who interact with the community. Community health representatives are thought to be an important interface with the community to gain community buy-in. The IHS electronic health record (EHR) already includes a fairly robust clinical decision support for most adult immunizations, but they are only age-based. IHS is working to expand that into risk-based forecasting for Hepatitis A and B for chronic liver disease patients in those with hepatitis C, hepatitis B for those with an HIV diagnosis, and PCV13 for the immunocompromised.

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

Dr. Gellin reported for Dr. Orenstein during this ACIP meeting, blending the NVAC and NVPO reports. An NVAC meeting was convened earlier in February. One of themes addressed during that meeting was the implementation of ACA, focusing on some of the challenges of implementation. As those issues arise, he will be glad to submit them to NVAC for further deliberation. There was a major focus on HPV vaccine in the context of Healthy People 2020 goals. This is an area in which NVAC was asked by the Assistant Secretary for Health to assess Healthy People 2020 goals, particularly those that are not on track. There is now an NVAC working group that will focus on this issue to try to better understand the root causes, evaluate current efforts, and make recommendations on further actions. NVAC also has a Global Immunizations Working Group that is focused on Goal 4 of the National Vaccine Plan (NVP), with a range of recommendations that will be presented later in 2013. A Vaccine Hesitancy Working Group has also been established. Recognizing that vaccine hesitancy can occur throughout the lifespan, the focus of this group initially will be on uptake of childhood vaccines. Both NVAC and the NVPO have a major focus on adult immunizations, which feeds into the summit in May 2013 in Atlanta. The Flu Vaccine Finder has been morphed into the Adult Vaccine Finder, which can be found at HealthMap. This offers an opportunity to learn what vaccines adults should receive, as well as where to acquire them within the radius of one's zip code. Another component of NVAC's work pertains to healthcare worker (HCW) immunizations. A recent issue of *Public Health Reports* featured NVAC recommendations in an editorial from Dr. Koh. NVAC continues to assess this within the system and throughout the healthcare system. There were presentations on this issue from CDC, CMS, and the Joint Commission on some of the activities going forward. With regard to two other pieces related to NVPO's work with the Institute of Medicine (IOM), in the past ACIP heard a presentation from

IOM on its Strategic Multi-Attribute Ranking Tool for Vaccines (SMART Vaccines) Program. IOM convened a stakeholders meeting in November 2012, and currently is working on the second phase. Software will be made available in the fall. The focus of this program is on decision making and a decision framework for vaccine research and development. A project that NVPO and CDC supported assessed the safety of the vaccine schedule, for which there would be a presentation by IOM during this ACIP meeting.

National Institutes of Health (NIH)

Dr. Gorman reported that there had been one senior leadership change, with Dr. Gary Nabel having left the Vaccine Research Center to serve as the Chief Scientific Officer at sanofi pasteur. At this time, the rotavirus mix and match study was 6 weeks from completing enrollment at 1300 babies, and will assess all of the variations of potential rotavirus vaccine mix and match vaccination schedules. Enrollment for an on-going study has completed for a study on the H3N2 variant influenza virus that was an issue at state fairs during the spring and summer. A study has been completed and will soon be presented at a national public meeting on maternal pertussis vaccination, which will help inform and perhaps strengthen the recommendation from ACIP on pertussis vaccination and pregnancy. A candidate hepatitis C vaccine has just completed Phase I of a Phase I-II study, and 70 eligible subjects will be presented to the FDA and the Data Safety Monitoring Board (DSMB) to determine whether that study can move forward.

Pneumococcal Vaccines

Introduction

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

Dr. Bennett indicated that the Pneumococcal Vaccines Working Group's terms of reference were to:

- Review data on immunogenicity, efficacy, and cost-effectiveness of pneumococcal conjugate vaccines
- Determine whether data available to date on PCV13 immunogenicity, effectiveness, and efficacy are sufficient to determine value of immunizing with PCV13
- Develop a revised statement on pneumococcal immunization as necessary

The group has been working its way through these terms of reference for the last several months. They reviewed and presented to ACIP evidence for PCV13 use among adults ≥50 years of age. At that time, they elected to defer the recommendation until more data were available for two reasons. The first was to be able to review results of the Community Acquired Pneumonia Immunization Trial in Adults (CAPITA), and second was to be able to review the indirect effects of PCV13 use in children. ACIP did vote to recommend PCV13 for adults 19 years of age or older with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants.

On January 25, 2013, the FDA approved Prevnar 13® for use in people 6 years through 17 years of age based on immunogenicity studies in healthy children. For this age group, PCV13 is indicated for prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

During this session, presentations were given on the impact of PCV13 use in children; evidence supporting PCV13 use for children 6 through 18 years old with immunocompromising conditions (review of data and GRADE); and recommendations for PCV13 use among immunocompromised children 6 through 18 years old. The objectives of this session were for the working group to propose to change the current permissive (e.g., GRADE category B) recommendation for PCV13-naïve high-risk children 6 through 18 years old to a routine recommendation (GRADE category A); and for ACIP to review the presented evidence and consider a vote on the proposed recommendation.

Impact of PCV13 Use in Children

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

Dr. Moore offered a brief update on the status of the introduction on PCV13 in children, and its impact on the incidence of invasive pneumococcal disease in children and in adults. Substantial reductions (>90%) have been observed in PCV7-type invasive pneumococcal disease (IPD) among adults within the first 7 to 8 years of PCV7 introduction for children in 2000. As Dr. Bennett mentioned, age-based recommendations for PCV13 use among adults were deferred pending the results of the randomized controlled trial (RCT) in the Netherlands (CAPITA) and the evaluation of indirect effects of PCV13 use among children. CDC monitors the incidence of IPD in 10 areas around the US using an active, population-based surveillance system called Active Bacterial Core Surveillance (ABCs).

PCV6-type invasive disease are cases of invasive pneumococcal disease that are included in PCV13 but are not included in PCV7. For 2006 through 2008 and 2010 through 2012 in children less than 2 years of age, the number of cases of pneumococcal disease increased somewhat rapidly during the late winter and early spring months and tend to level out during the late spring and early summer. Cases increase again in the fall and winter of the subsequent year. In 2010, when PCV13 was introduced, cases of pneumococcal disease in children under 2 years of age continued to increase, then leveled off, and ultimately failed to continue to rise at the same rate that they had in previous years, and then leveled off substantially. In 2011, it was much clearer that there was a marked reduction in the incidence of disease. Until the end of June 2012, reductions in the incidence of disease continued to be observed in this population

In adults in 50 through 64 years of age, a similar pattern was observed in terms of the seasonality of disease. However, rather than seeing a change of incidence in disease in 2010 as was observed in children, it was not until late 2011 that a slight change was observed in the accumulation of cases. This became even more obvious in 2012. In adults over 64 years of age, a very similar pattern of rates of disease was observed in late 2011 that dramatically tailed off in 2012 [CDC Unpublished, Active Bacterial Core surveillance; Note: Excludes 2009 pandemic year].

Some modeling has been done with regard to these changes in order to determine the percentage reductions in the incidence of disease. In children under 2 years of age and children 2 through 4 years of age, the incidence of disease caused by the additional serotypes in PCV13 has declined dramatically by over 80%. Even in the adult age groups, substantial reductions of at least 50% have been observed. Importantly, about 75% of the averted cases to date have been prevented in adults.

In conclusion, very positive results have been observed from the introduction of the PCV13 vaccine in children, both in children and adults. There is clear evidence of reductions in IPD caused by the additional serotypes included in PCV13. This was first evident among children under 2 years of age in the 4th quarter of 2010, and among adults ≥50 years old in the 4th quarter of 2011. In the 10 areas throughout the US, it is estimated that over 2000 cases of IPD have already been averted, primarily in adults. Monitoring of surveillance data will continue to be evaluated for future trends, and the working group will report back to ACIP during future meetings.

Discussion Points

Dr. Temte inquired about the relationship between influenza cases in adults, especially older adults, and secondary pneumococcal infections.

Dr. Moore indicated that they will assess this and report back to ACIP.

Dr. Keitel asked whether they were able to stratify according to other underlying risk conditions and rate reductions.

Dr. Moore replied that they had not yet been able to do this.

Dr. Neuzil (IDSA) requested clarification regarding whether the 2000 case estimate was just from ABCs, or if that was extrapolated to a broader population.

Dr. Moore responded that it was only from ABCs; however, they are working to extrapolate to a total US population, and in order to do this, racial differences, the incidence of disease, and other important issues have to be taken into consideration.

PCV13 For Children 6 through 18 Years of Age With Immunocompromising Conditions: GRADE

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

Dr. Pilishvili indicated that the policy question considered by the Pneumococcal Working Group was, “Should ACIP make a routine recommendation for PCV13 use among immunocompromised PCV13-naïve children 6 through 18 years of age?”

ACIP routinely recommends PCV13 use in high risk children 6 weeks through 71 months of age. In addition, the 2010 recommendations indicated that 1 dose of PCV13 *may be* given to children aged 6 through 18 years of age with anatomic or functional asplenia (including sickle cell disease: SSD); cochlear implant; CSF leaks; HIV infection; chronic renal failure and nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation

therapy, including malignant neoplasms, leukemias, lymphomas and Hodgkin disease or solid organ transplantation; or congenital immunodeficiency. In addition, children with underlying medical conditions should receive pneumococcal polysaccharide vaccine (PPV23) after PCV13. One dose of PPV23 is recommended for children age 2 years or older, and PPV23 is recommended at least 8 weeks after the last PCV13 dose [*MMWR* Dec 2010]. If the GRADE language had been applied to the permissive recommendations for PCV13 for children 6 through 18 years of age, it would be a Category B recommendation. In addition, the recommendations were off-label as the vaccine was not licensed for these age groups at that time.

In June 2012, ACIP made Category A recommendations for PCV13 use in high risk adults. One dose of PCV13 is recommended for adults 19 years of age or older with anatomic or functional asplenia (including sickle cell), cochlear implant, CSF leaks, or immunocompromised (e.g., HIV, nephrotic syndrome). The existing PPSV23 recommendations were not changed in 2012. For PPSV-naïve adults, at least 1 dose of PCV13 was recommended followed by the existing regimen of PPSV23 starting at least 8 weeks after PCV13. For adults who have received PPSV23 previously, 1 dose of PCV13 is recommended at least one year after PPSV23. If additional PPSV23 doses are needed, they should be administered at least 8 weeks after the PCV13 dose and at least 5 years after a previous PPSV23 dose. This was a Category A recommendation [*MMWR* Oct 2012].

The rationale for the working group proposal to have strong routine PCV13 recommendation for use in high risk children and adolescents was that on January 25, 2013, FDA licensed PCV13 for all children 6 through 17 years of age. In addition, children with immunocompromising conditions represent a small proportion of the population with very high risk of disease, so there is an opportunity to provide protection in addition to currently recommended PPSV23 in this age group. A strong routine recommendation may improve vaccine uptake in these high-risk populations, and this will offer an opportunity to harmonize the language with PCV13 recommendations for high risk adults that were recently made.

The incidence of IPD disease is very high among persons with immunocompromising conditions. The incidence of IPD in children aged 6 through 18 years with and without selected underlying conditions in the US for 2007 through 2009 was evaluated, and individuals with hematological cancer have the highest risk for IPD, with over a 1000-fold increased rate of disease compared to persons without these conditions. People with HIV/AIDS have over a 150-fold increased rate of disease compared to persons without HIV. Individuals with sickle cell disease have over 40-fold increased rate of disease compared to persons without sickle cell disease. These data demonstrate high rates of disease for immunocompromised persons despite the indirect effects of PCV7 [CDC unpublished data].

The study evaluating the risk of pneumococcal disease in persons ≥5 years of age with different underlying conditions, stratified by risk groups, is a retrospective cohort study using US healthcare insurance claims data. Dr. Pilishvili presented IPD rates for this study by age group among persons with underlying conditions, such as immunodeficiency, anatomic or functional asplenia, cochlear implant, nephrotic syndrome, chronic renal failure, malignancy, treatment with immunosuppressive or radiation therapy, compared to those with chronic immunocompetent conditions and healthy persons. Overall, these rates are lower than the rates obtained through the use of surveillance data (e.g., ABCs). These data represent a privately insured population, which is a population with higher than average socio-economic status. However, rates follow the same age-distribution as demonstrated by the routine surveillance data and show large disparities in IPD rates between persons with high risk

conditions and healthy persons. The IPD rate ratios comparing children 6 through 17 years of age with high risk conditions to healthy persons in the same age group ranged from around 30 to 45 [Courtesy of David Strutton, Pfizer].

With regard to the proportion of IPD caused by serotypes included in each vaccine, among children with immunocompromising conditions, 38% of IPD in this group is caused by PCV13 serotypes. The serotypes in PPSV23 which are not found in PCV13 account for an additional 33% of IPD in immunocompromised adults. Therefore, there is an opportunity for broader serotype protection through use of both vaccines in this age group [CDC, ABCs, unpublished, 2011].

The working group followed these GRADE steps:

1. Formulate specific policy question
2. Identify and rank relative importance of outcomes
3. Summarize all evidence for critical and important outcomes including number needed to vaccinate (NNV), where possible
4. Assess quality of evidence for each outcome
5. Summarize quality of evidence across outcomes
6. Review health economic data
7. Assess the balance of risks and benefits
8. Determine the recommendation category

The policy question that the working group GRADED was, “Should PCV13 be administered routinely to children 6 through 18 years of age with immunocompromising conditions?” The population of interest is children 6 through 18 years of age with immunocompromising conditions, functional or anatomic asplenia (including SCD), CSF leaks or cochlear implants. The intervention the working group wanted to evaluate was a single dose of PCV13. The control group was a placebo. The next step was to decide which disease outcomes should be considered and the relative importance of preventing each of them. The group agreed that invasive pneumococcal disease, pneumococcal pneumonia, hospitalizations, deaths, immune response, and serious and systemic adverse events were all outcomes of critical importance. There were no data available to evaluate hospitalizations. All other critical outcomes were included in the evidence review.

For each critical outcome considered, the working group summarized the evidence included and then assessed the quality of evidence. There was one study among adults that evaluated the critical outcome of invasive pneumococcal disease, defined by isolation of pneumococcus from a normally sterile site. This was a double blind randomized placebo-controlled trial among HIV-infected adults in Malawi. All 496 enrolled subjects had recovered from documented IPD. Study participants were given 2 doses of PCV7 4 weeks apart as opposed to the GRADE intervention of 1 dose of PCV13. The vaccine efficacy against PCV7 serotype IPD was 74%, and this finding was statistically significant [French N, et.al. *N Engl J Med* 2010;362:812-22]. The second efficacy trial included for the critical outcome of invasive pneumococcal disease was a double blind randomized placebo-controlled trial among HIV-infected and HIV-uninfected infants in South Africa. The same definition of IPD was applied. Infants were randomized to receive a 9-valent vaccine (PCV9) or a placebo at 6, 10, and 14 weeks of age. The vaccine efficacy against PCV9 serotype IPD among HIV-infected children was 65%, and this was statistically significant [Klugman, K et.al. *N Engl J Med* 2003]. The overall efficacy for the two clinical trials included for IPD outcome was estimated at 69%, and the results of the test of

heterogeneity suggest that the data were homogeneous and the results are consistent between the trials in terms of the point estimate of the efficacy.

In order to calculate number needed to vaccinate, the working group applied the combined efficacy of 69% estimated from the 2 clinical trials to the US incidence of PCV13-type IPD in HIV-infected children <19 years of age. An estimated rate of 1265 IPD cases with HIV per 100,000 persons with AIDS was used based on 2007-2009 data. Assuming 69% efficacy and 100% coverage, a rate of 392 cased per 100,000 was estimated in vaccinated HIV-infected persons. The estimated number needed to vaccinate to prevent one IPD case would be 115. As a point of reference, Dr. Pilishvili reminded ACIP members that when the same estimates were made for HIV+ adults 19 through 64 years of age, the number needed to vaccinate was estimated to be approximately 2000.

One observational study was included for the critical outcome of invasive pneumococcal disease. This was an observational population-based study assessing the effects of PCV7 on IPD rates among children with sickle cell disease. PCV7 histories were linked to IPD data for over 1200 children ≤10 years of age with confirmed hemoglobinopathies. The investigators conducted a stratified survival analysis to estimate PCV7 effect on IPD rates while adjusting for herd effects. The vaccine effectiveness against PCV7 serotype IPD, adjusted for the presence of herd protection , was estimated to be 81% in the two years after licensure, and this was statistically significant [Adamkiewicz et al. *Pediatrics* 2008].

In assessing the quality of evidence for IPD outcome, the working group felt there were very serious concerns with indirectness or generalizability of the results because the populations studied were adults in Malawi, with only 13% of the participants on anti-retroviral therapy, or infants in South Africa. Additionally, there was a difference in regimens with 2 doses of PCV7 or 3 doses of PCV9 studied. Therefore, the evidence quality for the 2 RCTs was downgraded to type 3. No serious concerns about the risk of bias, indirectness, or imprecision were raised around the one observational study, so the evidence type remained at 3.

For the critical outcomes of pneumonia and death, the results of the efficacy trial among HIV-infected and HIV-uninfected infants in South Africa were included. The vaccine efficacy against radiologically-confirmed pneumonia among HIV-infected infants was 13%, and this was not statistically significant. A 6% reduction in all-cause mortality among HIV-infected infants and a 4% reduction in mortality attributable to pneumonia were found. Neither estimate was statistically significant [Klugman, K et.al. *N Engl J Med* 2003]. Due to very serious concerns with indirectness (e.g., different populations studied and different vaccine formulation and dosing studied) the evidence quality for pneumonia and death was determined to be type 3.

In evaluating the evidence for the critical outcome of immunogenicity, the working group included a Phase III, open-label, single-arm study in children 6 through 17 years of age diagnosed with SCD who were previously immunized with PPSV23 more than 6 months prior to enrollment. Participants in the study received 2 doses of the 13-valent vaccine, given approximately 6 months apart. Blood samples were collected prior to and at 1 month (28 to 42 days) after each dose of PCV13. Serotype-specific immunoglobulin G (IgG) concentrations to the 13 serotypes and serum opsonophagocytic assay (OPA) titers were determined [Courtesy of Pfizer; Protocol 6096A1-3014-WW (B1851013)].

Because of the policy question under consideration, Dr. Pilishvili presented only the results following a single dose of PCV13. Serotype-specific OPA geometric mean titers (GMTs) and geometric mean fold rises (GMFRs) post dose 1 were presented. The OPA GMTs 1 month after dose 1 were higher than the OPA GMTs before dose 1 for all serotypes. GMFRs from before and after dose 1 ranged from 3.5 for serotype 14 to 40.3 for serotype 23F. In terms of the serotype-specific IgG geometric mean concentrations (GMCs) before and after dose 1, the IgG GMCs 1 month after dose 1 were higher than the IgG GMCs before dose 1. GMFRs from before dose 1 to 1 month after dose 1 ranged from 1.74 for serotype 5 to 6.91 for serotype 4. Both serotype-specific IgG concentrations and functional antibodies, measured through OPA, increased after a single dose of PCV13 [Courtesy of Pfizer; Protocol 6096A1-3014-WW (B1851013)].

Also included in the working group's review were 2 RCTs in HIV-infected infants (e.g., one study with a 4-dose schedule of PCV7 and one study with a 3-dose PCV9 schedule), and 4 RCTs among HIV-infected adults and one pre/post immunogenicity study in HIV+ children 2 through 18 years old which evaluated a 2 dose PCV7 schedule. In all of these studies, the CD4 count was greater than or equal to 200. Some of the comparisons that were evaluated in the adult study were compared to placebo and others were compared to PPSV23. The overall conclusions of the working group from the review of these studies were that PCV does elicit an immune response in HIV-infected children and adults; there was a significantly higher response in the PCV arm versus the placebo arm; and response following a single dose of PCV is as good or better than PPSV23 in vaccine naive or previously vaccinated adults. Thus, the quality of evidence for the important outcome of immunogenicity was 3. The 4 published immunogenicity studies in adults used PCV7, the two RCTs in children used different regimens of PCV7 or PCV9. Therefore, the evidence quality was downgraded from 1 to 3. The 2 pre-post studies were, by definition, quality type 3.

In evaluating the safety outcome, the working group included 2 RCTs of PCV7 and PCV9 among HIV-infected infants and 3 RCTs among HIV-infected adults. In the studies considered, no serious adverse events were reported. For the serious systemic events reported, no statistically significant differences were noted between the study and the control arm. Mild, self-limited secondary effects (e.g., local pain, fever, myalgias) were reported in adults studies, with no statistical differences between the arms. A phase III, single-arm study in children 6 through 17 years of age with SCD was included to evaluate safety outcomes. Most commonly reported systemic events following a single dose were headache (53.6%), fatigue (66.1%), and muscle pain (74.8%). Severe systemic events reported by more than 10% of subjects after dose 1 included headache (11 subjects, 12.0%), fatigue (13 subjects, 14.4%), and muscle pain (9 subjects, 10.1%). The most frequently reported adverse events were sickle cell anemia with crisis (15.8%), followed by pyrexia (6.3%), headache (3.2%), and vascular occlusion (3.2%). After dose 1, 13 (8.2%) subjects reported severe adverse events. The most frequently reported severe AEs were sickle cell anemia with crisis (7 subjects [4.4%]), acute chest syndrome (2 subjects) and pyrexia (2 subjects). No life-threatening adverse events were reported during the study period [Courtesy of Pfizer, Safety and Immunogenicity of Prevnar 13 in Children with Sickle Cell Disease (SCD) Previously Immunized with PPSV23].

To evaluate the quality of evidence for the critical outcome of serious and systemic adverse events, 5 RCTs among adults and children and one pre-post immunogenicity study were considered in total. The only serious concerns involved indirectness because the RCTs in children included a different vaccine formulation, and the RCTs among adults included a different comparison (PPSV). The quality of evidence for this outcome was type 3. Next, the working group summarized the quality of evidence across all critical outcomes. The quality of evidence for all critical outcomes considered was 3. Therefore, the working group assessed the overall evidence type to be 3.

The next step in the GRADE process involved the review of health economic data. Cost-effectiveness was evaluated for adults with certain immunocompromising conditions, and the results were presented to ACIP when considering the PCV13 recommendations for high risk adults. The cost-effectiveness assessment indicated that PCV13 immunization is cost-saving for the four selected sub-populations evaluated in the model. Given that the policy question being considered today includes a relatively small group of the population at a very high risk for disease, this recommendation will have a time-limited utility as it applies to PCV13-naïve persons only. The working group did not evaluate cost-effectiveness for children 6 through 18 years of with immunocompromising conditions.

In order to determine the recommendation category, the working group considered the following questions:

- Is the evidence quality "Lower?" Yes. The working group thought that there were very serious concerns with the indirectness of evidence from the RCTs, as well as low quality of evidence, by definition, through observational studies.

- Is there uncertainty about the balance of benefits versus harms and burdens? No. The working group agreed that the very high burden of disease in the immunocompromised, despite the indirect effects from PCV7, demonstrate the potential for a high net benefit from PCV13 use in the immunocompromised populations.

- Is there variability or uncertainty in what is important? No. The working group reached consensus regarding which outcomes are critical to prevent.

- Is there uncertainty about whether the net benefits are worth the costs? Yes, there is uncertainty regarding the cost-effectiveness of PCV13 in these groups.

The working group concluded that there remains an extremely high burden of pneumococcal disease among immunocompromised children 6 through 18 years of age. The GRADE process led the working group to conclude that PCV13 is likely effective in this group and that benefits likely outweigh harms. No additional data are expected to influence the GRADE conclusions for the immunocompromised group. As observed with adults, the indirect effects of PCV13 use in children are unlikely to eliminate PCV13 serotypes from immunocompromised population. While there was insufficient power for this particular age group to evaluate this question, the data in adults do support this statement. Thus, the working group decided that the benefits likely outweigh harms, and PCV13 should be routinely recommended for PCV13-naïve children 6 through 18 years old with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants. The working group reached the decision that this should be a Category A recommendation based on Evidence Type 3.

Discussion Points

Ms. Rosenbaum requested information about the implications for access to coverage through VFC and private insurers if the classification was left as Category B (permissive) and it remained an off-label use.

Ms. Pilishvili responded that it would not be off-label because the vaccine is already licensed for 6 through 18 years of age. VFC covers this vaccine, even with the Category B (permissive) recommendations. The language was included in the VFC language for these high risk individuals.

Dr. Netoskie (AHIP) responded that private insurance coverage would likely be variable, because some companies allow permissive use if a condition exists to which it should be applied and others are fairly strict around utilization only for those for whom there is a routine recommendation.

Dr. Temte commended the working group for a clear presentation using GRADE, noting that the GRADE process was beginning to feel somewhat routine.

Dr. Sun (FDA) clarified that the vaccine is not currently approved for adults 18 through 50 years of age.

Dr. Pickering added that this recommendation would be through 18 years of age, which follows the immunization schedule, but is licensed for ages 2 months through 17 years. Therefore, this would be an off-label recommendation for 18 year olds.

Ms. Pilishvili reiterated that the previous recommendation covered adults 19 years of age and older, so the 2012 recommendations are off-label for 19 through 49 year olds. The FDA approval was through 17 years of age. The recommendations are consistent with the pediatric tables, so the recommendation for 18 year olds would still be off-label.

Dr. Keitel inquired as to whether the manufacturer could provide information about whether they were able to tease out the time since receipt of polysaccharide vaccine and its effect on immunogenicity.

Ms. Pilishvili indicated that the question was raised with regard to the sickle cell disease study, and the manufacturer was able to provide data correlating the response by time since the receipt of the polysaccharide vaccine, and it does not seem to make a difference in terms of the response and there appears to be no correlation between time since PPSV receipt and antibody response to PCV13 in patients with sickle cell disease.

PCV13 Recommendations for Children 6 through 13 Years Old with Immunocompromising Conditions

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

Ms. Pilishvili reminded everyone that the working group proposed to include the following conditions as indications for PCV13 for children 6 through 18 years of age who are PCV13-naïve:

- Anatomic or functional asplenia, including sickle cell disease
- HIV infection
- Chronic renal failure and nephrotic syndrome
- Diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin's disease; or solid organ transplantation
- Congenital immunodeficiency
- Cochlear implant, CSF leaks

The proposed recommendation for prevention of pneumococcal disease among children 6 through 18 years old with immunocompromising conditions follows:

- A single dose of PCV13 is recommended for children aged 6 through 18 years who have not received PCV13 previously and who are at increased risk for invasive pneumococcal disease because of anatomic or functional asplenia, including sickle cell disease, immunocompromising conditions such as HIV-infection, cochlear implant, or cerebrospinal fluid leaks, regardless of whether they have previously received PCV7 or PPSV23.

- Recommendations for PPSV23 use for children in this age group remain unchanged.

The current recommendations, which are not changing, for the combined use of PCV13 and PPSV23 are as follow:

- PPSV23-naïve children:
  - PCV13 dose is recommended to be given before PPSV23, whenever possible
  - PPSV23 should be given at least 8 weeks after a dose of PCV13 (*MMWR* 2010)
  - Recommendations for 2nd dose of PPSV remain unchanged (*MMWR* 2010)

- PPSV23-immunized children:
  - A dose of PCV13 should be given at least 8 weeks after the PPSV23 dose (*MMWR* 2010)
  - Total number and interval between PPSV23 doses unchanged from existing recommendations (*MMWR* 2010)

The current ACIP PPSV23 recommendations for use among high-risk children aged 2 through 18 years of age include the following, and also would remain unchanged [*MMWR* 2010]:

- Administration of PPSV23 After PCV13 Among Children Aged 2–through 18 Years Who Are at Increased Risk for Pneumococcal Disease
  - Children aged ≥2 years with underlying medical conditions should receive PPSV23 after completing all recommended doses of PCV13. These children should be administered 1 dose of PPSV23 at age ≥2 years and at least 8 weeks after the most recent dose of PCV13
  - Children who have received PPSV23 previously also should receive recommended PCV13 doses

- Revaccination With PPSV23 Among Children at Highest Risk
  - A second dose of PPSV23 is recommended 5 years after the first dose of PPSV23 for children who have anatomic or functional asplenia, including SCD, HIV infection, or other immunocompromising conditions. No more than 2 PPSV23 doses are recommended

Based on the presented information, the working group proposed the following recommendation language for a vote for PCV13-naïve children 6 through 18 years of age:

> *"We recommend that children 6 through 18 years of age with immunocompromising conditions, functional or anatomic asplenia, CSF leaks or cochlear implants, and who have not previously received PCV13 receive a single dose of PCV13, regardless of whether they have previously received PCV7 or PPSV23."*

Discussion Points

Ms. Rosenbaum pointed out that given the wording of the ACA, it would be important to specifically use the word "routine," which did not appear in the proposed language. She emphasized the importance of clarifying that this would be a routine immunization for immunocompromised children.

Dr. Sawyer requested clarification regarding the recommendation for people who were previously immunized with polysaccharide with regard to interval to the subsequent conjugate vaccine. He recalled that for adults, the recommendation was to wait 1 year, but for children they would be recommending 8 weeks. If that was correct, he asked for an explanation of the difference and whether that interval was part of what they were being asked to vote.

Ms. Pilishvili replied that the interval would remain unchanged from the 2010 recommendations for pediatric recommendations. For adult recommendations, the committee voted on the interval of 1 year, so there is a discrepancy in terms of the waiting period following PPSV23 between the adult and pediatric recommendations. The data available for the adult recommendations were limited in that none of the studies used for evidence were designed to evaluate the optimal interval. Based on expert opinion, it was decided that a 1-year waiting period would be sufficient to potentially overcome any potential risk of hyper-responsiveness if the vaccines were given too close to each other. She was not involved in the recommendations for children, but there is no evidence available about the optimal interval. According to the 2010 recommendations, 8 weeks was considered to be the optimal waiting period.

Dr. Temte requested that Dr. Loehr comment on whether this would pose a problem, or if children with these conditions are rare enough that they would not be seen in usual practice.

Dr. Loehr (AAFP) responded that this is so unusual, physicians will look it up every time.

Dr. Harrison inquired as to whether the number needed to vaccinate was incremental to the receipt of the polysaccharide vaccine.

Ms. Pilishvili replied that PPSV pre-vaccination was not considered in the efficacy estimate or in the estimation of number needed to vaccinate. There are not sufficient data to evaluate this. Assumptions would have to be made about PPSV efficacy in this population in order to estimate the incremental effect. The number needed to vaccinate estimate was based on naïve children.

Dr. Campos-Outcalt wondered whether the proposed recommendation would be combined with the recommendation for ages 2 and above to have one recommendation for children aged 2 through 18, given that the recommendations are essentially the same.

Ms. Pilishvili replied that the ultimate goal of the working group was to revise and combine all of the recommendations. They are currently working on children 6 through 18 years of age. The previous recommendations focused also on naïve adults 19 years of age and older, and there is a group of children 2 through 5 years of age. The reason the working group focused on children 6 through 18 year of age is because this is the age for which permissive recommendations were made in 2010. Through the age of 5 years, there are already strong recommendations for the same group of children. Essentially, if they revise the recommendations into one document, it will cover children 2 through 18 years of age.

Dr. Duchin inquired as to what would happen to all of the recommendations that do not include the word “routine” under ACA. He was not sure he understood the inclusion of the word “routine” in the recommendation upon which they were being asked to vote.

Ms. Rosenbaum clarified that in implementing HHS regulations for the preventive services benefit under ACA, the regulations clearly tie coverage of immunizations to routine recommendations of the ACIP. If the word “routine” is not used, given the fact that this immunization has been treated as permissive, they would risk the possibility of significant variation in coverage policies because permissive language has been understood as such by clinicians and insurers. Therefore, she strongly recommended that if ACIP was moving from a recommendation for clinical judgment about whether to give an immunization to a standard that certain immunocompromised children should routinely receive this immunization, they should use the language of the implementing federal regulations of this agency.

Dr. Keitel’s understanding was that the use of the word “may” implied judgment and use of the word “should” implied routine in ACIP language. She suggested assessing their various recommendations to determine when the word “routine” is used versus the word “should.”

Ms. Rosenbaum stressed the importance of not leaving any doubt for CDC’s director, who makes the final decision about whether to issue this as a routine vaccine and thereby trigger the coverage requirements. It is important to be clear that what ACIP intends is a recommendation at a level that will leave no question about the fact that it goes onto a schedule for coverage purposes.

Dr. Temte noted that “routine use” for Category A recommendations is implicit, and the question regarded whether a word needed to be inserted for the implementation of ACA.

Dr. Campos-Outcalt agreed that because this is a Category A recommendation, and Category A is defined, this should cover intended implementation.

Vote: PCV13 Recommendation for Children 6 through 18 Years Old with Immunocompromising Conditions

Dr. Duchin made a motion to approve the proposed language in the PCV13 recommendation for children 6 through 18 years old with immunocompromising conditions as written. Dr. Sawyer seconded the motion. Let the record show that for purposes of coverage standards under the ACA, the intent of the ACIP language as written is to be understood as a routine recommendation for children 6 through 18 years old with these underlying conditions. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

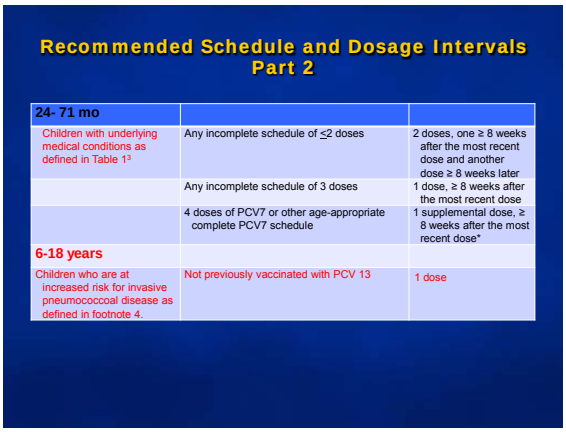
15 Favored: Bennett, Bocchini, Campos-Outcalt, Coyne-Beasley, Duchin, Harriman, Harrison, Karron, Jenkins, Keitel, Rosenbaum, Rubin, Sawyer, Temte, and Vazquez
0 Opposed: N/A
0 **Abstained:** N/A

Vaccines for Children

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

Dr. Santoli reminded everyone that the VFC resolution for pneumococcal vaccines contains two components, the PCV component and the PPV23 component. This update pertains only to the PCV component of the resolution. No changes were proposed to the PPV23 component. The purpose of this resolution was to update recommendations regarding the use of this vaccine in PCV13-naïve children aged 6 through 18 years. The current wording for eligible groups will remain unchanged, which follows:

- All infants and children at least six weeks through 59 months of age and children 60 through 71 months with certain underlying medical conditions listed in the table below.
- Children 6 through 18 years of age who are at increased risk for invasive pneumococcal disease because of sickle cell disease, HIV-infection, or other immunocompromising condition, cochlear implant, or cerebrospinal fluid leak.
- Table 2 remains unchanged. Changes to the scheduled doses and intervals are depicted in red in the following table:



The table footnotes remain unchanged with the exception of the following addition:

> 4) Includes children with anatomic or functional asplenia, including sickle cell disease, HIV-infection or other immunocompromising condition, cochlear implant, or cerebrospinal fluid leak.

The current wording for the recommended dosage remains unchanged. Contraindications and Precautions have been updated with the following link to the published recommendations:

> Contraindications and precautions can be found at:
> http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5911a1.htm

In terms of the statement regarding update based on published documents, if an ACIP recommendation regarding pneumococcal vaccination is published within 12 months following this resolution, the relevant language above (except in the eligible groups sections) will be replaced with the language in the recommendation and incorporated by reference to the publication URL.

VFC Vote

Dr. Sawyer made a motion to approve the proposed language in the VFC resolution as written. Dr. Coyne-Beasley 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, Keitel, Rosenbaum, Rubin, Sawyer, Temte, and Vazquez
0 Opposed: N/A
0 Abstained: N/A

Haemophilus Influenzae (HIB) Vaccines

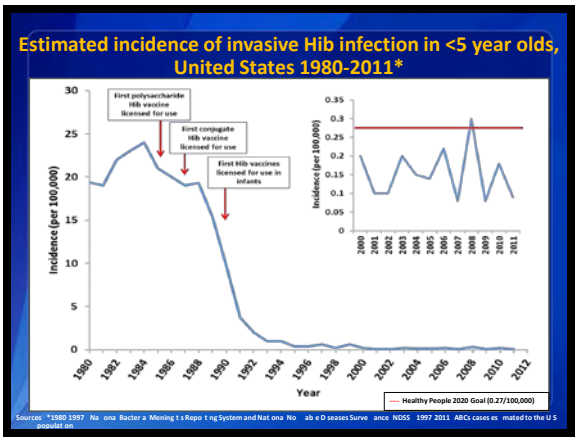
Introduction

Lorry Rubin, MD, Chair
ACIP Meningococcal and *Haemophilus Influenzae* Type B Vaccine Working Group

Dr. Rubin recognized several members who were rotating off of this working group, including: Geoff Evans (HRSA), Amy Middleman (SAM), and Marietta Vasquez (ACIP).

He indicated that during this session an overview would be presented of the draft Hib statement, followed by an ACIP vote on that statement. Considerations also would be presented for including HibMenCY in the Hib VFC Resolution, followed by an ACIP vote on that resolution. Dr. Rubin reminded everyone that during the last ACIP meeting, consideration was given to HibMenCY as a meningococcal vaccine, and that during this session, consideration would be given to HibMenCY as a Hib B Vaccine.

To give some historical background on Hib B invasive disease, Dr. Rubin shared the following graphic:



The first Hib B vaccine was licensed in 1985, which was a capsular polysaccharide vaccine. The first conjugate vaccines were licensed in 1989 for routine use in children 15 months of age and older. The incidence of invasive disease began to decline even before the first vaccines were licensed for use in infants beginning at 2 months of age. Rates during the 2000s have been consistently quite low.

The last routine Hib recommendations were published in 1993. Guidance for special populations was not included in the 1993 statement, and limited guidance for chemoprophylaxis was included in the 1993 statement.

Updated Hib Vaccine Recommendations

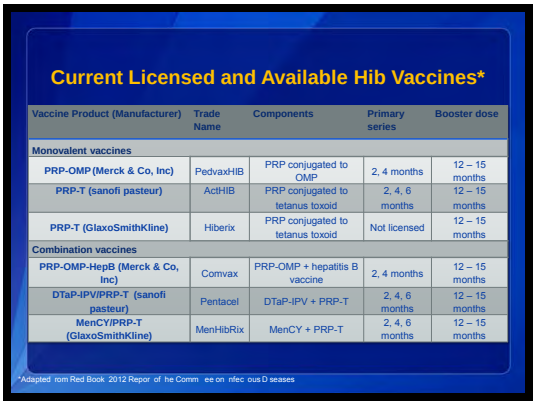
Elizabeth Briere, MD, MPH
LCDR, US Public Health Service

During this session, Dr. Briere reviewed the objectives of the updated Hib statement, summarized the sections in the updated statement, and entertained a vote to affirm the statement as a whole. She also discussed considerations for including HibMenCY in the Hib VFC resolution.

Since the last Hib statement in 1993, the epidemiology of Hib disease has changed. One of the objectives of updating the Hib statement was to provide an overview of current Hib epidemiology. The figure that Dr. Rubin presented will be included in the statement. Several Hib-containing vaccines have been licensed since the 1993 statement, and several are no longer available, so another objective was to provide an updated list of the Hib vaccines currently licensed and available in the US. The working group also wanted to provide recommendations for routine vaccination, guidance for special populations, and guidance for chemoprophylaxis of contacts all in one document.

Statement revision activities included reviewing all previously published Hib vaccine recommendations, including ACIP General Recommendations, ACIP recommendations for HIV and immunocompromised patients, the Red Book, and the draft of the 2013 evidence-based Infectious Disease Society of America (IDSA) Clinical Practice Guidelines for Vaccination of the Immunocompromsed Host. The working group also reviewed peer-reviewed literature and surveillance data from ABCs and National Notifiable Diseases Surveillance System (NNDSS). The working group reviewed the draft statement, and comments were discussed by teleconference meeting. The ACIP voting members reviewed the draft and provided comments. The statement was revised based on these comments and was provided for voting members prior to this meeting.

The following table also will be included in the statement and lists the current licensed and available Hib vaccines:



Current Licensed and Available Hib Vaccines*

Vaccine Product (Manufacturer)	Trade Name	Components	Primary series	Booster dose
Monovalent vaccines				
PRP-OMP (Merck & Co, Inc)	PedvaxHIB	PRP conjugated to OMP	2, 4 months	12 – 15 months
PRP-T (sanofi pasteur)	ActHIB	PRP conjugated to tetanus toxoid	2, 4, 6 months	12 – 15 months
PRP-T (GlaxoSmithKline)	Hiberix	PRP conjugated to tetanus toxoid	Not licensed	12 – 15 months
Combination vaccines				
PRP-OMP-HepB (Merck & Co, Inc)	Comvax	PRP-OMP + hepatitis B vaccine	2, 4 months	12 – 15 months
DTaP-IPV/PRP-T (sanofi pasteur)	Pentacel	DTaP-IPV + PRP-T	2, 4, 6 months	12 – 15 months
MenCY/PRP-T (GlaxoSmithKline)	MenHibRix	MenCY + PRP-T	2, 4, 6 months	12 – 15 months

*Adapted from Red Book 2012 Report of the Committee on Infectious Diseases

Hiberix®, Comvax®, Pentacel®, and MenHibRix® were licensed since the 1993 Hib statement. All of these vaccines are licensed for the primary series except for Hiberix®, which is licensed only as a booster dose. A footnote in the statement will clarify that the MenCY component of MenHibRix® is only routinely recommended for high-risk groups.

In the updated statement, no changes were made to the routine Hib vaccine recommendations. Although guidance for special populations was not included in the 1993 statement, guidance has been published in other statements and the guidance included in the updated statement is consistent with that in the 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised (not yet published), 2012 Red Book, 2011 ACIP General Recommendations on Immunizations, and 2009 ACIP Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents.

Regarding Hib vaccine, special populations include Alaskan Natives/American Indians; children <24 months of age with invasive Hib disease; preterm infants; and other high-risk groups, which includes patients with functional or anatomic asplenia, HIV infection, immunoglobulin deficiency including IgG2 subclass deficiency, or early component complement deficiency, recipients of a hematopoietic stem cell transplant (HSCT), and those receiving chemotherapy for malignant neoplasms. The updated statement includes a brief history of Alaskan Native/American Indian experience with Hib vaccines and the rationale for recommending PRP-OMP vaccines for these children. Children <24 months of age who develop invasive Hib disease remain at risk of a second episode. Therefore, these groups should be considered unvaccinated and be revaccinated. Preterm infants should follow the routine Hib schedule, starting at 2 months of age based on chronological age.

Guidance for patients at increased risk for invasive disease is broken down by age and high-risk group. The following two tables will be included in the updated statement:

Guidance for High-Risk Groups

High-risk group*	Hib Vaccine Guidance
Patient <12 months of age	Follow routine Hib vaccination recommendations
Patients 12 through 59 months of age	If unimmunized or received 0 or 1 dose before age 12 months: 2 doses 2 months apart If received 2 or more doses before age 12 months: 1 dose If completed a primary series and received a booster dose at age 12 months or older: no additional doses

Guidance for High-Risk Groups

High-risk group*	Hib Vaccine Guidance
Patients undergoing chemotherapy or radiation therapy, age <59 months	If routine Hib doses given 14 or more days before starting therapy: revaccination not required If dose given within 14 days of starting therapy or given during therapy: repeat doses starting at least 3 months following therapy completion
Patients undergoing elective splenectomy, age ≥ 15 months	If unimmunized: 1 dose prior to procedure
Asplenic patients >59 months of age and adults	If unimmunized: 1 dose
HIV-infected children>59 months of age	If unimmunized: 1 dose
HIV-infected adults	Hib vaccination is not recommended
Recipients of hematopoietic stem cell transplant, all ages	Regardless of Hib vaccination history: 3 doses (at least 1 month apart) beginning 6-12 months after transplant

Again, this guidance is consistent with other published guidance. No changes were made. For all high-risk patients less than 12 months of age, the routine Hib vaccine recommendations are followed. For all high-risk patients 12 months through 59 months of age, those who are unimmunized or received 0 or 1 dose before age 12 months should receive 2 doses of Hib vaccine 2 months apart. Those who received 2 or more doses before age 12 months only need 1 dose and those who received a primary series and a booster dose at age 12 months or older need no additional doses.

All high-risk patients <59 months of age who are undergoing chemo or radiation therapy need revaccination only if prior doses were given within 14 days of starting therapy or were given during therapy. All high-risk patients greater than or equal to 15 months of age who are undergoing elective splenectomy, asplenic patients >59 months of age, and HIV-infected children >59 months of age, should receive 1 dose of Hib vaccine if they are unimmunized. Hib vaccine is not recommended for HIV-infected adults, regardless of vaccine history. All recipients of hematopoietic stem cell transplant should receive 3 doses of Hib vaccine starting 6 to 12 months after transplant, regardless of prior vaccine history.

Limited guidance for chemoprophylaxis was included in the last Hib statement. The guidance in the updated statement is consistent with the 2012 Red Book. Rifampin is the recommended choice for chemoprophylaxis of Hib cases. For patients with invasive Hib disease who are treated with an antibiotic other than cefotaxime or ceftriaxone and are less than 2 years of age, rifampin should be given prior to hospital discharge. Rifampin chemoprophylaxis is recommended for all household contacts in households with members <4 years of age who are not fully vaccinated or members who are immunocompromised, regardless of their vaccination status. Rifampin chemoprophylaxis is recommended in childcare settings when 2 or more cases of invasive Hib disease have occurred within 60 days and unimmunized or under-immunized children attend the facility.

Dr. Briere reminded everyone that the vote would be to affirm the updated Hib statement. Since no new vaccine recommendations were proposed, the vote would be to affirm the statement as a whole.

Discussion Points

Dr. Sawyer asked about the difference between adults and children with regard to HIV-infected patients. The new statement recommends Hib vaccine through 18 years of age for HIV-infected individuals, but for adults there is not a complementary recommendation.

Dr. Briere responded that this was correct.

Ms. Rosenbaum noted that the word “routine” appeared in the revised statement. She emphasized that consideration should be given to being routine in the use of the word “routine.” There should be a clear understanding of what ACIP means by “routine” because it is this kind of variation that gives rise to the inference that other recommendations are not for routine immunization.

Dr. Pickering noted that IDSA has a document, which is now in clearance, prepared by a panel that Dr. Rubin chaired, that assesses primary and secondary immune deficiencies and vaccination of people with these deficiencies. He asked if ACIP could assume that the revised ACIP recommendations for children in those categories were exactly the same as the recommendations to be included in the IDSA document.

Dr. Rubin confirmed that the revised ACIP recommendation would align with the IDSA document.

Regarding HIV-infected persons, it was Dr. Keitel’s recollection that prior recommendations were softer, stating that consideration could be given to a single dose for HIV-infected adults; whereas, the revised statement indicated that this “is not recommended.” She wondered what the thought process was behind making that transition.

Dr. Briere believed that several of the guidelines the working group reviewed stated that the Hib vaccine is not recommended for adults.

Dr. Temte said he thought the Hib statement was the oldest existing statement that ACIP had not revisited. ACIP is charged with periodically renewing, reaffirming, or retiring vaccine recommendations. This is almost a 20 year old recommendation, and no new recommendations were embodied in the revised statement. Therefore, the GRADE process was not used for this particular recommendation.

Dr. Briere added that because the working group referred to the IDSA document, the recommendations for the high risk groups were evidence-based.

Dr. Jenkins inquired as to whether the presumption was made that the revised recommendation for HIV-infected patients would be through age 18.

Dr. Briere replied that this was correct.

Vote: Revised Hib Vaccine Statement

Dr. Bocchini made a motion to approve the proposed language in the revised Hib vaccine statement as written. Dr. Jenkins 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, Keitel, Rosenbaum, Rubin, Sawyer, Temte, and Vazquez
0 Opposed:	N/A
0 **Abstained:**	N/A

Considerations for Including HibMenCY in the Revised Hib VFC Resolution

Elizabeth Briere, MD, MPH
LCDR, US Public Health Service

In terms of considerations for including HibMenCY in the updated Hib VFC Resolution, Dr. Briere reminded everyone that HibMenCY is a combination vaccine that provides protection against both Hib and meningococcal serogroups C and Y. It was licensed in June 2012 as a 4-dose infant series, and is expected to be available in late summer 2013. In October 2012, ACIP voted to recommend HibMenCY for routine use only in infants at high-risk for meningococcal disease and to include it in the meningococcal VFC resolution only for high-risk infants. HibMenCY may be used for routine Hib vaccination in any infant.

Since all new combination vaccines require ACIP vote for VFC inclusion, a vote is needed to include HibMenCY in the Hib VFC resolution. Of note, this is the first combination vaccine with one component routinely recommended for all infants and the second component recommended only for high-risk groups.

HibMenCY is both immunogenic and safe. These data have been presented at past ACIP meetings. The Hib portion of HibMenCY has been found to be non-inferior to monovalent Hib vaccines for the infant and toddler doses and provides excellent duration of protection 1,3, and 5 years post 4th dose. Based on data from over 10,000 infants, HibMenCY is safe with few serious adverse events, mild, local reactions, and systemic reactions similar to other monovalent Hib vaccines.

Vaccines for Children

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

Dr. Santoli indicated that the purpose of this resolution was to update the list of Hib-containing vaccines that can be used to prevent Hib disease; correct the catch up recommendations; and add information about use of Hib-containing vaccines in special populations. Eligible groups include all children 6 weeks through 18 years of age to prevent type B Hib disease. The recommended schedule includes 3 or 4 doses of a Hib-containing vaccine, depending on the specific vaccine, as shown in Table 1 as follows:

Table 1. Schedule for administering doses of Hib-containing vaccines*

Vaccine Product (Manufacturer)	Trade Name	Components	Primary series	Booster dose
Monovalent vaccines				
PRP-OMP[a,b] (Merck & Co, Inc)	PedvaxHIB	PRP conjugated to OMP	2, 4 months	12 – 15 months
PRP-T (sanofi pasteur)	ActHIB	PRP conjugated to tetanus toxoid	2, 4, 6 months	12 – 15 months
PRP-T (GlaxoSmithKline)	Hiberix	PRP conjugated to tetanus toxoid	Not licensed	12 – 15 months
Combination vaccines				
PRP-OMP-HepB[a,b] (Merck & Co, Inc)	Comvax	PRP-OMP + hepatitis B vaccine	2, 4 months	12 – 15 months
DTaP-IPV/PRP-T (sanofi pasteur)	Pentacel	DTaP-IPV + PRP-T	2, 4, 6 months	12 – 15 months
MenCY/PRP-T[c] (GlaxoSmithKline)	MenHibRix	MenCY + PRP-T	2, 4, 6 months	12 – 15 months

*Adapted from Red Book 2012 Report of the Committee on Infectious Diseases

This table will be included in the statement and lists the current licensed and available Hib vaccines. Hiberix®, Comvax®, Pentacel®, and MenHibRix® were licensed since the 1993 Hib statement. All are licensed for the primary series except for Hiberix®, which is licensed only as a booster dose. Footnotes for Table 1 are as follows:

a. If a PRP-OMP vaccine is not administered as both doses in the primary series or there is uncertainty about which products were previously administered, a third dose of Hib conjugate vaccine is needed to complete the primary series.
b. Preferred for American Indian/Alaska Native children
c. Recommendations for the MenCY component of MenHIbRix can be found at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6203a3.htm?s_cid=mm6203a3_w

NOTE: Use of brand names in Table 1 is not meant to preclude the use of other licensed Hib vaccines with similar active components.

Recommended Schedule/ Dosage Intervals are as follows:

- The ACIP recommends Hib vaccine for all children through 5 years of age. In addition, children less than 24 months of age who develop invasive Hib disease should be considered unvaccinated and receive Hib vaccine doses according to the age-appropriate schedule for unimmunized children. Vaccination or re-vaccination of children <24 months of age who develop invasive Hib disease should begin 4 weeks after disease.
- If Hib vaccination is not initiated by 6 months of age, use the following schedule shown in Table 3:

Table 3. Catch up Vaccination Schedule

Age at first vaccination	Primary series	Booster
7 11 months	2 doses, at least 4 weeks apart	Age 12 15 months at least 8 weeks after the second dose*
12 14 months	2 doses, at least 8 weeks apart	N/A
15 59 months	1 dose	N/A

*A booster dose at 12 15 months of age is only necessary if 2 or 3 pr mary doses (depending on vaccine type used) were administered before age 12 months.

This catch-up schedule is corrected from the earlier resolution to add a footnote for the booster for the 7 through 11 month old children, which indicates that a booster dose at 12 through 15 months of age is only necessary if 2 or 3 primary doses, depending on the vaccine type used, were administered before age 12 months. The other correction is among 12 through 14 month old children, where the primary series indicates 2 doses at least 8 weeks apart. The previous resolution indicated 1 dose in the primary series and 1 dose in the booster column.

Table 4 is the guidance for patients at increased risk for invasive disease, which is broken down by age and high-risk group. Again, this guidance is consistent with other published guidance. No changes were made other than making the cutoff age 18. The footnotes for Table 4 are the same as in the statement and are as follows:

*Patients with functional or anatomic asplenia, HIV infection, immunoglobulin deficiency including Immunoglobulin G2 subclass deficiency, or early component complement deficiency, recipients of a hematopoietic stem cell transplant (HSCT), and those receiving chemotherapy for malignant neoplasms.
† Some experts suggest conducting serologic testing for these patients.
‡Some experts suggest vaccination at least 14 days before the procedure; some experts suggest administering a dose prior to elective splenectomy regardless of prior vaccination history.
§ Patients who have received a primary series and booster dose or at least 1 dose of Hib vaccine after 14 months of age are considered immunized.

The wording for the recommended dosage is unchanged and refers to the product package inserts. Wording for precautions and contraindications provides the link, which is: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833

The statement regarding update based on published documents indicates that if an ACIP recommendation regarding Hib vaccination is published within 12 months following this resolution, the relevant language above (except in the eligible groups sections) will be replaced with the language in the recommendation and incorporated by reference to the publication URL.

Discussion Points

Dr. Karron requested clarification regarding whether HibMenCY vaccine could be used interchangeably in all children under VFC if the language was approved, or if it could only be used for high risk children under VFC.

Dr. Santoli responded that by including HibMenCY in this particularly resolution, it could be used in all VFC-eligible children.

Dr. Campos-Outcalt pointed out that they were treading new ground, and that last time they voted not to make this vaccine a B level recommendation. However, it seemed to him that by putting it in the VFC, they were making it a B level recommendation in essence.

Dr. Keitel thought it would actually be an A recommendation if it could be used interchangeably for routine immunization in infants.

Dr. Campos-Outcalt maintained that it would be a B because it would be a clinical option. A Category A would mean that ACIP routinely recommends the vaccine. By placing it in the VFC for the VFC population, someone could choose to use it.

Dr. Keitel said she would interpret it as a Category A because several other vaccines are included that can be used interchangeably. The language is that all of these particular products can be used interchangeably for otherwise healthy infants, which would be a Category A recommendation.

Dr. Sawyer inquired as to why including the combination vaccine in the VFC resolution now made it available to everyone; whereas, during the last ACIP vote it did not. It was unclear to him what had changed.

Dr. Santoli clarified that the last vote regarded the meningococcal resolution, and there it was defined as a vaccine indicated for high risk children. In the Hib resolution, it was included in the table of all of the Hib-containing vaccines that can be used in children to prevent *Haemophilus Influenza*.

Dr. Temte noted that because of the previous resolution, there was federal purchase of HibMenCY for distribution to recipients of VFC vaccine. He thought the Hib resolution simply said that HibMenCY could be used for a dose of Hib vaccine should it be desired by the clinician. This basically would codify and unify the use, but did not change the underlying recommendation that had already been put forth as a Category B recommendation for the MenCY component.

Dr. Duchin expressed confusion. It seemed to him that if ACIP did not recommend the use of the MenCY-containing vaccine, and several other non-MenCY-containing vaccines, it was not clear why they would include it as an option for use when ACIP did not recommend its use.

Dr. Bennett also expressed confusion, because this seemed to create a scenario in which children who are covered by VFC would potentially receive this vaccine as a replacement for other Hib-containing vaccines, but children who are privately covered may not because it is not a routine recommendation. That is, because it is not a Category A level recommendation, it potentially would not be covered by private insurers.

Dr. Briere clarified that HibMenCY could be used as a Hib vaccine in the private sector, because it can be used for Hib protection.

Ms. Rosenbaum thought they were creating a lot of uncertainty about the coverage standard and whether this would make it into the coverage standard that derived from what ACIP recommends. If they wanted this vaccine to be routinely available as an approach to coverage as opposed to the prior approach to coverage, they would have to make that clear. Otherwise, VFC would adopt the coverage policy but private insurers potentially would not because it is not clear what ACIP is doing.

Dr. Campos-Outcalt said he could understand this better if there was a shortage of Hib vaccines and they needed an alternative for Hib. Short of that, it seems like they had done before what they needed to do at this point, which was to include the vaccine in VFC for those for whom ACIP recommended it. By approving this resolution, they would make the vaccine available for those for whom ACIP did not recommend the vaccine. Given that there was no shortage, he did not see a need to do this. He was leaning toward not favoring the resolution for those two reasons.

Dr. Loehr (AAFP) indicated that as a VFC provider, he could currently acquire HibMenCY for his high risk patients. If the resolution passed, he would be able to obtain HibMenCY for his regular patients, which would not be appropriate. He suggested that ACIP state that it could be used and would count toward a Hib vaccine in the regular schedule, but he did not think they should recommend this as a routine part of the process.

Dr. Wharton clarified that this resolution was not intended to specify a preference for the product. The intent was for providers to elect to use HibMenCY vaccine as a Hib vaccine in accordance with its FDA label indications if they choose to do so with their private and VFC patients.

Dr. Temte inquired as to how CDC would approach the federal purchase plan for this vaccine as a component within the full supply in the VFC.

Dr. Wharton replied that the terms of the contract would be a programmatic decision of the Procurement and Grants Office (PGO).

Dr. Whitley-Williams (NMA) pointed out that this raised other questions on the part of providers for infants who receive a HibMenCY vaccine, such as what this means in terms of protection if these infants travel, how long protection lasts, et cetera. Some of these questions were addressed in the guidelines in the most recent *MMWR*, but in the practice setting, in terms of making a decision about which vaccine to use, this creates many questions. If an infant received four doses and was traveling, a practitioner would question whether this is protective,

which it is not. She did not think the resolution spelled this out clearly enough, and that this was just one example of a number of questions that this raised.

Dr. Briere added that this vaccine would not be used for travel to meningitis belt countries, and that all of this was spelled out in the recently updated meningococcal statement.

Dr. Netoskie (AHIP) indicated that HibMenCY is generally covered as part of the routine options for private pay for high risk patients.

On behalf of immunization programs, Dr. Moore (AIM) echoed the confusion about how this resolution would be implemented in practice. The concern for immunization programs regards whether providers would force a move to a lot more purchase of this vaccine. Typically, providers prefer to carry just one kind or streamline the number of types of vaccine they carry in their refrigerators for simplicity in taking care of their patients. This could become a de facto routine practice because practitioners want to stay consistent and not pick and choose.

Dr. Brady (AAP) pointed out that on the list of other potential combination vaccines, all of the other ones included only products that are routinely recommended; whereas, the menincogoccal CY products are only recommended for special circumstances. Including it with those combination vaccines is likely to create a lot of confusion. Therefore, he wondered whether there could be a second VFC resolution related just to that.

Dr. Santoli clarified that the VFC resolution for meningococcal protection explicitly covers this vaccine for high risk children.

Dr. Campos-Outcalt emphasized that once they added this, it would set in motion a series of events that they would not be able to reverse later. He thought at this point there was too much confusion; it seemed like they were now making this an option for routine vaccine, which they voted not to do; and there were no shortages. Therefore, there did not seem to be any rush to add this as a VFC vaccine. This made him inclined to make a motion not to accept the proposed resolution.

Dr. Englund (PIDS) thought that they were confusing two different things. The table showing current licensed and available vaccines simply showed what was available. However, that did not mean that all available vaccines should be given to all children. She suggested including two tables to solve the problem.

Dr. Keitel thought it was specifically stated that HibMenCY could be used as an alternative Hib vaccine, but that that would drive the use of this vaccine for routine purposes. Perhaps a footnote could be included to state that HibMenCY could be used as an alternative in high risk patients for whom MenCY is recommended.

Reflecting on Dr. Wharton's comment that the intent of the VFC program and this resolution was to allow providers to be able to obtain and administer this combination vaccine to their individual patients, Dr. Sawyer thought the language regarding the combination vaccine currently allowed the provider to use some judgment in deciding to do so. For example, for a family with a child who previously had meningococcal disease, a practitioner might choose to immunize the rest of the family. While vacillating on his own personal opinion about how to vote on this, he wanted to offer for consideration that by not approving the resolution, providers would not be free to use the vaccine in that way.

Dr. Karron expressed confusion about Dr. Sawyer's last point. Practitioners are able to do this already because of the meningococcal recommendations.

Dr. Sawyer clarified that he was talking about immunization of a child who is not high risk, but maybe is in a circumstance in which the practitioner would still choose to vaccinate the child.

Dr. Karron noted that this would potentially create an inequity, because a VFC provider could make that decision for a VFC child in that circumstance; however, a child in that circumstance who has private insurance may not be covered.

Dr. Sawyer pointed out that the opposite inequity would be that the family of the child in that circumstance with private insurance might be able to pay for it out of pocket, while the family of the child under VFC could not.

Dr. Temte requested that Dr. Netoskie comment on the ramifications from the insurance industry for an insured child in this scenario.

Dr. Netoskie (AHIP) responded that he would have to acquire some additional information to answer that question. His feeling was that coverage would apply in most situations, and a lot of systems would not be able to distinguish whether a child has high risk issues linked to vaccine coverage.

Dr. Campos-Outcalt pointed out that Dr. Sawyer's question was the exact one ACIP faced when voting whether to make the recommendation a Category B subject to clinical decision-making under certain circumstances. They voted not to do that and should not reverse that decision now unless they formally wanted to reverse the vote. They were voting it de facto by including it in the VFC.

Ms. Rosenbaum emphasized that there would always be uncertainty in the private sector regardless of what was done on VFC, and that an insurer would elect not to make the vaccine available. If the vaccine is very costly, private insurers may make the decision not to cover it. If ACIP felt strongly that this should be a covered vaccine available under VFC under certain circumstances, when a clinician in his or her judgment decides that it is appropriate because of family history, Ms. Rosenbaum believed strongly that ACIP should be making the same recommendation across the board so that families with qualified health plan coverage in small group or individual markets who have modest incomes and are faced with the high cost of a vaccine will not be in a situation with certainty about whether their providers cannot make the same decisions for them. As a result of health reform, consideration needs to be given to what is clinically appropriate. This is one case in federal law in which the coverage standard is supposed to be aligned with what is clinically appropriate. What is decided on one side should carry over to the other.

Speaking as a physician, if Dr. Loehr (AAFP) decided that he wanted to give HibMenCY, insurance companies and VFC are probably not going to question him. His concern was broadening the use of HibMenCY as a Hib vaccine as opposed to using it only in special circumstances as a Hib vaccine.

Ms. Rosenbaum stressed that there must be a way to word this resolution so that they did not unnecessarily increase costs and use of a product that is not clinically necessary, while making it clear that when a decision is reached that it is appropriate, it should be routinely covered in those situations. What they are really saying is that coverage should follow the clinical decision to use this vaccine in certain cases.

Recalling Dr. Englund's earlier suggestion, Dr. Brady (AAP) inquired as to whether it would be possible to have a table that includes HibMenCY as an available vaccine and a second table that lists only those vaccines that should be approved by VFC for routine use.

Dr. Santoli indicated that if ACIP desired a different table in the resolution, CDC could create one to include the products the committee wanted in the table.

Dr. Temte asked whether there was any precedent for including a vaccine in the VFC and then removing it at a later date versus a vaccine that is not approved, but is added later.

Dr. Wharton replied that she did not know of a vaccine being removed from the VFC, but the resolution can be changed at any time. She also pointed out that inclusion in the VFC requires a federal contract.

Dr. Harriman expressed confusion regarding concerns about inclusion in the VFC. HibMenCY is known to be a safe and effective vaccine, and to offer infants additional protection against meningococcal serogroups C and Y disease. It was unclear whether they wanted to limit the vaccine's use to only these few high risk children when the vaccine certainly could benefit other children as well.

Dr. Campos-Outcalt stressed that this was exactly the decision ACIP made last time—not to make this a B recommendation.

Dr. Harrison viewed these as separate issues and did not fully understand the conflict. Based on the epidemiology of meningococcal disease, ACIP voted to only recommend the vaccine for high risk infants. Now they were saying the vaccine would be of viable use for coverage for situations in which a clinician might select this vaccine, such as the scenario suggested by Dr. Sawyer.

Ms. Brewer (ANA) emphasized that ACIP decided that this vaccine could not be used routinely for meningococcal prevention, but now they were discussing Hib prevention. She sensed that there was concern that the committee would be creating a loophole for use of this vaccine routinely that they did not intend to do with the meningococcal recommendation. She wondered whether they made any mention of use of this vaccine for routine use for Hib prevention in the statement by including the table in the new Hib statement. If the language was in the statement that the vaccine was not for use for routine Hib prevention, that should close the loophole for people trying to subvert the system.

Dr. Briere responded that HibMenCY can be used for routine Hib vaccination. The infant meningococcal statement indicates that as well. The table includes a footnote that references the infant meningococcal statement that indicates that it can be used for meningococcal coverage in high risk children.

Ms. Rosenbaum wondered whether there was a way to express the recommendation to indicate that it meets the testing of "should be covered" and that it is appropriate to substitute with this in certain circumstances such as Dr. Sawyer highlighted.

Dr. Rubin stressed that this is a safe and effective Hib B vaccine, and the meningococcal component is somewhat secondary though offers some added benefit. It was difficult for him to accept that this would not be an acceptable Hib B vaccine.

Dr. Temte pointed out that how much of the vaccine flowed into the VFC would depend upon federal purchase. If a decision was made to replace all Hib-containing vaccine with this vaccine that would be one issue, but if there was enough to meet the needs of those who see high risk children, that would be a different issue. Three separate manufacturers are making vaccines, so there is not a risk of having insufficient selection.

Dr. Sawyer clarified that the currently published meningococcal vaccine statement indicates that ACIP does not recommend routine meningococcal vaccine in infants who are not at increased risk. However, the next sentence states, "HibMenCY may be used in any infant for routine vaccination against Hib and will offer some protection against serogroups C and Y meningococcal disease." Thus, they left a loophole in the statement even if that was not the intent.

Dr. Duchin's understanding was that the last sentence was only to acknowledge the fact that HibMenCY is a licensed product, not that it is a recommended product by the ACIP for that indication.

Ms. Brewer (ANA) stressed that this was her point. If they were discussing when to use the vaccine as appropriate, it belonged in the statement not the VFC resolution. If it appeared in the statement someplace, it would not be incorrect to order this vaccine for their patients.

Dr. Clark (SME) pointed out that it would set a precedent to have a licensed, safe, effective Hib vaccine not under the VFC resolution. There could be some discussion about the contracting mechanisms, because one could envision a scenario in which contracting would be advantageous to the government for that vaccine. Of course, it also might be disadvantageous.

Dr. Pickering emphasized that ACIP does not GRADE vaccine financing as part of making vaccine recommendations. ACIP decisions are based on the science of the vaccines. If this were a single antigen Hib vaccine, ACIP probably would not be having this discussion. The focus should be on whether this Hib vaccine is safe to give to children, and by FDA licensure it appears to be, and whether having the meningococcal component is detrimental enough not to put this vaccine into the VFC program.

Dr. Campos-Outcalt clarified that last time they voted not to make this a Category B recommendation, but to include it for high risk. He wondered whether they followed that with a VFC resolution to include the vaccine for high risk children.

Dr. Santoli responded that it was included in the meningococcal resolution.

Dr. Campos-Outcalt pointed out that the Hib vaccine that is in HibMenCY is a Hib vaccine on its own without MenCY, so that vaccine is available through the VFC without the MenCY component.

Dr. Rubin noted that it is not licensed for the primary series.

Dr. Briere responded that the component in HibMenCY is Hibrix®, which is only a booster dose.

Dr. Friedland (GSK) clarified that this vaccine is called MenHibrix®, which has Hib and CY meningococcal serogroups combined. It is not available as a monovalent Hib vaccine. The other GSK vaccine, Hibrix®, is a very different vaccine. It happens to have the same PRP component, but it is a separate licensed vaccine. MenHibrix® is not available for use as a Hib vaccine. It is only available as MenHibrix®, the combination vaccine.

Dr. Thomas (GSK) clarified that GSK priced HibCY at the same level as monovalent Hib vaccines at the low $20 per dose range. He appreciated that they were not facing a current shortage of Hib vaccines, but noted that having lived through the last shortage, shortages do not come with a lot of warning. They occur because of bioprocess problems that occur very quickly. Dr. Thomas stressed that he did not intend to make a threat or ultimatum in any way, but GSK has to make decisions about the viability of manufacturing this vaccine. This product was initially developed about 10 years ago for the US market because of the epidemiology at that time, and it will be distributed nowhere else in the world. He fully respected the decisions that ACIP had to make about recommendations related to high risk, and now this difficult discussion about Hib vaccination. However, depending upon the volume of manufacturing that GSK can anticipate, if it is not sustainable economically for the company, they will have to consider that. That is simply the reality of vaccine manufacturing.

Dr. Temte emphasized that there were existing recommendations for use of Hib and meningococcal vaccines as shown on the routine immunization schedule for children from 0 through 18 years of age. Those recommendations are very clear, and most clinicians follow that well. ACIP's purview is to make recommendations based on the safety and efficacy of vaccines that are licensed for use in the civilian population in the US, and not the financing aspects.

Dr. Bennett thought it sounded as though the concern of the committee regarding the inclusion of the vaccine in the VFC was that it would drive the use of this vaccine more than ACIP actually wished to drive use. Rather than including the vaccine in the table of routine products for Hib protection, perhaps they should indicate that it may be used as a substitution in appropriate circumstances.

Dr. Harrison fully agreed that the burden of meningococcal disease was not sufficient to have a routine recommendation for infants; however, for routine use for Hib, the coverage for meningococcal disease would be a downside. That was not his feeling, so he was not quite as concerned as others.

Dr. Bocchini thought since the vaccine was already approved by ACIP for use in children who have a high risk of meningococcal disease, perhaps it could be stated that this vaccine is currently recommended for those children who are at high risk of meningococcal disease, who can also be immunized by Hib at the same time with the HibMenCY vaccine. If it is broken out that way, the VFC recommendation would not really be changed, but it would be clearly identified as a vaccine only for that risk group. ACIP's recommendation for combination vaccines is that they can be used when all components are needed by the patient.

Dr. Keitel pointed out that while ACIP does not formally consider pricing or cost, they are definitely asked to address the cost-effectiveness of vaccines. In view of the comment that there are two monovalent vaccines for primary immunization against Hib that are similarly priced, any cost-effectiveness analysis would look the same. Therefore, the VFC would be getting two for the price of one with the HibMenCY vaccine. In addition, safety is not a concern.

Dr. Harriman agreed with Drs. Harrison and Keitel, and did not see the downside to this resolution.

Dr. Friedland (GSK) stressed that GSK had every intent to market this vaccine and educate practitioners in complete accordance with all of the recommendations and guidances coming out of ACIP.

Ms. Groom (Indian Health Services) agreed with Ms. Brewer's comment that the change needed to be made in the recommendation, not in the VFC table. From the AI/AN point of view, it is printed in the table that the PRP-OMP product is preferred. What Indian Health Services is most concerned with in terms of this vaccine is that providers will focus on "two for the price of one," which for their population could have very serious consequences. While they will continue to educate their providers, they prefer the PRP-OMP formulation and believe that this vaccine should not be used for routine use for Hib in this population.

Dr. Temte said he thought that point was also made very nicely in the statement that ACIP just approved.

Dr. Duchin wondered whether it would be possible to annotate in the VFC statement and the new revised Hib statement that this combination vaccine is appropriate for use in those children who have indications for the meningococcal component, and then reference the meningococcal statement so that there is no confusion that this is being recommended either as a Category B or otherwise implicitly as an option for Hib protection regardless of the risk of meningococcal disease.

Dr. Santoli replied that identical footnotes could be added to the recommendation and the VFC resolution to indicate that.

Dr. Briere suggested that they could add to footnote C, which currently just referenced the infant meningococcal statement by including the words in the document.

Dr. Duchin said that would be acceptable to him, because the vaccine is already available in the VFC program for children who have the indication for meningococcal protection. This would basically be the same language saying that this vaccine can be used for protection of Hib and meningococcal disease if children have indication for protection against both of those according to the recommendations, but not exclusively for Hib.

Dr. Loehr (AAFP) asked how ACIP would feel if all of the other Hib vaccines were replaced by HibMenCY. It is a real possibility that physicians will elect to administer HibMenCY.

Dr. Englund (PIDS) indicated that since their practices are so commonly using combination vaccines, she wondered whether they were making a bigger deal of this than necessary.

Dr. Wharton reiterated that they were talking about participating in the VFC program, which is part of the federal contracting process. They decide what contracts they are going to sign at what price, and there are other terms included in the contracts as well. This is not a wide open process that does not have any parameters around it. They can decide as part of the contracting process how much they are willing to pay, and how much they choose to buy.

Dr. Santoli added that they are typically informed in how much they will purchase by state vaccine spend plans. States are asked to plan for how they will use the product, which helps to determine how much is requested in contract maximums.

Dr. Pickering requested that Dr. Wharton comment on marketing share and that it is not a consideration for ACIP.

Dr. Wharton replied that clearly, it is within the best interest of public health in the US to have a robust vaccine supply with multiple manufacturers in the market. It is difficult to predict what the impact of a single product will have on overall market share. She encouraged ACIP not to make a decision based on that.

Dr. Sawyer made a motion to approve the VFC resolution language as presented, with the proviso that the Hib language is clarified based upon the issues raised. Dr. Bennett seconded the motion.

Dr. Wharton requested clarification regarding whether it was the intent of the motion to restrict use in the VFC program to those children previously identified at high risk.

Dr. Sawyer clarified that his motion was to accept the addition of this vaccine as a Hib vaccine, and that a footnote or comment be included that guides the clinician to the current recommendations for use of meningococcal vaccine. It does not restrict them from using it.

Dr. Wharton confirmed that the intent was to provide guidance about current ACIP recommendations.

Dr. Duchin indicated that this was not consistent with the language he proposed. He thought they should go ahead with Dr. Sawyer's proposal, but his intent was that this vaccine would be used only for those who had indications for the meningococcal component.

Dr. Temte clarified that the motion was that VFC inclusion of the HibMenCY vaccine was for coverage for use as a Hib vaccine, and as part of that the resolution would refer to the ACIP recommendation for both Hib and meningococcal vaccines. Implicit in that, meningococcal vaccines are not recommended for routine use, except for high risk children.

Dr. Clark (SME) thought this seemed very ambiguous. He thought the resolution was that HibMenCY be included in the VFC resolution among other changes. There is already guidance for use in many documents, and they can connect to it. However, changing the guidance for use would be a different discussion.

Dr. Harrison asked for clarity regarding whether the motion was intended to say that they were going to refer to the previously approved ACIP recommendations from the last meeting pertaining to meningococcal disease.

Dr. Santoli responded that this was already in Footnote C, but that it did not indicate that it was limited to that group. She asked whether more language was preferred than what was already included, and if so, she thought it would be helpful to talk out what the language would be. She felt somewhat confused and did not want to misstate the proposed language.

Dr. Sawyer restated the motion, which was to accept this vaccine as a Hib vaccine, and refer to the guidance already in existence for use of Hib and meningococcal vaccines. Footnote C would include the wording from the current meningococcal statement about not recommending the vaccine routinely, including the second sentence which states that it can be used as a Hib vaccine.

Reflecting on the Hib vaccine guidance, Dr. Keitel thought that HibMenCY was an alternative Hib vaccine without any particular prohibition on its use as a primary Hib vaccine. Therefore, this did not seem to solve any of the issues with which they were grappling.

Dr. Harrison wanted to make sure that they avoided somehow discouraging the use of this vaccine for people who want to provide universal, routine coverage for Hib. Meningococcal is a bad disease, so he liked the idea of approving the vaccine for routine use but for educational purposes referring to the meningococcal recommendation.

Dr. Duchin emphasized that during the last meeting, ACIP voted that this vaccine should be used only for the prevention of disease in children at high risk for meningococcal disease, and that was incorporated into the meningococcal statement. Now the same vaccine was being considered under a different cover, and stating that it was okay to use it for Hib. That did not make sense to him, and he thought they needed to refer to their last decision, which was the way in which they intended the vaccine to be used.

As she understood it, Ms. Rosenbaum thought they were saying that when HibMenCY was being given for Hib reasons, it should only be used in the most narrow circumstances. When giving the same vaccine for meningococcal reasons, then it should be given only to high risk children. The issue pertained to donor intent and the clinician's starting point (e.g., the point of view of immunizing against Hib as opposed to immunizing against meningococcal disease). In either case, it was really not a recommendation issue. It was simply a practice management or clinical approaches issue. Also in either case they were saying that the vaccine should be covered, but the decision to use it should be driven by the reason the clinician is giving the vaccination (e.g., child at risk for Hib, or meningococcal, or both).

It seemed to Dr. Duchin that the Hib and meningococcal statements were inconsistent on this point, which was problematic. The Hib statement would be permissive for the use of this vaccine; whereas, the meningococcal statement restricts it to children at high risk.

Dr. Clark (SME) clarified that this vaccine is recommended and is safe, effective, and licensed for routine use in infants at increased risk for meningococcal disease. The Hib statement would say the same thing, that it is among the licensed Hib vaccines. Perhaps they were trying to go too far in a VFC resolution.

Dr. Moore (AIM) pointed out that the general recommendations say that combination vaccines can be used when even one component is necessary. Even though she knew it might cause confusion in offices, that is the general principle that applies.

Regarding Dr. Duchin's concern about inconsistency, Dr. Keitel pointed out that the meningococcal guidelines say that if the subject is at risk for meningococcal, this would be the preferred vaccine; whereas, the Hib recommendations say that any vaccines that have been shown to be safe for prevention of Hib can be used. It is not really inconsistent. She thought they were grappling with another issue.

Dr. Clark (SME) indicated that there is another quadrivalent meningococcal conjugate vaccine under review for the same 2-,4-, 6-month indication, so this probably is a temporary period of time when this vaccine is the only one that can be used.

Dr. Campos-Outcalt added that there is another meningococcal vaccine for 9 months of age and after 12 months of age, and ACIP has not stated a preference for either of the two, but has said that both should not be used routinely. It is getting to be very confusing.

Dr. Jenkins emphasized that if ACIP was experiencing this much confusion making a statement about it, practitioners are not going to be able to figure it out easily. If there is a reason not to have meningococcal vaccine used and counted in that immunization schedule, she thought they should consider that as an issue.

Dr. Temte said he had been in practice for about 20 years, during which he has referred to the ACIP immunization schedule and footnotes enumerable times. He has never gone to VFC resolutions for any guidance whatsoever. He thought they needed to keep the recommendations and the VFC separate.

As the layperson on the group, Ms. Rosenbaum felt that they were talking about two different things. One regarded what vaccines should be available for use. ACIP's recommendations really do drive the coverage rules. The discussion struck her as focusing on what she would call sub-regulatory guidance in terms of what ACIP recommended practices do. She thought what they were saying was that ACIP does not want the combination vaccine to be used in a child who presents for the Hib immunization unless there is also a high risk of meningococcal. However, a high risk child presents meningococcal coverage, ACIP wants the combination vaccine to be used.

Dr. Pickering stated that Dr. Santoli has reminded ACIP many times that the VFC resolution is not the place to make recommendations. Recommendations should be in the statement, and VFC resolution should be a mirror image of those recommendations.

Dr. Bocchini thought Dr. Sawyer's motion solved the problem if the footnote was changed to clearly indicate that the current guidelines for the use of the combination vaccine are based on the meningococcal component.

Dr. Sawyer restated his motion, which was to include the combination vaccine as an acceptable Hib vaccine, and have it on the table, but that an effort be made to refer to the current recommendations guidance for both Hib and meningococcal in the VFC resolution such that it is obvious to people.

Dr. Bocchini requested clarity regarding whether the recommendation language should actually be included in the footnote.

Dr. Sawyer said he was going to stop short of dictating exactly what wording should be included, but the intent was to include an explicit restatement of the guidance plus a referral to the fine details of the guidance.

Dr. Wharton requested clarity regarding whether the intent was for the VFC resolution for this product to be limited to those children who are covered by the meningococcal resolution for this vaccine, or if it was to be included in the VFC resolution with a reference to the current recommendations for use.

Dr. Sawyer replied that the latter was what he was trying to get at so that it would be painfully obvious to the clinician should they have any question about the guidance.

Dr. Jenkins reported that the working group for the high risk schedule is working on a high risk table.

VFC Vote: Hib Vaccine

Dr. Sawyer made a motion to approve the VFC Hib resolution as presented, with the proviso that the footnote include an explicit restatement of the guidance and a referral to the fine details of the current guidance for both Hib and meningococcal coverage, and that the ACIP members have an opportunity to review the exact language so that they could understand how it would guide practitioners regarding meningococcal vaccine. Dr. Bennett seconded the motion. The motion carried with 12 affirmative votes, 3 negative votes, and 0 abstentions. The disposition of the vote was as follows:

12 Favored:	Bennett, Bocchini, Coyne-Beasley, Harriman, Harrison, Karron, Keitel, Rosenbaum, Rubin, Sawyer, Temte, and Vazquez
3 Opposed:	Campos-Outcalt, Duchin, and Jenkins
0 Abstained:	N/A

Proposed Table 1 Footnotes for Inclusion in the Hib VFC Resolution

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

Based on the Hib discussion, changes were made to the footnote for Table 1 and were distributed to ACIP members for review. Some members thought Option #1 was fine as presented, while others thought it contained too many lines and too much information, which might make it confusing. Removal was suggested of the bracketed, underlined segment shown in Option #1. Based on that feedback, Option #2 was created. Members were asked to review, discuss, and vote upon the options written as follows:

Option #1: Footnotes for Table 1:

a. If a PRP-OMP vaccine is not administered as both doses in the primary series or there is uncertainty about which products were previously administered, a third dose of Hib conjugate vaccine is needed to complete the primary series.
b. Preferred for American Indian/Alaska Native children
c. Infants at increased risk for meningococcal disease should be vaccinated with a 4-dose series of Hib-MenCY-TT. These include infants with recognized persistent complement pathway deficiencies and infants who have anatomic or functional asplenia including sickle cell disease. [HibMenCY is only recommended for routine meningococcal vaccination for infants who are at increased risk for meningococcal disease. Hib-MenCY-TT is safe and immunogenic against Hib and N. meningitis serogroups C and Y and may be used in any infant for routine vaccination against Hib and will offer some protection against serogroup C and Y meningococcal disease.] Recommendations for the MenCY component of MenHIbRix can be found at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6203a3.htm?s_cid=mm6203a3_w

Option #2: Footnotes for Table 1:

a. If a PRP-OMP vaccine is not administered as both doses in the primary series or there is uncertainty about which products were previously administered, a third dose of Hib conjugate vaccine is needed to complete the primary series.
b. Preferred for American Indian/Alaska Native children
c. HibMenCY is only recommended for routine meningococcal vaccination for infants who are at increased risk for meningococcal disease. These include infants with recognized persistent complement pathway deficiencies and infants who have anatomic or functional asplenia including sickle cell disease. Recommendations for the MenCY component of MenHIbRix can be found at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6203a3.htm?s_cid=mm6203a3_w

Revised Vote: Hib Vaccine Statement and VFC Resolution

Dr. Rubin made a motion to approve footnote Option 2 for the VFC Hib resolution and the Hib statement as presented. Dr. Bocchini 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, Jenkins, Karron, Keitel, Rosenbaum, Rubin, Sawyer, Temte, and Vazquez
0 Opposed:	N/A
0 Abstained:	N/A

Japanese Encephalitis Vaccine

Joseph A. Bocchini, Jr, MD, Chair
Japanese Encephalitis Vaccine Working Group

Dr. Bocchini reminded everyone that currently, there is one licensed and available Japanese Encephalitis (JE) vaccine in the US, which is an inactivated Vero cell culture-derived JE vaccine (JE-VC). This vaccine is licensed for use in persons ≥17 years of age and older. Thus, there is no JE vaccine currently licensed and available in the US for use in children. Intercell Biomedical, the manufacturer of JE-VC, submitted a BLA for use of JE-VC in children 2 months through 16 years of age and a decision on that BLA is anticipated in May 2013. The same indication for use of JE-VC in children was approved by the European Medicines Agency (EMA) earlier in February 2013. Based on the submission of the BLA, the Japanese Encephalitis Vaccine Working Group was reactivated in October 2012, and has met five times thus far to review safety and immunogenicity data for JE-VC in children. The working group is in the process of developing recommendations for use of JE-VC in children with an expected ACIP vote in June 2013 pending the decision of the FDA prior to that meeting. During this session, background information was presented to ACIP on JE risk and current ACIP recommendations for use of JE vaccine for travelers.

Japanese Encephalitis Vaccine for US Travelers

Marc Fischer, MD, MPH
Arboviral Diseases Branch, Division of Vector-Borne Diseases
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Dr. Fischer presented an overview of JE and JE vaccine for US travelers. JE virus is a mosquito-borne flavivirus that is closely related to dengue and West Nile viruses, and is a leading cause of encephalitis in Asia. JE virus is maintained in an enzootic cycle between mosquitoes and amplifying hosts, primarily pigs and wading birds. The virus is transmitted through the bite of infected mosquitoes. Humans are incidental or dead-end hosts, because they usually do not develop high enough concentrations of JE virus in their bloodstreams to infect feeding mosquitoes. *Culex* mosquitoes are the principal JE virus vectors throughout Asia. *Culex tritaeniorhynchus* is the most important vector for transmission of the virus to humans. *Culex tritaeniorhynchus* is an evening- and nighttime-biting mosquito that feeds most often outdoors. Larvae are found in rice fields and marshes, with the greatest densities occurring from June through November.

Most JE virus infections in humans are asymptomatic, with less than 1% of infected people developing clinical illness. However, when clinical disease does occur, it is often severe. Based on a recent estimate, there are approximately 68,000 JE cases annually. Of these, 20% to 30% of patients die, and 30% to 50% of survivors have significant neurologic, cognitive, or behavioral sequelae. There is no specific antiviral therapy. Treatment consists of supportive care. JE occurs primarily in rural agricultural areas. Transmission is often associated with rice production and flood irrigation. However, in some areas of Asia, these ecologic conditions may occur near urban areas. In most endemic areas, JE is primarily a disease of children, with annual incidences of 5 to 50 cases per 100,000 children. Because of the high asymptomatic

infection rate, many adults in endemic areas have protective immunity. However, because travelers from non-endemic countries usually do not have JE virus antibodies, travel-associated JE can occur among persons of any age. In the most temperate areas of Asia, JE virus transmission is seasonal and human disease usually peaks in summer and fall, sometimes with large outbreaks. In the subtropics and tropics, transmission patterns vary and human disease often peaks during the rainy season, but may occur sporadically or year round. JE occurs throughout most of Asia and parts of the Western Pacific. Local transmission of JE virus has not been identified in Europe, Africa, or the Americas. However, more than 3 billion people live in JE-endemic countries.

Several JE vaccines are available in Asia, and vaccination has been expanding in recent years. JE vaccine programs vary in endemic Asian countries. China, India, Japan, South Korea, Nepal, Sri Lanka, Taiwan, Thailand, and Vietnam have comprehensive JE vaccine programs. Cambodia, Laos, Malaysia, and North Korea have partial programs. Bangladesh, Bhutan, Brunei, Indonesia, Myanmar, Papua New Guinea, Philippines, and Timor Leste have no JE vaccination programs. However, it is hoped that this will change in the next few years.

For most travelers to Asia, the risk for JE is very low, but varies based on destination, duration, season, and activities. Over 300 JE cases were reported among US military personnel during the Vietnam and Korean Wars. From 1973 through 2012, there were 65 cases of travel-associated JE among persons from non-endemic areas reported in literature. This includes reports that are in press or submitted for publication. Of these cases, 6 (9%) were in children under 17 years of age. During this timeframe, there was a median of 1 case reported per year, with a range of 0 to 6 annual cases. About half of all JE-associated cases were male, and the distribution among males and females was similar among children and adults. The median age of all cases was 34 years, and patients ranged from 1 to 91 years of age. Of the adult cases, 40% were 20 to 39 years old. Among the 6 pediatric cases, the median age was 9 years with a range from 1 to 11 years.

The month of disease onset is known for 47 of the 65 travel-associated cases. Although the number of cases peaked from June through August, cases occurred throughout the year. Overall, 20% of the reported travel-associated cases were fatal. Of the survivors, 43% experienced neurologic, cognitive, or behavioral sequelae and 23% had no sequelae. Among the 6 pediatric cases, 2 were fatal and the 3 survivors with known outcomes had sequelae at last follow-up. Reported travel-associated cases were likely acquired in 13 different countries. The largest numbers of cases were among people traveling to Thailand followed by China, Indonesia, and the Philippines. This distribution likely reflects the numbers of travelers to these countries, as well as the risk of exposure in the countries themselves. Travel-associated cases occurred among citizens from 17 different countries, with 19 of the cases being US citizens, including 3 of the children.

Of the travel-associated cases, 62% occurred among tourists. This includes at least 6 people who were returning to their country of origin to visit friends or relatives and 2 students who were studying abroad. Of the cases, 18% were expatriates living in Asia and 9% were soldiers. Type of travel was unknown for another 11%. None of the cases were reported to have received JE vaccine. Of the 65 travel-associated cases, the itineraries were known for 47 cases. The range of travel for these 47 cases was from 10 days to 34 years. Of these cases, 30 (64%) were traveling for a month or longer. Of the 17 shorter-term travelers, 13 (27%) had a trip duration of 2 to 4 weeks and 4 (8%) were traveling for 10 days to 2 weeks. Among the shorter-term travelers, 4 (24%) had known extensive rural exposures, 10 (59%) took shorter trips to rural

areas, 3 (18%) stayed primarily in coastal areas, and no cases were reported among short-term travelers who visited only urban areas.

There are several similarities in the epidemiology of JE among travelers compared to JE in resident populations. Both are associated primarily with rural exposures in endemic areas. JE disease in travelers and in resident populations both result in high case fatality rates and substantial sequelae among survivors. However, there are several important differences. In most endemic areas, JE is primarily a disease of children. In contrast, most travel-associated JE occurs in adults and reflects the age distribution of exposed travelers. Cases among travelers have less seasonal variation, likely because there are more travelers to tropical areas where transmission may occur year round. Travel-associated cases also often occur in countries where there are few recognized cases due to poor surveillance or routine vaccination. The incidence of JE among travelers is generally much lower than resident populations, but the risk does depend upon the traveler's itinerary and exposures.

There are several important limitations of using travel-associated JE cases to estimate JE risk for travelers. First, the numerator of travel-associated cases is incomplete and may not be representative of all cases. There may be published cases that are not identified, and there are almost certainly cases that are not diagnosed, reported, or published. Travel details are missing for about a quarter of the known cases, especially those that occurred prior to 1992. The reported cases that are known may be clinically or epidemiologically different from those that are not reported. It is also difficult to estimate the risk of travel-associated JE because the denominators are unclear or unknown. For example, it is difficult to estimate the total numbers of travelers to Asia, the proportion of those travelers who may have longer-term or higher risk itineraries, and the proportion of travelers who are not at risk because they are immunized.

There is some information regarding the proportion of those travelers who may have longer-term or higher risk itineraries, and the proportion of travelers who are not at risk because they are immunized from a survey of US travelers to JE-endemic areas in 2007. Almost 1700 US travelers boarding direct flights to Asia were surveyed. Of those, 25% reported higher JE risk itineraries, including 20% who said they planned to spend 1 month or more in Asia and 5% who planned to spend less than 1 month but were going to spend the majority of time in rural areas. Among high risk travelers, 11% reported receiving JE vaccine, while only 2% of lower risk travelers reported receiving JE vaccine [Duffy, *J Travel Med*, In press].

Despite these limitations, an attempt can be made to estimate the incidence of JE for travelers to Asia in two different ways. First, extrapolation can be made from the incidence of disease in unimmunized children in endemic areas and assumed that the risk is equally distributed throughout the year. Using those estimates, the overall risk for JE for travelers may be as high as 1 to 10 cases per million travelers per week. As we have seen, seasonality varies by location, and the risk may be higher or lower depending upon the destination and the time of year of travel. In addition, most travelers do not have itineraries or exposures that put them at risk similar to the resident populations. Over the past 40 years, only 19 cases of JE have been reported among US travelers to Asia. In 2004, there were an estimated 5.5 million entries of US travelers into JE-endemic countries. Using these figures, for all US travelers to Asia the estimated overall risk would be less than 1 case per million trips to Asia.

After reviewing the relevant data, the working group concluded that the overall risk of JE for most travelers to Asia is very low but that the risk varies based on destination, duration, season, and activities. Prolonged travel in rural areas with active JE virus transmission may confer similar risk as that for susceptible resident populations. Shorter term travelers may still be at risk if their itinerary includes outdoor or nighttime exposure in rural areas during periods of active transmission. Short-term travel restricted to major urban areas confers minimal risk for JE.

Two JE vaccines are licensed in the US. The inactivated mouse brain-derived JE vaccine (JE-MB) was marketed with the trade name JE-VAX®. It was manufactured in Japan by Biken and was distributed in the US by sanofi pasteur, but is no longer produced or available. The inactivated Vero cell culture-derived JE vaccine (JE-VC) is marketed under the trade name IXIARO®. It is manufactured in Scotland by Intercell Biomedical and is distributed in the US private market by Novartis. This is the only JE vaccine currently licensed and available in the US.

The JE-MB vaccine was first developed and manufactured in Japan in the 1940s and 1950s. Beginning in the 1960s and 1970s, this type of vaccine was used to control JE in several endemic countries, such as Japan, Taiwan, South Korea, and Thailand. Efficacy of the mouse brain-derived JE vaccine was demonstrated in a randomized controlled trial in over 65,000 children in Thailand in 1984 through 1986. Study participants were randomized to receive 2 doses of JE vaccine or tetanus toxoid. After two years, the vaccine had an efficacy of 91%. In 1992, formulation of this vaccine was licensed in the US for use in people 1 year of age and older. In the 1990s, rare neurologic and hypersensitivity reactions were described. In 2006, Biken discontinued production and all remaining doses expired in 2011.

The JE-VC vaccine was licensed for use in adults in the US, Europe, and Australia in 2009. ACIP recommendations for adults 17 years of age and older were approved in June 2009, and booster dose recommendations were approved in February 2011. There are no efficacy data for JE-VC. The availability of several effective JE vaccines in Asia made a randomized controlled efficacy trial impractical and unethical. However, JE virus plaque reduction neutralization test (PRNT) titer of 10 or greater is the established immunologic correlate of protection [Hombach, *Vaccine*, 2005; Markoff, *Vaccine*, 2000]. JE-VC was licensed based on its ability to induce neutralizing antibodies in a non-inferiority comparison to JE-MB. Safety evaluations were also performed in approximately 5000 adults.

JE-VC is a formalin inactivated vaccine derived from the attenuated SA_{14}-14-2 JE virus strain propagated in Vero cells. The final liquid preparation contains aluminum hydroxide as an adjuvant. Unlike the mouse brain-derived vaccine, JE-VC does not contain gelatin or thimerosal. The primary immunization series consists of 2 doses administered intramuscularly at 0 and 28 days.

A pivotal non-inferiority study for licensure of JE-VC compared 2 doses of JE-VC to 3 doses of JE-MB among adults in the US, Austria, and Germany. The primary outcome measure was the proportion of vaccinees who developed JE virus neutralizing antibodies based on 50% plaque reduction neutralization ($PRNT_{50}$). The immunogenicity analysis was performed on 735 subjects who met all protocol criteria, including having no JE virus neutralizing antibody prior to vaccination. A safety analysis was performed on 863 subjects who received at least 1 dose of the vaccine. Of JE-VC recipients, 98% developed a neutralizing antibody titer of 10 or greater compared to 95% of JE-MB recipients. This met the study criteria for non-inferiority. The GMT was 245 among recipients of JE-VC compared to 102 among recipients of JE-MB. In the same

study, severe pain or tenderness at the injection site was uncommon and occurred in less than 2% of the recipients of either vaccine. However, severe redness or swelling at the injection site was significantly less common among recipients of the Vero cell-derived vaccine. The frequency of systemic adverse events was similar between the two groups [Tauber, *Lancet,* 2007].

A pivotal safety study compared 1993 subjects who received 2 doses of JE-VC to 657 subjects who received 2 doses of a placebo adjuvant composed of phosphate buffered saline and aluminum hydroxide. Adverse events were monitored for 56 days following the first dose. The proportion of vaccinees who reported any adverse events, medically attended adverse events, serious adverse events, or an adverse event that resulted in termination from the study were similar between the two groups. None of the serious adverse events in the JE-VC recipients were considered related to vaccination. Among the 12 subjects who terminated the study due to adverse events, 2 of the events were classified as severe, including 1 case of gastroenteritis and 1 rash. Eight of the adverse events leading to termination were considered possibly related to the study vaccine, including 2 subjects with headaches, and 1 each with influenza-like illness, injection site pain, nausea, fatigue, rash, and allergic dermatitis [Tauber, *J Infect Dis*, 2008].

When JE-VC was first licensed in 2009, the need for and timing of a booster dose was unknown. Since that time, three studies have been published evaluating the duration of protection after JE-VC primary series and response to a booster dose. Three studies evaluated duration of JE-VC seroprotection*†‡. Of the 495 total participants in these three studies, between 17% and 42% had no detectable neutralizing antibodies at 12 to 15 months after receiving the 2-dose primary series. In two of the studies, subjects received booster doses at 11-23 months after the primary series†‡. Of 238 subjects total, all were seroprotected at 1 month after booster, and 98% remained protected at 12 months after booster [*Schuller. Vaccine 2008*; †Dubischar-Kastner. Vaccine 2010; ‡Eder. Vaccine 2011]. A response to the booster dose administered more than 2 years after the primary series has not been studied, and there are no data on the need for and timing of subsequent booster doses.

As noted, the initial clinical trials for JE-VC were conducted in approximately 5000 adults. However, since licensure in 2009, several hundred thousand doses total have been distributed worldwide, with over 300,000 doses distributed in the US alone. To date, no important safety concerns have been identified in passive post-licensure surveillance [Schuller, *Vaccine*, 2011].

In summary, JE-VC is the only JE vaccine licensed and available in the US. It was licensed in 2009 for use in adults based on non-inferiority comparison to a licensed vaccine and an established serologic correlate of protection. JE-VC showed a good immunogenicity and reactogenicity profile in these approximately 5000 adults in randomized controlled clinical trials. In addition, no safety concerns have been identified in post-licensure surveillance to date. The vaccine is administered in a 2-dose primary series, and costs approximately $200 per dose.

Recommendations regarding the use of JE vaccines for travelers must weigh the risk of travel-associated JE with the benefits and potential risks of JE vaccine. The overall risk for travelers to Asia is very low but risk varies based on location, duration, season, and activities. JE is a severe disease with substantial morbidity and mortality, and there is no specific treatment. A safe and effective vaccine is available; however, the vaccine is relatively expensive and the possibility of rare serious adverse events cannot be excluded. Because humans are not amplifying hosts, JE vaccine protects the person who receives the vaccine, but does not prevent importation or spread of JE virus.

Given these considerations, in June 2009, ACIP approved the following recommendations for the prevention of JE among travelers [CDC, *MMWR,* 2010]:

1. Travelers to JE-endemic countries should be advised of the risks of JE disease and the importance of measures to reduce mosquito bites
2. JE vaccine is recommended for travelers who plan to spend a month or longer in endemic areas during the JE virus transmission season
3. JE vaccine should be considered for short-term travelers to endemic areas if they will travel outside of an urban area and their activities will increase the risk of JE virus exposure
4. JE vaccine is not recommended for short-term travelers whose visit will be restricted to urban areas or times outside of a well-defined JE virus transmission season

In February 2011, ACIP approved the following recommendations for a booster dose of JE-VC [CDC, *MMWR*, 2011]:

1. If ≥1 year since the primary series, a booster dose may be given prior to potential JE virus exposure
2. Data on the need for and timing of additional booster doses are not available

With regard to the status of JE vaccine for children, no JE vaccine is licensed and available in the US for use in children under 17 years of age. JE-VC has been evaluated in three pediatric clinical trials, including two in endemic areas and one in travelers from non-endemic countries. In July 2012, Intercell submitted a BLA amendment to FDA for use of JE-VC in children aged 2 months through 16 years. The action due date for the BLA amendment is May 2013. Pediatric indications were approved by the EMA in February 2013. During the June 2013 ACIP meeting, the Japanese Encephalitis Vaccine Working Group plans to present JE-VC pediatric clinical trial data that was recently submitted for licensure, and to present and vote on proposed recommendations and evidence-based ratings for the use of JE-VC in children.

Discussion Points

Dr. Keitel inquired as to whether Dr. Fischer had information on the number of travelers in the pediatric age group to the areas at risk and their duration of travel.

Dr. Fischer replied that he was not aware of any data that specifically breaks down the travelers by age. It is known that when the mouse brain-derived vaccine was licensed for use in children over 1 year of age and adults, an estimated 3500 doses of vaccine were used for pediatric use. That is a very rough estimate and there are no data specifically from the travel sites of how may pediatric travelers there are to Asia.

Dr. Turner (ACHA) reported that he has a network of college health services that contribute de-identified clinical data to a central network, and over 2 years from 21 schools representing 671,000 students, 415 doses of the vaccine were given. Since it is a 2-dose series, he assumed that was about 200 students total out of 671,000 who traveled abroad and received the vaccine. It is a tiny percentage, and pediatrics would be a fraction of that.

Dr. Temte indicated that the resources for cost-effectiveness studies are limited. This is an uncommon vaccine that is not universally recommended, it is an uncommonly administered vaccine, and it is unlikely to be covered by insurance policies or the VFC. With those issues in mind, he recalled that the agreement was that no formal cost-effectiveness study would be conducted for this vaccine.

Dr. Fischer added that when the recommendations were approved, the same rationale was given. While very rough estimates can be made of risks for travelers and numbers of travelers who will need this vaccine, the proportion of travelers are in the higher risk group for whom ACIP recommendations would be in place, or what proportion of travelers are immunized. This makes it very difficult to come up with cost-effectiveness estimates. As Dr. Temte noted, this vaccine is not routinely covered under insurance, but is a travel vaccine that is usually paid out-of-pocket.

Dr. Pickering asked Dr. Fischer to comment on when the BLA was filed, so that they would have some idea about whether it would be licensed before the next ACIP meeting.

Dr. Fischer responded that the BLA was filed in July 2012, and some changes were made to it at the end of 2012. However, the action due date did not change from May 2013.

Dr. Duchin wondered about people who received one booster dose, but who make subsequent trips years after the first booster, and whether there were any concerns about safety with regard to booster doses.

Dr. Fischer replied that for the mouse brain-derived vaccine, there was never a recommendation for more than one booster dose and there were never any data to support that. That is currently the same for the JE-VC vaccine. There are some modeling data to suggest that neutralizing antibody data should last for several years following a booster dose, but there are not actual hard data at this point, so no recommendations can really be made regarding the need for subsequent booster doses. Based on studies of subjects who have received multiple doses, there is no reason to believe there would be safety issues for subsequent doses.

Dr. Keitel asked whether anything was known about the practice of immunization of children in endemic areas in terms of the recommendations for booster and / or estimates for duration of protection.

Dr. Fischer indicated that there are several vaccines that were developed in different countries in Asia, so the recommendations vary based on those vaccines. The most commonly used vaccine is a live attenuated vaccine made in China. Some countries use a 1-dose regimen and some use a 2-dose regimen. The studies available suggest that efficacy lasts for at least 5 years.

Dr. Whitley-Williams (NMA) wondered whether there were any data regarding simultaneous administration with some of the more common childhood vaccinations, understanding that by 2 years of age hopefully most children in this country would have completed their primary series and even booster doses.

Dr. Fischer said he was not aware of any data on concomitant use of this vaccine with routine pediatric immunizations. For adults, there was a study that assessed the use of the vaccine in adults who received Hepatitis A, and no interference or safety issues were observed.

Pertussis Vaccines

Introduction

Mark Sawyer, MD
Chair, Pertussis Vaccine Working Group

Dr. Sawyer reminded everyone that the terms of reference under which the Pertussis Working Group is currently constituted are as follows:

- ❑ Review existing statements on infants and young children (1997), adolescents (2006), adults (2006), and pregnant and postpartum women and their infants (2008) and consolidate these into a single statement.

- ❑ Review new data on Tdap including:
  - ➢ Effectiveness of ACIP recommendations
  - ➢ Interval between Td booster and Tdap
  - ➢ Use of Tdap in adults ages 65 years and older
  - ➢ Pregnant and breastfeeding women
    - Use of Tdap
    - Cocooning strategies
  - ➢ Vaccinated HCP and need for post-exposure prophylaxis
  - ➢ Tdap revaccination
    - Pregnant Women

- ❑ Review updated epidemiology of tetanus and diphtheria

The policy regarding repeat Tdap vaccination during pregnancy was scheduled to be published in the *MMWR* on February 22, 2013 titled, "Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis (Tdap) Vaccine in Pregnant Women—Advisory Committee on Immunization Practices (ACIP), 2012."

Topics to be covered during this session included the following:

- ❑ Update on the immunization safety plan for Tdap use in pregnant women

- ❑ Pertussis in the US and Tdap revaccination
  - → Update on epidemiology of pertussis
  - → Tdap effectiveness
  - → Antibody persistence following a single Tdap
  - → Safety and immunogenicity after a second Tdap
  - → Framework for a decision and cost effectiveness analysis for Tdap revaccination

In terms of licensure and composition, there are currently two licensed Tdap products in the US (e.g., Adacel® by sanofi pasteur and Boostrix® by GSK). These are recommended and approved by FDA beginning at 10 or 11 years of age and up. One vaccine has no upper age limit (Boostrix®), while the other is currently licensed through age 64 (Adacel®). These are combined vaccines with diphtheria and tetanus toxoid, which to some extent limits the ability to use them repeatedly at short intervals. Regarding ACIP recommendations, a single Tdap dose should be administered beginning routinely in adolescents aged 11 through 18 years, with a preference at 11 or 12 years of age. All adults should receive at least one dose of vaccine at age 19 years and older. Further guidance will be forthcoming on the timing of revaccination in persons who have received Tdap previously. Pregnant women should receive a Tdap vaccination with each pregnancy.

Considerations of the working group as they have dealt with the topic of Tdap revaccination of the general population include the following:

- ❑ Current Tdap policy and objectives
- ❑ Epidemiology of pertussis and state of the vaccination program
- ❑ Summary of Tdap vaccine performance
    - Antibody persistence
    - Effectiveness/duration of protection
    - Revaccination
        - Safety
        - Immunogenicity
- ❑ Revaccination options
    - Framework for decision and cost-effectiveness analysis
- ❑ Programmatic feasibility and acceptability

The next steps for the working group are to bring the topic of revaccination back to ACIP in June 2013 with complete decision and cost-effectiveness analyses, apply the GRADE process to the data that the working group has begun to evaluate, and draft updated DTaP and Tdap statements as part of that process.

Update on Immunization Safety Monitoring:
Tdap Administered to Pregnant Women

Frank DeStefano, MD, MPH
Immunization Safety Office
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention

Dr. DeStefano presented an overview of Immunization Safety Office (ISO) post-licensure safety monitoring activities, and ISO monitoring of safety of Tdap administered during pregnancy. The mission of the ISO is to assess the safety of vaccines administered to children, adolescents, and adults in the US. ISO's comprehensive approach to vaccine safety includes surveillance to detect possible adverse events following vaccination in a timely way; investigation of possible adverse events following vaccination to determine causality and risk factors; development of strategies for prevention of adverse events following vaccination; vaccine safety research; and timely communication and education to partners and the public. ISO works with other federal agencies and other organizations to further its vaccine safety mission.

Basically, ISO has three main projects in its office that are designed to evaluate various stages of vaccine safety:

- The Vaccine Adverse Event Reporting System (VAERS), which CDC manages collaboratively with FDA, is the US frontline spontaneous reporting system to detect potential vaccine safety problems. The main purpose of this system is to detect potential vaccine safety problems, sometimes referred to as signals.
- The Vaccine Safety Datalink (VSD), which is a collaborative project that CDC has with several healthcare organizations. This system provides a large linked database system that is used for active surveillance and research.
- The Clinical Immunization Safety Assessment (CISA) Project is a CDC collaboration with several academic centers that provide expert collaboration to conduct individual clinical vaccine safety assessments and clinical research.

More specifically, VAERS is a spontaneous reporting system for adverse events after vaccination. Its main strengths are that it is national and thus can protect potential problems in the most timely fashion probably of the systems in place. It accepts reports from anyone (e.g., providers, patients, parents of patients, manufacturers, and others). This system also makes data available to the public. As a voluntary reporting system, VAERS is subject to the limitations of such systems, including under-reporting, biased reporting, and inconsistent data quality and completeness. In general, for these various reasons, the system cannot be used to assess causality. It serves primarily as an early warning system to indicate that there may be a potential problem that requires further investigation. In addition, pregnancy is inconsistently reported. That is, the reporting form does not include a specific field to indicate that a woman was pregnant at the time of vaccination.

The VSD is a collaboration between CDC and 9 health plans. It has data on over 9 million persons per year, and thus provides near real time surveillance data on these individuals. This is a large linked database system that links vaccination data to health outcomes from all medical care settings (e.g., outpatient, emergency department, inpatient), and it also provides demographic data. The strengths of the VSD are that all medical encounters are available, each plan has vaccine registry data that provides complete and detailed information on individual vaccinations administered, rates can be calculated since a demonstrator population is available, and medical records are available that allow for more detailed studies and validation of results. Specific to pregnancy, the VSD has a tested algorithm to identify women who are pregnant who may have received vaccinations during pregnancy. The annual birth cohort is approximately 100,000. The VSD does have some limitations. Even with 9 million currently enrolled members, sample sizes may be inadequate for very rare events; vaccines administered outside of the medical home may not be captured; and there is a potential for lack of socioeconomic diversity.

The Clinical Immunization Safety Assessment (CISA) Project is a collaborative effort between CDC and 7 academic centers that conducts clinical evaluation and research. The strengths of CISA are that it can implement prospective, multi-site clinical studies on the order of hundreds of subjects. It provides expertise in vaccinology, vaccine safety, and many clinical areas, including obstetrics and gynecology. It provides access to pregnant women who are receiving vaccines, and has the ability to collect detailed clinical data on the mother and the baby. CISA can also collect biological specimens, and has the ability to recruit controls. The limitations of CISA are that the sample size is limited to study rare adverse events, there are potential challenges to recruit and retain pregnant women, there may not be access to vaccine records for vaccines given outside of the site, there is a potential for lack of geographic or

race/ethnicity diversity, and clinical studies may be labor and resource-intensive. CISA project sites and principal investigators (PI) at these sites include the following:

- Boston Medical Center, MA
  - PI: Colin D. Marchant, MD
- Cincinnati Children's Hospital Medical Center, OH
  - PI: Steven Black, MD
- Columbia University, NY
  - PI: Dr. Anne Gershon, MD and Philip LaRussa, MD
- Duke Clinical Research Institute, Duke University, NC
  - PI: Emmanuel "Chip" Walter, MD, MPH
- Johns Hopkins University, MD
  - PI: Neal Halsey MD
- Kaiser Permanente Northern California (KPNC), CA
  - PI: Roger Baxter, MD and Nicola Klein, MD, PhD
- Vanderbilt Medical Center, TN
  - PI: Kathryn M. Edwards, MD

Activities in monitoring the safety of Tdap administered during pregnancy are conducted primarily using VAERS and VSD. From VAERS an initial assessment has been conducted covering the years 2005 through 2010, before the time when a routine recommendation was made for Tdap vaccination in pregnancy. This study identified 132 reports to VAERS in women who received Tdap[a] during pregnancy or infants exposed in utero[b] during that time period. Of these reports, 77% had Tdap during the first trimester and 42% described no adverse events. Many of these women were vaccinated at a time when they were not aware that they were pregnant. Reports of no adverse events probably reflects that the reporter was primarily compiling this report to document an inadvertent vaccination during a time when there was not routine recommendation for the vaccine. This study identified no unusual or unexpected patterns of maternal, fetal, or infant outcomes. Monitoring is continuing [[a]Zheteyeva et al. Safety of Tdap in pregnancy. Am. J. Obstet Gynecol. 2012;207:59.e1-7;
[b]Before routine recommendation for Tdap in pregnant women; Adacel or Boostrix was administered].

The Tdap in pregnancy VSD study just began recently. Resource support was received from NVPO for this study. It is intended to be a 3-phase study. Phase 1 is just getting underway and is anticipated to complete in August 2013. The primary purpose of this phase is to assess Tdap vaccine coverage among pregnant women from 2007 through 2011. Phase 2 has an anticipated completion no later than July 2015. This phase is designed as a cohort safety study with matched vaccinated / unvaccinated pregnant women. Outcomes will be evaluated for acute events (e.g., allergic reactions, injection site reactions, et cetera), maternal health outcomes (e.g., preeclampsia and eclampsia), and selected birth outcomes (e.g., premature and low birth weight). This phase will focus on data that are currently available from 2007 through 2011. Phase 3 is anticipated to be completed by July 2015. This phase will include 2012 and 2013 data for the Phase 2 outcomes. If there is sufficient power, analyses will be done to evaluate stillbirths and select congenital anomalies. Coverage data will be reassessed at that time as well. It is too soon to know whether it will be possible to evaluate vaccination timing between Tdap vaccinations or previous tetanus toxoid-containing vaccinations.

In summary, ACIP recommendations for Tdap administration during pregnancy are relatively recent, so low Tdap vaccination coverage among pregnant women currently is to be expected. As Dr. Liang presented during the last ACIP meeting, recent estimates are that about 2.6% of women in the US have had a Tdap vaccination during pregnancy. Monitoring in VAERS is ongoing, and monitoring has been enhanced by trying to obtain additional clinical detail and determine vaccination history on all Tdap vaccination reports during pregnancy. The available exposure data currently are limited, but safety studies in VSD have been initiated. The CISA project does provide a potential for targeted prospective clinical studies should the need arise.

Discussion Points

Dr. Harriman wondered whether there were any plans to add a field to collect pregnancy status in the VAERS system.

Dr. DeStefano replied that they are in the process of revising the form to add a subject field.

Given that influenza vaccine has been added to the recommended vaccines that pregnant women should receive, Dr. Jenkins wondered whether evaluation would be made of concomitant administration of vaccinations, such as during the influenza season, or for other exposures that pregnant women might have.

Dr. DeStefano replied that as part of the VSD, they will have data on all of the vaccines women receive, so that is an issue they could address. Depending upon how many women, they may be able to do a strictly descriptive study or they may be able to do an analytic study.

Noting that the presentation was focused primarily on numerators, Dr. Schaffner (NFID) wondered whether Dr. DeStefano could offer a sense of the denominators and how they could assess the frequency of various clinical events that would be reported in the larger pregnant population.

Dr. DeStefano indicated that in planning the 3-phase study, it was estimated that for Phase 1 and Phase 2 with the 2007 through 2011 data there would be about 10,000 Tdap vaccinated women. By the end of Phase 3, the estimate is 30,000.

Dr. Schaffner (NFID) clarified that he was actually thinking of Tdap pregnant unvaccinated women, and how they would acquire the data from the unreported women.

Dr. DeStefano replied that they have data on all women who are enrolled in these managed care organizations, vaccinated or unvaccinated. If they have 10,000 or so vaccinated women, they will have about 90,000 or so unvaccinated women.

Dr. Temte asked whether the anticipated percent for August was anticipated to differ from the 2.6% estimate from the internet survey.

Dr. DeStefano thought they may do better than the 2.6% estimate from the internet survey, because their two largest health organizations are in California, and were at the forefront of starting vaccinate with Tdap, including during pregnancy.

Considerations for Tdap Revaccination

Thomas Clark, MD, MPH
For the ACIP Pertussis Vaccines Working Group

Dr. Clark reported that the working group has been reviewing published and unpublished data on revaccination with Tdap. As Dr. Sawyer mentioned earlier, the working group has been reviewing current Tdap policy and objectives; the epidemiology of pertussis and status of the vaccination program; a summary of Tdap vaccine performance (e.g., antibody persistence, effectiveness/duration of protection, the safety and immunogenicity of revaccination); revaccination options and a framework for decision and cost-effectiveness analysis; and programmatic feasibility and acceptability.

ACIP's current recommendation is a single Tdap dose for adolescents aged 11 through 18 years, with a dose preferred at age 11 or 12 years. A catch-up dose is recommended for every person aged 19 years and older who did not receive a dose at age 11 or 12. Further guidance will be forthcoming on the timing of revaccination in persons who have received Tdap previously. Pregnant women are now recommended to have a Tdap with every pregnancy. However, anyone else who has received Tdap and needs Td vaccination either routinely or for wound management would receive Td booster. Both products are licensed for a single dose. It is important to remember that the primary objective of the Tdap vaccination policy is to protect vaccinated persons against pertussis. It is hoped that there will be herd protection or reduction in the reservoir of disease or of transmission to infants, the most vulnerable population, but that was not the purpose for the recommendation [CDC. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for use of Tdap among health-care personnel. *MMWR* 2006;55(No. RR-17)].

There has been a tremendous reduction in the occurrence of pertussis in the US with the advent and implementation of vaccination. Approximately 20,000 children used to die every year from pertussis, so the burden has been reduced substantially. However, in recent years, more pertussis has been observed, with notable epidemic years in 2004, 2005, 2010, and 2012. Based on preliminary data, the overall incidence in 2012 was 13.4% (n=41,880 cases reported). Rates varied by state, but were as high as 100 cases per 100,000 in some states, Wisconsin especially. Washington State had a notable epidemic last year [CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System and 1922-1949, passive reports to the Public Health Service].

In 2012, every state except California had increases in pertussis over 2011 numbers. In many cases, those were greater than 3-fold increases. While 41,880 cases were reported through the end of January 2012, by the time the final dataset was closed, 20% to 25% more cases are typically observed. Therefore, more cases are expected to be observed when the numbers are closed in the summer [Cases reported through Week 52 in 2011 were compared with cases reported through Week 52 in 2012; fold-changes were calculated for each state]. Fortunately, there were only 18 reported deaths in 2012. Of these, 13 were in children less than 3 months of age [2012 data are provisional; CDC. National Notifiable Diseases Surveillance System, 2012].

Use of whole-cell preparations of pertussis vaccines in the US began in the 1940s. Those were phased out in the 1990s and were replaced by acellular vaccines. Those products were initially licensed and recommended for the booster doses given at 15 to 18 months and 4 to 6 years. Subsequently, the entire series was recommended as acellular vaccines beginning in 1997. There was a washout period, so by about 2000 there was no more whole-cell vaccine used in the US. The Tdap vaccines with reduced antigen content pertussis were licensed and recommended beginning in 2005.

The US has high coverage with childhood vaccinations, and sustained high coverage with pertussis vaccinations. Based on the last survey, 96% of children 19 through 35 months had 3 or more doses and 85% had 4 or more doses of DTaP vaccines [CDC National Immunization Survey]. There have been substantial increases in coverage with the Tdap recommendations. Based on the last survey, there was 78.2% coverage in 2011 among 13 through 17 year olds[1]. However, adult coverage is not so successful. The most recent survey showed 12.5% coverage. Important to note is that for children and teenagers these are provider verified data, while the adult data are self-reported. Many adults report having received Tdap or DTaP, but do not know which one [[1]CDC. National, State, and Local Area Vaccination Coverage Among Adolescents Aged 13-17 Years - United States, 2008. MMWR 2008;58(36);997-1001; CDC. Vaccination Coverage Among Adolescents Aged 13-17 Years – United States, 2007. MMWR 2008;57(40)1100-1103; CDC. Vaccination Coverage Among Adolescents Aged 13-17 Years– United States, 2006. MMWR 2007;56(34) 885-888; CDC. National, State, and Local Area Vaccination Coverage among Adolescents Aged 13-17 Years - United States, 2009 MMWR 2010;59(32);1018-1023; [2]CDC. Tetanus and Pertussis Vaccination Coverage Among Adults Aged ≥18 Years --- United States, 1999 and 2008. MMWR 59(40);1302-1306; CDC. Adult Vaccination Coverage — United States, 2010. MMWR 61(04);66-72; CDC. Noninfluenza Vaccination Coverage Among Adults — United States, 2011. MMWR 62(04);66-72].

In terms of tetanus vaccination coverage within the preceding 10 years by age group, there is generally 60% coverage or so and dropping below that at ages 65 to 74, and less than that at 75[1]. Infants continue to have the highest risk for pertussis and they are also most likely to be hospitalized with severe pertussis, and that is where most of the fatalities occur. Historically, the relative contributions in each age group have remained about the same. However, during the 1990s, there was an emergence of adolescent disease. Peaks in adolescents in 2004 and 2005 led to the Tdap recommendation. In the 2000s, there was significant discussion regarding the emergence of disease in fully vaccinated school-aged children 7 through 10 years of age, with more adolescent disease being observed again in 2012[2] [[1]CDC. 2009 Adult Vaccination Coverage, NHIS. http://www.cdc.gov/vaccines/stats-surv/nhis/2009-nhis.htm; [2]2012 data are provisional. CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System. Despite increasing and good adolescent vaccination coverage, the rates of disease in infants are actually higher now than before the Tdap recommendation. Thus, there does not appear to be a strong herd effect with Tdap coverage in adolescents.

In terms of the peak of disease in 2004, there was a relatively sustained low level of disease across childhood, increases in early adolescents, peaks at age 13, and then a decline after that. All of the whole-cell vaccines were out of the US system by 2000, so children about 4 years of age and younger would have received only acellular vaccines. There was a group in transition, and then anybody above 8 years of age would have received some whole-cell vaccine. The 2010 peak of 27,500 cases was quite different. There was more disease in the youngest age groups, an increase in disease in children 7 through 10 years of age that appeared and progressed as the acellular-vaccinated cohort aged, and a reduction in 11 to 12 year olds and older adolescents. The occurrence of that pattern of disease in the US data, and especially in

the epidemic in California, prompted the first case-control study evaluating the effectiveness by year of receipt of the entire 5-dose vaccination series and its performance over time. There were approximately 600 fully vaccinated cases who received 5 doses and about 2000 controls. Overall, the vaccine effectiveness of 5 doses was 88.7%, within the first year of receipt it was 98%, by 3 or more years it was less than 90%, and by 5 or more years it was 71%. Thus, there was excellent short-term effectiveness but waning of protection consistent with the epidemiology[1]. By 2012, the acellular group aged and there was an increase in disease among 13 and 14 year olds. These data include national incidence with and without the epidemic in Washington State to show that this was present in Washington State and the US and not accounted for only by Washington State, which probably changed vaccines more rapidly[2] [[1]JAMA. 2012;308:2126-2132; [2]CDC. MMWR 2012;61(28);517-522].

In summary, pertussis incidence has increased since the 1980s. The resurgence of childhood disease in 2000 in vaccinated school-aged children is occurring probably because of waning protection from the acellular vaccines. A re-emergence of adolescent disease has been observed despite high coverage with Tdap, suggesting that Tdap boosting in children who received aP vaccines as children may wane more quickly than as anticipated. The working hypothesis is that the switch to aP vaccines may be changing pertussis epidemiology, and that what is being observed is really a problem of susceptibility despite vaccination. Therefore, the working group has reviewed the persistence of antibody from Tdap vaccination. There are several published studies of almost 2000 total vaccinated subjects, both observational studies and clinical trials assessing revaccination. The time of evaluating the kinetics includes 1 year, 3 years, 5 years, and 10 years.

In a study of Adacel® in adolescents, just assessing diphtheria and tetanus, rapid rises were observed in the Tdap groups in the declines over the first year, with relative plateaus through 10 years of age. The pattern is pretty consistent in adults, and is similar for Boostrix®. In summary of persistence of diphtheria and tetanus responses and kinetics in Tdap vaccinated individuals, for diphtheria there are high levels of seroprotection above the defined cutoffs associated with protection against disease at well over 90% at 3 to 5 years in children and adults. This drops to about 80% seroprotection at 10 years. Generally, adolescents have higher levels of protection than adults, probably because they often receive Menactra® with diphtheria toxoid. These results are consistent with Td only vaccines. For tetanus, there are very high levels of seroprotection among vaccinated people persisting to 10 years, and those are sustained.

There is also probably a substantial decline for pertussis antibodies in the first year to two years, and a slower decline through 10 years and less of a plateau, so antibody levels continue to fall. For Adacel® adults are comparable to adolescents. Similar results are observed for Boostrix®. The general assessment of antibody kinetics in persistence for pertussis antibodies is that there is a rapid decline in the first 1 to 2 years after vaccination, with a slower decline over the subsequent 5 through 10 years. However, antibody levels are generally higher than pre-vaccination levels, but are close to pre-vaccination levels at 10 years. It is believed that antibody protects or contributes to protection, but there is no cutoff like there is for diphtheria and tetanus of absolute antibody known to correlate with protection, or a combination of correlation levels known to absolutely correlate with protection.

Based on a review of these data, the working group members were reassured that protection against tetanus and diphtheria persists for certainly through 10 years post-Tdap vaccination. The working group was concerned regarding the decay of pertussis antibody in the first few years, but it is difficult to reconcile the rapidity of antibody decay with what is being observed in vaccine effectiveness data.

In terms of the effectiveness data, at the time of licensure, Pichichero et al demonstrated that the immune response to Tdap was noninferior to the immune response of infants receiving DTaP. Based on sero-bridging studies, initial Tdap effectiveness was assumed to be 85% to 89%. From the adult pertussis clinical trial by Ward et al, overall vaccine efficacy of an acellular pertussis vaccine was 92%. More recent post-licensure studies of Tdap show vaccine effectiveness between 66% and 78%. However, 4 studies highlighted in blue all involve adolescents who received some whole-cell vaccines as children. Only the study by Terranella et al includes a subset of children who received all acellular vaccines. All of these observational studies are limited by sample size and methodology. Currently, Tdap effectiveness among adolescents who received all acellular vaccines in childhood is unknown. Duration of protection offered by Tdap for recipients of both acellular and whole-cell childhood vaccines is also unknown.

The Adult Pertussis Trial (APERT) studied the 3-component acellular pertussis. This was a randomized controlled trial with 2 years of follow-up (July 1997 through December 1999). There were 2781 subjects aged 15 through 65 years. There is no definitive history on the primary series, but by age, these are people who would have received whole-cell vaccines. In this study, the effectiveness of the vaccine was 92% (95% CI: 32-99), but that was based on 1 vaccinated case and 9 unvaccinated cases [Ward JI et al. N Engl J Med. 2005 Oct 13;353(15):1555-63].

A field evaluation of Tdap assessed the mass Tdap vaccination program for adolescents through schools in New South Wales, Australia. They also used a 3-component Tdap vaccine, and vaccination took place from May through December of 2004. Similarly, these are not verified receipt of vaccination, but these are children who would have received whole-cell vaccines in Australia. The study included about 272,000 high school students aged 12 through 19 years. The case reports were through the routine surveillance system from January through December of 2005. By the screening method, vaccine effectiveness was 78.0% (95%CI: 60.7-87.6) based on 167 cases of whom 26% were vaccinated [Rank C, et al. Pediatr Infect Dis J. 2009 Feb;28(2):152-3].

A field evaluation was conducted on Tdap in St. Croix, US Virgin Islands on a pertussis school outbreak with children in nursery through grade 12 grade from September through December 2007. The study focused on Tdap in children 11 years of age and older. There were 266 students in that age group of whom 98% were verified to have received 4 or more childhood doses and would have received some whole-cell vaccine, and 12% of whom had received Tdap. The vaccine effectiveness was 65.6% (95% CI: -35.8-91.3), which was based on 2 cases among 33 vaccinated children and 41 cases among 233 unvaccinated children [Wei SC, et al. CID 2010; 51(3):315-321].

A Tdap vaccine effectiveness case-control study was conducted in Minnesota on a routine adolescent vaccination program from October 2007 through June 2008 or September through December 2008. The study included adolescents aged 11 through 17 years. Cases were polymerase chain reaction (PCR) or culture-confirmed with a cough of 7 days more, which was a somewhat more inclusive case definition. These data do not take into consideration confirmed primary series receipt, but most would have received some whole-cell and some aP vaccines. Vaccine effectiveness was 72.0% (95% CI: 38.0-87.3) in this group of 99 cases and 187 controls [Skoff et al. NIC 2011, Washington, DC].

A field evaluation of Tdap was conducted in Maine where there were two pertussis outbreaks in 2 schools focused on adolescents in a retrospective cohort study from August 15 through November 26, 2011. The study included 314 students aged 11 through 19 years of age, most of whom would have received acellular vaccines, but some whole-cell. Vaccine effectiveness was 68.5% (37.7 - 86.2%) based on 8 cases among 159 vaccinated and 21 cases among 155 unvaccinated [CDC unpublished data].

A field evaluation of Tdap was conducted on a statewide pertussis epidemic in Washington State occurring from January 1 through June 30, 2012, which is the first study to assess durability of protection in acellular vaccinated children. This was a case-control study that enrolled 909 cases among adolescents aged 11 through 19 years in 7 counties. There were 2661 controls matched on birth year and healthcare provider office. The analysis was restricted to complete data on subjects aged 11 through 14 years born between 1998 and 2000 who would have received acellular vaccines as children. The overall vaccine effectiveness in that group was 66% (52 - 76%), which is very consistent with the field estimates. For the first time, this was able to be broken down by less than 12 months, 1 to 2 years, and 2 to 4 years. Approximately 90% of data collection is complete, and evidence of waning protection is being observed in the acellular vaccinated groups, which is consistent with what is being observed in the epidemiology of a lot of disease in 13 and 14 year old children [CDC unpublished data].

In summary, studies in the field are quite consistent overall. Tdap effectiveness seems to be approximately 66% to 78% in field observational studies. Preliminary data suggest that effectiveness wanes within 3 to 4 years among children who received acellular vaccines. This is believed to be consistent with the observed epidemiology. No strong evidence had been observed for herd immunity or an added benefit of high vaccination coverage.

With regard to Tdap revaccination, the working group reviewed the available published clinical trials on revaccination. Many of these are in other countries, though some were conducted partially in the US. Many of the studies have the benefit of being revaccination in children and adults after their first dose, so there is an internal comparison group. The manufacturers were kind enough to share unpublished data, and are both conducting trials in the US. To summarize the safety, in general, local reactions are common in these groups in tetanus-containing vaccines. Systemic reactions like malaise and fatigue are less common. Generally, the solicited adverse events are mild to moderate and are self-limited. The frequency is comparable to the first Tdap vaccination, and is comparable to Td vaccines in general. Serious adverse events are rare, and those that did occur in the trials were determined not to be related to vaccine. The working group felt that data from trials conducted fully in the US probably would not differ from the available data. As a reminder, the working group has reviewed observational studies for other considerations which support the safety of Tdap with intervals of less than 5 years after a tetanus-containing vaccine.

In terms of immunogenicity for tetanus and diphtheria, two groups were broken down for diphtheria by those adolescents who received Menactra® or diphtheria toxoid-containing vaccines. Between the first and second doses at 5-year intervals, the 4-fold responses were somewhat lower, but the baseline levels were higher. They do respond robustly, and essentially everyone is protected. This is comparable in adults following Boostrix®, with essentially everyone being protected for tetanus and diphtheria [Booy 2010]. So, the working group concluded that that the responses to tetanus and diphtheria were robust at 5 and 10 years, and that very high levels of seroprotection are observed.

In a pertussis study of Adacel® with a 5-year interval, robust responses were observed to all pertussis antibodies. The second Tdap antibody response was similar to the first Tdap antibody response, and antibody levels were similar in cohorts boosted after 5 or 10 years. The 4-fold rises were lower, but it was a 5-year interval so their baseline levels were higher[1]. In an assessment of a second 10-year dose of Adacel® versus contemporaneous first-dose adult recipients of a similar age, the response was somewhat different comparable to one another[2]. The same results were found with Boostrix® after 10 years, with Tdap compared to Td plus aP separately [[1]Halperin 2011; [2]Halperin SA et al, *Pediatr Infect Dis J* 2000;19:276–283;[3]Mertsola 2010].

The working group concluded that the antibody responses to revaccination to pertussis are robust at 5 and 10 years. The second dose responses are comparable to the first dose responses, and antibody levels in cohorts boosted after 5 or 10 years are comparable. The working group believes that the clinical trial data support the safety of 5- and 10-year booster intervals, but that observational data supported shorter intervals. Immunogenicity is observed with 5- and 10-year intervals. A 10-year interval is probably sufficient for tetanus and diphtheria, but perhaps is not sufficient for pertussis. In terms of the discussion about the impact of various strategies, the working group feels strongly that the overall effectiveness of the vaccines and the waning of protection will be the most influential in the burden of prevented disease. Data are available for a second dose after a first dose of Tdap, but not for subsequent doses because no one has received a third dose in these trials. The working group anticipates that these considerations for revaccination recommendations will be off-label indications.

A decision and cost-effectiveness analysis of various potential strategies for Tdap routine revaccination in the general population is underway and will be presented to both the working group and to ACIP when complete. The reason to embark on this cost-effectiveness analysis is the high incidence of pertussis among adolescents and adults, and the realization that the duration of protection of Tdap vaccine may be short among acellular vaccine recipients. The objective is to evaluate the cost-effectiveness and the preventable burden of disease by different scenarios of revaccination of Tdap for healthy adolescents and adults.

The cost-effectiveness model will compare a Tdap revaccination strategy to no revaccination. The model constructed includes an 11-year old hypothetical birth cohort that is followed for the lifespan of a hypothetical 11-year old. The outcomes to be assessed include disease, outpatient visits, hospitalizations, and deaths. Costs will be examined from a health system and societal perspective, as well as the quality adjusted life years or QALYs. The model itself is pretty straightforward: revaccinated or not, disease or not, outpatient disease, hospitalization, and death. The key vaccine parameters to be included in the model of the model include the following:

- Incidence rates by age or age group
- Vaccine effectiveness
- Waning immunity
- Vaccine coverage
- Revaccination rate
- Infection rate of non-vaccinated
- Pertussis patient's probability of visiting outpatient clinic and hospitalization
- Case fatality rate
- Natural death rate of each age

- Cost
  - Direct medical cost of cases (inpatient and outpatient)
  - Indirect cost (wage loss and productivity loss)
  - Revaccination program cost

Consideration was given to how this fits into the existing Tdap schedule. There is a Tdap recommendation for every pregnancy, there is an existing decennial Td booster recommendation, and there is an adolescent platform at 11, 12, and 16 years because of the meningococcal conjugate vaccine booster dose recommendation, and that is also a time supported for HPV catch-up. With all of this in mind, the following three scenarios were considered:

- Scenario #1: Replace Td, which is recommended every 10 years for adults, with Tdap

- Scenario #2: Replace the first dose of Td with Tdap at 21 to 22 years of age and afterwards recommended Td every 10 years

- Scenario #3: Add an additional booster Tdap dose for adolescents

Regarding next steps, the working group hopes to present information regarding several items during the June 2013 ACIP meeting, including the following:

- Final results from the Washington State case-control study of Tdap vaccine effectiveness and duration study numbers by time since vaccination, and some comparison of effectiveness in acellular versus whole-cell recipients
- Decision and cost-effectiveness analysis results
- GRADE results in anticipation of a recommendation and vote, though the questions to be GRADEd have not yet been determined

Depending upon the proposed recommendation, consideration may have to be given to other at-risk populations (e.g., healthcare workers, cocooning and post-partum doses, gap for under-vaccinated children aged 7 through 10 years).

In terms of final thoughts, pertussis vaccines protect. DTaP vaccine in the short-term is highly effective, though protection wanes. Tdap is effective, though protection may be wearing off. The vaccine protects well against severe disease, fatal disease, and hospitalizations in those most vulnerable—infants. The resurgence of pertussis is expected to continue. The goal is to prevent infant morbidity and mortality, and also to limit burden of pertussis. It is known that high coverage in adolescents can be achieved, but that attaining high coverage among adults remains a challenge. There is no evidence yet of a strong herd effect.

Current work focuses on maximizing the vaccination program and expanding the evidence for new vaccines. There are numerous activities underway, such as a significant amount of communication exchange of information among the federal partners. A meeting is planned for March 2013 that will bring the research together with the federal partners to discuss what is known, what is not known, and what the right next steps are in terms of understanding pertussis and a path to new vaccines. Many studies are underway, with a couple aimed at assessing protection from Tdap and waning over time. There is an ongoing system in 6 sites for which CDC supports enhanced surveillance with better information collection and laboratory confirmation. Hopefully, the first few years of data will soon be published. The molecular epidemiology of circulating pertussis strains is being assessed, and the enhanced sites allow for

much better isolate collection. The cocooning and pregnancy recommendations are being evaluated to assess the effectiveness in a case-control study design of post-partum and maternal vaccination of preventing infant disease. The burden of other *bordetella* species is being assessed by evaluating PCR-confirmed cases with PCR that allows for the identification of other species. A serosurvey has been proposed through NHANES to assess the levels of antibodies consistent with recent pertussis in the population, and the proportion of the population that is susceptible. National hospital discharge data are being assessed to evaluate any changes in the severe burden of pertussis, under-reporting, or hospitalized pertussis. Those data will also feed into an economic analysis to evaluate the cost of pertussis in the US.

Dr. Clark posed the following questions for discussion:

- Are we considering appropriate strategies?
- Should we consider additional strategies?
- What additional data would ACIP like to see?

Discussion Points

Dr. Duchin inquired as to whether the different vaccine preparations were being assessed, and if so whether they anticipated being able to make any statement or conduct any analyses about potential differential effectiveness of the different vaccines.

Dr. Clark replied that in a quick look at the Washington State Tdap study results, no differences were observed. However, a lot of receipt of product must still be confirmed. There is a cohort study of HMO data that hopefully will include good data for receipt of a certain Tdap product and risk of pertussis. Given that no product or preparation differences have been observed thus far, the feeling is that it is a class problem versus a product problem.

Dr. Bennett requested information on the burden of disease in adults in terms of how many people actually come to medical attention when they have pertussis, and whether anything is known about testing practices. Her suspicion is that pertussis in the adult population continues to be under-recognized, which has major implications for any cost-effectiveness analyses.

Dr. Clark replied that there are only a couple of studies assessing pertussis testing in people with cough illness. Both suggest that the actual incidence in adolescents and adults is on the order of 300 to 500 per 100,000. That is much higher than the 1 per 100,000 that is reported. While it is believed that a lot of disease is under-recognized, it is not clear how to obtain better information. This definitely will influence the cost-effectiveness study, so the approach will be more of a decision analysis comparing the burden of disease or fraction of disease prevented.

Dr. Temte inquired as to whether there was any incidence information from the pre-vaccine era, and whether there was something biologically different in infants and adolescents compared to older people.

Dr. Clark indicated that in the pre-vaccination era, essentially everyone got pertussis by about 4 to 5 years of age. Thus, there was not a lot of reported disease in adults after that. There anecdotally was disease recognized in adults, so it was known that someone could get pertussis after having already had it. However, there is not a good estimate of rates. Some of what is observed historically in vaccination, disease-free interval, and return of disease in adolescents suggests the duration of protection. There is somewhat of a bump in disease in the 40-year old age group, which suggests some waning of protection from the adolescent bump in

disease before. The difference may be that challenge and re-challenge during one's lifetime leaves them relatively better protected than early in life, either from vaccination or disease.

Dr. Keitel noted that Dr. Clark repeatedly alluded to the fact that a herd effect had not been observed. It was worth pointing out that the pertussis disease has such a high number of cases from an infected persons, in order to achieve herd protection, 95% to 98% plus of the population at large would have to be effectively vaccinated. It is unlikely that the US can achieve this, because adults are not protected, they are not immunized, and they serve as a huge reservoir for infection of infants and children. Since the goal is to identify the need for better vaccines, she wondered whether Dr. Clark could comment on a pertussis-only vaccine.

Dr. Clark agreed that herd protection would require high levels of protection in the community. Even some modeling studies suggest slightly lower levels, but the bar is still high for protection across the population, which the US is probably unlikely to achieve, especially with vaccine coverage and the effectiveness being observed. CDC's understanding of a standalone aP vaccination was that that was what was initially evaluated in the APERT study. Those data would be potentially contributory toward licensure, but those were not the kind of clinical trials that are typically required for licensure. That is a potential vaccine that might have some use, given that it has no tetanus and diphtheria, but it would take some time to license a product and bring it to market. He requested that the manufacturers comment.

Dr. Decker (sanofi pasteur) indicated that a standalone aP vaccine would be the most straightforward product to develop. However, it is important to recognize that every year every vaccine company reviews all of its potential projects; ranks them by value to society, feasibility of success, and return on investment; and draws a line where the money runs out. Every year, aP is evaluated and has never gotten close to being above that line. It will likely remain below that line forever unless CDC can identify a specific new recommendation that the aP vaccine would serve. For example, if an 8-year old dose was going to be implemented, that would be a new recommendation that would provide the revenue to support the clinical development. Currently, an aP vaccine cannot rise above the line because there would be zero return on investment. That type of decision-making applies to all manufacturers. He knows that CDC and a lot of academics believe strongly that the entire existing global current class of aP vaccines is never going to offer what is wanted because they produce the wrong immunotype at first administration. What is really needed are entirely new aP vaccines that more accurately emulate the type of immune response that whole-cell vaccines created. There will never be such new acellular pertussis vaccine unless a couple of things occur that vaccine manufacturers cannot make happen. The major problem is that there is no pathway to licensure for a fundamentally new aP vaccine. The regulatory process used in North America and Europe to license aP vaccines cannot be used for a novel vaccine, and there exists no regulatory pathway currently accepted by either FDA or EMA to license a new vaccine. Regulators must change their rules, and it even could require Congressional action before there could be a new aP vaccination. The problem is that these vaccines are spectacularly effective initially. The new vaccine is needed from infancy, but since every country in the world now recommends pertussis vaccine, which was not the case when the aP vaccines were first studied, there is no country in which a placebo-control trial can be conducted. A comparative trial must be conducted, but the efficacy of the comparator is so high, there is no country in the world with a population large enough with which to conduct the study. Moreover, no one has enough funding to conduct such a study. Because there are no defined correlates of protection for pertussis vaccines, there is no pathway to licensure other than a direct clinical endpoint study. A human challenge study could be conducted, but this would not be permitted in infants. It would have to be conducted in adults, and there is no mechanism by which to bridge from such an adult study to infant

licensure. A country that does not recommend Tdap could possibly be found where a study could be conducted in adolescents or adults of Tdap, but there is no basis for bridging that to infants because the immune response in adolescents and adults is higher than the immune response in infants. Therefore, the study will be inferior and will be denied licensure. The final pathway potentially available in the US is the Animal Rule, but it has never been used to license anything other than a bioterrorism vaccine, and there are senior members of the regulatory community who say that the Animal Rule cannot be used for anything but a bioterrorism vaccine. No one is going to spend a penny on a vaccine that cannot be licensed.

Dr. Hahn (CSTE) pointed out that a major need is more data on the effectiveness of post-exposure prophylaxis. All states are handling this differently. It takes a lot of effort, and it is unclear whether this strategy is effective outside the household setting in which it has been studied.

Dr. Clark replied that CDC has tried to evaluate the existing data, but is limited for the impact of post-exposure prophylaxis on interrupting transmission or controlling outbreaks. In the setting of 42,000 report cases, it is too much work.

Dr. Wharton emphasized that one of the things CDC wanted to get out of this session was feedback on the questions posed by Dr. Clark. Given that there is a plan to do some modeling work, it was particularly important to make sure that the strategies being considered are the ones ACIP feels are appropriate.

With regard to the molecular epidemiology, Dr. Harrison inquired as to whether there was any evidence that there are changing vaccine antigens such that there is escape from the current vaccines.

Dr. Clark responded that currently circulating strains have generally different alleles than the strains used to develop the vaccines. However, there is a lot of diversity in the currently circulating strains and there is no evidence that effectiveness has changed because of that. In fact, studies over time have been remarkably consistent with regard to effectiveness as those strains have changed. The other issue is the new recognition of deletion of strains not expressing pertactin. There is evidence that those emerged very recently. CDC has examined its historic isolate collection before 2009 and has not found these, and is working to determine how common they are now. There are no data to show whether vaccine effectiveness is changed by missing pertactin, but current studies show consistent vaccine effectiveness. The vaccines contain other antigens and protective factors. CDC does not like the term “vaccine escape mutant” because strains with pertactin are causing vaccine failures as well.

Dr. Poland (ACP) reported that there are some intriguing data from Australia regarding the possibility of strains that seem to be resistant to vaccine. Certainly, there have been reports of some 12 pertactin-negative variants in Philadelphia. Regarding the proposed modeling, the Office of the Inspector General (OIG) report on safe handling of vaccines demonstrated that 76% of these vaccines were held outside the recommended temperature range for in excess of 5 hours. So, one consideration is that some or the majority of these vaccines have been handled such that they may be sub-immunogenic compared to what occurs in a clinical trial.

Dr. Clark responded that the agency is putting a lot of effort into appropriate storage and handling of vaccines that are publically purchased. There is no evidence that this is a problem that has contributed in large part to what is currently being observed. CDC is trying to determine the effectiveness of vaccines in current practice. There is a lot that is unknown about why vaccines fail in an individual, so that is one thing to assess. However, it is difficult to evaluate because it is hard to get histories of vaccinations, much less what temperature they were.

As a practicing physician, Dr. Fryhofer (AMA) noted that a recent excuse for adults not getting vaccinated is that they believe vaccines do not work that well. A letter in the *New England Journal of Medicine* (*NEJM*) discussed the cases in Philadelphia, and the evolution of pertussis has gotten some media attention that is making patients think that it is not a good vaccine. Those data need to be quantified and made clear to the public.

Dr. Messionier (SME) reported that CDC's web pages include many communication points about this. They have also been in contact with state health departments to help them develop communication points as well. She reminded everyone that this was not the first discussion of strain changes. In fact, in regard to the California outbreak, there was discussion that this was all due to strain mismatch. There are other evolving data that will hopefully clarify and quantitate the picture. CDC's analysis of this as well as the former strain changes is that while strain vaccine mismatch is not good, what is being observed cannot be solely attributed to vaccine strain mismatch. The vaccine efficacy being observed in the short-term matches almost exactly the vaccine efficacy observed 5 years ago, which does not lend itself to an explanation of strain vaccine mismatch or vaccine mishandling.

Dr. Stanly Plotkin (Vaccine Consultant) said he did not quite share all of Dr. Decker's pessimism, because the FDA did use serologic responses in the 1990s trials where efficacy was determined to bridge to vaccines for older age groups. That might well apply for vaccines with a new adjuvant. Concerning the importance of correlates, he agreed that there are no absolute correlates of protection. However, there is a general relationship with antibody response and protection. Therefore, CDC does have an opportunity to add to the possibility of licensure by trying to determine the serologic situations in failures as compared to adolescents or children who do not get pertussis. Those data could be very important. In that regard, he suggested considering the data in terms of not simply the median titers declining, but rather to do curves at different levels and correlate those curves with failures. In other words, what percentage of individuals have titers less than X amount of antibody in relation to the risk of pertussis. That would be much more helpful than just doing median concentration curves. In that regard, he did not see any data on the decline in the 10-year old group, which according to the curves is really the important epidemiologic group and probably is the group who is transmitting to infants rather than adolescents who probably do not have many infants in their immediate homes. He expressed hope that CDC would take on the task of trying to define the correlates better than now, which could include cellular immune responses. While this is more difficult technically, this has not really been investigated.

Dr. Clark responded that there has been a lot of discussion among the federal partners about additional immunologic studies, including cell-mediated immunity. CDC has one study that will help to understand the role of antibody and protection in vaccine failure, and there have been discussions about how to conduct others. The pathway to new vaccines and licensure is difficult; however, a new vaccine is not being considered. It is not an absolute requirement to have data from the US. The original vaccines were licensed with data from Sweden and elsewhere. The FDA has expressed interest in this, and their willingness to have these

discussions. A lot of disease is still being observed in school-aged children, but it is now being seen more in adolescents.

Dr. Stanly Plotkin noted that the curves showed the peak at 10 years, which is about 4 years after the last DTaP dose. He thought it was important to establish that the decrease in antibodies is similar in that group as it is in the adolescents who received DTaP.

Dr. Clark replied that this is what he meant in the difficulty in reconciling a fairly rapid decline in antibodies compared to a slower decline in vaccine effectiveness where effectiveness tails off even further out from being vaccinated. Tdap vaccines are reduced pertussis antigen concentration, so that may be involved. Although the responses seem brisk, at least as brisk as the children.

Dr. Stanly Plotkin noted that the curves shown included anti-fimbrial agglutinogens (Anti-FIM) as well.

Dr. Clark said he understood that people say that PT declines more quickly, but he saw them declining similarly across the antibodies. PT probably declines lower, but starts out lower. Much more remains unclear, which is why CDC proposed the revaccination strategies for discussion.

Regarding whether revaccination was an appropriate strategy, Dr. Gorman (NIH) referred to the data on pertussis rates by age in the US in 2012 [slide 20], which suggested that the result of a revaccination strategy would not be very encouraging. Also of concern to Dr. Gorman with regard to a revaccination strategy was the Washington State cohort, for which it appeared that in less than 2 years there would be about 50% protection, so more frequent vaccination would be required.

Dr. Clark agreed that this is the large scale public health result of vaccinating at 11 or 12 and seeing protection wane in the context of intense pertussis transmission. To maintain high levels of those cohorts protected, he agreed that more frequent vaccination would be required.

Regarding Revaccination Strategy #2, Dr. Warshawsky (NACI) wondered why they would not model a further 10-year dose during the childbearing years to cover the years when women are having children.

Dr. Clark thought there was a potential to model a third dose, but not lifespan. There was some discussion about the reported burden of disease and the frequency with which that could be addressed. Scenario #2 gets at a 10-year revaccination because it fits in the schedule and is the time for childbearing women, because it replaces Td and it is an easier program.

In terms of the fifth dose of DTaP recommended at 4 to 6 years of age, Dr. Bocchini wondered whether the children receiving the dose at 4 years of age were contributing to the 7 to 10 year old increased case rate. If so, perhaps this would offer an opportunity to delay that dose toward 6 years of age in order to better protect 7 to 10 year olds.

Dr. Clark replied that in the case-control study for the California epidemic, the majority (2/3) of the cases had received their fifth dose in their 4th year of life. That differs from what has been observed in other states. There has been a high burden of disease in Minnesota, where more children received their fifth dose in year 5. He did not believe that was the cause of what was

being observed. The analogy is that vaccination closer to 6 years of age would push the disease around, but would not really reduce the burden of disease.

Dr. Sun (FDA) said he did not want the impression left that there is no regulatory pathway for use of pertussis vaccine. In the face of public health need, the agency will find a way to address that need and does welcome vaccine developers to talk to the agency about potential pathways.

Dr. Duchin pointed out that depending upon whether the objective for the revaccinations scenarios were to reduce infant death or for personal protection would have some impact on which strategy to use.

Dr. Clark indicated that the primary strategy to minimize infant death and morbidity and mortality would be the pregnancy recommendation. There is potential also to employ the cocooning idea or vaccinating around the time of childbearing to have high antibody levels that might protect infants or interrupt transmission to infants. A fundamental question pertains to whether the burden of disease can really be reduced with current vaccines, or if it would be temporized by giving a dose at 15 or 16 years of age because there is a platform through which vaccines can be delivered and it might protect some adolescents versus giving every adult lifespan vaccination.

Dr. Duchin noted that this raised this issue of whether it would make sense to move incrementally to determine the effects on the major outcomes of interest instead of assessing every 10 years at the outset. It was not clear to him that every 10 years would make a difference compared to one of the more efficient scenarios. He would take every 10 years off of the table as an initial strategy and would start with a smaller scale strategy, such as 1 or 2 boosters at the most to determine what impact that has on the epidemiology and transmission. Another consideration with these large outbreaks occurring is that there will be many years of people developing some good natural immunity, which will complicate the interpretation of the implementation of a vaccination strategy as well.

Dr. Loehr (AAFP) expressed an interest in knowing more about the data regarding the burden of 300 to 500 per 100,000 that Dr. Clark mentioned, because if the burden is really that high, then decreasing that burden of disease would be an important component of the model.

Dr. Clark indicated that this had been discussed in the over 65 recommendations. There are a couple of studies that actively test cough illness and try to confirm pertussis. It is very different from what is reported in that age group, so there is a major discrepancy that absolutely will affect the cost-effectiveness study. They will bring that to the discussion in June 2013.

Dr. Pickering reported that in a recent *NEJM* editorial Jim Cherry raised the issue of a whole-cell pertussis vaccine, pointing out that if whole-cell pertussis vaccine were administered to the 4 to 6 year age group, pertussis would be wiped out for the next 10 years. He thought that would be a good approach, and wondered whether the manufacturers maintained their licensure for whole-cell vaccine.

Dr. Sun (FDA) replied that he did not know the current status of whole-cell pertussis vaccine licenses, but would find out so that he could report back to ACIP.

Dr. Clark said it was CDC's understanding that licensure had been withdrawn for whole-cell vaccines in the US, and that there are no licensed products.

It was Dr. Harriman's understanding that whole-cell pertussis vaccine would be most effective if it were given as the first dose. That seemed fairly unlikely unless a less reactogenic whole-cell vaccine could be developed.

Dr. Clark responded that it was unknown whether whole-cell vaccine administered after aP vaccine would perform the same as it would administered before aP vaccine.

Smallpox Vaccine Working Group

Introduction

Dr. Lee Harrison
ACIP, Smallpox Working Group Chair

Dr. Harrison offered a brief overview of the new Smallpox Vaccine Working Group. In terms of background, smallpox vaccine provides cross-protection against all of the orthopoxviruses (e.g., smallpox, monkeypox, vaccinia, and cowpox). Smallpox vaccine is used to protect clinical and research laboratory workers against these viruses. The ACIP recommendations for smallpox vaccination of laboratory workers have not been updated since 2003. There is now a new smallpox vaccine, ACAM2000™, which was licensed in 2007 and has replaced the previously used smallpox vaccine, Dryvax®. Both vaccines are derivatives of the New York City Board of Health strain. Dryvax® was freeze-dried calf lymph, while ACAM2000™ is a modern vaccine that is produced in Vero cells.

The Smallpox Vaccine Working Group 's terms of reference are as follows:

1. Review recommendations for smallpox vaccination for laboratory workers in 2001 statement and supplements from 2003:
   a. Review Biosafety in Microbiological and Biomedical Laboratories (BMBL) requirements for work with orthopoxviruses
   b. Review orthopoxvirus laboratory exposure cases and reports, a number of which are now in the literature

2. Review data on smallpox vaccine:
   a. ACAM2000™ safety and immunogenicity data, as well as adverse event rates with current stringent prescreening program
   b. Dryvax® publications on 2002 through 2004 pre-event smallpox vaccination program

3. Review human safety and animal model efficacy data for attenuated smallpox vaccine IMVAMUNE®, a new smallpox vaccine that is on the horizon that does not replicate in mammalian cells, and therefore, it is a potential vaccine for immunocompromised individuals; it is an unlicensed product and therefore review of these data is informational

4. Review data on recombinant vaccinia viruses in development or under investigation in clinical trials to provide guidance on need for smallpox vaccination in healthcare and/or laboratory personnel working with these viruses; Dr. Harrison shared photographs of laboratory-acquired smallpox

5. Revise existing statement and supplements for smallpox vaccination of laboratory workers into single ACIP Policy Note document

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 for adult hepatitis A vaccine, Pentacel® and DTaP, and Boostrix®.

Merck's adult hepatitis A vaccine is currently available for order as vials as well as pre-filled syringes. Availability of sanofi pasteur's Pentacel® and DAPTACEL® vaccines is currently reduced. Increased availability of supply is expected in April 2013. However, sanofi pasteur's single antigen inactivated polio and Hib vaccines continue to be available in sufficient supply to address historic usage of Pentacel® as well as the single antigen vaccines. Regarding DTaP-containing vaccines, production and supply of GSK's single and combination vaccines is currently sufficient to address anticipated supply gaps for DTaP-containing vaccines.

The prefilled Boostrix® syringe presentation is currently out of stock and supply interruptions are anticipated to continue until mid third quarter 2013. An ample supply of the single dose vial presentation is currently available for order. Supply is sufficient to meet historical demand for both presentations. GSK will continue to provide updates on the availability of the prefilled syringe presentation.

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

General Recommendations

Introduction

Dr. Jeff Duchin
ACIP General Recommendations Working Group Chair

Dr. Duchin reminded everyone that the General Recommendations document is published by the *MMWR* every 3 to 5 years, and addresses a broad range of immunization issues that are not specific to individual vaccines necessarily, but to immunization practice in general. General recommendations on immunization are directed to providers who are giving many different vaccines every day. Providers come from variable backgrounds (e.g., physicians, nurse-practitioners, nurses, pharmacists, medical assistants). Text, tables, and figures are included for quick reference.

General recommendations revision will encompass a number of topic areas, 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 to be addressed during this session included the following:

- ❑ Timing and spacing of immunobiologics, including:
  - → Timing and spacing of immunobiologics discussion focused on the grace period and the Live Vaccine Rule
  - → Simultaneous and non-simultaneous administration:
    - Inactivated influenza vaccine (IIV), Pneumococcal conjugate vaccine (PCV13) – Febrile Seizures
    - PCV13 and Meningococcal conjugate vaccine – D (MCV4-D)

- ❑ Contraindications and Precautions, including:
  - → Clarification of contraindications and precautions tables that will clarify Guillain-Barré syndrome and Arthus reactions
  - → Vaccination during acute illness, particularly around the time of hospitalization for surgery and anesthesia

- ❑ Special situations, including:
  - → Vaccination during pregnancy
  - → History of vaccination for persons vaccinated outside of the US

Update on Proposed Revisions for Three Sections of The General Recommendations

Dr. Andrew Kroger
General Recommendations Working Group

During this session, Dr. Kroger provided an update on the proposed revisions for the *Timing and Spacing of Immunobiologics*, *Contraindications and Precautions*, and *Special Situations* sections of the general recommendations. He noted that ACIP members should have draft documents for these sections. He also emphasized that all topics on which he was presenting during this session represented an attempt to incrementally describe to the ACIP the changes being made to the general recommendations document, and that there would be presentations during later ACIP meetings for other sections of the document, as well as a chance to revisit this content .

The *Timing and Spacing* section of the document deals with intervals between vaccines, doses of the same vaccine in series, and the timing and spacing that must be maintained between different vaccines and different doses of the same vaccine. The two topics on which Dr. Kroger focused were the grace period and simultaneous vaccination for PCV13 and IIV in terms of febrile seizures and spacing of PCV13 and MCV4-D.

The grace period is an ACIP recommendation that has been in place since 2002. It applies to sequential doses of the same vaccine in a single series for one patient. The general recommendations include Table 1, which lists all of the routinely recommended vaccines, and the grace period is applied to this and basically states that a vaccine can be administered four days short of the minimum age for that dose or the minimum interval from the previous dose. The reason a grace period exists is a programmatic one. It reduces missed opportunities for vaccination if a patient is in the office for some other reason and a provider notes that they could give a dose of vaccine, it can be given even though it is not necessarily a well-child visit. Also very important with respect to the grace period is that it can be used when looking back on past doses, not only for the provider to make a decision about when to administer the dose, but also to assess past doses to determine whether that dose was in fact valid.

The Immunization Information Systems Branch is committed to programming its algorithms to align with ACIP recommendations, so they want to ensure that they are programming correctly. The grace period is part of ACIP recommendations. A challenge that has arisen recently in discussions with the Immunization Information Systems Branch pertains to the separate rule called the Live Vaccine Rule. This is a rule that applies to different live vaccines that requires a spacing of 28 days between two live vaccines. The reason there is a desire to space two live vaccines is because it is believed that there is an effect of the vaccine given first, which replicates and produces a number of cellular mediators of immunization, one being interferon, on the vaccine given second. There are data dating back to the 1960s showing that the measles vaccine can reduce the immunogenicity of smallpox vaccine. More recent data show that breakthrough varicella can occur if two different live vaccines (MMR and varicella vaccine) are given too close together. If MMR vaccine is given first and varicella vaccine is given at less than the 28-day minimum interval, there was an effect on the vaccine given second.

There is now a newly available combination vaccine, MMRV vaccine, that contains live components (e.g., measles, mumps, rubella, and varicella) in one vaccine. This raised the issue regarding whether the grace period could be applied to the new combination vaccine, because traditionally the grace period has programmatically been applied to single component vaccines. All of the routinely recommended vaccines appear on Table 1, and there is a programmatic policy that says the grace period can be reduced by 4 days from 28 days to 24 days. Notably, MMR and varicella are given as two doses in series, and therein lies the rub for this. To better illustrate the grace period, Dr. Kroger shared several sample scenarios:

- If MMR is given at time one, it must be separated from varicella vaccine by 28 days. A grace period would not be applied to the two doses of MMR vaccine because of the Live Vaccine Rule.

- For MMRV or varicella vaccine, the same rationale could be applied that the grace period should not be applied to MMR. It should be separated by 28 days, not 24 days.

- If beginning with varicella vaccine, MMRV should be completely delayed with no grace period due to the same rationale. The Live Vaccine Rule must be applied here as well.

The working group decided that the Live Vaccine Rule should trump the grace period, and therefore, time-one and time-two for all these circumstances would be treated equally. The grace period would not be allowed between these two vaccines. This was the merging of a programmatic rationale for allowing the grace period between two doses of MMR vaccine alone, which would still be allowed. However, the consensus of the General Recommendations Working Group is that the same rationale cannot be applied to administration of MMRV. The following language is in the text, from which Dr. Kroger read the underlined language [Page 9, Line 1 (P9, L1) of "Timing and Spacing"]:

> Two or more injectable or nasally administered live vaccines not administered on the same day should be separated by at least 4 weeks (Table 3), to minimize the potential risk for interference. If two such vaccines are separated by <4 weeks, the second vaccine administered should not be counted and the dose should be repeated at least 4 weeks later.
>
> The 4-day grace period discussed earlier, which may be used to shorten the minimum interval between doses of the same vaccine, should not be applied to this 4-week interval between two different live vaccines. Confusion about this prohibition may arise when two live vaccines whose intervals are identical are administered simultaneously. For example, if MMR and varicella vaccines are administered on the same day, the second dose of each vaccine could come due 4 weeks later (depending on the patient's age). If either vaccine had been given alone at both timepoints, the 4-day grace period could be applied to the second dose. <u>But in this situation the live vaccine rule prevents the grace period from being applied to the second dose of either vaccine, because Varicella-2 could potentially be affected by MMR1 if administered earlier than 4 weeks, and MMR-2 could be affected by Varicella-1</u>. Note that this prohibition also applies if the combination MMRV is used rather than individual MMR and varicella vaccines. Live oral vaccines (Ty21a typhoid vaccine and rotavirus) may be administered simultaneously with, or at any interval before or after, any other live vaccines.

The rest of the *Timing and Spacing* section is focused on keeping the general recommendations in line with vaccine-specific recommendations that are published along the way, so there is a section on simultaneous vaccination of two different vaccines. Language is included on the issue of febrile seizures in association with IIV and PCV13. This was first identified with respect to vaccines used in the US during the 2010-2011 influenza season with Fluzone® and other vaccines. The strongest signal at that time linked Fluzone® with PCV13 with respect to an association with febrile seizures. The Febrile Seizure Subgroup discussed this issue in some detail, and this involved assessing risk and benefit issues with respect to febrile seizures occurring with simultaneous vaccination contrasted with the benefit of being able to provide vaccines without missing an opportunity, namely IIV and PCV13. Febrile seizures are generally benign and generally do not lead to poor neurologic outcomes, and invasive pneumococcal disease and influenza cause significant morbidity in infants and toddlers. After reviewing all of the data, it was specifically decided that the attributable risk suggested that one additional febrile seizure could be expected for every 2200 simultaneous vaccinations with IIV and PCV13 in children between 12 and 23 months of age. ACIP concluded that the importance of vaccination to prevent pneumococcal and influenza disease outweighed the risks of febrile seizures, and made no change in guidance for the immunization schedule or simultaneous administration of these vaccines.

Another topic for simultaneous vaccination includes some exceptions to the rule. There is a general rule that two different vaccines can be given simultaneously, but there is now a specific exception to that rule with MenACWY-D (Menactra® brand of meningococcal conjugate vaccine) and PCV13 in patients with asplenia. It is known that there is interference with PCV13 immune response to 3 of the serogroups of pneumococcous when these two vaccines are given simultaneously, so a one month interval is recommended between PCV13 and Menactra®, and it is also recommended that PCV13 be given first. There is language in the general recommendations on Page 4, Line 14 and Page 8, Line 8 of the general recommendations in the *Timing and Spacing* section.

Moving to the *Contraindications and Precautions* section, there are three topics beginning with the precaution in the recommendation that addresses the issue of vaccination when someone is severely or moderately acutely ill. There was a general recommendation that a dose of vaccine could be deferred when someone is severely or moderately acutely ill. There is also a tendency to state in training messages that if someone is mildly ill, they can receive a dose of vaccine. The new issue pertains to hospitalization and revolves around anesthesia and surgery during hospitalization. The other topic regards a clarification to contraindication and precaution tables with respect to a previously listed precaution regarding the history of Arthus reactions, with regard to GBS as well.

Regarding the issue of vaccination of someone while acutely Ill, persons who are hospitalized may be mildly, moderately, or severely ill. There is really only a recommendation to defer a dose of vaccination for severe or moderate acute illness. However, a number of circumstances have presented challenges to this issue. In terms of vaccination during a hospitalization, CMS uses as a performance measure the offering of inactivated influenza vaccine (TIV) and pneumococcal polysaccharide vaccine (PPSV23) during hospitalization. That transcends ACIP and is ongoing within CDC. This issue in isolation did not drive the work of the General Recommendations Working Group, and was really a secondary issue. What really drove the General Recommendations Working Group to take this on in the first place were a number of events that occurred, primarily involving the pediatric context for vaccination, but involving adults as well, in terms of elective procedures involving vaccination prior to anesthesia. In January 2011, CDC first received a request from anesthetists in Ireland to closely assess this topic. Dating further back than that, previous working group chairs had requested that the issue of vaccination during anesthesia be addressed, but that was discussed during the October 2011 ACIP meeting at which time the suggestion was made to focus more on the issue of vaccination in the context of elective procedures involving anesthesia and procedures in the future.

The working group considered this and framed the question, “Does there need to be an interval between surgery, anesthesia, and vaccination?” There is some background to this topic. Current ACIP/CDC recommendations and guidance indicate that if someone is severely or moderately acutely ill, vaccination should be deferred until convalescence. That argues for vaccination around the time of discharge. The current recommendations also state that a provider may give PCV13, PPSV23, MenACWY, or Hib ideally two weeks before surgery to remove the spleen, if feasible. There are a number of other examples as well. For example, the desire to avoid missing an opportunity to vaccinate a Tdap naïve pregnant women to cocoon in the post-partum period, would argue for giving a dose of vaccine at discharge following a cesarean section. The examples vary by specific vaccine.

There is discussion in the general recommendations regarding important outcomes, including the following:

- In the adult context, should a dose of vaccine be withheld following a surgical/anesthesia event? Is there an interval that should be applied following surgery?

- In the pediatric context, should a dose of vaccine be withheld because of upcoming elective surgery? Is there an interval that should be applied prior to the surgery?

As the working group began to assess the literature on this topic, it became clear that the available data focus on vaccine efficacy as opposed to the issue of a dose of vaccine causing an expected event like fever, and the impact of that on decisions to have elective surgeries or the consequences of a fever occurring because of a vaccine after a surgical procedure. There is limited information in the literature regarding the topic of vaccination and anesthesia, and the primary focus is typically the efficacy of the vaccine. There were 20 papers addressing the hospitalized patient and the immune response, only 5 of which addressed the immune response to vaccination with respect to concurrent or previous surgery or anesthesia. The remaining 15 papers do assess immune response, but they are not specifically about immune response following vaccination.

The 5 papers that address the immune response to vaccination following a dose of anesthesia consisted of one systematic review, one editorial, and three letters in response. There were no randomized controlled trials among these 5. The review article cites a number of provider surveys and studies that evaluate immune parameters, but not the immune response to vaccination. The citations for these 5 papers are as follows:

- Siebert JN, Posfay-Barbe KM, Habre W, et. Al. Influence of anesthesia on immune responses and its effect on vaccination in children: review of evidence. Pediatric Anesthesia. 2007: 17, 410-420.

- Currie J. Vaccination: is it a real problem for anesthesia and surgery? Pediatric Anesthesia. 2006: 16, 501-503.

- Siebert J, Posfay-Barbe KM, Habre W, et. Al. Author's Reply. Pediatric Anesthesia. 2007: 17, 1215-1227.

- Nafiu OO, Lewis I. Vaccination and anesthesia: more questions than answers. Pediatric Anesthesia. 2007: 17, 1215-1227.

- Short JA, Van der Walt JH, Zoanetti, DC. Author's Reply. Pediatric Anesthesia. 2007: 17, 1215-1217.

The remaining 15 articles address anesthesia and the immune response, but not immune response to vaccination. Two RCTs addressed anesthesia and the immune response, but these trials compare different types of anesthesia:

- Mattila-Vuori A, Salo M, Iisalo E. Immune response in infants undergoing application of cast: comparison of halothane and balanced anesthesia. Can J Anesth. 1999: **46**(11), 1036-1042.

- Vuori A, Salo M, Viljanto J, et. Al. Effects of post-operative pain treatment using non-steroidal anti-inflammatory analgesics, opioids or epidural blockade on systemic and local immune responses in children. Acta Anaesthesiol Scand. 2004: **48**, 738-749.

In terms of the strength of the evidence, the review article does posit that an interval can be applied. However, the letters in response say that no interval should be applied. The overall evidence is weak. It is imprecise in that all of the studies have small sample sizes; indirect in that the papers discuss immune response but not immune response to vaccination; and they focus on different age groups and the results are inconsistent. Of the studies, 6 studies assessed both infants and children and found different results with respect to the response for

infants and children. Of these 6 studies, 3 showed an increase in immune cell parameters in both age groups, 1 showed a decrease in immune cell numbers in both age groups, 2 showed a decrease in immune cell numbers for infants and an increase in immune cell numbers for children, 11 studies looked at more than one parameter (e.g., antibodies, T-cells), 8 showed variation among parameters, and 3 did not show variation but each of the studies showed something different. For example, 1 study showed a decrease in lymphoproliferation based on a number of immune parameters [ConA and PWM], 1 showed no change in PMN chemotaxis and actin polymeration, and 1 showed an increase PMN phagocytosis and oxidative burst.

On the basis of the strength of the evidence, the working group found no compelling reason to recommend a specific interval generally. Given that the current recommendation is to defer vaccination while severely or moderately acutely ill and that much of the general recommendation evidence is going to be at the discretion of the provider, the working group felt that it was preferable to vaccinate after anesthesia and surgery as opposed to before anesthesia and surgery. Concerns were expressed among many of the pediatricians on the working group with respect to elective procedures and the effect of an immune response on that, so generally the working group thought it was better to state a preference to vaccinate after as opposed to before. The following language is in the text, from which Dr. Kroger read the underlined language [P2, L18 of "Contraindications and Precautions"]:

> It is reasonable to vaccinate patients during hospitalization if they are not acutely ill. Health-care facilities are held to standards of offering influenza vaccine for hospitalized patients, so providers are incentivized to vaccinate these patients at some point during hospitalization. Likewise patients admitted for elective procedures will not be acutely ill during all times during their hospitalization. The hospitalization should be used as an opportunity to provide recommended vaccinations. Most studies that explore the effect of surgery or anesthesia on the immune system consist primarily of observational studies, are small, and are indirect in that they do not look at the immune effect on the response to vaccination specifically. Studies that examine the effect of anesthesia on the response to vaccination consist only of a systematic review and expert opinion pieces which vary on the need for or duration of an interval. The optimal time for vaccination may be hospital discharge to avoid superimposing any vaccine-induced adverse effects on underlying conditions or avoid confusion in determining the etiology for conditions that occur or are exacerbated during the hospitalization. For patients who are deemed moderately or severely ill at the time of discharge, vaccination should occur at the earliest opportunity (i.e., during immediate post-hospitalization follow-up care, including home or office visits) when patients' clinical symptoms have improved.

Regarding some of the topics in the Contraindications and Precautions Table, Guillain-Barré Syndrome (GBS) is a topic that exists in many vaccine-specific ACIP statements. It has been associated with some vaccines, but has multifactorial causes. Current ACIP recommendations state that a history of Guillain-Barré Syndrome within 6 weeks of a dose of influenza vaccine or tetanus toxoid-containing vaccine is a precaution to influenza vaccine or tetanus-toxoid vaccine respectively. These are split out in the table separately. GBS used to be what was called a "relative contraindication" for meningococcal conjugate vaccine. In June 2010, ACIP removed GBS as a contraindication and as a precaution for meningococcal conjugate vaccine.

However, the General Recommendations Working Group was tasked with the determination regarding whether such precautions or lack of precautions could be applied more broadly to all vaccines. The working group consulted with ISO and CISA, which reviewed specific data that suggests that past history of GBS is not a risk for recurrent GBS following a vaccination [(e.g., Baxter, *CID,* 2012]. They evaluated 279 individuals who experienced GBS previously and received a current dose of vaccine. Of those individuals, 25 experienced GBS following a previous dose of vaccine. Of those 25, none experienced GBS following their current dose of vaccine. It is important to note that of the other individuals in the study, in addition to the 254 individuals who had previous GBS, a current dose of vaccine and no previous dose of vaccine, there were 271 individuals who had previous GBS, and neither a previous or a current dose of vaccine. Of all of these individuals who experienced GBS previously but did not receive a dose of vaccine previously with their episode of GBS (n=525), there were only 6 recurrent GBS

episodes. While one of these 6 episodes was in an individual who received a current dose of vaccine (1/254), five were in individuals who had not received a current dose (5/271) and none of these 6 were in individuals who had received a previous dose of vaccine. Based on these data, CISA made the following suggestions to the General Recommendations Working Group:

1. Add data from the Baxter et al paper (CID, 2012) to the ACIP recommendations for influenza vaccine, stating that these data are reassuring, although the power is limited given the rarity of the condition.

2. Use similar and parallel language regarding recurrence of GBS following both tetanus and influenza vaccines, since these vaccines are the only ones associated with possible recurrence.

3. The experts in the group were comfortable that meningococcal vaccine should no longer be mentioned as a risk factor for recurrent GBS. That has been replicated or will be replicated in future specific statements.

4. Include clear language in the relevant ACIP recommendation documents stating that there is little evidence to support a problem with GBS recurrence after tetanus/influenza vaccination, yet it cannot be ruled out.

4. Be explicit in the general recommendation about guidance for vaccination of persons with a history of GBS. Specifically, precautions only apply if the GBS occurred within 6 weeks of influenza or tetanus-containing vaccine administration. There is no precaution to any other vaccine for patients with history of GBS.

A change was made to Table 7 as a result of the discussion on GBS, which is not specifically the Contraindications and Precautions Table. This is the Misperceptions Table, which states that vaccines may be given under these conditions. At the bottom of the table is the history of GBS with footnotes stating the exception

TABLE 7. Conditions Incorrectly Perceived as Contraindications to Vaccination (vaccines may be given under these conditions)

Conditions commonly misperceived as contraindications (i.e., vaccination may be administered under these conditions)

Mild acute illness with or without fever

Mild-to-moderate local reaction (i.e., swelling, redness, soreness); low-grade or moderate fever after previous dose

Lack of previous physical examination in well-appearing person

Current antimicrobial therapy*

Convalescent phase of illness

Preterm birth (hepatitis B vaccine is an exception in certain circumstances)†

Recent exposure to an infectious disease

History of penicillin allergy, other nonvaccine allergies, relatives with allergies, or receiving allergen extract immunotherapy

History of Guillain-Barré Syndrome§§

§§§§An exception is Guillain-Barré Syndrome within six weeks of a dose of influenza vaccine or tetanus-toxoid containing vaccine, which are precautions for influenza vaccines and tetanus-toxoid containing vaccines, respectively.

Regarding Arthus reactions, a revision was made to the Contraindications and Precaution Table for tetanus-toxoid containing vaccines. Arthus reactions are type III hypersensitivity reactions that result in circulating/local antigen-antibody complexes and cause severe local pain, severe erythema, and sometimes local necrosis. Arthus reactions have historically been associated with giving multiple sub-sized doses of vaccines at shorter than recommended intervals, which makes sense because an individual is given a dose, they generate an antibody response, and then another dose of antigen is given too soon. Revision was needed under tetanus-toxoid containing vaccines, which is an issue relevant to tetanus-toxoid containing and diphtheria-toxoid containing vaccines. The language revised thus far is specific only to the tetanus-toxoid containing vaccines. No specific changes have been made for meningococcal conjugate vaccines yet, but this addition needed to be made under the entry for tetanus-toxoid containing and diphtheria-toxoid containing vaccines. The specific addition is underlined in the following paragraph:

> History of arthus-type hypersensitivity reactions after a previous dose of <u>diphtheria toxoid—containing or</u> tetanus toxoid--containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid-containing vaccine

The addition is only “diphtheria toxoid-containing” vaccine, but only where it is underlined. There may be more to do here in terms of whether to recommend increased intervals following previous doses of meningococcal conjugate vaccine when further doses may be indicated later. However, the working group has not gotten that far yet.

Two topics were addressed in the *Special Situations* section, vaccination during pregnancy and persons vaccinated outside of the US. Regarding vaccination during pregnancy, the working group decided that there was a need to incorporate new Tdap in pregnancy recommendations, which are not yet published but will be soon. The specific language will replicate the language that is in the Tdap-specific recommendations and will be published first.

Persons vaccinated outside of the US was a popular topic in the working group. This topic originally dealt with internationally adopted children. However, in 2006 this section was broadened to include all persons vaccinated outside of the US. At issue are persons with records, but the records are uncertain or difficult to decipher. For the most part, if someone does not have a record, there is a general recommendation to give a dose of vaccine. Some of the topics that must be dealt with pertain to uncertain records. In light of the expansion to all age groups vaccinated outside of the US, there is a need to address pertussis epidemiology and the current recommendations. The current recommendations from 2011 state that in light of uncertain records, tetanus and diphtheria serology can be used to make decisions about whether previous doses of tetanus-toxoid containing vaccines, including DTaP have been given. There are no correlates of protection for pertussis, so this section has relied on tetanus and diphtheria serology as a proxy. This has been in the general recommendations since 2002; however, with rising numbers of pertussis cases in the US, consideration had to be given to whether this is this still appropriate. The working group consulted with the WHO which provided a website that lists vaccines given in other countries as a guide. In truth, few countries use DT vaccine, so it was deemed to be still appropriate to use tetanus and diphtheria serology as a proxy in this sense. Therefore, no change was made to this recommendation.

The issue of uncertain records raised the topic of establishing history of vaccination. There are recommendations in the *Special Situations* section and the *Timing and Spacing* section that allow self-report for influenza vaccine and pneumococcal polysaccharide vaccine to establish documentation of immunity. These are exceptions to the recommendation that if it was not documented, it was not given. This has been carried forward in the *Special Situations* and *Timing and Spacing* sections. The rationale for why self-report is allowed for these two vaccines is that influenza requires reliance on memory lasting for one year, and pneumococcal polysaccharide vaccine has a high rate of adverse reactions if doses are given at less than a five-year interval. The discussion among working members revolved around pneumococcal polysaccharide vaccine. It was determined that for the *Special Situations* section, pneumococcal polysaccharide vaccine would be removed from the self-report list for persons vaccinated outside of the US. Only about 25% of countries give this vaccine, so the judgment of the working group was that this change can probably be made without concern for an increased risk of local reactions.

Discussion Points

Regarding vaccination while acutely ill, Ms. Rosenbaum recalled that Dr. Kroger pointed out that CMS is currently using a performance measure for hospital performance. As she understood the working group's recommendation, they were reaffirming the current recommendation to defer vaccination while severely or moderately ill. She wondered what the CMS reaction was, and whether issues might be revisited in terms of hospital performance measures.

Dr. Hance (CMS) responded that she had not been involved in the conversations with the side of CMS that established this performance measure. However, she will follow up and will report back to ACIP and will assure that these connections are made so that everyone is speaking with one voice.

Dr. Kroger added that this is ongoing with CDC as well. There are many complicating factors to this decision because of new pneumococcal vaccines, so the situation is dynamic. That is why the general recommendations focused more on the anesthesia issue in its deliberations.

Dr. Temte pointed out that a number of the recommendations Dr. Kroger covered, specifically issues such as the Live Vaccine Rule and GBS, fit into a Category A recommendation as items ACIP would routinely recommend. Most of these are based on what would be categorized as Category 4 or fairly low quality evidence. He had no problem making a strong recommendation for spacing even though it is based on expert opinion, and they may never have any better evidence. However, he wondered whether this should bring the framework for GRADE into the general recommendations in terms of the transparency.

Dr. Kroger responded that one of the pitfalls is the level of evidence that can be expected from the outset with a set of recommendations based on all vaccines as opposed to one particular vaccine. Specific issues may arise on which they may be able to focus. There may be topics in the general recommendations for which it is impossible to really link the strength of the evidence to the strength of the recommendation because they deal with all vaccines. At the outset, there may be a presumption that there are no data.

Dr. Temte noted that they do not necessarily have to link the strength of the evidence to the strength of the recommendation. Looking through the general recommendations, some fall more within the realm of administrative rules, such as people vaccinated outside of the US. However, there are other issues about which they are making a recommendation. He was very comfortable as a clinician using a spacing rule based simply on expert opinion, and it has very little consequence. However, it opens the door to being very transparent about where that is coming from. It would be a worthwhile effort to bring everything slowly in line.

Dr. Duchin agreed that while they could not GRADE all of the hundreds of recommendations that go into the general recommendations document, they could be more explicit about the decision-making process.

Regarding Arthus reaction, Dr. Poland inquired as to whether the working group meant to not include pneumococcal vaccine.

Dr. Kroger responded that so far in that discussion, they have been addressing specifically the meningococcal conjugate vaccine because it contains diphtheria-toxoid. The contraindication stated for the tetanus-toxoid containing vaccines is an Arthus reaction following a dose of a vaccine tetanus or diphtheria toxoid.

Dr. Poland noted that Arthus type reactions are observed with frequent pneumococcal polysaccharide vaccine use. Regarding GRADE, he agreed that it may be difficult, but it would be good to have a footnote so stating that GRADE criteria could not be applied and therefore this represents expert opinion. At his institution, using tetanus or diphtheria serology would cost approximately $200 to $300. It might be worth mentioning that this is an expensive alternative as opposed to simply providing a dose of the vaccine. He requested clarity regarding whether the working group was proposing removal of just pneumococcal from the self-report, not that self-report would be accepted of other non-influenza or non-pneumococcal vaccines.

Dr. Kroger pointed out that using diphtheria and tetanus serologic assays was an alternative approach. One of the approaches in the table is just to revaccinate. It does not require serology by any means, and in fact, in the document there are numerous places in the *Timing and Spacing* section that move away from serology.

Dr. Poland clarified that he was not interpreting it that way, but was suggesting adding a comment about the cost. Otherwise, some clinicians would order serology and have no idea of the cost.

To clarify the issue of self-report for pneumococcal polysaccharide vaccine, Dr. Kroger indicated that it was felt that they should focus on only *Special Situations*, and within *Special Situations* to focus only on pneumococcal polysaccharide vaccine, and take that out of self-report. That would be one along with all of the other vaccines besides influenza vaccine for which self-report is not accepted.

Dr. Vazquez noted how subjective it is to determine which children are moderately ill or severely ill, and the association with anesthesia and how that may influence children and adults with chronic illnesses who do not see their physician and how that can be translated into missed vaccine opportunities. It is usually those who are sicker who have transplants. If they are not vaccinated when mildly ill, they lose their opportunity for live vaccines. Dr. Vazquez was concerned that chronically ill individuals might “fall through the crack.” She also pointed out that what is mild or moderately ill is different depending upon the person.

Dr. Kroger replied that the sections in the general recommendations he discussed during this session were primarily issues of acute illness. Chronic illness carries its own considerations. Typically deferral is made to the provider at the point of care when they are seeing patient to assess whether the patient is acutely ill at that time. If the patient is mildly acutely ill, a dose of vaccine can be given. If the patient seemed moderately or severely acutely ill, deferral of a dose would be permissible. This probably could be stated more clearly in the recommendations. Because what constitutes mild or moderately ill depends upon the person, discretion on the part of the provider must be emphasized.

Dr. Warshawsky (NACI) wondered if consideration had been given to whether the Live Vaccine Rule should or should not apply to intranasal and parenteral vaccines.

Dr. Kroger responded that the general recommendation is that any vaccines can be given simultaneously, with the exceptions of the few he spoke of earlier. The issue regarding live vaccines pertained to non-simultaneous vaccination, but within a narrow window of less than 28 days. Intranasal vaccines are included among live vaccines, so an intranasal and a parenteral live vaccine should be separated by 28 days. That decision was made around the time of licensure of LIAV and how that would be applied in the general recommendations, and the recommendation does expand to that. For oral vaccines, there does not have to be a 28-day separation. There is a lot of history with the recommendations for oral polio vaccine. When oral polio vaccine was being used, this was decided.

Dr. Warshawsky (NACI) reported that NACI is currently assessing that as well, particularly the LIAV and parenteral vaccines, and whether it really makes sense to have a 28-day window if they are not given simultaneously. She also thought the rate of recurrence of GBS after a vaccine seemed like a really high rate of recurrence in general.

Dr. Kroger clarified that it was recurrence after a previous GBS episode. Because of the study design, the investigators assessed individuals who were receiving current doses of vaccines who had current episodes of GBS. All of the individuals had previous episodes of GBS, but very few had previous episodes of GBS and a previous dose of vaccine at that time. This sheds more light in recurrence of GBS.

Dr. Warshawsky (NACI) asked whether that was considered to be the average rate of recurrence of GBS regardless of vaccine, because it seemed high.

Dr. Kroger responded that the study authors found it to be low. In the safety discussions, this seemed to be what was expected.

Dr. Gorman (NIH) felt the 10% GBS recurrence rate was fairly high to be considered low for a serious disease like GBS. However, he said he would defer to the working group's recommendations after reviewing that.

Dr. Kroger replied that for a number of the GBS cases that occurred following previous GBS, the timing did not lend itself to being associated to the dose of vaccine. That is, they occurred at an interval of time from the current dose of vaccine.

Dr. Broder clarified that there were no cases of recurrent GBS identified in people who had received a vaccine within two months. The numbers were too small to draw definitive conclusions about risk, but they were reassuring overall.

Dr. Gorman (NIH) expressed confusion about "moderately" and "severely" ill and "anesthesia" and "surgery." Approximately 70% of hospital-based surgery is now done in and out, same day surgery, or ambulatory surgery depending upon what definition is used of those. It would be hard to imagine that those people are seriously ill if they are in and out of the hospital on the same day. They may be moderately ill. He thought the separation between those two conditions might be delineated in a different way. Notwithstanding the factor that anesthesia may blunt immune responses, he did not perceive those people as being ill because they go home the same day.

Dr. Sawyer requested clarification on the issue of eliminating history of polysaccharide pneumococcal vaccine. Though Dr. Kroger discussed eliminating polysaccharide pneumococcal vaccine from the section regarding people vaccinated outside of the US, he did not recall whether there had been discussion about not eliminating it for people vaccinated in the US. Conjugate vaccine has now been added for at least a subgroup of adults, so this could become very confusing. Perhaps it should be eliminated in that case as well.

Dr. Kroger responded that this was discussed briefly, but the conclusion of the working group was to remove polysaccharide pneumococcal vaccine from persons vaccinated outside the US. Consideration for removing it from self-report for all persons raises the issue of local reactions because that vaccine is still being given in the US.

Dr. Gellin (NVPO) wondered how the Live Virus Rule aligned with the convalescent phase of illness. With two vaccines, the antigens being presented are known. However, someone convalescing from an acute illness may be suffering similar immunologic issues that interfere with efficacy.

Dr. Kroger replied that the Live Vaccine Rule is very specifically data-driven. The question is posed from time to time about varicella disease and whether someone can be subsequently immunized with MMR vaccine within 28 days following varicella disease. The response has been yes. A data-driven approach is taken to this recommendation to withhold a dose of vaccine and does not apply it to chicken pox disease specifically. That is a direct example in which the rule is applied to varicella vaccine, but not varicella disease. This is primarily due to the fact that there are no data.

Dr. Campos-Outcalt requested that Dr. Kroger send the article regarding GBS to ACIP members so that they could better understand what occurred.

Dr. Brady (AAP) noted that prior to the advent of the electronic medical record, surgeons and anesthesiologists were doing elective surgery on children who received vaccines all of the time. They just did not have any records of the vaccines and they did not care. Now that they see the records, they are constantly cancelling elective surgeries in healthy children who have recently received vaccines. Given the fact that there are no data to show that this is a problem, the way the recommendation is worded is likely to be more harmful than helpful. He thought they needed to honestly say that there are no data to support the fact that vaccines given prior to surgery or anesthesia have any adverse effects, and let practitioners use their clinical judgment about what they want to do.

Dr. Kimberlin (AAP) drew attention to the wording regarding febrile seizures that stated that "febrile seizures are generally benign, and generally do not lead to poor neurologic outcomes." In discussions with the MMRV working group a number of years ago, and in discussion within AAP as a consequence of those considerations, the AAP has come down much more strongly

that febrile seizures are benign. They are not "generally benign" they "are benign." The specific wording included in the MMRV AAP statement is that "Febrile seizures do not predispose to epilepsy or neurodevelopmental delays later in life. Although they are frightening for parents, febrile seizures are not associated with long-term health impairment for the affected child." He encouraged ACIP to adopt similarly decisive language.

Dr. Fryhofer (AMA) requested further clarity about timing of vaccinations prior to surgery. For example, if a patient presents in her office for a pre-operative evaluation for elective surgery in one to two weeks, but the patient has not had their influenza vaccine, she would have to have them return after their surgery for their influenza vaccination based on what was presented. As a clinician who would have to read the recommendation and determine what to do, she was very confused by this and requested more specific guidance about timing. The focus seemed to be on the anesthesia / surgery issues versus acute illness.

Dr. Kroger replied that the recommendations as rewritten still give discretion to the provider to determine the status of acute illness at that time.

Dr. Temte pointed out that most hospital rules require a pre-operative history / physical within 30 days of a planned procedure. That is an opportunity for him to review all of the health maintenance for his patients and catch-up on immunizations, which he readily does all of the time. This is also a great time for an influenza vaccine in order to reduce the risk of becoming ill prior to the surgery and having to cancel because of it.

Ms. Stinchfield (NAPNAP) reported that in her institution, a couple of times a month they have a parent who requests vaccines while the patient is having surgery and is anesthetized. Because there are not a lot of data and guidelines, every institution has to develop their own recommendations. Beyond post-operative fever and anesthesia impacting immune response, there are a lot of practical considerations pertaining to storage, handling, understanding doses, proper administration technique, and documentation. There is a lot to think about in terms of vaccinating in the surgical setting. In addition, there are numerous types of anesthesia (e.g., topical anesthesia, general anesthesia, nitrous oxide). More data are needed on vaccination and the various types of anesthesia, and there needs to be more precision about this.

Dr. Duchin acknowledged that it was difficult to be precise when there were unknowns, which was one of the problems, and some good suggestions had been offered during this discussion. One of the counterpoints to the suggestion about deferring vaccination before procedures was that he has had people who had their elective cardiac surgeries cancelled because they had an influenza vaccination, got a fever, and the team refused to operate on them. The working group was not trying to imply that the vaccination would cause any sort of significant clinical problem, but that it may cause a fever or other adverse event that could be confused with a clinical problem, and therefore interfere with a planned surgery or be interpreted as a complication of the surgery or procedure. The timing component needs to be narrowed down, but there is a rationale for not giving a vaccination too close to an elective surgery, for example.

Dr. Brady (AAP) agreed that there may be some issues related to receiving a vaccine, but the number of people who have those events is relatively small. In pediatrics, since many vaccines are given, it does create a tremendous problem when the pediatrician does the right thing and brings a child current with vaccines, but a procedure is cancelled as a result because there are no data to support this.

Dr. Duchin emphasized that nothing written in the recommendation would suggest cancelling an elective procedure.

Dr. Brady (AAP) said he could guarantee that because of the way it was worded, that vaccines should be given after surgery, anesthesiologist would say, "See, we were right. It should be done after surgery."

Dr. Duchin thought that the inclusion of more context would be helpful.

Dr. Harriman stressed that the CMS requirements posed a major issue, because at the state level they are receiving many calls from hospitals that are trying to implement this. They want a definition of what constitutes mild, moderate, and severe. They also have concerns about post-op fever from a vaccine and how that will play out. There is a lot to do in a 2- to 3-day admission, so this is a major struggle. Many questions about this are on the National Infection Control listservs as well.

Dr. Duchin expressed appreciation for Dr. Kroger's leadership on the working group, emphasizing that this is a very tough issue to deal with, given that there is a lot of uncertainty and there is not a solid evidence base upon which to proceed.

Measles and Rubella Initiative

Lisa Cairns, MD, MPH, Deputy Branch Chief
Disease Eradication and Elimination Branch
Global Immunization Division, Center for Global Health

During this session, Dr. Cairns presented an update on the Measles and Rubella (MR) Initiative, which has been a remarkable success story. Between 2000-2010, a 74% reduction in measles deaths was observed. This reduction in measles deaths contributed 20% to the overall reduction observed in childhood mortality, addressing WHO's Millennium Development Goal (MDG) 4 to reduce by two-thirds, between 1990 and 2015, the under-five mortality rate [Simons E et al. Assessment of the 2010 global measles mortality reduction goal: results from a model of surveillance data. Lancet 2012; 379(9832):2173-8].

Dr. Cairns explained that the MR Initiative is a partnership with five founding partners, including the American Red Cross, CDC, United Nations (UN) Foundation, United Nations Children's Fund (UNICEF), and WHO. Other participating members include civil society organizations at the national level, national governments, private donors and foundations, and public donors. MR Initiative has a number of major functions. At the global level, it has coordinated global efforts to reduce eliminate measles and more recently rubella, including fundraising and in advocating. It offers technical assistance to countries, and recently it has tried to incorporate research that is considered important for meeting control and elimination goals through its activities. The MR Initiative also plays a major role in monitoring, evaluation, and reporting functions.

The impetus for the founding of the MR Initiative in 2001 was the success of measles elimination in the region of the Americas (PAHO) and the success in measles mortality reduction in Southern Africa – based on the same strategy as that used in PAHO. In 2012, what began as the Measles Initiative changed its name to the Measles and Rubella Initiative in recognition of the increasingly important role of rubella control and elimination.

In 2010, a Global Consultation on the Feasibility of Measles Eradication was held. The final conclusion was that measles can and should be eradicated, but that this should be done in the context of strengthening immunization and primary health care systems. At this consultation, measles eradication and the existing measles elimination efforts were recognized as an opportunity to accelerate rubella control and the prevention of congenital rubella syndrome (CRS). There was discussion that 2020 would be a feasible target date if interim targets were met.

Since 2010, a number of significant changes have occurred. One of these was the publication of a new WHO position paper on rubella in 2011 stating that, "In light of the remaining global burden of CRS and proven efficacy and safety of RCVs, WHO recommends that countries take the opportunity offered by accelerated measles control and elimination activities to introduce RCVs." This was the first time that there had been a broad endorsement at the global level for rubella-containing vaccines (RCVs) to be used. The position paper noted that "The preferred approach is to begin with an MR vaccine or MMR vaccine in a wide-age range campaign followed immediately with introduction in the routine programme. Countries introducing RCV should achieve and maintain immunization coverage of 80% or greater with RCV delivered through routine services and/or regular SIAs."

As a result of this position paper, GAVI decided to offer major support for introducing rubella in the form of MR. As a result, support for rubella vaccine introduction also translated into major support for measles activities. GAVI has offered support of more than $750 million through 2018 to support a number of efforts. The first is the introduction of rubella vaccine with catch-up supplementary immunization activities (SIAs) in children 9 months through 14 years of age. The next is performance-based funding to improve first dose measles coverage. The details of how this performance-based funding will function are still under discussion. GAVI also supports grants to introduce a second dose of measles vaccine into the routine program, as, in many countries, a first dose of measles vaccine is given through the routine immunization system, but there is not yet a second dose delivered through the routine system. In these countries, when a second dose is given, it is historically been given through vaccination campaigns. In recent years, there has been a movement to introduce a routine second dose into the immunization program; GAVI is supporting this. GAVI has also offered support for measles follow-up SIAs in 6 large countries that were thought to be at very high risk for measles outbreaks. These are countries with infrastructure challenges (e.g., Chad, Nigeria, Ethiopia, Democratic Republic of the Congo, Pakistan, and Afghanistan). Finally, GAVI has also offered support for measles outbreak response. This was really lacking at the global level in the past, so when there were large measles outbreaks, there was no source of global funding to respond to these.

In 2012, the MR Initiative published the *Global Measles and Rubella Strategic Plan, 2012-2020*. This plan was endorsed by the heads of the five founding agencies, including Dr. Frieden. The vision of this strategic plan is to, "Achieve and maintain a world without measles, rubella and congenital rubella syndrome." The goals are: by the end of 2015 to reduce global measles mortality by at least 95% compared with 2000 estimates; achieve regional measles and rubella/CRS elimination goals; and by the end of 2020 achieve measles and rubella elimination in at least five WHO regions. This is really quite ambitious.

More "granular" measles and rubella targets have also been set. The first is the World Health Assembly 2015 Global Targets, which include a measles mortality reduction of 95% versus 2000; measles reported incidence of less than 5 cases per million; and measles vaccination coverage of 90% at the national level and 80% in every district. There are currently five regions

that have measles elimination goals. The following are the dates of their goals: AMRO (2000), WPRO (2012), EURO and EMRO (2015), and AFRO (2020). During the same week of this ACIP meeting, a meeting was held in Kathmandu during which there was to be a discussion of establishing a measles elimination goal for the Southeast Asian Region (SEARO). If the Southeast Region established a goal, then all six global WHO regions would have an elimination goal. Two WHO regions also have rubella elimination goals, including AMRO (2010) and EURO (2015). The Global Vaccine Action Plan (GVAP) includes a goal of measles and rubella elimination in five WHO regions by 2020.

Regarding progress on achieving these goals, from 1980 through 2011, there has been a reduction in measles global annual reported cases and an increase in coverage. However, there has been a lot of leveling off in the past few years. The estimated 74% reduction in measles deaths from 2000 through 2010 is based on modeling, because in many of the countries where there is the highest mortality, there is not good surveillance for measles mortality. Therefore, it is necessary to rely on modeled estimates. In terms of estimated measles deaths by WHO region from 2000 through 2010, there has been a major variation across the regions in the extent to which they have been able to reduce their measles mortality. Most of the regions have progressed quite well. Excluding India, the Southeast Asia Region is estimated to have reduced measles mortality by 78%. By 2010, India had achieved comparatively little reduction in estimated measles deaths. Because of the size of the population of India, this had a major impact on the whole Southeast Asia Region. However, India has recently become much more actively engaged in reducing its cases and mortality through a combination of administration of a routine second dose and conducting supplementary immunization activities. [Simons E et al. Assessment of the 2010 global measles mortality reduction goal: results from a model of surveillance data. Lancet 2012; 379(9832):2173-8].

Despite the fact that a major reduction in mortality has been observed and there has been an increase in coverage, in 2011 there were a number of large measles outbreaks. There were some very large outbreaks in parts of Africa and in EMRO [Data sources: monthly surveillance DEF file and country reports received at WHO IVB. Data in HQ as of 30 May 2012. Data for Somalia and DRC from aggregate case reports, not monthly DEF file]. In terms of coverage with a first dose of measles-containing vaccines by region from 2000 through 2011, some of the regions, such as the African Region, have made pretty substantial progress over the past decade. However, in other situations, such as in Europe, the coverage has been fairly flat [Source: WHO/UNICEF coverage estimates 2011 revision. July 2012, 193 WHO Member States. Date of slide: 3 September 2012].

As mentioned, GAVI is funding the introduction of a second dose of measles vaccine through the routine immunization system. About a decade ago, the global recommendation for measles vaccination was one dose of vaccine, followed by giving every child a “second opportunity for vaccination” as opposed to a second dose of vaccine. For many children, that actually translated into one dose of vaccine—if they were lucky. However, a revised position paper published by WHO in 2009 clearly articulated the need for two doses of vaccine for each child. That is now the global standard, so a second dose is now used in all countries. A routine second dose has been introduced by 141 countries, and supplemental immunization activities are used in other countries that have not introduced a routine second dose [WHO/IVB database, 194 WHO Member States. Data as of July 2012]. With regard to some of the surveillance and reporting activities that are supported through the Measles and Rubella Initiative, there is an extensive laboratory network with oversight from WHO Geneva. Currently, there are about 690

laboratories in the network globally, including both national and regional reference labs. These labs test for measles and rubella.

Challenges in reaching measles control and elimination goals vary substantially according to the Region. The Americas eliminated indigenous measles in 2002, but is constantly being exposed to new importations just as the US. It is a challenge to maintain sufficient immunity to stop these importations from turning into outbreaks. In Africa the weak immunization and health systems struggle to reach high coverage with one dose of measles vaccine, let alone two. In this setting, one is often obliged to rely on supplementary immunization activities. However, it is difficult to organize those and to achieve the coverage necessary. In the Eastern Mediterranean Region, there are major security concerns that limit access to vaccines in countries like Afghanistan and Pakistan. In Europe, there is a lot of vaccine hesitancy. This had led to large outbreaks in some places such as France and the Ukraine. In Southeast Asia, there are a number of large federalized countries such as India and Indonesia. The political structure of these countries makes it challenging to have centralized disease control initiatives move forward. In the Western Pacific, although greatly reduced transmission has been observed in China, there continues to be transmission there. Because of the size of the population in China, this country's progress is key to bringing measles incidence to low levels in the Western Pacific Region. In all Regions it is a challenge to achieve and sustain high second dose coverage. Globally, we are increasingly seeing measles susceptibility gaps in the older population, which presents challenges. There is also an ongoing lack of human and financial resources.

In contrast to the measles situation, over the past decade there has not been very much change in the estimated burden of congenital rubella syndrome globally. In 1996, there were estimated to be 120,000 congenital rubella syndrome cases globally. In 2010, there were estimated to be 103,000 cases. It is striking, in this context, to see the very low number of reported cases. This reflects the fact that there is very little CRS surveillance conducted globally. As mentioned, rubella testing is done through the laboratory network. What is often done, but not always, is that when a rash and fever case is reported, it is first tested for measles and then if it tests negative for measles it is tested for rubella. The algorithm varies somewhat according to region, but that is the most frequently used algorithm. Most of the rubella cases reported to WHO from 2000 through 2011 were reported through the laboratory network.

The number of countries with rubella-containing vaccine (RCV) in the National Childhood Immunization Program remains relatively low. In 1996, there were 83 countries representing 13% of the global cohort using RCV. In 2011, there were 130 countries representing 41% of the global birth cohort. In most of Africa, Southeast Asia, and some parts of the Western Pacific Region a rubella-containing vaccine is not given. With the funding from GAVI, the expectation is that rubella vaccine will be introduced in many of these countries over the next five years. This produces some real challenges at the global level in terms of vaccine supply. The number of doses of vaccine that will be needed will depend upon when different countries introduce vaccine. These countries would all be conducting wide age range campaigns, and, after that, introducing rubella vaccine into their routine immunization systems.

The Measles and Rubella Initiative has been trying to focus more on a research agenda to look proactively at what the needs are going to be in the future to be able to meet the measles and rubella elimination and control goals. A meeting was convened in 2011, the results of which were published in *Vaccine* in 2012. There is also a sub-group of WHO Strategic Advisory Group of Experts (SAGE) working group on measles and rubella that addresses research issues.

In summary, it can be said that, since 2000, there has been remarkable progress made in terms of measles control, with a three-fourths reduction in measles deaths and reported incidence rates globally and with elimination of measles and rubella in the Americas. Recently, there has been substantial progress in India and great progress in China. There are new tools being developed for diagnosis, and there are new resources from GAVI and other partners. However, some real challenges remain. These include leveling off of coverage, incidence, and deaths; weak immunization systems that cannot be strengthened rapidly; conflict and emergency settings, which are always difficult to work in; and maintaining social and political will to continue this work.

Discussion Points

Dr. Pickering indicated that when CDC spoke with colleagues from El Salvador, they reviewed problems they are having with surveillance systems in El Salvador that hinder availability of data to make vaccine recommendations. Particularly with regard to the measles areas mentioned, he wondered how comfortable Dr. Cairns was with the surveillance systems in the various WHO Regions.

Dr. Cairns responded that if coverage is considered, surveillance is not particularly strong in general. That is an area in which a lot of work must be done in terms of improving the quality of both denominators and numerators to get good coverage figures. She thinks surveillance in terms of disease incidence is fairly good overall. That she knows of, no studies have been done to evaluate reporting efficiency. However, laboratories in the extensive network are routinely reporting.

Dr. Smith inquired as to whether Dr. Cairns defined “elimination.”

Dr. Cairns replied that basically the definition is the same that was used in the US, which is the absence of circulating endemic virus for a year. There was a period of time during which there was discussion of using less than 1 per million incidence for measles as a definition; however, that has been refuted.

Dr. Plotkin (Vaccine Consultant) observed that from his point of view, one of the major defects of the attempt to eliminate rubella was the lack of serologic studies, particularly in women of childbearing age, so that something is known about the circulation of the virus. Although surveillance for congenital rubella syndrome can be done through cataract surveillance relatively easily, it does not appear that this is being done systematically either. However, both are very important. He also has concern about introduction of rubella-containing vaccines in India, a country that has been notorious for its lack of efficient vaccination. If rubella is gradually introduced into India in three different years as shown, the possibility of a perverse effect in terms of reducing circulation sufficiently so that women grow up without antibodies becomes important. That can be eliminated by a high rate of infantile immunization, but there are some grave doubts about the ability of India to do that. One way to get around that would be to introduce vaccination of women subsequent to childbirth. That would be an efficient way of reducing the risk to pregnant women, and even in India that could probably be accomplished.

Dr. Cairns agreed fully that there were issues, particularly with serosurveillance. The focus on rubella is relatively recent and has brought awareness to the need for improving CRS surveillance, and there are efforts in that direction. Regarding the possibility of using cataract surveillance to search for CRS, Disease Eradication and Elimination Branch is involved in a couple of research studies to assess that more closely. Hopefully that will offer a simplified

algorithm. One of the challenges is that CRS surveillance is somewhat different from a lot of traditional vaccine-preventable disease surveillance and can be challenging for countries to implement. Therefore, finding a simplified algorithm that is easy to use in some resource-limited settings is going to be important. The points about India are well-taken.

Global Polio Eradication Initiative

Dr. Robert Linkins, Chief
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Dr. Temte called attention to a letter from the Independent Monitoring Board (IMB) to Dr. Margaret Chan acknowledging that the 2012 polio eradication goal was not achieved, but that nevertheless, very good progress had been made toward polio eradication in 2012 with just 223 cases of polio. That represents one third of the total for 2011. The letter also addressed the polio eradication campaign workers who were killed in Pakistan and Nigeria for providing polio vaccines.

Dr. Linkins acknowledge Dr. Jean Smith, ACIP's Secretariat, who was a pioneer in the early days of the polio eradication program at CDC through the mid-1990s. For 10 years, she worked in India and Nepal and was instrumental in setting up Acute Flaccid Paralysis (AFP) surveillance in Southeast Asia. She made a tremendous impact before coming to the ACIP. Dr. Linkins said he wanted to make sure that everyone knew that Jean Smith was a very special person for those in polio. He then presented an update on the Global Polio Eradication Initiative (GPEI).

A very dramatic and impressive decrease has occurred in the number of cases since the 1980s. In 1988, the world decided that it had had enough of 1000 children getting polio each day. In May 1988, the World Health Assembly (WHA) resolved to set its efforts on eradicating polio globally. Also, that created the Global Polio Eradication Initiative (GPEI). In the 1990s, a 99% decrease was observed in the incidence of polio globally. Polio was eliminated from the Western Hemisphere. Absolutely astounding was the eradication of one of the three types of polio (WPV2). Types 1 and 3 are still circulating, but eradication of Type 2 was an amazing achievement. In terms of the 21st Century, the incidence of wild polio virus cases ranged between 500 and 2000 per year through 2011.

Two seminal events occurred in 2011. For many in the public health community, there was finally proof that polio eradication was, indeed, possible with the interruption of polio virus circulation in India. Despite very aggressive surveillance that continues to this day, no cases have been detected to date since January 13, 2011. That really is quite an achievement. The Indians have really led the globe in showing that a virus like polio can be eradicated in an incredibly difficult environment. The second major achievement had less to do with program outcome than with program management. The GPEI's Independent Monitoring Board (IMB) released a report in October 2011 that woke up the global polio eradication community. The IMB concluded the following, "The Programme is not on track for its end-2012 goal, or for any time soon after unless fundamental problems are tackled. This Programme needs greater global priority and funding. Failure would be a disaster. We are convinced that polio can – and

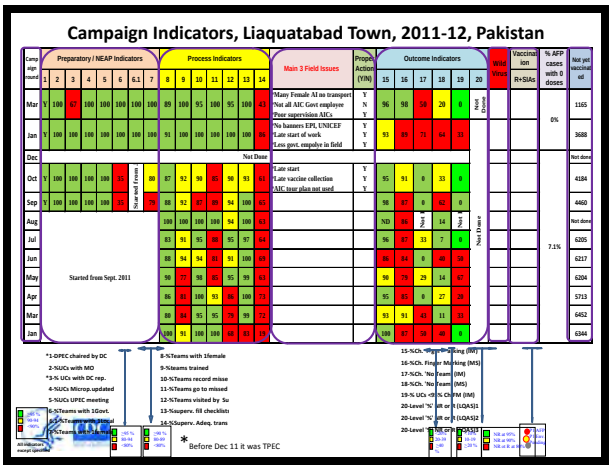
must – be eradicated. We are equally convinced that it will not be eradicated on the current trajectory."

The IMB's conclusions precipitated a meeting in late 2011 in Atlanta of the core polio partners: WHO, UNICEF, CDC, Rotary, and the Bill and Melinda Gates Foundation. One of many conclusions reached in that meeting, which Dr. Linkins believes was a game changer, was that business as usual was no longer an option in the polio eradication program. Dr. Frieden has been quoted as saying that, "At this point in the program, polio eradication has become a lifestyle rather than a goal that we are all working toward." People were so used to this program continuing on, and on, and on that there was not a sense of urgency in the program that the job must be finished. At CDC, Dr. Frieden also had the courage to be the first head of the partner agencies to activate its Emergency Operations Center (EOC), which has helped to intensify and consolidate CDC's emergency response to the GPEI.

At the end of 2011, there were no cases of polio in India. However, there was continued endemic circulation in Nigeria, Afghanistan, and Pakistan. There was re-established transmission (e.g., transmission occurring for 12 months after an absence of transmission in a country) in Angola, Democratic Republic of Congo, and Chad. There were 11 different outbreaks in 9 countries. In total, there were 650 cases seen in 16 countries. The situation actually looked much better at the end of 2012. There were large decreases in case counts in Afghanistan and Pakistan, but there was a worrying doubling of cases in Nigeria. No cases were reported since 2011 in Angola or the Democratic Republic of the Congo, and no cases were reported in Chad since June 2012. This suggested the interruption of transmission in the three re-established transmission countries, which was very exciting news. Only one outbreak was reported, which was in Niger caused by a Nigeria virus that resulted in only one case, with the onset of paralysis in November. In total, cases decreased from 650 in 2011 to 223 in 2012.

While cases have decreased in Pakistan over the last four months, there has been no circulation in Baluchistan and there has been only limited circulation in Sindh, which includes the City of Karachi. However, circulation continues in FATA and in Khyber Pakhtunkhwa. Eradication challenges in Pakistan include poor management; corruption; insecurity and violence against vaccinators; and inaccessibility to children in some areas, particularly in North and South Waziristan.

Major changes to the Pakistan program since early 2011 have included new program leadership, particularly by CDC staff secunded to the WHO in the Eastern Mediterranean Region (Dr. Elias Durry), as well as by Special Assistant to Pakistan's Prime Minister (Shahnaz Wazir Ali). There has also been implementation of a new dashboard system that assesses district readiness to conduct polio immunization campaigns. Polio control rooms were established to centralize and closely monitor activities. A National STOP (NSTOP) team was established, which is modeled after CDC's STOP program, but that is comprised of national polio eradication staff. Many of these staff members are Field Epidemiology and Laboratory Training Program (FELTP) graduates in that country. They are trained and are then sent to high risk areas in Pakistan where Westerners cannot work. The following is an example of Pakistan's dashboard:



On the dashboard, readiness to conduct polio campaigns is assessed using a red, yellow, green stoplight approach. This has actually proved to be very effective. In districts judged to be unprepared, polio immunization campaigns are postponed until remedial actions are taken to ensure high immunization coverage during the campaign. This strengthened program management and accountability has led to measurable increases in campaign coverage. In two different sampling methodologies implemented over time from January 2011 through October 2012 to assess campaign coverage, both show increasingly improved coverage over time.

Moving to neighboring Afghanistan, it is important to note that while Afghanistan's Eastern region is continually being re-infected with Pakistan virus, Afghanistan has its own endemic circulation in the Southern provinces of Kandahar and Helmand. Like Pakistan, Afghanistan's challenges include poor program management, insecurity, and inaccessibility in the Southern region. There has also been slow implementation of their polio emergency action plan. In the last year, Afghanistan has identified 13 high-risk districts all in the South, and is intensifying activities there with the deployment of permanent polio immunization teams that provide house-to-house social mobilization activities throughout the year. In the East, there is a new focus on synchronized cross-border activities with Pakistan and at the national level, a push to work with new partners like the agricultural sector. The problem in Kandahar and Helmand is that there are too many missed children; that is, children who are accessible but who are missed in polio immunization campaigns. Hopefully, Afghanistan's increased focus on program management and accountability will go a long way toward solving this problem.

There has been a continuing challenge in Northern Nigeria. Nigeria has three transmission zones, which include the Northwest, North Central, and Northeast and has seen Types 1 and 3 polio circulation as well as vaccine-derived Type 2 circulation. Nigeria is perhaps the toughest area, and is the current priority focus of the GPEI. It may actually be the only country in Africa right now where polio continues to circulate. As mentioned earlier, cases were double in 2012 what they were in 2011. Unlike the progress observed in Pakistan and Afghanistan, there is less hope for what is going on currently in Nigeria, although there is some recent indication that the situation might actually be improving. Major transformations are occurring in Nigeria to turn this increasing polio incidence around. Partners are doing a better job of coordinating their activities at the global, national, and local levels. This collaboration includes training and deploying more than 4000 field staff and over 100 NSTOP program staff in close collaboration with Nigeria's FELTP program; developing emergency operations centers to centralize polio operations and management in the highest risk areas; and employing new tools to identify previously unknown nomadic communities with large numbers of completely unvaccinated

children, not just with polio, but with other EPI antigens, and who also have unreported cases of acute flaccid paralysis. New tools to monitor before, during, and after campaigns include dashboards similar to those used in Pakistan and India, and exciting new GIS techniques to intensify house-based micro-planning.

Nigeria is also implementing lessons learned in Pakistan and India to improve its program, and recently hosted its second group of surveillance medical officers from India to share eradication lessons learned in India. There has been a recent upturn in violence targeted at public health workers in Nigeria. While there is absolutely no denying that this is a tragedy and a real risk to the program, the government is increasing security during campaigns and messaging the critical nature of completing the eradication job in that country.

In terms of moving forward, work is currently underway in what is hoped to be the very last polio eradication strategic plan, which covers 2013 through 2018. Major milestones in this plan include the end of wild virus circulation by the end of 2014, the introduction of at least one dose of IPV in the routine immunization program by the end of 2015, a switch from trivalent oral polio vaccine to bivalent oral polio vaccine by the end of 2016, and the end of all oral polio vaccine use by the end of 2019.

In summary, substantial progress has been made over last year, but more must be done. There have been major program improvements in Pakistan, but there has been less impressive progress in Afghanistan. Continued challenges in Nigeria are being met with major program transformation, and perhaps interrupted polio virus transmission elsewhere. Maintaining the population immunity needed to keep these areas polio free will be a continuing challenge, particularly in the face of weak routine immunization programs; poor management and corruption in many countries at risk for polio; and ongoing challenges with insecurity, national politics, and maintaining an adequate vaccine supply.

Discussion Points

Dr. Coyne-Beasley inquired as to why the children were missed in Kandahar.

Dr. Linkins replied that part of the challenge is the quality of immunization program delivery. For example, some vaccinators do not make the extra effort to go down Street B when Street A is so much easier to get to. One of the partner organizations, UNICEF, conducts post-campaign surveys targeted at why children are missed. Among the reasons they always find is not so much blatant refusals by parents to vaccinate, but other excuses such as the child is sick, sleeping, out in the field, et cetera—more indirect refusals to vaccination. The surveys have gone a long way in helping to target messages and strategies to make sure that those children are not missed in the future. Nevertheless, some of it is inaccessibility. These are very tough places to work, so local community volunteers are enlisted in the program to help deliver vaccine.

Given that there are many needs in the countries discussed, Dr. Jenkins could not imagine how polio vaccination rises to the top. She wondered what types of incentives are offered to workers, especially public health workers, to meet some of these goals.

Dr. Linkins responded that the IMB publishes quarterly reports regarding their assessment of the status of the polio eradication program. In one of their recent reports, they made the major point that the program needs to place more value on vaccinators at the local level. The people who are really “rolling up their sleeves” and going house-to-house are the real heroes of this

program. One incentive that has been used is to acknowledge the job they are doing. Another, which is really very important, is to increase their pay. Afghanistan and Pakistan compare their salaries, so part of the effort at the global level has been to ensure that there is just pay for the work being done.

Dr. Wassilak (SME) added that a lot has to do with the quality of the supervisor, so the better the supervisor, the more motivated the staff are.

Dr. Linkins noted that assessment is being done of the efficiency of the program, which includes the efficiency and effectiveness of the training conducted for vaccinators. More value is being placed on training, and more respect is being provided for these people than has been offered in the past. That is an important lesson that the IMB has highlighted.

Dr. Sun (FDA) wondered whether there were any surprises in the polio campaign as compared to the smallpox effort in terms of obstacles.

Dr. Linkins thought one lesson they learn every single day is how hard this is. This is a tough job. Many people thought, "Smallpox is doable. We did it. We showed the world that we can eradicate a virus. We can do polio." It is a lot more difficult than anticipated. One of the lessons learned has been not to leave the hardest countries for last. Those should be targeted first, and early, and hard. Another lesson learned is to ensure that there is political will from the top down in every community. To get the job done, it must be made a priority for everyone.

Dr. Wassilak (SME) emphasized that there are many challenges for polio that differ from smallpox. The vaccine is much less effective for polio than for smallpox, multiple doses are required, surveillance captures only the "tip of a very large iceberg," and there is a lack of appreciation among these communities that polio is a serious disease that deserves prevention. There are lessons learned and that continue to be learned from the "house on fire," but they are still different enough that retooling was required for these particular issues. Lack of ownership and lack of political have really been hindrances in all of these trouble areas.

Dr. Linkins added that this has gone on for so long that everyone in Atlanta is tired, and if everyone is tired in Atlanta, imagine how everyone feels in Kandahar when they are told every month or every two months that there is another campaign and they need to get out there and find these children or the job is not going to get done. It is very important to finish this job and move on. There is a lot of exciting evidence to suggest that this is possible and is happening. Dr. Linkins stressed that it is an honor to work in this program with great people like Jean Smith.

Dr. Temte indicated that a little over a year ago, the US was recertified as being free of measles, rubella, and CRS. He requested input on the last case of polio in the US, pointing out that these campaigns were a testament to what can be done.

Dr. Wassilak (SME) reported that the last cases of polio in the US were in 1979, and PAHO certification was in 1992.

Day 1: Public Comment

Karen Ernst
Voices for Vaccines

I have no conflicts of interest. I come from Voices for Vaccines. We are made up of anyone who is interested in protecting children from vaccine-preventable diseases. We are parents, we are doctors, we are nurses, we are grandparents, we are aunts and uncles, we are anyone who cares about a child. We are an organization that is putting together the means to help all of these people advocate for better conversations, better media coverage, and better policies and legislation involving vaccines. I would like all of you today to go to the voicesforvaccines.org site and join. Thank you.

Deborah Wexler
Immunization Action Coalition

I receive funding from the Centers for Disease Control and Prevention, from three foundations, and several vaccine companies. We are proud recipients of support from all of these organizations, including vaccine companies. My brief announcement today is that the Immunization Action Coalition launched a new website in addition to immunize.org. Just a couple of weeks ago we launched a new website, well actually it's an old website that we re-launched. It's called vaccineinformation.org. It's our website for the public. It's really nice. I urge you to talk to your patients about it. It's a really great place to get vaccine information by age (infants, children, pre-teens, teens, adults). The site is full of personal stories about people who have suffered or died from vaccine-preventable diseases. There are over a hundred video clips and more coming that you can use in presentations. So, those are all available on the website in addition to disease-specific information. It's pretty simple, straightforward, and easy to navigate. I urge you all to please sign up and become members of Voices for Vaccines. It's a wonderful organization led by two young parents, and they are doing a terrific job, and I think we should all support them. LJ Tan could not attend today because he got stuck in Hong Kong from an engine failure as they were taking off in the plane, so the flight takeoff was aborted. But LJ Tan has left the AMA and joined the Immunization Action Coalition effective the beginning of January. He is our chief strategy officer. We are very proud to have him. I would like to also add that Dr. William Atkinson, who retired recently from the Centers for Disease Control and Prevention is also now a consultant at IAC as our Associate Director for Immunization Education.

Distinguished Service Medal Presentation

Melinda Wharton, MD, MPH, Acting Director
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Wharton indicated that the Distinguished Service Medal is the highest Public Health Service Commissioned Corps award. This award is given to commissioned officers for outstanding contributions to the mission of the Public Health Service. Such achievements may range from

the management of a major health program, to an initiative resulting in a major impact on the health of the nation. It can also be conferred for a one-time heroic act resulting in great savings to life, health, or property. During this session, Dr. Wharton presented a Distinguished Service Medal to a US Public Health Service Commissioned Officer who recently retired. She read the following excerpt from this award nomination:

> "The US Immunization Program is one of the top public health successes. Thousands of deaths a year are prevented in children and adults due to the vaccines given throughout the lifespan. CDC's Advisory Committee on Immunization Practices sets standards of care for the Public Health Service and the nation through its recommendations for prevention and control of vaccine-preventable diseases. These recommendations are complex and can change rapidly for many reasons, including epidemics, outbreaks, other public health emergencies; vaccine shortages; new product licensures; or safety concerns. Educating clinicians and public health practitioners on the constantly evolving recommendations has been a critical component of the enormous success of the US Immunization Program. Since 1995, this officer almost single-handedly raised the standards and approach toward vaccine education to new heights as the leader of CDC's Immunization Education Team. This officer led ACIP policy development for several vaccines, and made major contributions to others. Additionally, this officer was a national leader in educating providers and public health practitioners on current vaccination policy and vaccine safety. Because of this officer's persistent, innovative, and invaluable efforts, the officer became the public face of CDC's Immunization Program. This officer is recently retired Captain Bill Atkinson.

Dr. Wharton invited Dr. Atkinson to come forward to accept his award. He accepted the award and expressed his gratitude.

Farewell to Sara Rosenbaum

Dr. Jonathan Temte
Chair, ACIP

Dr. Temte mentioned that to everyone's great regret, this would be Sara Rosenbaum's last ACIP meeting. She has been with ACIP as a voting member since January 1, 2010. Ms. Rosenbaum is Jane Hirsh Professor of Health Law and Policy at George Washington University. She has been invaluable in helping ACIP understand the nuances and intricacies of the Affordable Care Act, as someone who was intimately involved in its creation. She has a position on ACIP that will be greatly difficult to fill with anyone who has similar expertise. Typically, the last meeting for members rotating off the committee is in June. However, Ms. Rosenbaum will be unable to attend the June meeting. Dr. Temte offered public gratitude from himself, Dr. Pickering, Dr. Smith, the rest of the ACIP members, and everyone involved at CDC and beyond. He thanked Ms. Rosenbaum for her service, and requested that she make a few comments.

Sara Rosenbaum, JD
ACIP Member

Ms. Rosenbaum thanked Dr. Temte. She said she could not say enough about what an honor it has been to be a member of ACIP, and to be able to spend this much time regularly with CDC and the wonderful ACIP staff, particularly Drs. Smith and Pickering. Of all the work she has done over the last 20 years, her work with ACIP has been the most tremendous. Everybody on ACIP is excellent. She noted that she is an insurance lawyer by training, so her knowledge base goes to using the evidence that entities such as ACIP create to consider legal issues. Being on ACIP represented her first opportunity to serve as a member of an evidence-making body. She has been thrilled to have this kind of opportunity, and has learned so much about the making of really great scientific evidence. Children and adults who need immunizations are in good hands with the ACIP.

IOM Immunization Schedule Report

Ada Sue Hinshaw, RN, PhD,
Dean and Professor
Graduate School of Nursing,
Uniformed Services University of the Health Sciences
IOM Committee Chair

Dr. Hinshaw presented information on the recently published IOM reported titled, "The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies." This was a shift in thinking, and will perhaps be a shift in thinking for many in the vaccine community who are assessing immunization and vaccines. Many of the people who testified for IOM during the public meetings and several IOM members had to be reminded continually that the issue was the immunization schedule—not individual vaccines or adverse events in relationships to individual vaccines. This study resulted from the following 2009 recommendation from the NVAC Safety Working Group:

> *"For an external expert committee, such as a committee convened by the Institute of Medicine (IOM), with broad expertise in research methodologies, study design, and the ethical conduct of research to consider the strengths and weaknesses, ethical issues and feasibility including timelines and cost of various study designs to examine outcomes in unvaccinated, vaccine-delayed and vaccinated children and report back to the NVAC."*

The Statement of Task came directly from the NVAC Safety Working Group, and stated that the IOM would convene an expert committee to: 1) Review scientific findings and stakeholder concerns related to the safety of the recommended childhood immunization schedule; 2) Identify potential research approaches, methodologies, and study designs that could inform this question, including an assessment of the potential strengths and limitations of each approach, methodology and design, as well as the financial and ethical feasibility of doing them; and 3) Issue a report summarizing their findings. The committee members were carefully chosen for particular areas of background that were in the Statement of Task (e.g., stakeholders, well-known research methodologists, ethicists, individuals interested in health outcomes, and individuals who were interested in stakeholder concerns).

In terms of the committee process, three information-gathering meetings were convened that were open to the public. During these meetings, presentations were delivered from clinicians; representatives of federal and international state agencies, including public health agencies; vaccine safety researchers; advocacy groups; vaccine manufacturers; and methodological experts. Information was gathered about public perspectives, and the scientific literature regarding the safety of the childhood immunization schedule was reviewed. An independent paper was commissioned to inform the committee and solicit feedback from the public about the study designs for the safety evaluation of different childhood immunization schedules. Written and oral comments were received from a variety of stakeholders.

The identified stakeholders included academic researchers; advocacy groups; federal government agencies, departments, and federal advisory committees; the general public, including parents; health care systems and providers; international organizations; media; non-governmental organizations; philanthropic organizations; state, local, and tribal governments and public health agencies; the travel industry; vaccine distributors; the vaccine industry; and vaccine investors. In terms of stakeholder concerns, the IOM committee endorsed the need for systematic research to understand the public's knowledge, beliefs, and concerns about the childhood immunization schedule and vaccine-preventable diseases. A subset of parents were documented as having the strongest safety concerns. A major problem for stakeholders was that they thought too many vaccines were given too fast, particularly in the first two years. Communication was another major issue that threaded through all of the literature, as well as the public testimony received. Of those who parents trust to communicate information, 26% of parents in a recent survey listen to celebrities. Based on the stakeholder concerns, the IOM committee made Recommendation 4-1 as follows:

> *The committee recommends that NVPO systematically collect and assess evidence regarding public confidence in and concerns about the entire childhood immunization schedule, with the goal to improve communication with health care professionals, and between health care professionals and the public regarding the safety of the schedule.*

In terms of the scientific evidence to understand safety of the childhood immunization schedule, the committee searched for, assembled, and summarized information on the association between aspects of the schedule and specific health conditions already available in the literature. The concept of the immunization schedule is not well-developed in the scientific literature. The field needs valid and accepted metrics of the entire immunization schedule (the exposure) and clearer definitions of health outcomes linked to stakeholders' concerns (the outcomes). Evidence from assessments of health outcomes in potentially susceptible subpopulations of children who may have an increased risk of adverse reactions was limited, and is characterized by uncertainty about the definition of populations of interest. Based on this information, the committee made Recommendation 5-1 as follows:

> *To improve the utility of studies of the entire childhood immunization schedule, the committee recommends that NVPO develop a framework that clarifies and standardizes definitions of:*
>
> - *key elements of the schedule,*
> - *relevant health outcomes, and*
> - *populations that are potentially susceptible to adverse events.*

This led to the issue of future studies. The committee agreed that stakeholders' concerns should be one of the central elements used to drive searches for scientific evidence; however, these concerns alone, absent epidemiological or biological evidence, do not warrant the initiation of further study. Epidemiological evidence of potential adverse health outcomes associated with elements of the immunization schedule, such as post-marketing signals or indications of elevated risk from observational studies, should exist. Biological plausibility supporting hypotheses linking specific aspects of the immunization schedule with particular adverse health outcomes should also be present. With this in mind, the committee made Recommendation 6-1 as follows:

> *The committee recommends that HHS incorporate study of the safety of the overall childhood immunization schedule into its processes for setting priorities for research, recognizing stakeholders' concerns and establishing the priorities on the basis of epidemiological evidence, biological plausibility, and feasibility.*

Also with regard to future studies, there are many existing systems for the detection of adverse events that provide confidence that the existing schedule is safe. The committee recognized that the federal government invests considerable resources to ensure vaccine safety. The committee also took a very firm stand that any study that places children in a study group that does not receive vaccines according to existing guidance would be exposing them to greater risk for contracting vaccine-preventable illnesses and is, therefore, unethical. To address these issues, the committee made Recommendation 6-2 as follows:

> *HHS should refrain from initiating randomized controlled trials of the childhood immunization schedule that compare safety outcomes in fully vaccinated children with those in unvaccinated children or those vaccinated by use of an alternative schedule.*

The committee agreed that secondary analyses of existing systems are more promising approaches to examination of the research questions that the committee identified in future studies, and concluded that the VSD is currently the best-suited source of data for studying the childhood immunization schedule. Its utility will be expanded with the addition of more detailed demographic data and family medical histories. Newer data collection and surveillance systems, such as FDA's Postlicensure Rapid Immunization Safety Monitoring System (PRISM), offer potential for future studies. To address these issues, Recommendation 6-3 was made:

> *The committee recommends that the HHS and its partners continue to fund and support VSD to study the safety of the recommended immunization schedule. Furthermore, HHS should consider expanding the collaboration with new health plan members and enhancing the data to improve its utility and generalizability.*

In conclusion, Dr. Hinshaw shared the website address where the full IOM report can be accessed: www.iom.edu/childimmunizationschedule.

Discussion Points

Regarding Recommendation 6-3, Ms. Rosenbaum said she had thought for a long time that the reporting plans for safety studies are extremely limited. She asked Dr. Hinshaw to elaborate on whether other plans have not been included or were unwilling to participate. It struck her that the bellwether plans chosen were very non-diverse, with a very low number of participants in public insurance programs. She also wondered whether the trend toward HIT might offer another angle for this in terms of whether, as the care settings come on line more, it would be

worth going to them all. Currently, 75% of all Medicaid beneficiaries are in managed care plans. The number of children in these plans is probably closer to 85% to 95% of all children. Given the fact that Medicaid is now insuring about 1 of 3 children in the US, it might be worth going back to some of the very large plans.

Dr. Hinshaw responded that one of their concerns was that only private managed care organizations were included in that plan with CDC, that the low income population was not included, and that some of the Deep South states were not represented. The committee's concern was that those areas needed to be strengthened and enhanced. People who knew that database were very concerned that if they want to link it to susceptible populations, which is a major issue for the stakeholders, consideration must be given to how to define "susceptible" populations and assess them in the secondary analysis. Having family medical histories would be needed to do that, which is the linkage that is being made on some of those pieces.

Dr. DeStefano added that the composition of the current plans that are in the VSD is guided primarily by the data requirements that CDC set for it. Plans are needed that have good linkable databases, solid vaccine registries with detailed vaccination information, and the ability to link those with all levels of care. Consideration has been given several times to how to expand the VSD, and pilot efforts have been conducted with large health insurance plans. Having scoured the country, the plans that are included are the ones that have the types of data needed. While he agreed that they should consider the possibility of including other plans with more representation of lower income public health plans, the issue has been data quality. The FDA PRISM system is trying to use the larger health plans, with a focus on quantity versus quality. Those plans have somewhat limited information in terms of the depths of detail regarding immunization, and more difficulty in getting more detailed information if it is needed from medical records. In terms of the increasing utilization of healthcare medical records, the VSD and such systems will continue to evolve and will take Ms. Rosenbaum's recommendation to heart regarding going back to the large plans.

Given the challenges of some of the stakeholders in terms of dissemination of the summary of the report, Dr. Jenkins wondered whether there had been any discussion about translating it into some message that would be acceptable to the public.

Dr. Hinshaw agreed that this is always a concern, but noted that the IOM is primarily a policy organization, not a distribution organization. However, to address this to some extent, they have given testimony to Congress and the press, and have tried to get the press involved in talking about the report. They are also talking to groups such as ACIP, as well as policy groups.

With regard to Dr. Temte's inquiry about the public response to date and whether IOM planned to make any effort to review, collate, and disseminate the public comments flowing back in, Suzanne Landi (IOM) indicated that after the report was released, there was wonderful press coverage in some major news networks that were all very positive. Few public comments were received after the report was released, but when the commission paper was published early in the study process, over 900 public comments were received. There is certainly a lot of interest, and a lot of concerns from parents. Some of their concerns can be found in Chapter 4 of the report, which includes discussion about the reports received. The public comments are all listed in the IOM's Public Access File, which can be requested. She was not sure whether there would be any additional effort beyond the summarization of public comments in the report, but this can be considered.

Ms. Stinchfield (NAPNAP) asked whether Ms. Landi could characterize the themes of the comments in terms of whether they were supportive, disbelieving of the report, et cetera.

Ms. Landi (IOM) responded that one of the overwhelming concerns regarded immune system overload in terms of whether receipt of too many vaccines at once could have a detrimental effect on a child's immune system or leave them susceptible to autoimmune diseases, allergies, et cetera. Since the report was published, few comments have been received on that subject.

Regarding Recommendation 6-2, Dr. Sun (FDA) wondered why the committee thought that the phrase "those vaccinated by use of an alternative schedule" was necessary. He said he asked because the FDA labels with vaccine schedules are usually done as schedules in the pivotal trial, so any reduction in those schedules will have to rely on adequate, well-controlled studies. The inability to do that would prevent any consideration of reductions in schedules that may be just as safe and effective.

Dr. Hinshaw responded that the committee felt strongly about that because of the limited research that is available in terms of addressing particular stakeholder concerns about the schedule that could be assessed over so many years with so many studies, and because such studies would be very expensive and would not come to fruition for a long period of time. The major issue regarded the unethical nature of such studies. If there was some epidemiological information from the large datasets that suggested that this is a plausible issue, this could lead to an RCT that varies the schedule in some way. However, anything that would deny a child certain vaccinations that are known to be valuable and prevent certain diseases would be unethical. The IOM was not saying to never conduct these studies, but was saying to refrain from them now because epidemiological and biological plausibility data are needed to suggest where to target such studies, if they are appropriate.

Dr. Pickering noted that ACIP has 31 liaison organizations, and would be happy to work with IOM to disseminate this report in a manner that is understandable that could then be further communicated to their memberships. He inquired as to how IOM defined and selected the stakeholder representatives for the committee, and what the most contentious issues were with which the committee dealt.

Dr. Hinshaw replied that in terms of selection of stakeholders, they were particularly seeking people who deal with large populations and are responsible for vaccination schedules for entire populations, such as public health officials like Dr. Aragón. They were highly concerned about the issue of community immunity, and wanted someone with that type of background. People were also chosen who are not heavily into vaccine work and background settings, but who have good knowledge of vaccine work in that sense because there was an attempt to keep biases from moving from one committee to another. IOM has conducted 60 studies in the area of vaccines, so they are very careful not to duplicate committee membership any more than is appropriate. The parent stakeholder was highly recommended because she has a child with an illness that is believed by some to be a vaccine-related adverse event, and in the process of that is someone who has given a lot of careful thought to the issue and was willing to do the same with the IOM. Probably the most difficult issue was trying to sort out the priorities for research in this area, because it was very difficult to obtain biological plausibility and epidemiological data. Therefore, it was necessary to build off of the stakeholders' concerns, particularly parents. Another issue was to prioritize the studies that need to be conducted.

Dr. Harrison noted that many of the outcomes mentioned and the safety of individual vaccines had already been evaluated extensively. In the absence of scientific evidence, it was unclear to him why they were even talking about altering a schedule that was based on the best scientific evidence available. He said he was uncomfortable in the way this seemed to be drifting.

Dr. Hinshaw responded that the IOM was not talking about an alternative schedule in that sense. The committee talked about ways to study an alternative schedule if people wanted to do so without endangering children or their parents. In all of the data the committee reviewed, there were no data to suggest that the current schedule is unsafe. The committee has repeatedly stated this in press conferences and Congressional testimonies. The issue regarded the extent to which schedules have been studied, and whether other questions needed to be asked. If so, they must consider the three criteria recommended by the committee. She assumed that NVAC requested that the IOM address this issue and consider other methodologies because they thought other questions needed to be asked. For example, Jason Glanz found a relationship between delayed vaccinations and healthcare utilization issues, in that children with delayed vaccinations have higher rates of hospitalizations. People are beginning to ask questions about the entire schedule or parts of it in that sense.

Dr. Harriman requested clarification with regard to delayed vaccinations having higher rates of hospitalizations and whether that was any hospitalizations, or hospitalizations specific to vaccine-preventable diseases.

Dr. Hinshaw replied that this was any hospitalizations. The investigator literally reviewed healthcare utilization statistics. In terms of the evidence that those two are linked, clearly in the statistics they are. However, further study is required to determine whether that can be replicated and an understanding of why that would happen. His data also shows that people who have delayed vaccines have fewer outpatient visits. That makes sense because they did not go for their vaccinations every time. The issue of a relationship between delayed vaccinations and hospitalization raises as many questions as it answers.

Dr. DeStefano added that Jason Glanz's work is being done as part of the VSD, and this particular paper was primarily addressing the issue of differences in healthcare utilization between parents who choose different vaccine schedules or delay vaccinations for their children. One of the main thrusts of the paper was to highlight the difficulties in terms of studying the issues of health outcomes because in general, the health utilization patterns of these parents are different. This raises a number of comparability / confounding issues. Dr. Glanz has also done some sub-analyses that have shown that children who receive delayed pertussis vaccination have increased risk of pertussis disease.

Dr. Gorman (NIH) inquired as to whether the terminology "according to existing guidance" was chosen carefully so that it was not "according to present labeling." ACIP often makes recommendations and issues guidance that are not concordant with the existing labeling of vaccines, and he has often watched this group struggle when there are vaccine shortages to make recommendations regarding how to administer the diminished supply of vaccines. He also asked which groups offered guidance that is authoritative.

Dr. Hinshaw responded that this was why the IOM committee was trying to recommend research methodologies and study designs by which those questions could be asked. They did not talk about specific situations.

Adult Immunization

Introduction

Dr. Tamara Coyne-Beasley
ACIP Working Group Chair

Dr. Coyne-Beasley introduced the Adult Immunization Working Group Session, noting that Dr. Carolyn Bridges would provide a summary of the presentation at the conclusion of the session. She acknowledged the many individuals who worked tirelessly on this working group, indicated that the schedule had been published in the February *MMWR* Surveillance Summaries, and reviewed the topics to be covered during this session.

Updated Adult Immunization Coverage

Walter W. Williams, MD, MPH
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Dr. Williams reported that to assess vaccination coverage levels among adults aged 19 and older, CDC analyzed data from the 2011 National Health Interview Survey (NHIS) for pneumococcal, tetanus toxoid-containing, hepatitis A, hepatitis B, and HPV vaccines. During this session, Dr. Williams described the data source used for this report, the coverage highlights, and the specific adult vaccination coverage estimates for each of the vaccines by selected characteristics.

NHIS is an annual, in-house survey of the US's non-institutionalized civilian population. Respondents are polled in their households. Questions regarding receipt of recommended vaccinations for adults are asked of one randomly selected adult in each family in the household. The presence of high-risk conditions are based on ACIP recommendations, and were polled using questions in the 2011 NHIS. High-risk status for hepatitis A and B was not collected in the 2011 NHIS. Information on high-risk status was based on recommendations from ACIP. The final sample adult component response rate for the 2011 NHIS was 66.3%.

Compared with the 2010 NHIS, there were modest increases only for at least one dose of HPV vaccine of 8.8% to 29.5% in women 19 through 26 years of age. For Tdap vaccination among persons 19 through 64 years, there was a 4.3% increase to 12.5%. Coverage overall for tetanus-containing vaccination for the past 10 years remained unchanged. Compared with the 2010 NHIS, there were limited increases for pneumococcal vaccination of adults 65 years of age and older, hepatitis B vaccination of adults 19 through 49 years of age, hepatitis A vaccination of adults 19 through 49 years of age, pneumococcal vaccination of high-risk adults 19 through 64 years, receipt of at least one dose of HPV vaccination for men 19 through 26 years of age, and herpes zoster vaccination of adults 60 years of age and older.

Dr. Williams clarified that while there are two pneumococcal vaccines (e.g., the 23-valent polysaccharide vaccine, and the 13-valent conjugate vaccine) the results he was presenting were based on the PPSV23 vaccine only. In adults aged 19 through 64 years with high-risk conditions, vaccination overall was 20.1%, which was a 1.6% increase compared to 2010.

White, non-Hispanics had higher vaccination coverage levels than Hispanics and non-Hispanic Asians. For persons 65 years and older, overall coverage was 62.3%, which was a 2.6% increase compared to 2010. White, non-Hispanics had higher coverage rates than non-Hispanic blacks, Hispanics, and non-Hispanic Asians.

With regard to tetanus vaccination for the past 10 years, coverage overall for persons 19 through 49 years was 64.5%. There were no changes compared with 2010. White, non-Hispanics had higher coverage than Black, non-Hispanics, Hispanics, and non-Hispanic Asians. In persons 50 through 64 years for the past 10 years, tetanus vaccination coverage overall was 63.9%. Again, there was no change from 2010. Whites had better coverage than Blacks, Hispanics, and non-Hispanic Asians. For tetanus vaccination the past 10 years for persons 65 and older, coverage overall was 54.4%. Again, this reflected no difference from 2010. Whites had higher coverage than non-Hispanic blacks, Hispanics, and non-Hispanic Asians.

Overall, Tdap coverage remained low at 12.5% despite a 4.3% increase. There were increases in Tdap vaccination coverage for all racial/ethnic groups with the exception of non-Hispanic Asians. The highest increase occurred among persons who reported a race other than Asian, Black, White, or non-Hispanic ethnicity. There was also a large increase of 10.9% among persons living in a household with an infant aged less than one year. This is of programmatic importance, given that Tdap vaccination of persons who have close contact with infants less than one year of age provides protection against risk for transmission to unprotected infants.

It is important to note that Tdap estimates have a high potential for biased. Among the 25,000 plus respondents, about 32% were excluded. This included those without a “yes” or “no” response for tetanus vaccination in the past 10 years, those without a response to tetanus vaccination during 2005-2011, and those who reported tetanus vaccination but were not told what type or did not know the vaccine type. A sensitivity analysis was conducted to determine the impact of these exclusions on the potential for biased. Depending upon the actual proportion of persons who received Tdap vaccination, the coverage could range from 8% to 36.4%. In terms of the proportion of Tdap among all tetanus vaccinations received, 55.9% of adults 19 through 64 years of age were not told by their physician or provider what type of vaccination they received and 8.9% could not recall. Among the remaining 35% of adults 19 through 64 years, 61.1% received Tdap. Among healthcare worker respondents, 38.8% were not told by their provider what type of tetanus vaccination they received, and 5.4% could not recall. Tetanus vaccination among healthcare personnel was 66.8%. Regarding tetanus vaccination among healthcare personnel compared to non-healthcare personnel, the proportion among healthcare personnel was higher statistically.

Hepatitis A vaccination was higher for persons who had traveled outside the US to countries with a high prevalence of hepatitis A compared to those who had not traveled to a country of high endemicity. Coverage was 20.1% in travelers, which was an increase of 3.5% over 2010. Hepatitis A vaccination of at least 2 doses among persons 19 through 49 years overall was 12.5%, which was an increase of 1.8% from 2010. There was a 1.9% increase among non-Hispanic Whites. The group with the highest coverage was persons who reported a race other than Asian; Black; or White, non-Hispanic ethnicity. Non-Hispanic Asians had the second highest coverage for hepatitis A vaccination at 19.1%.

Hepatitis B vaccination coverage overall for persons 19 through 49 years was 35.9%, which was a 2.1% increase compared to 2010. White, non-Hispanics had higher Hepatitis B coverage than Blacks and Hispanics, despite a 3.6% increase among Hispanics. For persons with diabetes 19 through 59 years of age and 60 years of age and over, there were no changes compared to 2010 coverage estimates.

Zoster coverage for persons 60 years and older was 15.8%. There was no change compared to 2010. Black, non-Hispanics and Hispanics had increases of over 3%, but still had lower coverage compared to White, non-Hispanics.

HPV coverage among females aged 19 through 26 years of age was 29.5% overall, which was an 8.8% increase compared to 2010. The highest increase occurred among women 19 through 21 years of age, with a 14.9% increase to 43.1%. This finding might reflect receipt of vaccine during eligibility for the VFC program of those 18 years of age and younger, and those 19 years of age and older when these respondents were interviewed. HPV vaccination among males 19 through 26 years of age was 2.1% overall, which reflected a 1.5% increase compared to 2010. In October of 2011, recommendations were made for vaccinating males against HPV through 21 years of age, with a permissive recommendation for male adults 22 through 26 years of age. These coverage estimates do not reflect that recommendation.

Tetanus vaccination among healthcare workers for the past 6 years, including pertussis vaccine, was 26.8%, a 6.25% increase compared to 2010. White, non-Hispanics had higher vaccination coverage levels than Black, non-Hispanics. There was an increase among Hispanics of 16.3% to 30.1%, and this coverage estimate was similar to that among Whites. Overall hepatitis B vaccination coverage for healthcare personnel 19 and older was 63.8%. There was no difference between 2010 and 2011. Non-Hispanic Asians had higher coverage compared to Whites, and Whites had higher coverage compared to non-Hispanic Blacks and Hispanics.

These coverage reports have several limitations. The NHIS excludes persons in the military and those residing in institutions, which can result in under- or over-estimation of coverage. The response rate was 63.3%. A low response rate can result in sampling bias if the non-response is unequal among the participants regarding vaccination. Self-reported vaccination is subject to recall bias; however, it is known that self-report of pneumococcal vaccination has been found to be sensitive and specific. The Tdap estimates are subject to biased due to the many exclusions described. In addition, the age of vaccination is not known for vaccines reported as “ever received.” That includes HPV and hepatitis B vaccination, so it is unclear whether vaccination occurred as an adult or as part of a child or adolescent program.

In conclusion, coverage remains low for the three vaccines included in *Healthy People 2020* (e.g., pneumococcal, zoster, and hepatitis B vaccines). There was some improvement compared to 2010, with modest increases for HPV in women and Tdap vaccination for those 19 through 64 years of age. However, there were limited increases in other vaccines and racial and ethnic disparities remain. Obviously, much remains to be done to increase vaccine utilization among adults and to eliminate disparities.

Provider Survey Results on Adult Immunization

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Dr. Hurley said she thought the University of Colorado's data would provide some insight into the low coverage Dr. Williams reported. She explained that the study objectives were to assess the following in a nationally representative sample of family medicine physicians (FM) and general internists (GIM):

- Current practices regarding assessing patient need for and stocking of recommended adult vaccines
- Barriers to stocking and administering adult vaccines
- Characteristics of physicians who perceive greater financial barriers to delivering vaccines
- Practices, experiences, and attitudes regarding vaccination outside of the medical home
- Attitudes regarding the ACIP Adult Immunization Schedule

The investigators used sentinel physician networks to complete rapid turnaround surveys to gain information to inform vaccine policy decisions. Sentinel physician networks were recruited from random samples of the ACP and AAFP. Quota sampling based on region, practice location, and practice type were done to ensure that networks were similar to overall AAFP and ACP memberships. A previous study demonstrated that this method produced comparable results to the commonly used method of surveying random samples of the AMA Masterfile with respect to physician demographics, practice characteristics, and attitudes regarding vaccine-related issues.

In terms of the survey design and administration, questions were developed jointly with CDC and were modified based on input from advisory committees of general internists and family physicians from 6 states. The survey questions were then pre-tested and piloted among primary care physicians across the country. The survey was administered by internet and mail from March through June of 2012 using methods known to produce high response rates.

Given that the results were generally similar for FM and GIM, Dr. Hurley presented the results together for ease of presentation, but highlighted any significant differences. Descriptive, bivariate, and multivariate analyses were conducted to assess the primary outcome of perception of financial burden of delivering vaccines. A 71% response rate was achieved overall (79% for general internists and 62% for family physicians). Respondents were similar to non-respondents with respect to gender, age, region, practice location, practice setting, and number of providers in the practice.

In terms of the first objective of describing current practices regarding assessing need for and stocking recommended adult vaccines, physicians were asked: When do you usually assess an adult patient's immunization status for routinely recommended vaccines other than seasonal influenza? Almost all physicians reported that they asses immunization status at an annual (97%) and at an initial visit (92%), but only 30% reported that they do so at every visit. Physicians were also asked how they assessed an adult patient's vaccination status. Almost all physicians reported that they check their own medical record and ask the patient verbally, three-fourths reported that they review outside medical records, 61% have the staff member ask the

patient verbally, about half ask questions on a questionnaire regarding immunization status, 30% have staff review outside medical records, and only 20% reported checking a state or regional immunization information system to determine immunization status. Of note, 92% of physicians reported using three or more ways to assess immunization status. Only 2% relied exclusively on patient-supplied information, and of particular note, family medicine physicians reported they were more likely to use an immunization information system to determine immunization status.

Almost all physicians reported assessing the need for and stocking seasonal influenza and pneumococcal vaccines. Similarly, almost all physicians reported assessing need for and stocking Td and Tdap vaccines. While most physicians reported assessing the need for herpes zoster vaccine, only about half of the physicians reported actually stocking herpes zoster vaccine. Fewer physicians reported assessing the need for and stocking hepatitis vaccines. Family medicine physicians were more likely to assess the need for and stock hepatitis B vaccine, and family physicians were more likely to assess the need for hepatitis A vaccines. The differences between the specialties were significantly different. About half of general internists reported assessing the need for and stocking HPV vaccine, which compares to about three-quarters of family medicine physicians reporting assessing the need for and stocking HPV vaccine. These are statistically significant differences. For all three of the vaccines considered to be "catch up" vaccines or vaccines that individuals should have received in childhood (e.g., meningococcal, MMR, and varicella vaccine), family medicine physicians were more likely to assess the need for and stock these vaccines. Thirty-one percent of family medicine and 20% of general internal medicine reported stocking all routinely recommended vaccines.

Moving to the second objective, the top five reported barriers were all financial, with 44% to 60% of physicians reporting these barriers to be major or moderate. These included lack of adequate reimbursement for vaccine purchase, difficulty determining if a patient's insurance will reimburse for a vaccine, patients not having insurance coverage for vaccines, lack of adequate reimbursement for vaccine administration, and upfront cost of buying vaccines. Because about 50% of physicians reported that financial barriers were "major" or "moderate," a multivariable analysis was conducted to evaluate what demographic and practice characteristics were associated with perceiving greater financial burden. Being from the Southern region, working in private practice, working in smaller practices, and having a greater proportion of patients with Medicare Part D were associated with perceiving a greater financial burden to administering vaccines. Gender, age of the provider, practice location, proportion of patients with Medicare Part B, and proportion of patients with Medicaid were not associated with perceiving a greater financial burden to delivering vaccines.

Regarding the third objective (relationship with outside vaccinators or vaccinators outside of the medical home), physicians were asked where they most commonly refer a patient for a vaccine if they do not stock it or cannot deliver it for another reason. The most common place to refer to was a pharmacy or a retail store, with 25% of physicians reporting they often or always do this and 36% reporting that they sometimes do this. The second most common place to refer was to a public health department, with 21% of physicians saying they often or always refer there and 40% saying they sometimes refer there. Physicians were also asked, "Why do you refer to an outside vaccinator?" The most common reported reason was that a patient's insurance does not cover the vaccine, with 18% saying they often or always do this and 43% saying they sometimes refer for this reason. The second most common reason to refer was that patient's insurance covers the vaccine, but the provider perceives that the reimbursement is inadequate. Of the reporting physicians, 11% said that they often or always refer for this reason and 29% reported that they sometimes refer for this reason.

While physicians were open to multiple methods of receiving information from other vaccinators, the most preferred method was for the information to be sent to the provider by the vaccinator. Among 84% of physicians reporting this, 33% preferred to look up the information in the state or regional IIS and 18% preferred to have the information relayed when the patient next had a doctor's visit. Of note, 44% of family medicine compared to 25% of GIM, preferred to use the IIS. In terms of physicians who reported receiving information regarding vaccines administered outside of the medical home by other vaccinators less than 50% of the time, 59% said that they hear back from a pharmacy or retail store less than 50% of the time, and 83% said that they hear back from a public health department less than 50% of the time. Communication was not necessarily better from the other locations.

With regard to attitudes regarding the role of different adult vaccine providers, responses ranged from strongly agree to strongly disagree. Of note, almost all physicians agreed (74% strongly) that it was the primary care physician's responsibility to see that patients receive recommended vaccines even if received somewhere else. Most agreed (47% strongly) that patients prefer to receive vaccines at the office rather than a pharmacy or retail store. Most agreed (34% strongly) that vaccinations are a shared responsibility between themselves and other providers the patient sees. About half of physicians agreed (25% strongly) it was not their responsibility to stock "catch up" vaccines. There was a statistical difference between family medicine and general internal medicine, with general internal medicine being more likely to agree that it is not their responsibility to stock "catch up" vaccines. Regarding attitudes about the sub-specialist's role, most physicians agreed that it was problematic when sub-specialists provided vaccines because of lack of documentation of receipt of vaccine. Only 29% agreed (4% strongly) that many patients received vaccinations in this setting. Most physicians agreed (21% strongly) that it is helpful to have pharmacists share the role of vaccinating adults. Of reporting physicians, 27% agreed (7% strongly) that pharmacists do not have adequate training to administer vaccines. There was also a specialty difference, with family medicine being more likely to agree that pharmacists do not have adequate training to deliver vaccines. Only 7% of physicians agreed (3% strongly) that pharmacists are not able to deliver vaccines in their area.

In terms of the last objective, attitudes regarding the ACIP adult immunization schedule, most physicians agreed (42% strongly) that the schedule is easily accessible when needed. Most agreed (28% strongly) that the schedule provides clear guidelines on "catch up" vaccinations. The majority agreed (26% strongly) that the schedule provides clear guidance about what to do when immunization status is unknown. Most agreed (19% strongly) that the footnote section of the schedule is clear and concise. Twenty-five percent of physicians agreed (only 4% strongly) that the age-based indications for immunizations are difficult to follow. Twenty-nine percent agreed (only 3% strongly) that the medical condition-based indications are difficult to follow. Only 12% agreed (3% strongly) that they do not use the schedule to guide their vaccine recommendations.

There are several limitations to this study. Respondents may have differed slightly from non-respondents, sentinel physicians may differ from physicians overall, and these survey results represent reported practice—actual practice was not observed.

In summary, physicians are not assessing and/or stocking several recommended adult vaccines. A minority of physicians, particularly general internal medicine physicians, are using immunization information systems to track vaccines for adult patients. The top-reported barriers to delivering adult vaccines were financial, and physicians from the South in private practice, in smaller practices, and with higher proportions of patients with Medicare Part D perceived higher

financial burden to delivering vaccines. Physicians are referring patients to other vaccinators, but there is no systematic approach, and communication regarding vaccinations is perceived as poor. Primary care physicians perceived themselves as having a central role in ensuring patients receive vaccines. Attitudes regarding the adult immunization schedule were generally favorable, but some physicians find aspects of the schedule unclear or are unfamiliar with it.

Consumer Awareness Regarding Adult Immunization

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During this session, Dr. Sheedy shared a few highlights from a recent survey of US adults on the consumer perspective and CDC communication efforts regarding adult immunization, described a new communication program at CDC to help promote adult immunizations, and discussed recent communication activities and available resources.

The Styles Surveys have been a helpful mechanism to obtain information regarding the consumer perspective on childhood and influenza immunization issues over the years. Before 2011, Porter Novelli Styles Surveys were an annual series of self-administered mail surveys sampled through an opt-in panel of approximately 200,000 US households. Beginning in 2011, they moved to online surveys administered through Knowledge Networks' samples from their probability-based panel of 50,000 US households. Internet access, computers, and technical assistance are offered to panelists to avoid bias. The data Dr. Sheedy shared were from the FallStyles Survey, which was administered in September and October 2012. This was a re-contact survey sent to a random sample of over 6000 households that had returned the larger ConsumerStyles Survey conducted earlier in 2012. The re-contact survey response rate was about 80%, and the data are weighted according to the 2009 Current Population Survey of the US Census by gender, age, race, ethnicity, household income, and household size. Dr. Sheedy shared a summary of the demographics of the approximately 3500 participants.

In addition to immunization questions, respondents were asked how many times they visited a primary care doctor or specialist in the past 12 months. Of the respondents, 74%, almost three-quarters of adults, reported seeing a primary care doctor at least once in the last 12 months. Many reported seeing a primary care doctor multiple times. Only 38% percent reported seeing a specialist in the past 12 months. Respondents were asked, "Are any of the following vaccines recommended for you as an adult?" It is challenging to know how many of the "yes" and "no" responses are correct regarding hepatitis A, hepatitis B, and pneumococcal vaccines, but Dr. Sheedy said she wanted to share this information because of the high percentage of respondents who reported that they did not know if the vaccines were recommended for them. This is not necessarily surprising, given the complexity of the adult immunization recommendations and the limited attention those recommendations have received in US public discourse compared to infant and influenza immunizations.

Next, respondents were asked, “Have you received the following vaccine as an adult?” Dr. Sheedy emphasized that NHIS is the source for official coverage estimates, and that these results simply represent respondents’ perceptions and recollections of whether they received the vaccines as adults. With the exception of influenza, few adults believe they have received adult vaccines, specifically older adults receiving Tdap and Zoster. The inability for adults to recall whether they have received vaccine underscores the potentially important role that immunization information systems could play in helping the public keep track of the vaccines they have received. Participants were also asked, “In the past year, has the following vaccine been recommended for you by a medical professional?” Again, with the exception of influenza vaccine, few adults believe that a medical professional recommended vaccines to them in the past year. If their perceptions are correct, opportunities are being missed to discuss vaccines with adults. If the perceptions are not correct and providers are recommending vaccines more frequently, they may not be doing so in a memorable or meaningful way from the patient’s perspective.

In terms of the findings related to respondent’s attitudes related to adult immunizations, participants were asked, “How important do you think vaccines are when it comes to protecting your health?” The vast majority of respondents (about 82%) said they think vaccines are “important” or “very important” for protecting their health. Next they were asked, “How important do you think vaccines are when it comes to protecting your family and loved one’s health?” Of the respondents, 73% said “important” or “very important.” When asked, “How important do you think vaccines are when it comes to protecting your community’s health?” a majority (68%) said “important” or “very important.” All of the 10 attitudinal variables assessing adult attitudes toward vaccines in general show the same encouraging patterns of directionality. An important implication of this is that providers engaging in adult immunization conversations with their patients will be doing so with a population that is generally supportive of the value of vaccines.

Finally, respondents were asked, “Which of the following are important to you when you’re making decisions about which adult vaccines you should get?” A provider recommendation was the most frequently selected factor in influencing vaccination decisions. Like findings from research conducted about childhood, adolescent, and influenza vaccines, a long track record of safety is also an important component of the adult vaccination decision. Therefore, it is important to ensure that adults and their providers have clear, credible, and timely information about vaccine safety. Cost and convenience are important components as well, which is a reminder that it will take more than communication and awareness-raising to increase adult vaccination coverage. Most respondents agreed that vaccines are important for protecting health and preventing spread of disease. A healthcare provider recommendation was the number one reported factor in influencing vaccination decisions. Three-fourths of adults reported having visited a primary care practitioner at least once in the past year; however, adults perceive receiving few recommendations for adult vaccines from healthcare professionals, and an awareness of recommended vaccines other than influenza appears to be quite low.

Turning to the new Adult Immunization Communication Education effort underway at CDC, Dr. Sheedy emphasized that communication is only one piece of the overall approach to increasing adult immunization. Communication cannot be expected to address barriers that only policy and system change can overcome. These are very critical pieces on which the National Adult Immunization Summit (NAIS), HHS’s Adult Immunization Task Force, and other partners are working. What communication can do is increase the demand for adult immunization through provider and consumer behavior change efforts. The health communication strategies that can be used to affect behavior change among adults and healthcare professionals to increase

community demand for immunization range from increasing consumer awareness to development and dissemination of provider education resources.

CDC's new adult immunization program is aimed at raising awareness and promoting timely immunization according to the recommended schedule by targeting both adults and healthcare professionals. As the first such program at CDC with an initial funding for just two years, the hope is to lay a strong foundation for a branded, general campaign that can inform and support the work of the National Adult Immunization Summit and other partners. The intent is to continue to build on that foundation long-term as the agency has done with its influenza and infant immunization communication efforts, with whatever resources are available. The goal is to develop a brand that can be adapted for all adult audiences and to develop clear, science-based, and actionable messages to increase awareness of, and interest in adult vaccines generally.

While it is important to reach all adults given the low rates of awareness and low coverage rates, it is also known that the most successful communication is tailored to specific audience segments. One of the challenges is that there are distinct groups within the US adult population who required such targeted communications. Over time, CDC would like to have resources tailored for all or most of them. However, given considerations such as budget, staffing, and consideration of gaps already being filled by partners, the agency decided to start with groups who are at high risk for complications of vaccine-preventable diseases and who are also more likely to see a healthcare professional. This includes adults age 40 and older with chronic health conditions, specifically heart disease, diabetes, chronic obstructive pulmonary disease (COPD), and asthma; as well as adults age 60 and older. Pregnant women are being targeted through other efforts with the American College of Obstetricians and Gynecologists (ACOG) and other partners.

It is known that healthcare professionals play the critical role in adult vaccination. CDC's focus will be on those responsible for administering vaccines, including primary care physicians, physician assistants, and nurses. Adults with chronic disease are often under the care of specialists who help to manage their conditions, and who they may see more regularly than their primary care doctor. While specialists may not have the capacity to provide vaccines in their offices, they can play a significant role by educating patients about the need for vaccines and referring them to appropriate healthcare professionals. CDC will work with associations of specialists (e.g., cardiologists, endocrinologists, and others) to encourage their members to recommend vaccines to patients and to vaccinate or refer them. Given that many adults lack a medical home and not all medical practices administer all vaccines, pharmacists can also play a critical role in ensuring that adults are immunized. According to the FallStyles 2012 results, approximately 20% of all adults visit a pharmacist at least once a year. That number may be higher for people with chronic health conditions. Retail and large pharmacies have the capacity and interest in promoting adult immunization, so CDC looks forward to expanding the work the agency has done with American Pharmacists Association (APhA) and retail pharmacy chains on influenza vaccination to include other adult immunizations.

Regarding the general approach, the program will be designed following social marketing and risk communication principles and the results of formative research with target audiences. Print, radio, and digital media products will be developed and tested with target audiences prior to distribution through paid and unpaid placements. The communication messages, materials, and products will be culturally and linguistically appropriate, written in plain language, and delivered through trusted sources and effective channels for each target audience segment. CDC will

work closely with NAIS and partner with other relevant national medical associations and consumer groups to support this communication program.

With regard to formative research, as a first step a literature review was conducted. Key gaps in the research identified related to adult immunization communication included what adults know and think about the adult immunization schedule, what types of messages and creative approaches could motivate adults to get vaccinated, what information adults want to know about immunization and how they prefer to receive it, what can be done to support healthcare professionals in making vaccination a routine part of preventive care, and communicating a strong recommendation for vaccination. To address these gaps, CDC will be conducting focused, formative research with adults and healthcare professionals. Research with adult audiences will be conducted through a number of focus groups across the country. These will be segmented by chronic condition, including adults with and without those conditions, age, and race ethnicity. Through these focus groups, the agency hopes to better understand not only what adults know and feel about adult vaccination, but also how they can be effectively educated and motivated to get vaccinated. Research with priority groups of healthcare providers will be done through in-depth interviews. Through these interviews, CDC hopes to better understand the additional barriers healthcare professionals face in assessing adult vaccination status, recommending vaccines, and administering them. They also hope to identify ways to support providers so that they can effectively educate patients and make strong recommendations for vaccination.

The next steps are too numerous to list, but a few include sharing available research findings at the Adult Immunization Summit meeting in May; using formative research as the foundation to build a branded communication program targeting high-risk adults and health care professionals; developing educational and multi-media resources to increase awareness about the importance of adult immunization and encourage timely vaccination; using earned and limited paid media coverage through media round tables, radio media tours, print ads, et cetera; and engaging other organizations that can support communication efforts at national, state, and local levels.

A few recent efforts and successes related to garnering attention to the release of the 2013 Adult Immunization Schedule and the 2011 Adult Immunization Coverage Estimates included launching a new adult vaccination website; holding a press conference, which got more national and local media attention than expected; and conducting a radio media tour with approximately 40 radio stations across the country. Dr. Sheedy offered special thanks to Drs. Schaffner and Fryhofer for participating in that activity. She reminded everyone that CDC currently has some helpful resources available, including the Online Adult Vaccination Quiz and many other products.

Conclusion

Dr. Carolyn Bridges
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

In conclusion of this session, Dr. Bridges added some summary thoughts and information. While coverage among adults continues to lag, surveys of providers and the general public highlight opportunities. Providers see immunizations as important, and most adult patients are willing to accept vaccinations when recommended by their providers. Clearly, there are some important areas that need improvement. Increasing awareness and use of immunization

information systems (e.g., registries) by adult vaccine providers are needed to improve documentation and communication among providers. It is also important to identify ways to either reduce the barriers for coverage and payment, or to identify ways to help providers understand ways to reduce those barriers. Awareness must be increased about adult vaccines among the public, and adult patient vaccine needs assessment must be increased as part of routine care by providers.

Given the importance of provider recommendation, Dr. Bridges shared some data highlights from the CDC Internet Panel Survey. The results have been very consistent among pregnant women whose providers recommended and offer influenza vaccination. Coverage was 75% among pregnant women who received a recommendation from their provider. If the vaccine was not offered at the visit, coverage was only 37.5%. If there was no recommendation by the provider, coverage was only 10%. Studies from the pharmacist community also demonstrate that that recommendations from a pharmacist can be very helpful. The Diabetes Ten City Challenge was a study in which patients with diabetes were enrolled to receive additional counseling from their pharmacist. Participants usually had two or more visits. Compared to Year 1, influenza vaccination increased from 32% among these patients with diabetes to 65% in Year 2.

One of the efforts CDC has undertaken is the National Adult Immunization Summit. The influenza summit started in 2000 and is now in its 13th year. The adult summit started in 2012. For the May 14-16 2013 summit, the two are being combined into the National Adult and Influenza Immunization Summit. While there will continue to be an emphasis on influenza vaccine, about half of the meeting will be devoted to adult immunization issues. This is a partnership of over 150 organizations, with a goal to increase coverage of ACIP-recommended vaccines through identification and work on actions that can lead to improved uptake. There are five working groups, four of which align with the HHS Interagency Task Force on Adult Immunizations. There is good exchange of information among those groups. One of the action items that the Adult Summit thought was important to undertake is to update the adult immunization standards. A number of people on the summit have been working on a new outline to update the standards. The update was felt to be needed because of the increasing range of types of providers involved, which was not a significant part of the prior standards, and to encourage more communication and documentation of adult vaccination among the various providers for adults. The revision of the standards is being handed off from the summit to NVAC. A draft report is anticipated over the next several months. The overarching message of the adult standards is that adult providers have a role in assessing the vaccination status of their patients, recommending needed vaccines, and ideally vaccinating, or if they do not stock vaccines, referring to vaccine providers and following up to make sure that vaccine was received.

Discussion Points

Dr. Keitel inquired as to whether Dr. Sheedy had any further specificity with regard to how many adult visits in the previous year were for an acute care-related issue as opposed to a routine visit. Dr. Sheedy replied that they do not have this information.

In response to Dr. Keitel's question regarding how accurate adult recall is for immunization for vaccines other than influenza and pneumococcal, Dr. Williams indicated that Jim Singleton is conducting a study that may provide more information about vaccines other than influenza and pneumococcal. While he did not have the details regarding the data from that study, he expressed hope that it would be available for this group sometime in the future.

Ms. Rosenbaum inquired as to whether there are data from healthcare financing studies to indicate the average cost to a physician to stock enough pharmaceutical product to manage a current adult practice; whether a new survey should be conducted to have physicians respond to a question about whether they understand the new ACA provisions, and whether it would change any of their decisions about whether to stock and shelve vaccine now that there is coverage with first dollar payment; whether any of the presenters had thought about a field survey of primary care practices in medically under-served communities; and whether there was specific survey information about how health information technology is changing the way the physicians think about their practices.

Dr. Brooks thought it would be a great idea to survey physicians about their understanding of the provisions of the ACA. There are opportunities in the future to conduct surveys of primary care practitioners, and this topic has also arisen in discussions with the summit about how to educate providers about that. One of the barriers with one provision of the ACA might be the concern about the in-network providers. In terms of primary care practitioners not stocking all vaccines, it can be difficult and expensive financially to obtain vaccines from pharmacists. HRSA is a very active participant in the Adult Interagency Working Group, and is considering ways in which to assess under-served areas. The Indian Health Service has had success using standing orders and tracking adult immunizations, and this is a testament to what can be done with resources, efforts, and champions who work on adult issues. In terms of how the EHR and Meaningful Use issues might impact adult immunizations, the Adult Summit and the Interagency Working Group have had several conversations. Efforts are in the early stages to ensure that vaccines are part of the system.

Dr. Sawyer asked Dr. Hurley about the completeness of information currently available from IISs regarding adults. He thought some state systems had only recently begun to include adults. He also asked whether they were able to stratify results about the use of information systems by state and compared to the population, or the percent of the adult population in those registries, and further stratify by practices that have interfaces between their electronic health record and their IIS.

Dr. Hurley's understanding was that 47 out of 50 states have IISs. She was not sure how much of that information is entered as a result of an adult vaccination or a childhood vaccination. Regarding stratification, she did not know how much information would be available for use as a research group to stratify the results by the capabilities of each state IIS. She agreed that it was a great question, and offered to look into it.

Dr. Bridges added that up to 47 states now have the capability of accepting adult immunization information into their IIS. Some of those are opt-in versus opt-out that requires some sort of consent to add their information. That can certainly be a potential barrier. As reported, the proportion of internists who are familiar with the registries is pretty low, so there is a lot of room for improvement there. A number of states require that pharmacists who vaccinate enter data into registries, so that should assist with collection of adult data.

Dr. Groome (IHS) indicated that the Indian Health Service has been engaged in data exchange with a number of state immunization registries. They started with childhood and now have the ability to send adult data. The challenge is that some of the state registries are not currently able to accept the volume of data that Indian Health Services is trying to send them. Another challenge is the issue of opt-in versus opt-out, because sometimes that differs for children than

for adults. Differing rules pertaining to opt-in and opt-out complicate matters for providers who just want to submit their data.

Dr. Temte noted that he is in a system with a fairly mature state-based immunization registry that is integrated with his EHR, which he uses on nearly a daily basis. For all of his adult patients, he routinely reviews that component because he can get to it easily. He is at about 85% saturation of his adult patients in terms of administering all the appropriate vaccines because it is easy to do. Once the information is there and the recommendation is made, he finds that there is a high likelihood his patients will accept that vaccine. Thus, he made plea for interoperability between the immunization information systems and EHRs.

Dr. Poland (ACP) congratulated CDC for taking a new way forward. He was delighted to hear that a communications specialist has been assigned to this effort, noting that he had been pleading to bring others to the effort as well (e.g., cultural anthropologists, psychologists, et cetera). He emphasized how woefully short they were of reaching the 2020 goals for adults, and expressed his hope that there would be an increasing focus on fundamental, structural changes. Medical education for internists is also woefully inadequate. The medical sub-specialties are inadequately involved, and there are payer issues. Perhaps they need to be talking about not only a VFC, but also a "Vaccines for Adults" (VFA) program. He pointed out that nearly three years ago, the ACP and its Council of Medical Sub-specialties endorsed a clinical practice standard that called for all physicians caring for adult patients to inquire about immunization status with their patients, and either provide them with vaccines or refer them for vaccines. In terms of easy access to the information, ACP has an immunization advisor app that is free and easy to use.

Dr. Sheedy clarified that there are more than 8 health communication specialists at CDC, and said she thought Dr. Poland would be pleased with the multi-disciplinary team that is working on this effort. CDC is also working with ICF International on this, which brings a tremendous amount to the table.

Dr. Bennett lamented that the take-home message from the presentation was the same as it had been for many years, and that it was disappointing and depressing. She agreed with Dr. Poland that when reflecting on adult versus childhood immunization, there is an enormous difference. She suggested that there were three critical areas that could be shored up to truly strengthen the adult program: 1) Measure real data for adult immunization; 2) Address and become involved in existing systems and changes, including information systems, what is occurring in practices, and medical homes; and 3) Address vaccine finance for adults.

Dr. Bridges responded that part of the idea behind the Adult Immunization Summit is that they work closely with the professional medical organizations that are working with their membership on issues such as the patient-centered medical home. She invited Drs. Poland and Fryhofer to comment on training efforts to educate their memberships.

Dr. Fryhofer first offered public gratitude to Drs. Bridges and Williams for all they did to coordinate this effort, particularly with regard to instituting embargos to ensure that this was released with a splash. It was so helpful to have the new schedule available at the same time Dr. Williams published his report card of last year's successes and non-successes. This added a lot of urgency and illustrated what needs to be done. She thought that added to media acceptance. In terms of the immunization app, Apple accepted all of the updates. The PSA video is now available for release that will help to get the word out about this app. They are

really excited about new ACP initiatives over the next year to try to link the certification requirements to attention to vaccinations.

Dr. Zahn (NAACHO) asked whether the data offered any sense of whether providers are in situations in which they feel like they do not have someplace to which they can refer patients. As local health departments get defunded, they will cease providing direct vaccinations and other direct patient care. This may be worse in smaller communities.

Dr. Hurley responded that their data would not address that question, even though it is a good question. She works in a clinic near a public health department where she can refer patients. However, there is not necessarily a health department readily available to refer to across the State of Colorado.

Dr. Bridges noted that at the same time the adult schedule and coverage were released, Harvard opened their adult vaccine finder site, so she encouraged state and local health departments to reach out to the vaccinators in their community to add their information to that site to help people find vaccines.

Dr. Duchin inquired as to what proportion of adults across the US receive care from smaller practices. Depending upon the type of practice, different solutions will be needed.

Dr. Hurley has looked for descriptive data about who is seen by smaller practices, larger practices, sub-specialists, and primary care practitioners. This information would add to a manuscript she has written, so she invited input from anyone in the room with that type of information.

Dr. Jenkins asked Dr. Williams whether he was able to assess the impact of having versus not having insurance, or having versus not having a primary care practitioner.

Dr. Williams responded that the NHIS has covariates related to physician visits, number of physician visits during the previous year, whether the respondent has insurance, type of insurance, et cetera. They did not conduct that detailed analysis for this report just to keep it simple and make it a report card, but those types of analyses are routinely done. When they have assessed whether a respondent has a medical home or insurance, vaccination coverage levels are higher among those who have a medical home and those who have some type of insurance.

Dr. Schaffner (NFID) said he was puzzled by Dr. Hurley's survey results that indicated that 78% of responding physicians agreed that they were comfortable with the adult immunization schedule and that it was useful, and only 10% to 20% said they were unfamiliar with it. When he gives his unofficial, anecdotal survey to continuing education programs for physicians who are interested enough to attend continuing education programs, he always begin by asking for a show of hands of individuals in the audience who are familiar with the schedule. His results are exactly the reverse of Dr. Hurley's. In fact, the proportion of physicians in the audiences he addresses who are familiar with the adult immunization schedule is less than 10%.

Dr. Hurley said she thought there was an element of social desirability bias inherent to survey research. The physicians knew they were being surveyed about vaccines, so they might have been more knowledgeable about the schedule. While it is not comforting to know that, it might be the explanation. She delivers resident education on vaccines at her institution, and her

anecdotal experience aligned with her results. However, she agreed that there is likely some variability nationally.

Stan Grogg (AOA) suggested that one incentive for healthcare providers who do not stock vaccines in their offices would be some type of financial compensation for referring patients to other venues where vaccines are given.

Dr. Netoskie (AHIP) noted that there is likely variation in physician acquisition, storage, vaccines management. There may be opportunity to educate physicians about how to purchase more effectively, which would address some of the cost issue as well.

Dr. Moore (AIM) pointed out that an issue which had not been raised was that a barrier to local health departments in filling the gap for adults is that they are not considered to be in-network providers. They are working to improve their ability to bill private insurance and are ready and willing to fill the gaps, but until health departments are uniformly classified as in-network providers, they will not be able to do so.

Dr. Hurley added that ACA coverage will not help those who are not in-network providers.

Influenza

Introduction

Wendy Keitel, MD
Chair, Influenza Working Group

Dr. Keitel reported that over the last several months, the Influenza Working Group's discussions have included updates on ongoing studies and data related to febrile seizures, use of influenza vaccines in pregnancy, and influenza vaccine and egg allergy; the newly approved recombinant hemagglutinin vaccine (FluBlok®); vaccine efficacy over time through influenza season; and 2012-2013 mid-season vaccine effectiveness estimates.

Introduction

Dr. Lisa Dunkle
Protein Sciences Corporation

Dr. Dunkle indicated that Protein Sciences Corporation is a small company of approximately 100 employees. The company has been in business for about 30 years, and is largely based on a single platform technology, the Baculovirus Expression Vector System (BEVS). Three core franchises utilize that technology: Flublok®, developmental partners for whom a number of proteins are produced, and the research antigen business that provides a host of purified recombinant proteins to a very diverse customer base. They believe this technology has been validated in some fashion with recent licenses from Merck and Boehringer Ingelheim. Protein Sciences Corporation has worked very collaboratively and productively with Biomedical Advanced Research and Development Authority (BARDA) on a contract to support Panblok® and Flublok® vaccine development over the last two years.

In response to the H1N1 pandemic in 2009-2010, the President's Council of Advisors on Science and Technology (PCAST) evaluated the medical and community response to the pandemic. Regarding the perception that the response was slow and inadequate, PCAST concluded that the "the fault was not with the execution of the response, but in inherent shortcomings of current technologies for development and production of influenza vaccines." The limitation is that most US influenza vaccines are currently produced in embryonated chicken eggs, which results in a delayed response time, limited capacity, and limited flexibility. PCAST recommended short-term improvements in surveillance, strain development, testing, and fill/finish. PCAST concluded that, "The greatest potential for substantially shortening the time and increasing the reliability of influenza vaccine production lies in the use of recombinant DNA technologies." This is what Protein Sciences Corporation does.

Flublok® was approved by the FDA on January 16, 2013 for the prevention of influenza in adults 18 through 49 years of age. This was considered by the FDA and published not as an evolution of an influenza vaccine, but a revolution of influenza vaccine [The Evolution, and Revolution, of Flu Vaccines; http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm336267.htm]. It is the first recombinant purified protein influenza vaccine, and is perceived to be the only solution to a rapid response to an emerging pandemic. The major surface protein for influenza is hemagglutinin (HA), which is the protein that Protein Sciences Corporation makes with its BEVS technology. In terms of the BEVS process, basically the gene of interest is cloned into a baculovirus highly specific to insect cells with a powerful promoter that allows the generation of a high yield of protein. Cell expression is performed in insect cells in a bioreactor. It takes approximately 48 to 72 hours to produce high levels of protein. This protein is then purified to well in excess of 90% purity in the final product. From the time a gene is identified for the hemagglutinin of interest to production takes 21days. This permits Protein Sciences Corporation to have a released product within approximately 6 weeks after a virus is identified as an emerging threat.

Flublok® has some very interesting characteristics that make it different. As noted, it is a recombinant hemagglutinin protein. The single vaccine dose of hemagglutinin is 45µg/rHA antigen, which is three times as much antigen as the currently available standard vaccines. As mentioned, it is produced in insect cell cultures and is a highly purified protein. The vaccine contains no egg protein, adjuvants, preservatives, antibiotics, or latex and has a very low endotoxin content. There is a short production cycle that uses no live or infectious influenza viruses; therefore, no biocontainment is required. The high yield process allows for higher doses of hemagglutinin, which does seem to enhance immunogenicity.

The two BLA trials that supported approval of Flublok® were PSC01 from 2004-2005 (Phase II) and PSC04 from 2007-2008 (Phase III). The Phase II efficacy and safety trial assessed two different dose levels of recombinant hemagglutinin versus placebo in healthy adults 18 through 49 years of age. This was confirmed in the Phase III field trial that assessed clinical efficacy and immunogenicity in a subset of roughly 4600 patients 18 through 49 years of age. The BLA was also supported with two additional Phase III trials in older adults: PSC03 from 2006-2007 and PSC06 2007-2008. PSC03 was a non-inferiority immunogenicity/safety study conducted in healthy adults age 65 years and older. Approximately 860 adults were enrolled in this study. PSC06 filled in the gap between adults ages 49 and 65. This was a non-inferiority/ immunogenicity safety study in healthy adults 50 through 64 years of age. Both of these trials were designed to show non-inferior immunogenicity to that produced by Fluzone®, which was used as the active control.

All of the studies were randomized, modified double-blind design (e.g., observer-blinded studies of all subjects, site staff, and laboratory personnel were blinded, except for the vaccine administrator). These were multicenter studies that were all conducted in the US. The two pivotal trials were conducted in healthy adults 18 through 49 years of age, while the two supportive studies (PSC03 and PSC06) were conducted in medically stable adults 65 years of age and older and 50 through 64 years of age, respectively. Safety data were collected using a standardized memory aid for solicited adverse reactions described during the first 7 days following immunization. Unsolicited adverse events were collected through Day 28 after immunization, and there was a final safety follow-up 6 months following immunization. Standardized definitions in MedDRA Medical Dictionary for Regulatory Activities (MedDRA) coding were utilized. Immunogenicity was measured using a validated hemagglutinin inhibition (HI) antibody assay performed at central laboratory. Those data were analyzed using serological endpoint criteria specified in FDA and EMA guidances. In terms of demographics, for the 18 through 49 year old population for whom Flublok® is currently indicated, the mean age was 32. For the 50 through 64 year old population, the mean was 56 years. For the 65 and older population, the mean was 73 years. In the PFC03 study, one of the patients was in his 90s. There was fairly even distribution in terms of gender, with 40% males and 60% females. Ethnicity was approximately 70% to 80% Caucasian; approximately 20% to 25% Black, Asian, or Latino; and approximately 5% Other.

Study PSC04 to determine the protective efficacy of Flublok® was conducted in 2007-2008 when 96% of the circulating strains were drifted from the strains that were recommended in the vaccine. Therefore, for the primary endpoint that was intended to match to the strains in the vaccine, there were very few cases. It appeared that Flublok® was quite effective, but with very wide confidence limits. In terms of CDC-ILI with all strains, including drifted strains, Flublok® still demonstrated 45% vaccine efficacy. This was somewhat higher in the A strains (54.4%) than in the B strains (23.1%), but both were still statistically significant. In PSC04, there were very high levels of seroconversion to all three strains in the Flublok® recipients versus the placebo recipients. For PSC01, titers were done slightly differently utilizing a 1:32 level rather than 1:40, but a very high level of seroconversion was observed nevertheless in the full dose (135µg) Flublok® recipients versus placebo. For all three strains in PSC04, seroprotection in Flublok® recipients well-exceeded the 70% confidence limit that is required by FDA guidance for licensure. The same was true in PSC01 in which good results were observed with the full dose (135µg) Flublok® recipients. Flublok® basically met licensure criteria for all of the strains in terms of seroprotection and seroconversion, with the exception of the B strain in PSC01.

With regard to the older patients 50 through 64 year olds in study PSC06, there was a nice seroconversion rate. The B strain was not quite as good as the A strains; however, Fluzone® did not meet the licensure criteria either. In PSC03 of patients older than 65 years of age, there was a good response by and large to the A strains and not quite so good a response for the B strains. This was a complicated year because the strain that was selected by the Vaccine and Related Biologic Products Advisory Committee (VRBPAC) was the B/Ohio strain, which is what Protein Sciences Corporation cloned and made the vaccine with. This was a strain that manufacturers were not able to grow in eggs, so they used B/Malaysia. The reference antigen from FDA was B/Malaysia and Flublok® did not react quite as well to that as Fluzone® did. However, an exploratory analysis was conducted in a subset of patients in this same study who were over 75 years of age. In this group, there was a very nice response to Flublok® for the A strains that was somewhat better than the response to the comparator vaccine. The same issues occurred with the B strain as in the larger population. Seroprotection in patients 50 through 64 years of age was very high, and was quite comparable to Fluzone®. For the older patients, there were very high levels of seroprotection that were comparable to Fluzone®.

Comparing the results of GMTs and the proportion of seroconversions in the two older populations, 11 of the 12 comparisons of the response to Flublok® were statistically superior to that of Fluzone®. It was only in the B strain in the population over 65 years of age where Fluzone® became superior to Flublok®.

The results were very good in terms of safety in the two pivotal trials (PSC01, PSC04) among those 18 through 49 years of age. By and large, there was little difference between Flublok® and placebo. The one difference was in terms of pain at the injection site. The relatively high rates of complaints of pain in the PSC01 study are believed to be attributed to the fact that the first study included a Day 3 visit for evaluation of safety, which was not included in the PSC04 study. The same was true for systemic reactions, with higher rates in PSC01 probably due to the Day 3 visit and additional data collection. Beyond that, there was almost no difference between Flublok® and placebo for any of the systemic complaints. In terms of spontaneous adverse events, the proportion of non-serious reports was essentially the same between Flublok® and placebo. The number of serious adverse events was very low in both arms. A few women became pregnant or were vaccinated at a time before they knew they were pregnant. Important to note is that of the serious adverse events in Flublok® recipients, only one was judged as possibly related to Flublok®. This was an episode of pericarditis and pleurisy, for which an etiology was never fully determined. Because of that and because of the cell line that was new for the FDA to be considering, at the time of the VRBPAC meeting for Flublok®, the FDA presented their analysis of potential hypersensitivity events in the safety database. There were perhaps fewer incidents of potential hypersensitivity reactions with Flublok® compared to the active comparator. None of the events was judged to be serious or severe, and only the one pleuropericarditis was considered to be possibly related to Flublok®.

Of the 20 women who received Flublok® while they were pregnant, 15 (75%) were followed up. There were no birth defects in the live births, and there were no vaccine-related adverse events. A full battery of reproductive toxicology studies were conducted in rats, which if not unique is certainly unusual among the influenza vaccine. The full 135 µg dose was injected twice prior to and once during gestation. No effect was found on fertility, implantation, or fetal growth. There was no evidence of birth defects or of effects on pups through the time of weaning. At the FDA's request and in Protein Science Corporation's post-marketing commitment, a formal pregnancy registry will be initiated in 2014.

In summary of safety data, the commercial formulation was evaluated in a total of 3233 adults in four randomized, controlled trials. Of these, 2497 were 18 through 49 years of age and 736 were 50 years of age and older. The patients in all four studies are represented in the Summary Basis for Regulatory Action (SBRA) that the FDA recently posted on their website. There was excellent tolerability with Flublok®, as well as a good safety profile. Adverse event rates were generally similar to the active comparator, Fluzone®, in two studies. Only one treatment-related serious adverse event occurred, which was an episode of syncope and one serious adverse event possibly-related Flublok® (pericardial/pleural effusion) was reported.

Flublok® became available on February 15, 2013. Before starting influenza clinics, approximately 100,000 to 125,000 doses were available. Recipients have been targeted who have self-identified as being egg-allergic. Some college-age groups have been targeted as well, because they have a particularly dismal rate of influenza vaccination. Most of these individuals are currently registered with Protein Science Corporation. For the 2013-2014 season, Protein Science Corporation expects to manufacture the vaccine in a new expanded manufacturing facility, with which they have received remarkable assistance from their HHS

colleagues at BARDA, and expects to be able to produce 3 to 5 million doses in that facility. While the distributor has not been identified, this year's distributor is FFF Enterprises.

Additional trials must be conducted post-marketing. The first two are intended to expand the age indication. A short-term safety study will be conducted in 2500 adults 50 years of age and older in the second quarter of 2013 with a trivalent inactivated vaccine (TIV) control to assess hypersensitivity reactions. This is expected to support approval for the over 50 age group for the 2013-2014 season. A safety and immunogenicity study will be conducted in approximately 700 children 6 through 17 years of age, which is required by the Pediatric Research Equity Act (PREA). This will also be a TIV-controlled non-inferiority study. This study will be initiated by October 2013 and will include 6 to 12 months of safety follow-up. The other post-marketing commitments include the pregnancy registry to be initiated in 2014, which will enroll 600 pregnant women, of whom at least 300 are Flublok® recipients. These women will be followed throughout their pregnancy complications and outcome. Live newborns will be followed to the first well-baby visit. The intent is to have some concurrent non-Flublok® recipient controls, but it may take up to 5 years for enrollment. The last post-marketing commitment is an observational safety study of 25,000 Flublok® recipients, with controls to be non-Flublok® recipients. This study is intended to begin in the fall of 2013 with a large health maintenance organization (HMO). These study participants will be followed for medically attended adverse events, adverse events, and adverse events of special interest. This study is expected to be completed in a single influenza season.

In conclusion, Flublok® is the first purified, recombinant hemagglutinin protein influenza vaccine in which no infectious influenza virus is used in the manufacturing process. It contains 45µg of each of the antigens to improve immunogenicity. Safety and protective efficacy have been demonstrated in adults 18 through 49 years of age. The vaccine contains no egg protein, preservative, antibiotics, or latex. A full battery of reproductive toxicology studies were conducted that were negative. Pregnancy monitoring will be ongoing, with the formal registry to begin in 2014. Single-dose vials will be available for targeted populations in 2013, with 3 to 5 million doses expected for the 2013-2014 season. Continued growth is expected after that time. Additional studies are being conducted to expand the age range to those 50 years and older and those 6 through 17 years of age.

Discussion Points

In terms of the serology for the B strain, Dr. Temte inquired as to whether there was any understanding of why the seroconversion rates were so much lower compared to Fluzone® standard dose.

Dr. Dunkle replied that there was not. In general, the B serotypes are not as great a health threat, at least to adults as the A strains. The company is very happy with the response to H3N2, since it seems to cause the most public health risk.

Dr. Duchin asked whether they use the entire hemagglutinin molecule and if not, how they select which pieces of the molecule to be used, or if they have considered using any other proteins.

Dr. Dunkle responded that they could consider using other proteins. They have produced neuraminidase in the past, which is one of the possible directions to go with development. That would necessitate an understanding of how much neuraminidase was required. No one knows how much is in any of the vaccines, so this is somewhat complicated. She cannot explain the

lack of apparent dose response to the B strain. The gene that is cloned into the expression vector is just the head of the hemagglutinin, and it does form very nice rosettes. It is not clear what additional proteins they might want to add, stock or one of the transmembrane proteins that could contribute another form of immunogenic response.

Dr. Karron noted that in the 18 through 49 year old age group who received 45µg, there is really not a statistically significant difference in immunogenicity compared to 15µg of other vaccines. In follow up to that, she wondered whether in the early development stages dose response was evaluated to assess various doses, and whether there was a reason this particular dose was chosen.

Dr. Dunkle responded that there were a number of studies early in the development of hemagglutinin that utilized monovalent or bivalent hemagglutinin. Some of those studies did include dose response assessments. The Phase II PSC01 study had another arm that had a lower concentration of hemagglutinin, and there did seem to be an added benefit to using the full 45µg. Up to as much as 405µg have been administered in some populations, particularly elderly and immunocompromised patients, quite safely and with a good response.

Dr. Offit (Children's Hospital of Philadelphia) inquired as to whether Protein Sciences Corporation has an interest in the near future in developing a quadrivalent recombinant vaccine.

Dr. Dunkle responded that the company has already conducted the preliminary work to demonstrate that the four antigens together have good stability, and anticipates introducing a quadrivalent as quickly as feasible.

Dr. Zahn (NACCHO) asked what pre-defined vaccine efficacy success threshold was used for the pre-licensure study. He also wondered how long the development process would take on an annual basis.

Dr. Dunkle indicated that they used the FDA's criterion, which is that versus placebo, it needed to be statistically significantly superior and that the lower confidence limit should be around 40%. In regard to the development process, it is actually possible to go from cloning the gene to being prepared to put it into the bioreactors and make product in three weeks. They did that 4 or 5 times in the last year for 3 different H3N2 variant strains that were identified with the influenza issues that occurred at fairs. They also recently did this with the A/Texas/77 (H3N2), which she understands WHO plans to recommend for next year's strain. It is routine to do that. How quickly the transfected cells are put into the bioreactor to start cranking out protein depends upon the urgency.

Dr. Temte asked whether shelf-life is similar to other inactivated vaccines. Dr. Dunkle responded that the current shelf-life is 16 weeks in the label, which is quite short. They have been doing a lot of work over the last year to extend that. They have data on all of the strains in this year's vaccine as well as last year's vaccine, indicating 12 months of stability. However, the FDA has asked the company to provide data from multiple years and multiple different antigens to officially extend the shelf-life. They have no doubt that it will be the same shelf life as others.

For study PSC04, Dr. Plotkin (Vaccine Consultant) requested clarity regarding the difference between the categories shown of "CDC ILI, All Strains" and "All Strains." He also wondered whether the correlation between HA titers and protection had been assessed in the efficacy studies.

Dr. Dunkle responded that the "All Strains" included anybody who presented to the clinic and had a culture done that grew an influenza virus. "CDC ILI, All Strains" included anyone whose clinical presentation met the criteria for CDC-defined influenza-like illness (ILI). Regarding the correlation between HA titers and protection, Protein Sciences Corporation has not yet evaluated correlates of protection with its own strains.

Dr. Fryhofer (AMA) inquired as to whether the quadrivalent version of the vaccine would be available for next season. Dr. Dunkle responded that she could not predict whether the quadrivalent would be ready by next season. There are some issues with the reference antibodies for testing the potency, in that there is some cross-reactivity from the reference antigens that were attained from the FDA. Work is being done to improve that situation.

Dr. Loehr (AAFP) noted that there was nothing on the package insert to suggest that this cannot be given to pregnant women, and it is a Category B. He wondered whether there was anything to prevent them from administering the vaccine to pregnant women.

Dr. Dunkle responded that the language in the label regarding pregnancy is basically the standard language for all influenza vaccines. The fact that the company has conducted good quality reproductive toxicology studies is the reason that the vaccine is a Category B rather than C.

Dr. Coyne-Beasley inquired as to what the cost per dose was known. Dr. Dunkle replied that the company anticipates the cost to be at somewhat of a premium, because it is considered to be a premium product. While she did not have the exact cost, she thought it would likely be somewhat more than the standard egg-derived vaccine.

Epidemiology and Surveillance Update

Lynnette Brammer, MPH
Influenza Division
Epidemiology and Prevention Branch
Influenza Surveillance and Outbreak Response Team
Centers for Disease Control and Prevention

Dr. Brammer reminded everyone that CDC collects data from approximately 140 US WHO collaborating laboratories in the National Respiratory and Enteric Virus Surveillance System (NREVSS) across the country. Those laboratories report to CDC each week how many specimens they have tested for influenza, and how many of those were positive for influenza by virus type and, when available, virus subtype. As of the week ended February 9, the data collected from the laboratories show that the percent of those specimens testing positive for influenza peaked during the last week of December at 38.1%, and the percent testing positive has declined since to 19.7%.

Approximately 80% of the influenza positives reported to CDC this season have been influenza A viruses. Of the viruses that have been sub-typed, approximately 97% were A(H3N2) viruses. The WHO collaborating laboratories send a subset of viruses that they identify to CDC for further antigentic characterization. To date, all of the 2009 H1N1 viruses submitted to CDC are similar to the 2012-2013 vaccine virus A/California/7/2009. Greater than 99% of the H3N2 are similar to A/Victoria/361/2011, which is in the current vaccine. The influenza B viruses can be divided into two antigenically distinct lineages. The vaccine strain for this season is in the Yamagata lineage. Of the viruses tested so far, 71% are from the Yamagata lineage and are

similar to the vaccine B/Wisconsin/1/2010. With regard to antiviral resistance testing that has been done so far this season, all of the influenza A(H3N2) viruses and the influenza B viruses tested are sensitive to oseltamivir and zanamivir. Of the 234 2009 H1N1 viruses tested for sensitivity, 2 (0.9%) have been found to be resistant to oseltamivir. All of the viruses tested against zanamivir are sensitive to zanamivir.

CDC has a network of approximately 3000 healthcare providers across the country who report to CDC each week the number of patients they have seen, and how many of those patients have ILI-like illness. From that data, CDC creates a percentage of patient visits for influenza-like Illness. Similar to the laboratory data, the peak in ILI occurred in the last week of December. Of the patient visits during that week, 6.1% were for ILI-like illness. During this season, there was a lot more activity than observed last season. In terms of timing, this year was more similar to the 2003-2004 season, but was less severe than that season, which peaked at 7.6%. The magnitude of the season was much more similar to 2007-2008 season. In addition to calculating a percent of visits for ILI, CDC also calculates ILI activity level for each state, which offers a measure of how much ILI is occurring within each state. As of February 9, 11 states and New York were still reporting high influenza activity, 10 states were reporting moderate activity, 13 states and the District of Columbia were reporting low activity, and 16 states had dropped back to minimal influenza activity.

CDC also collects population-based rates of laboratory-confirmed influenza-associated hospitalizations from the agency's FluSurvNet system, which covers about 9% of the US population. This year was a more severe year for persons 65 years of age and older. The overall cumulative rate so far of hospitalization for the population as a whole is 32.1 per 100,000. For people 65 years of age and older, that rate is 146 per 100,000. Compared to last year, that is considerably higher. Last year, the end of season rate for people 65 years of age and older was 30.5 per 100,000.

With regard to mortality surveillance data, so far this season 64 influenza-associated pediatric deaths have been reported to CDC. While this is higher than what was observed last year, it is still lower than the 2010-2011 season. Given that activity is falling fairly rapidly, it is unlikely that the 2010-2011 level will be reached this season. As would be expected from the higher rate of hospitalizations in the elderly, in terms of mortality on the population level, increases in excess influenza-associated deaths have been observed as measured through the 122 Cities Pneumonia and Influenza Mortality reporting system. In this system, the percentage of deaths that had pneumonia or influenza listed anywhere on the death certificates exceeded the epidemic threshold for the first time during the first week of 2013. It remained above baseline for 6 consecutive weeks and peaked during the third week of the year at 9.9%. The majority of these pneumonia and influenza deaths occurred among persons over 65 years of age.

CDC gets a measure of the geographic spread of influenza through its state and territorial epidemiologist reports. For the week ending February 9, widespread activity was still being reported by 31 states. The peak occurred several weeks prior when 48 states reported widespread activity. In addition to the 31 states reporting widespread activity, 14 states and Puerto Rico reported regional activity, 4 states and the District of Columbia reported local activity, and 1 state reported sporadic activity. No states have yet dropped back to no activity.

In summary, influenza activity in the US during the 2012–2013 season began approximately 4 weeks earlier than usual, and occurred at moderately high levels. Activity increased in late November and peaked in late December. Activity continues in much of the country, especially in the West. Influenza A(H3N2) viruses have predominated overall, but influenza B viruses

have also circulated. This influenza season has been moderately severe with high rates of influenza hospitalization in the elderly, and a large proportion of deaths attributed to pneumonia and influenza.

Discussion Points

Dr. Vázquez inquired as to whether the pneumonia and influenza deaths were excess deaths in patients with influenza-associated pneumonias or with bacterial co-infections. She also wondered whether Dr. Brammer could comment on influenza vaccination rates in these patients.

Dr. Brammer replied that unfortunately, the data are very sparse and are based strictly on the number of death certificates filed with the Vital Statistics Office and how many of those death certificates had pneumonia or influenza listed anywhere on the death certificate. A large number of those actually had influenza listed. It was just under 90 for a couple of weeks. However, it is unknown how many of these had secondary bacterial pneumonia. It would be expected that quite a few did, but the data available is not detailed enough to offer a lot of information.

Dr. Vázquez wondered whether anyone was assessing this to determine cause, and whether Dr. Brammer could speculate on why there was increased severity in persons over 60 years of age as opposed to young children.

Dr. Brammer replied that CDC will get a small amount of data on the underlying complications for deaths that occurred this year from the hospitalization surveillance, but that is a small subset. When the full mortality data are available from the National Center for Health Statistics (NCHS), other conditions listed on the death certificate can be assessed. In terms of the increased rates in persons over the age of 60, usually 90% or more of influenza-associated deaths occur in people over 65 years of age, presumably because they are more frail, their immune systems are not working as well, and they just do not “bounce back” from it.

Dr. Keitel added that some insight might be gained into why there was increased severity in persons over 60 years of age as opposed to young children as they proceeded through the session.

Dr. Temte wondered how hospitalization rates looked for a similar H3 year compared to an H1 year, which was fairly unimpressive and seemed to affect children in a greater magnitude than older adults.

Dr. Brammer replied that unfortunately, CDC does not have the hospitalization data for adults for very many years. They can only go back to the 2005-2006 season. Compared to the seasons for which there are data, this is the highest rate that has been observed in the elderly.

Dr. Duchin inquired as to whether Dr. Brammer could comment about co-circulation of other notably wintertime ILI-like viruses and how they may impact the ILI curves and morbidity. He was particularly interested in human metapneumovirus (hMPV) in light of a recent publication that suggested it was a significant cause of morbidity in the older age group. It might be interesting to track that along with influenza.

Dr. Brammer indicated that CDC has only a very small project with a really small subset of ILI reporters from which systematic sampling is received. The specimens from those sites are tested for an array of respiratory viruses. Small signals due to other respiratory viruses are sometimes picked up, particularly respiratory syncytial virus (RSV) in the younger age group. The most current report showed that there was still significant RSV, human parainfluenza virus (hPIV), hMPV.

Dr. Keitel inquired as to whether there were any temporal trends with regard to the circulation of the different B lineages; that is, has there been a shift from the matched to the mismatched strain across the season.

Dr. Brammer replied that she had not assessed the characterization data for the B lineages as the season progressed, but as more viruses have been received and tested, the percentage matched to the vaccine has been increasing.

Reflecting on the session prior to this on adult immunization, Dr. Neuzil (IDSA) thought it could be quite catalytic if influenza-associated deaths in adults were a reportable condition. This suggestion has been made before, and she realized that it could be quite time- and labor-intensive. However, she thought it was important to consider. Perhaps they could begin incrementally, for example, with pregnant women or some other adult risk group and move from there.

Dr. Brammer said she would be happy to have better information on influenza-associated mortality, and this could definitely be considered.

Dr. Schaffner (NFID) echoed what Dr. Neuzil said, and keyed on something Dr. Bennett said in the previous session, “what gets measured, gets attention.” He observed that what gets displayed gets even more attention. A graph is needed concerning the number of influenza-associated adult deaths just as they do pediatric deaths. A couple of years ago, they began to pay attention to pregnancy-associated hospitalizations and deaths. That also needs to be displayed on a regular basis.

Dr. Warshawsky (NACI) noted that the observation has been made that when the influenza season begins early, it is often more significant. She wondered whether that was a confirmed trend, or just anecdotal observation.

Dr. Brammer responded that many people have that feeling, but a quick assessment of the data does not support this. It is probably just because it is not being evaluated in quite the right way. Early seasons can be the more severe seasons, but influenza is unpredictable and anything can happen.

Dr. Sun (FDA) asked whether CDC makes any attempt to relate influenza activity with regular pneumococcal pneumonia in surveillance to determine whether there is a relationship in a particular season.

Dr. Brammer replied that they have collaborated with its colleagues in bacterial diseases to conduct a couple of special studies to assess the correlation of influenza activity and pneumococcal disease, temporally at least. There is a slight correlation, but not as strong as would be expected.

Vaccine Supply / Distribution Update: 2012-2013 Season

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Dr. Santoli reviewed some of the highlights of supply and distribution for the 2012-2013 season. She reported that the final number of doses produced for the US market for the 2012-2013 season was 145 million. As of February 8, 134.8 million doses had been distributed to end users. There was increased demand for vaccine and an increase in distribution in January that has not occurred in recent years. This season had the second highest distribution number after the 2010-2011 season. Important to note is that there was an uptick in January that has not been observed previously. There is typically a leveling off during that timeframe. This represents a change in this year's distribution curve.

Influenza surveillance data indicated an earlier increase in disease incidence compared to recent seasons. Media coverage of influenza disease activity was extensive during the National Influenza Vaccination Week in early December and again in early January when disease activity significantly increased. This coverage likely contributed to increased vaccine demand. Spot shortages began to be reported in January 2013, a time when influenza vaccine distribution is typically largely complete. There were limited supplies for purchase of vaccine for young children. However, additional doses of the 0.25ml single dose syringe vaccine became available for sale during the first of February. In terms of the response, a number of activities were undertaken. Providers were pointed toward vaccine that was still available for purchase through a tool called http://www.preventinfluenza.org/ivats/ivats_healthcare.asp. This tool is supported by the National Influenza Vaccine Summit that allows distributors and manufacturers to submit information in one place about products that they have available, so that can be used as a place to send providers who are looking to purchase vaccine. Another part of the response was helping to point the public toward influenza vaccine clinics in their jurisdictions, since it was known that some providers might be out of their supplies of vaccines. The public was referred to the website http://flushot.healthmap.org/, which is a collaboration between HHS and Harvard that is a national influenza vaccine clinic locator. The estimates of vaccine production and distribution were confirmed with the manufacturers and distributors who provided data to ensure that there were no errors. There was significant communication as part of the response, and a brief survey was conducted of National Influenza Vaccination Summit Members to identify whether there truly was vaccine in the pipeline, and to understand people's experience with trying to purchase influenza vaccine.

In terms of looking ahead, several new products and types of influenza vaccines are anticipated for the 2013-2014 season. Quadrivalent vaccines will be available from several currently licensed US vaccine manufacturers. A new cell-based vaccine from Novartis was licensed in November 2012 and will be available. The new recombinant vaccine from Protein Sciences Corporation was licensed in January 2013 and will be available.

In conclusion, an increase in influenza vaccine distribution in January occurred for first time in the past decade. Tools for providers and the public can help to address vaccine demand late in the season when some providers have exhausted their vaccine supplies. Vaccine supply estimates for the 2013-2014 season are not yet available, but new products and brands are anticipated.

Discussion Points

Dr. Karron seemed to recall that information was presented regarding supplies and demand for the quadrivalent vaccine preparation, which suggested that because of an increase in capacity, demand can be met even when manufacturers are making quadrivalent vaccines, which decreases the number of doses they can make. She wondered if there were any different thoughts about that based on the past season, and whether there were any concerns about whether demand can be met in the coming years when quadrivalent vaccines are available.

Dr. Santoli indicated that CDC does not have quadrivalent numbers yet. One opportunity is that pre-booking for next season had already begun, and would inform what manufacturers do. Based on December and January of the current season, people will probably engage in early and more generous pre-booking than last year. That will offer a good indication of demand for the manufacturers who are producing product. She requested that manufacturers speak to that as well.

Dr. Hosbach (sanofi pasteur) indicated that their current trivalent capacity in the US is 150 million doses. They are looking forward to their quadrivalent vaccine being reviewed by FDA, and hopefully will have a license before the start of the influenza season and will be able to release at least some doses this year.

Dr. Mike Thomas (GSK) reported that GSK received approval late last year for its Fluarix® quadrivalent product, and estimates have been made for the coming season for the amount of TIV product that they can put into the market for the season. They have some flex capacity as well in case the estimates are incorrect. Clear communication from ACIP about the acceptability and reimbursability of QIV is going to be very important, because there is a short window of time over the next several weeks for pre-booking for the coming fall season. That will dictate whether GSK decides to make more vaccine or not.

Allyn Bandell (MedImmune) indicated that this year, MedImmune produced about 13 million doses of LAIV, some of which came to market upon requests in January. They have the capacity to make up to 35 million doses, but have not made a commitment for the coming season yet. All of the vaccine made in the US will be quadrivalent LAIV, and the number of doses made will be based on demand.

Clement Lewin (Novartis) reported that Novartis supplied about 36 million doses of trivalent vaccine last season, but that he could not comment on supply yet for the coming season because it is early in the season. Fluvirin® and Flucelvax® will be available next year.

Dr. Sawyer indicated that California was one of the locations that experienced a late season and spot shortages. California has a law prohibiting the use of thimerosal-containing vaccines in children under the age of three, and they had to request a waiver of that law from the Governor because the shortages were so bad. In early January, they were told by the manufacturer that there would be more vaccine, but not until February 1st. In addition, 11 million doses were produced but not distributed, so he assumed there was a process the manufacturers undergo at the end in terms of packaging and actually shipping vaccine. He wondered if this season provided any insight into how that could be anticipated better to avoid spot shortages, and whether anyone had any information regarding the oseltamivir shortage.

Dr. Hosbach (sanofi pasteur) replied that sanofi pasteur made vaccine based upon demand from each segment of the population, whether it was pediatric vaccine or high-dose vaccine for those 65 years of age and older. They always make more than anticipated in terms of the orders received early in the year. This year there was an excessive demand late in the season, so it is difficult to respond to that. Two things occurred. Luckily they had some of the vaccine available to be released and packaged at the 0.5ml preservative-free dose, and worked with CDC to repurchase the stockpile of 0.25ml syringes and were able to sell that back into the private sector. They also did the best they could to address a very late season demand, but they try to predict and project based on demand from physicians and historical demand. It was an unusual season due to the late spike, but he thought they were able to address a lot of it.

Dr. Santoli added that CDC has a moderately sized VFC stockpile that has been purchased every year since 2004-2005. The number of doses is not huge, but the agency has never previously used the entire stockpile. Therefore, beginning in December CDC reaches out to all of its state programs to find out whether they have additional need for VFC children's doses. They were given approximately a month to respond. That information is collected in mid-January, and as long as the agency can meet the need of those grantees for their VFC children, the doses are sent to the federal depot so they can be ordered for VFC children. Because of the situation this year, CDC then went to the manufacturers who had doses left and offered to them to be able to credit back the VFC program and have those doses to sell privately. That is how the 0.25ml doses became available in the February timeframe.

Dr. Bresee (SME) indicated that there were spot shortages of oseltamivir during the late part of the season in January. To his knowledge, those spot shortages were only for the suspension for pediatric use. CDC and FDA responded primarily to remind people that they could re-suspend the tablets or capsules in solution and provide directions for that. That seemed to mitigate the problem. There was discussion at CDC's Strategic National Stockpile (SNS) regarding whether the stockpile could be used to mitigate spot shortage, and those discussions will probably continue, but they did not have to use it this year.

Dr. Sawyer commented that the reconstitution of capsules into liquid is well known and is in the package insert. Despite that, there was a lot of difficulty at the local level convincing pharmacies to do that. He encouraged partners from the American Pharmacy Association to encourage pharmacists to consider doing that more.

Dr. Keitel asked whether there was any information on the uptake and/or distribution of newer vaccines, such as the high-dose vaccine and intradermal preparations.

Dr. Santoli responded that the distribution numbers CDC provides are an aggregate. They are not broken out by particular brand. CDC has some survey data about uptake, but she was not sure that would include information about brand either.

Dr. Hosbach (sanofi pasteur) reported that there was a substantial increase in uptake this year of the high-dose vaccine, which is in its third year of existence. He thought about 6 million doses plus were distributed of the high-dose. While he did not have the exact numbers for intradermal uptake, for which this was the first full year of launch, several million doses were utilized this year.

Vaccine Effectiveness

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Dr. Thompson reported that because of the early season, CDC released the crude, unadjusted numbers of the first few weeks of the influenza season. During this session, he shared the newly released adjusted and age-stratified estimates that included several additional weeks of data. These data come from CDC's US Influenza Vaccine Effectiveness Network (US Flu VE), which consists of five study sites across the US. The network enrolls children and adults with acute respiratory illness with cough in outpatient and urgent care settings. CDC assesses these by comparing the percentage vaccinated among cases who are influenza positive and controls who tested negative. The end-of-year estimates rely on medical record and registry-confirmed vaccination, but the interim estimate relied on self-report for 2 of the sites. Vaccination is defined as at least one dose of vaccine received 14 or more days from illness onset. About 40 individuals received vaccine less than 14 days before illness onset, so they were excluded. Standard covariates include age, site, and days from illness onset to enrollment, which have been potential confounders in the past. In this dataset, there was also some indication of confounding by race/ethnicity and self-rated health. Thus, the numbers were also adjusted for those.

Through the third week of January, approximately 1100 cases and 1500 controls were enrolled. It appears that these early estimates will represent about the first half of the season. Roughly a third of the cases were influenza B. Of those that have been subtyped, 97% were H3. Perhaps at the end of the season an H1 estimate can be done, but this was not available during this meeting. For all ages, 32% of the cases were vaccinated compared to 50% of the controls, which is an unadjusted vaccine effectiveness of 51%. Once adjusted for all of the variables, vaccine effectiveness is 56%. In terms of estimates by age category, vaccine effectiveness was significant, with significant in this case meaning that the confidence intervals do not overlap with zero. That was not the case among older adults. There were nice, respectable point estimates for B. There were not a lot of B cases among older adults, which explains the wide confidence intervals. The *MMWR* will show that the unadjusted numbers for that group were significant. It is just that adding a lot of covariates results in wide confidence intervals. For H3, there were somewhat consistent point estimates for the groups under age 64. However, the point estimate was not non-significant for those 65 years of age and older, which is disappointing.

In summary, adjusted vaccine estimates against influenza A and B was 56% (47%-63%), which was similar to the earlier unadjusted vaccine efficacy of 62% (51%-71%) against A and B. Vaccination reduced the risk of outpatient medical visits due to influenza A(H3N2) by half (47%), which was consistent for ages 64 and less. Vaccination reduced the risk of outpatient medical visits due to influenza B by two-thirds (67%), and appears to be consistent for all ages. This was similar to other interim estimates from this season for Europe and Canada. There was sub-optimal VE against A(H3N2) among adults aged 65 and older, which is similar to interim VE against A(H3N2) among the elderly in Denmark.

Enrollment continues, and assessment will be done again at the end of the season. At that point, there will be more data, including missing chronic medical conditions, vaccine type, and prior vaccination status. Additional potential confounders will be considered as well. In terms of implications, there is probably an opportunity to expand the benefits of vaccination, especially among younger age groups. It is important to recognize illness and treat with antiviral medications, especially among older adults. More effective vaccines, vaccination strategies, and a better understanding of factors that modify VE are needed. VE this season has to be considered in the context of other seasons, strains, and outcomes. This season does not differ very much from what has been observed over the past two seasons against circulating strains for those under 64 years of age. It is difficult to enroll older adults, so precision of estimates has always been an issue. VE among older adults is not observed to be significantly lower every year, but if this season turns out to be as it started, it may look more like the 2010-2011 season in which there was a substantial step-down for that age group.

Discussion Points

Dr. Temte lamented that the one vaccine that is well-promoted in older adults has fairly dismal efficacy in that group. In terms of vaccine policy issues, what struck him was that in his state, 32% of school-age children received an influenza vaccine this year. This is the one group he is convinced is responsible for the majority of transmission. This group is low on the list of who receives vaccine, but high on the list of efficacy. This presents an opportunity for community-based interventions. One problem is taking children to a visit every year when there are competing demands on time is really difficult. He wondered whether there was any information on vaccine efficacy from Australia, New Zealand, or South Africa.

Dr. Duchin congratulated CDC on these vaccine effectiveness studies, which are providing exactly the type of data needed to understand more about how well vaccines work, what the gaps are, and how thinking needs to be adjusted about policy in response. He did not think lumping influenza A and B for the mid-season and end-of-season presentations provided a very useful way of updating what is occurring. The majority of morbidity and mortality is in the elderly and is primarily due to the A strains, and particularly H3N2 this season. Vaccine effectiveness against that strain is particularly poor. The combined estimate is driven up by the relatively better effectiveness against influenza B, which is less of an issue clinically. He wondered whether these data were really generalizable, given that the numbers are based on a third of the isolates being influenza B. However, throughout the country he thought it was probably that a smaller proportion of disease is caused by influenza B, particularly a smaller portion of severe clinical disease. He made the case for presenting influenza A and B as if they are two different diseases.

Dr. Thompson responded that almost 50% of cases for a couple of sites have been comprised of influenza B, while in other sites there has been hardly any. “Site” is confounded with a lot of other issues, so when they control for that, they are collapsing across a lot of different variables.

Dr. Bennett noted that there are relatively few cases in the 65 year and older age group compared to some of the other age groups, and was curious about whether that was truly representative of the US population and the disease burden. She also wondered whether they were able to assess more refined age groups, given that many believe that 65 plus is no longer the most relevant cut point. In addition, she asked whether they controlled for chronic underlying health conditions.

Dr. Thompson replied that for the final assessment, they will have information about chronic underlying health conditions from medical records. Self-rated health data is easy to collect, and is definitely related to chronic conditions and is one of the best predictors of mortality. It is a decent proxy, but is not the same. The reason there are 100 plus cases is because the sites worked really hard to find the places where they could find older adults and reach them soon enough, especially for outpatient care where older adults are discouraged from coming in and when they do, it tends to be late. There has been a great deal of discussion about what it would take to have the size of a sample that would be needed so that they could control for all of the heterogeneity, functional status, et cetera. It is at least 10 times as hard and costs more for every older adult they eventually found.

Dr. Rubin wondered whether it would make a difference if a more stringent definition for being vaccinated was used for the earlier years.

Dr. Thompson responded that they would have to have vaccine histories to calculate this for children under nine years of age who are fully immunized. The numbers presented were from the single dose, which is generally what is used for VE estimates, and then a sub-analysis is usually done to determine whether full immunization resulted in a significantly different VE. It usually does, and this is usually an underestimation of the true benefit of full immunization. They certainly can assess more refined age groups. There are age variations among those 18 to 45 years of age, and the thought is that perhaps this can offer a clue about whether there is some exposure history that may be modifying the response, especially to H3. Perhaps that is a topic to present to the Immunization Working Group.

Dr. Karron wondered whether the Influenza Branch and others in the community were thinking about match issues, and whether we have the best tools currently for assessing what match is.

Dr. Bresee (SME) replied that a significant amount of consideration is given to this issue. There have been two WHO consultations that have tried to understand what match means and how best to measure that. He thought there would be a third consultation this year to try to determine this. In the meantime, it will be measured as it has been in the past.

Dr. Duchin added that the most common question he had had this season from his colleagues is, “If the match is so great, why are we seeing so much influenza among vaccinated patients and healthcare workers?” He thought this raised a number of questions about the correlates of protection and how they are measured and communicated. The serum measured for antigenic match is not well-characterized enough to be a predictor of vaccine effectiveness, so perhaps they should try to avoid this as a way of describing how effective or ineffective a vaccine may be.

Dr. Keitel wondered whether there were any plans to assess hospitalized cases among the elderly to assess effectiveness. There is at least one study that shows higher estimates of effectiveness when hospital data are evaluated. She asked whether they would be able to establish the time of vaccination and distance between when the person was vaccinated and when they became ill, and whether it is possible to compare influenza positive to positive for another virus. One of the limitations of influenza negative is that they may have had influenza but it cannot be detected.

Dr. Thompson agreed that all of those were great ideas. With the network, they narrowed down to just outpatient and urgent care because hospital enrollment was so costly. Instead, CDC funded separate studies. A study will be published that was conducted by Dr. Schaffner and colleagues at Vanderbilt that assess hospitalizations among adults. While this is a very different question, it is a very important one. One could imagine a scenario where these older adults against outpatient visits might be null, but in the same year it might be preventing more serious outcomes, which is important to assess. They will be able to evaluate calendar time and time varying VE from vaccination. A few of the sites are doing multiplex testing for other respiratory pathogens, and there has been some discussion regarding whether the most appropriate control is someone who is infected with something that can be identified that is not influenza. Right now, the platform does not support that for everyone so typically all they know is that someone does not have influenza.

Dr. Harrison thought there would be some impact of false negative real time reverse transcription polymerase chain reaction (RT-PCR) among the controls, and he wondered whether they tried to quantify that or do sensitivity analyses around that. He also wondered whether they were going to assess the high-dose product. He suspected that based on the numbers they heard, the coverage rates are sufficiently low to make even wider confidence intervals.

Dr. Thompson indicated that for the past couple of years, there has not been a high uptake of high-dose at the sites. They have debated about how to increase uptake, such as perhaps administering the vaccine for free. Regarding the impact of false negative real time PCR in the controls, one of the drivers is the distance from illness onset to enrollment. In addition for adjusting for that, they typically do sensitivity analyses to assess only the recently onset illness. Fortunately, RT-PCR is highly sensitive, and they use combined oral pharyngeal swabs, so they do not believe this is a significant concern, but it can be further evaluated at the end of the season.

Dr. Bresee (SME) indicated that CDC is exploring the idea of measuring product-specific VE, which is a pandemic preparedness issue. The idea would be to set up that capacity during the season so that it is in place to measure pandemic vaccine product by product. They certainly already produce and publish product-specific information, at least as it relates to LAIV versus TIV since there is only one LIAV product.

Dr. Neuzil (IDSA) emphasized that the point estimates of efficacy are relative and only have meaning to her if she understands the underlying absolute burden of illness, which would be a function of absolute disease rates and severity. She thought the 2012 estimate in the elderly probably prevented more disease than the 2011, because there was a much greater influenza season this year and much more disease. While she would love to see higher point estimates of efficacy, absolute numbers are needed in addition to relative numbers.

Dr. Temte added that the ability to couple the virology and the PCR results with severity and duration for disease to calculate the “area under the curve” is crucial. It is not easy to do and it is expensive, but it would be very helpful.

Dr. Foster (PhRMA) stressed that with the variety of vaccines available or soon to be available, lumping them together would make it very difficult to decide which is better. It would be very beneficial to break these out.

Dr. Thompson indicated that CDC's laboratory has a B assay, which permits them to assess B lineages, so they will have VE against those as well.

Dr. Riley (ACOG) inquired as to whether there were any data on how many of these people are pregnant. Even if it does not work that great, in pregnancy the ramifications of getting influenza are so much worse.

Dr. Thompson responded that among the enrollees, they typically capture about a dozen women who are pregnant at the time of enrollment. They have funded a separate study called "The Pregnancy Influenza Project," which specifically focuses on this. The first VE results of that will be available soon. He agreed that there are several subgroups who may require their own special investigations, and it is worth investing in this.

Upcoming Topics

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Dr. Grohskopf discussed some of the Influenza Working Group's ongoing and upcoming topics, and then presented some of the proposed recommendations for 2013-2014. One of the discussions the working group had relatively recently concerned evidence for waning of vaccine efficacy and effectiveness throughout the influenza season. Two recently published European case-control studies conducted during the 2011-2012 season noted a decrease in estimated vaccine efficacy with increased time since vaccination over the course of the season. The Castilla et al study conducted in Navarre, Spain noted decrease in overall vaccine effectiveness from 61% in the first 100 days post-vaccination, to 42% from days 110 to 119, to -35% thereafter. Most of this effect was related to decrease among those 65 years of age and older, among whom estimated vaccine effectiveness fell from 85% to 24% to ineffective thereafter. The Pebody study in the United Kingdom noted decline in vaccine effectiveness against A(H3N2) specifically from 53% among those vaccinated for less than three months to 12% among those vaccinated three months or more. In this study, the authors noted that the proportion of persons 65 and older was too small to detect a significant difference in decline in this age group.

Overall, one thing of note is that number of subjects is relatively small in both studies, as evidenced by the wide confidence intervals, with considerable overlap between point estimates, particularly among the elderly subgroup in the Castilla study. Nonetheless, the decline in point estimates of VE is important and warrants further discussion. In discussing this issue within the working group, several themes emerged. The working group considered the context of initial influenza vaccine shipments in recent seasons. Influenza vaccines have been available earlier in the last several seasons than in the past, as early as July for some providers. Data are not yet available on the proportion of people on a national basis who are going to be vaccinated that early, but it appears from what is known that the proportion is in the low single digits. Another issue is that the timing of onset and peak of influenza activity varies unpredictably from season to season, with localized outbreaks at the start of a season occurring as early as October in some years. As a result, the ideal time to vaccinate in any given season cannot be stated.

Overall, there was a sense that there is a need to balance the goal of maximizing the likelihood of persistence of protection through the season with avoiding lost opportunities to vaccinate, avoiding vaccinating after influenza circulation begins, and the feasibility of vaccinating a population in a more constrained time period. These aspects are reflected in the draft language related to timing of vaccination that will be discussed in the next section.

Proposed Recommendations

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Dr. Grohskopf explained that the current document, which was circulated to the ACIP members, is not yet a complete Recommendations and Reports. Some topics, will be discussed further within the working group and, if changes in the current guidance are proposed, they will be presented during the June 2013 ACIP meeting. For example, the working group will probably be discussing updated data on influenza vaccination for persons with egg allergies, and that will be brought back to the committee if it is believed further discussion and possibly changes are needed. For the time being, there is a reiteration of the recommendation for annual routine vaccination for all persons aged 6 months and older. There is a discussion of timing of vaccination. A summary of new vaccine abbreviations deserved its own space this time. A discussion of newly approved vaccines that are expected to be available during the 2013-2014 season is also prominent.

Regarding persons recommended for vaccination, essentially no change is proposed for the upcoming season in that annual vaccination continues to be recommended for persons aged 6 months and older. That will be the same as seasons since 2010. In terms of timing of vaccination, this section of the document notes the earlier timing of influenza vaccine availability in recent seasons, and discusses recent literature concerning waning of immunity, including the two European studies noted earlier. This section also discusses the potential implications of deferral of vaccination as they relate to unpredictability of onset of influenza activity, potential missed opportunities, and feasibility of vaccination given time constraints associated with delay.

The recommendation proposed is similar to that in the most recent full ACIP influenza statement from 2010 that basically states that in general, health-care providers should begin offering vaccination soon after vaccine becomes available, and if possible, by October. It is not possible to give a specific date, but the literature and background elements are discussed and general guidelines are offered. However, there is a specific recommendation for all children aged 6 months through 8 years who are recommended for 2 doses. These children should receive their first dose as soon as possible after vaccine becomes available, and children should receive the second dose at least 4 weeks later. It is noted that ACIP will continue to evaluate emerging data on change in effectiveness over time, and that these recommendations will be revisited as appropriate.

The draft statement contains a description of the new vaccine abbreviations. TIV, or trivalent inactivated influenza vaccine, which previously was used to refer to inactivated vaccines in general, is replaced with IIV, for inactivated influenza vaccine. IIV refers to these vaccines as a class. The numeric suffix, when present, refers to valence. IIVs include trivalent vaccines or IIV3s, both egg and cell culture-based, and IIV4, the new quadrivalent inactivated vaccine. Cell culture-based vaccine is specifically abbreviated as ccIIV or ccIIV3, and is currently available

only as a trivalent, or ccIIV3. RIV and RIV3 refer to recombinant HA influenza vaccine, currently available only as a trivalent, or RIV3. LAIV refers to live-attenuated influenza vaccine, anticipated to be all of the quadrivalent or LAIV 4 form next season, or LAIV4. The newly approved vaccines that are expected to be available next season are summarized and have been added to the table of available vaccines.

These include the two quadrivalent vaccines and the two vaccines that are produced using technologies that are new for US influenza vaccines:

- Quadrivalent Live-attenuated Influenza Vaccine (LAIV4)—Flumist® Quadrivalent (MedImmune)
- Quadrivalent Inactivated Influenza Vaccine (IIV4)—Fluarix® Quadrivalent (GSK)
- Cell-culture based inactivated influenza vaccine (ccIIV3)—Flucelvax® (Novartis)
- Recombinant hemagglutinin vaccine (RIV3)—FluBlok® (Protein Sciences)

In general, with regard to the newer vaccines, all newly approved influenza vaccines expected to be available for 2013-2014 are acceptable alternatives to other licensed vaccine products, within specified indications. No formal preferential recommendation is proposed at this time for one vaccine product over another, where more than one is appropriate for a given recipient. The reasons for this include that these are new products, post-marketing safety data are not yet available, and supplies are anticipated to be less relative to previously approved vaccines. Because of the large number of available vaccine preparations, and because some providers may have more than one option at their disposal, potential considerations are discussed for selecting a vaccine where more than one acceptable alternative is available to a provider. However, vaccination should not be delayed in order to obtain a specific product.

With regard to some of the newly approved vaccines, Quadrivalent LAIV, or LAIV4, will be available from MedImmune as Flumist® Quadrivalent. The same recommendations are proposed as for the trivalent formulation of Flumist®; that is, that it is recommended for healthy non-pregnant persons aged 2 through 49 years. It is an acceptable alternative to other licensed products for this group. There is no preferential recommendation proposed for LAIV over another appropriate licensed vaccine product. As noted earlier and at the last ACIP meeting, data from studies comparing trivalent LAIV to trivalent IIV indicate that LAIV is more effective in children. Providers may wish to LAIV over IIV for children, where both are available and otherwise appropriate. However, vaccination should not be delayed if LAIV is not available.

Quadrivalent inactivated influenza vaccine, or IIV4, will be available as Fluarix® Quadrivalent (GSK). Fluarix Quadrivlant is approved for persons aged 3 years and older. IIV4 is an acceptable alternative to other licensed products when used within indications. Among inactivated vaccines, both IIV3 and IIV4 will be available during 2013-2014. It is anticipated that most of the supply will be IIV3. Either IIV3 or IIV are acceptable for the indicated populations. No preferential recommendation is proposed. Given the potentially broader coverage of IIV4, providers who have access to both vaccines may wish choose IIV4 over IIV3. However, vaccination should not be delayed if IIV4 is not available.

The cell-culture-based trivalent inactivated influenza vaccine, or ccIIV3, is Flucelvax®, manufactured by Novartis. It is approved for persons aged 18 and older. ccIIV3 is an acceptable alternative to other licensed products when used within indications. With regard to ccIIV and other IIVs for those with a history of mild egg allergy, the vaccine viruses used in the production of ccIIV are not propagated in eggs. However, the initial reference strains from WHO have been passaged in eggs. The vaccine cannot therefore be considered to be egg-free;

however, it is expected to contain considerably less egg protein than other IIVs. The most recently approved vaccine is the trivalent recombinant hemagglutinin vaccine, Flublok®, which was discussed earlier. Flublok® is approved for persons aged 18 through 49 years. RIV3 is an acceptable alternative to other licensed products, used within indications, and can be considered egg-free.

With respect to the last 2 vaccines, Dr. Grohskopf briefly discussed egg allergy in the context of the current recommendations for vaccination of persons in this group. In June 2011, ACIP recommended that persons with mild egg allergy (e.g., those who have experienced only hives upon egg exposure) should receive inactivated influenza vaccine. No recommendation was made for selection of vaccine based upon a maximum ovalbumin threshold. Any age-appropriate inactivated vaccine could be used. Those with a history of other symptom or anaphylaxis to egg are recommended to be referred to a physician with expertise in the management of allergic conditions before vaccination. With regard to how ccIIV3 and RIV3 fit into these recommendations, first it is important to note that neither ccIIV nor RIV is approved for children under 18 years of age. Egg allergy is most prevalent in children, but children should not receive either vaccine. No recommendation is made for off-label use. For adults of appropriate ages, ccIIV3 is expected to contain considerably less egg protein than other IIVs. For this reason, providers may wish to use ccIIV over other IIVs for persons with mild egg allergy when both are available and otherwise appropriate, with the same additional safety precautions. However, vaccination should not be delayed if ccIIV3 is not available. Another IIV may be used. Production of RIV does not involve eggs, and the vaccine may be considered egg free. Providers may wish to use RIV3 over IIVs for persons with mild egg allergy, where both are available and otherwise appropriate. However, for those (again) with mild egg allergy, vaccination should not be delayed if RIV3 is not available; IIV may be used.
For those with a history of more severe reaction to egg, such as anaphylaxis, RIV3 is not contraindicated, and may be used.

Discussion Points

Regarding waning immunity during the season, it was not clear to Dr. Sawyer whether language would be included in the annual influenza statement referring to those studies. He would be reluctant to even suggest that there is waning immunity during the season unless they were quite confident in the results of the studies available, particularly given the last several years of emphasizing to patients that it is not too early to immunize. Regarding the preference statement for LAIV for children, he could not recall whether the GRADE analysis was done for LAIV for this group. If so, and the data were solid, the preference statement should stronger than the language presented that providers *should* give LAIV to young children.

Dr. Grohskopf indicated that the studies pertaining to waning were recently published, and were discussed among the working group about a week later. There was a sense that it is too early to make any decision to make a firm recommendation to begin vaccinating later. As is generally done in a full recommendation, it is customary to conduct a literature review and include this in the general recommendations to point out the strengths and limitations of the available literature.

Dr. Keitel suggested that the statement make mention of the studies in the spirit of transparency and the fact that there are data, with the caveat that further study is needed to confirm this before any strong changes in recommendations are made. She stressed that a very small proportion of individuals are receiving influenza vaccine before September.

Regarding LAIV versus IIV, Dr. Grohskopf noted that one of the issues that changed the path in the summer was the warning that the entire supply of LAIV for the coming season would be quadrivalent. While there is no reason at this point to anticipate that the safety profile would be any different, pre-marketing studies sometimes do not pick up issues that larger post-marketing data will. Her understanding is that a vaccine that is new to market generally will not receive a preferential recommendation prior to actually being released.

Dr. Keitel added that ACIP has not voted on a preferential recommendation. GRADE needs to be completed for trivalent vaccine, so that information can be used with the safety information that follows as quadrivalent vaccine is introduced.

Dr. Temte asked whether anyone had a sense of when that would be done in terms of the safety evaluation.

Dr. Grohskopf responded that the timeline is somewhat dependent on accrual of data, and this will need to be further discussed within the working group. The GRADE analysis that was presented in October 2012 related exclusively to the efficacy data.

Dr. Kimberlin (AAP) indicated that the AAP also was not prepared to make a preference for one product over another at this time.

Dr. Leger (AAPA) emphasized the importance of educating providers about timing of vaccination. She was unable to get her influenza vaccine until late in the season in January. When she went to see her physician, he tried to convince her not to be vaccinated even though he had the vaccine in his office. She was adamant that she wanted it, and he was shocked.

Dr. Englund pointed out that the issue of timing had been extensively discussed among working groups members and with its collaborating organizations, and that Dr. Grohskopf had summarized many weeks of meetings. She thought many working members would eventually like to make a statement, and the data are getting close to being sufficient. Having a new quadrivalent vaccine coming out does affect some people's thinking on the issue.

Dr. Temte commented that one of the major difficulties was the wonderful abundance of influenza products available compared to a few years ago. However, the number of preparations, manufacturing modalities, the number of presentations, and the ways to provide vaccine make it nearly impossible to conduct all of the studies they would wish to have done to have adequate evidence to make informed decisions. He did not believe this would be likely or possible in the near or more distant future. That being said, this is some of the indirectness they have to accept between trivalent and quadrivalent preparations. It was simply not clear to him how it would be technically possible to put all of this through a GRADE process.

While Dr. Loehr (AAFP) was one of the working group members who was looking forward to having a preferential recommendation, he reminded everyone that for at least 90% of the data, it was only clear that there was a preference for children 2 through 8. The data are not as clear for children ages 9 through 18.

Dr. Pickering noted that even if GRADEing was done for the trivalent vaccine, the quadrivalent will be used next year, and there are minimal safety data to extrapolate that preference to the quadrivalent vaccine.

Dr. Keitel said it was her personal opinion that it would be valuable to complete the GRADE of the trivalent product versus the other trivalent product, so that it can be used when there are data regarding large scale safety evaluation of the quadrivalent vaccine.

Dr. Grohskopf reviewed the new vaccines, indicating that the question upon which the committee would vote would be, "Are the recommendations for use as indicated and the supplemental language regarding considerations providers can make based on having choices agreeable to ACIP?" She reviewed each new vaccine.

Dr. Keitel indicated that the working group has reviewed the data and strongly said that there should be some specificity about which age groups providers might wish to prefer based on superior efficacy.

Dr. Grohskopf indicated that studies varied with regard to the age cutoffs. Methodologically, Clover had the lowest quality of evidence, primarily because it did not describe blinding procedures very well. The working group discussed this in terms of trying to use 2 through 8 years of age and 9 through 18 years of age primarily because 8 years is already an age cutoff for another clinical judgment (e.g., the last period of time for which 1 dose versus 2 for children must be considered). They could specify 2 through 8 years.

Dr. Temte thought that since data were presented that showed relative benefit in that age group and not in the older group, the statement could be modified to include that age group.

Dr. Duchin thought it might be useful also to add some language stating that the age 8 cutoff is not because there is evidence that it is not more effective, but that the data are insufficient. The assumption may be that it is equivalent if something is not added about why there is no mention after age 8.

Dr. Neuzil (IDSA) suggested being quite precise in the language. Dr. Grohskopf inquired as to whether citing an age range would satisfy that.

Dr. Keitel said that her greatest hesitation was that ACIP had not formally voted on the preferential recommendation. Relative effectiveness has not been addressed in that age group, so she would be very hesitant to make any comment whatsoever about that. The greatest data are in the younger children. To remain silent on older children would mean saying they do not have stronger data to support a preferential recommendation one way or the other, and that there is a practicality to the cutoff in that 8 is the natural age for 1 versus 2 doses and clinicians are thinking that way.

Dr. Temte inquired as to whether the evidence review was completed as presented during the October 2012 ACIP meeting. The difficulty was making the change in formulation to a quadrivalent and whether Dr. Keitel felt comfortable making a preference without knowing the post-licensure safety.

Dr. Keitel's understanding was that it was the requirement of the process that there be a formal assessment of vaccine safety before completing GRADE, because it is risk versus benefit. Now that there is a quadrivalent vaccine, the safety analysis has not been completed for the trivalent vaccine.

Dr. Temte said that if that was the case, he thought it was appropriate to leave the statement as it was without specifying an age range.

Dr. Sawyer wondered why they would even say what was in the statement, because many providers would interpret it as a preferential recommendation based on the way it was worded, and there were no safety data. Therefore, he thought they should not make any statement and use the standard language on this issue.

Dr. Campos-Outcalt inquired as to whether there would be a chance to revisit the language or if it would appear in the recommendations beginning in the summer.

Dr. Grohskopf responded that the language could be revisited. She thought the critical issue during this meeting would be at least the recognition of the new vaccines, their presence in the table, and that they are acceptable. The full scale recommendations contain a lot of literature review, and she has read most of them since 1960. Particularly for the past decade, there is a quite a lot of detail. This sort of information would be included in a literature review so that clinicians who read that section would know, and could make their own decisions about what to use. Some members of the working group wanted more specific information in the recommendation to assist clinicians in their choices, which is why the language was drafted as it was. However, that language could be removed.

Given that the hour was late, Dr. Wharton suggested that the important issue to address before the conclusion of the meeting was approval by ACIP of the list of vaccines that are acceptable for use for influenza vaccination for the upcoming season, without a lot of detail about their use, as well as reaffirming the basic recommendation for use of influenza vaccine in the US. There appeared to be a lot of complexity in the language as presented that they did not have time to address. Rather than making a recommendation with which they were not fully comfortable, perhaps they should step back and do a little less.

Dr. Groom (IHS) wondered if it was known when the codes would be made available for the cell-cultured and RAV vaccine so that those who have to program this could start working on it. Dr. Grohskopf said she believed the codes had been assigned. While she did not know the codes, she indicated that she would follow up and supply them.

Dr. Friedland (GSK) inquired as to how the list of approved vaccines would be disseminated to the public and payer community before the typical time in August.

Dr. Grohskopf replied that the plan is to issue a policy note on that shortly following the meeting, although she did not know a specific date. The currently available vaccines will also be listed on the influenza website.

Vote: Influenza Vaccine

Dr. Keitel made a motion that ACIP approve the list of newly introduced vaccines for age-appropriate use, and persist with the recommendation that eligible people who are at least 6 months of age be immunized annually against influenza. Dr. Coyne-Beasley seconded the motion. The motion carried with 14 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

14 Favored:	Bocchini, Campos-Outcalt, Coyne-Beasley, Duchin, Harriman, Harrison, Karron, Jenkins, Keitel, Rosenbaum, Rubin, Sawyer, Temte, and Vazquez
0 Opposed:	N/A
0 Abstained:	N/A

Day 2: Public Comment

No public comments were offered during this session.

Certification

Upon reviewing the foregoing version of the February 20-21, 2013 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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