

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

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



**Summary Report
June 22-23, 2011
Atlanta, Georgia**

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MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Centers for Disease Control and Prevention

1600 Clifton Road, NE, Tom Harkin Global Communications Center (Building 19), Atlanta, Georgia

June 22-23, 2011

<u>AGENDA ITEM</u>	<u>PURPOSE</u>	<u>PRESIDER/PRESENTER(S)</u>
Wednesday, June 22, 2011		
8:00 <u>Welcome & Introductions</u>		Dr. Carol Baker (ACIP Chair) Dr. Larry Pickering (ACIP Executive Secretary; CDC)
8:30 <u>Herpes Zoster Vaccine</u> <ul style="list-style-type: none">· Introduction· Merck vaccine supply status and projections· Licensure of Zostavax for adults of ages 50-59· Discussion	Information & Discussion	Dr. Paul Cieslak (ACIP, WG Chair) Dr. Eddy Bresnitz and Mr. Jim Robinson (Merck) Dr. Rafael Harpaz (CDC/NCIRD)
10:00 <u>Varicella</u> <ul style="list-style-type: none">· Update on varicella epidemiology since implementation of routine 2-dose varicella vaccination for children	Information	Dr. Stephanie Bialek (CDC/NCIRD)
10:15 <i>Break</i>		
10:45 <u>Meningococcal Vaccine</u> <ul style="list-style-type: none">· Introduction· Menactra indication for a two dose series in 9 and 12 month olds · Recommendations for infants at increased risk for meningococcal disease· Vaccines for Children (VFC) program vote· MenAfriVac™ (meningococcal A conjugate vaccine) introduction in Burkina Faso	Information Discussion & <u>Vote</u> <u>Vote</u> Information	Dr. Cody Meissner (ACIP, WG Chair) Dr. David Johnson (Sanofi) Dr. Amanda Cohn (CDC/NCIRD) Dr. Lance Rodewald (CDC/NCIRD) Dr. Thomas Clark (CDC/NCIRD)
11:40 <u>MMR Vaccine Work Group Update</u> <ul style="list-style-type: none">· Introduction· 2011 measles epidemiology update (U.S.)	Information	Dr. Jon Temte (ACIP, WG Chair) Dr. Huong McLean (CDC/NCIRD)
12:00 <i>Lunch</i>		
1:00 <u>Pertussis</u> <ul style="list-style-type: none">· Introduction· Safety of maternal vaccination to mother and fetus· Decision and cost-effectiveness analysis: maternal vaccination and cocooning· "Cocooning"· Timing of maternal vaccination: pregnancy or post-partum?· Proposed recommendations on maternal Tdap vaccination· Proposed recommendation on use of Tdap for contacts of newborns ("cocooning") and special situations· Tdap in pregnant and post-partum women through age 18 years · Emergence of pertussis in children aged 7 through 10 years and early evaluation of DTaP effectiveness in California	 <u>Vote</u> <u>Vote</u> <u>VFC Vote</u> Information & Discussion	Dr. Mark Sawyer (ACIP, WG Chair) Dr. Sonja Rasmussen (CDC/OID) Dr. Garrett Asay (CDC/NCIRD) Dr. Jennifer Liang (CDC/NCIRD) Dr. Jennifer Liang (CDC/NCIRD) Dr. Jennifer Liang (CDC/NCIRD) Dr. Jennifer Liang (CDC/NCIRD) Dr. Lance Rodewald (CDC/NCIRD) Dr. Lara Misegades (CDC/NCIRD)
2:45 <u>Vaccine Supply</u>	Information	Dr. Lance Rodewald (CDC/NCIRD)
3:00 <i>Break</i>		
3:30 <u>Human Papillomavirus Vaccines</u> <ul style="list-style-type: none">· Introduction· Background· Quadrivalent HPV vaccine: duration of protection· HPV-associated oropharyngeal cancer· Cost effectiveness issues for male vaccination· Policy considerations - HPV vaccine for males	Information & Discussion	Dr. Janet Englund (ACIP, WG Chair) Dr. Lauri Markowitz (CDC/NCHHSTP) Dr. Alfred Saah (Merck) Dr. Aimee Kreimer (NCI) Dr. Harrell Chesson (CDC/NCHHSTP) Dr. Eileen Dunne (CDC/NCHHSTP)
5:00 <u>Public Comment</u>		
5:15 <u>Adjourn</u>		

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<u>AGENDA ITEM</u>	<u>PURPOSE</u>	<u>PRESIDER/PRESENTER(S)</u>
Thursday, June 23, 2011		
8:00 <u>Unfinished Business</u>		Dr. Carol Baker (Chair, ACIP)
8:15 <u>Agency Updates</u> CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NVPO, NIH	Information	<i>Ex officio</i> members
8:30 <u>General Recommendations: Febrile Seizures</u> · Introduction · Clinical aspects of febrile seizures	Information	Dr. Jeff Duchin (ACIP, WG Chair) Dr. Harry Keyserling (WG Member, SHEA; Emory University School of Medicine)
· Safety data update · Burden of disease information; next steps	Discussion	Dr. Jerome Tokars (CDC/NCEZID) Dr. Andrew Kroger (CDC/NCIRD)
9:45 <i>Break</i>		
10:15 <u>Hepatitis B Vaccine</u> · Introduction · Update of hepatitis B incidence among persons with diabetes		Dr. Mark Sawyer (ACIP, WG Chair) Ms. Meredith Reilly (CDC/NCHHSTP)
· Cost effectiveness of hepatitis B vaccination among persons with diabetes · Next steps	Information & Discussion	Dr. Tom Hoerger (RTI International) Dr. Trudy Murphy (CDC/NCHHSTP)
11:15 <u>13-valent Pneumococcal Conjugate Vaccine (PCV13)</u> · Introduction · Public health and economic impact of PCV13 in US adults ≥50 years of age		Dr. Mike Marcy (ACIP, WG Chair) Dr. David Strutton (Pfizer)
· Current epidemiology of pneumococcal disease in adults · Considerations for PCV13 use among adults; summary of immunogenicity and efficacy; cost-effectiveness studies	Information & Discussion	Dr. Tamara Pilishvilli (CDC/NCIRD) Dr. Tamara Pilishvilli (CDC/NCIRD)
12:35 <i>Lunch</i>		
1:45 <u>Influenza</u> · Introduction · Influenza vaccine and egg allergies	Information	Dr. Wendy Keitel (ACIP, WG Chair) Dr. John Kelso (Scripps Clinic, University of California, San Diego); Dr. Matthew Greenhawt (University of Michigan Medical School, Ann Arbor); Dr. Matthew Fenton (NIAID, NIH) Dr. Lisa Grohskopf (CDC/NCIRD)
· Proposed recommendations · Intradermal influenza vaccine · Fluzone High Dose update	Vote Information & Discussion	Dr. David Johnson (sanofi pasteur) Dr. David Johnson (sanofi pasteur); Dr. Pedro Moro (CDC/NCEZID)
3:05 <u>Public Comment</u>		
3:20 <u>Adjourn</u>		

Acronyms

DTaP	Diphtheria, Tetanus, and Acellular Pertussis Vaccine
NCCDPHP	National Center for Chronic Disease Prevention and Health Promotion
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCI	National Cancer Institute
NCIRD	National Center for Immunization and Respiratory Diseases
OID	Office of Infectious Diseases
RTI	Research Triangle International
SHEA	Society for Healthcare Epidemiology of America
TBD	To be determined
Tdap	Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
WG	Work Group

Acronyms

AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core Surveillance
ACHA	American College Health Association
ACNM	American College of Nurses and Midwives
ACP	American College of Physicians
ACIP	Advisory Committee on Immunization Practices
ADL	Activities of Daily Living
AEs	Adverse Events
AHIP	America's Health Insurance Plans
AIM	Association of Immunization Managers
AIN	Anal Intraepithelial Neoplasia
AMA	American Medical Association
ANA	American Nurses Association
ASTHO	Association of State and Territorial Health Officials
BLA	Biologics License Application
BRFSS	Behavioral Risk Factor Surveillance System
CAP	Community Acquired Pneumonia
CDC	Centers for Disease Control and Prevention
CDPH	California Department of Public Health
CIN	Cervical Intraepithelial Neoplasia
cLIA	Competitive Luminex immunoassay
CMI	Cell-Mediated Immunity
CMS	Centers for Medicare and Medicaid Services
COI	Conflict of Interest
CUA	Cost-Utility Analysis
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DTaP	Diphtheria, Tetanus, and Pertussis
DVA	Department of Veterans Affairs
EBRWG	Evidence-Based Recommendations Work Group
ECMO	Extracorporeal Membrane Oxygenation
EIP	Emerging Infections Program
EIS	Epidemic Intelligence Service
ELISA	Enzyme-Linked Immunosorbent Assay
EMR	Electronic Medical Record
FDA	Food and Drug Administration
FIFO	First In First Out
GAO	Government Accounting Office
GMCs	Geometric Mean Concentrations
GMTs	Geometric Mean Titers
GRADE	Grades of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HCC	Hepatocellular Carcinoma
HCP	Healthcare Personnel
HCUP	Healthcare Cost and Utilization Project
HICPAC	Healthcare Infection Control Practices Advisory Committee
HepA	Hepatitis A
HepB	Hepatitis B
HHS	Department of Health and Human Services
Hib	<i>Haemophilus influenzae B</i>
HPV	Human Papillomavirus

HMO	Health Maintenance Organization
HZ	Herpes Zoster
HZV	Herpes Zoster Vaccine
HRSA	Health Resources and Services Administration
IARC	International Agency for Research on Cancer
ICURs	Incremental Cost-Utility Ratios
ICD-9	International Classification of Diseases, Ninth Revision
IDSA	Infectious Disease Society of America
IDU	Injection Drug Use
IgG	Immunoglobulin G
IHS	Indian Health Services
ILI	Influenza-Like Illness
ILINet	Influenza-Like Illness Surveillance Network
IOM	Institute of Medicine
IPD	Invasive Pneumococcal Disease
ISO	Immunization Safety Office
<i>JAMA</i>	<i>Journal of the American Medical Association</i>
LEEP	Loop Electrosurgical Excision Procedures
LTPS	Long Term Persistence Study
MCO	Managed Care Organization
MMR	Measles, Mumps, Rubella
MMRV	Measles, Mumps, Rubella, Varicella
<i>MMWR</i>	<i>Morbidity and Mortality Weekly Report</i>
MOMs	Moms on Meningitis
MSM	Men Who Have Sex With Men
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization
NBP	Nonbacteremic Pneumonia
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
NFID	National Foundation for Infectious Diseases
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIS	National Immunization Survey
NMA	National Medical Association
NNDSS	National Notifiable Diseases Surveillance System
NPP	Non-bacteremic Pneumococcal Pneumonia
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
OPA	Opsonophagocytic
PAHO	Pan American Health Organization
PBNA	Pseudovirion-Based Neutralization Assay
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PHN	Post-Herpetic Neuralgia
PPACA	Patient Protection and Affordable Care Act
PPV23	23-Valent Polysaccharide Vaccine
QALY	Quality-Adjusted Life Year
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
SAEs	Serious Adverse Events

SBA-HC	Bactericidal Assay Antibody Titers using Human Complement
SME	Subject Matter Expert
SPR	Seroprotection Rate
SPS	Shingles Prevention Studies
STPS	Short Term Persistence Study
Tdap	Tetanus and Reduced Diphtheria Toxoids
TIV	Trivalent Inactivated Influenza Vaccines
UK	United Kingdom
US	United States
USPHS	US Public Health Service
VAERS	Vaccine Adverse Event Reporting System
VFC	Vaccines for Children
VICP	Vaccine Injury Compensation Program
VIS	Vaccine Information Statement
VSD	Vaccine Safety Datalink
VZV	Varicella-Zoster Virus
WG	Working Group
WHO	World Health Organization
ZEST	Zostavax® Efficacy and Safety Trial

June 22, 2011

Welcome and Introductions

Dr. Carol Baker
Chair, ACIP

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

Dr. Baker called the meeting to order, welcoming those present. She then introduced Dr. Pickering who delivered the administrative announcements.

Dr. Pickering welcomed everyone to the June 2011 Advisory Committee on Immunization Practices (ACIP) meeting. As with previous ACIP meetings, 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. Notably, during the February 2011 meeting there were 27,570 sites watching.

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, Committee Management Specialist for ACIP; Natalie Greene, Maximum Technology Corporation; and Tanya Lennon, Special Assistant. Those with any questions were instructed to see him, any of these individuals, or Dr. Baker. He indicated that boxed lunches would be provided for a charge during the first day of the meeting in the hallway outside of the auditorium, and that coffee and tea would be available in the hallway for the duration of the meeting.

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 at this meeting will be posted on the ACIP website approximately one week after the meeting concludes, the live webcast will be posted within three weeks following the meeting, and meeting minutes will be available on the website within 90 days following this meeting. Members of the press interested in conducting interviews with various ACIP members were instructed to contact Tom Skinner, CDC Public Affairs Specialist, who was in attendance, for assistance in arranging the interviews.

Dr. Pickering recognized the following visitors:

From the World Health Organization's (WHO's) Pan American Health Organization (PAHO), and from Ministries of Health of PAHO member countries:

- Dr. Cara Janusz, PAHO Technical Officer, PAHO Office in Washington, DC
- Dr. Gloria Rey, Sub-director, Lab Network of the National Institute of Health in Colombia, liaison to the National Committee on Immunization Practices in Colombia
- Dr. Gabriel Wolf Oselka, Technical Advisory Committee on Immunizations in Brazil
- Dr. Misael Gómez, National Immunization Program in Mexico

- ❑ Dr. Cristina Marino, President of Colombian Association of Pediatricians, Member of the National Committee on Immunization Practices
- ❑ Dr. Rafael Haeussler, Director of Integrated Primary Care Programs at the Guatemalan Ministry of Health

From The Republic of Korea:

- ❑ Ms. Min Jung Seo, Assistant Director, Korea Centers for Disease Control & Prevention
- ❑ Ms. Kwang Suk Park, Research Scientific Officer, Korea Centers for Disease Control & Prevention
- ❑ Ms. Jonghee Kim, Technical Specialist, Korea Centers for Disease Control and Prevention

Those unable to attend this ACIP meeting for either or both days included the following:

Ex Officio Members

- ❑ Dr. Richard Gorman from National Institutes of Health was unable to attend; Dr. Mirjana Nesin attended on his behalf.
- ❑ Dr. Norman Baylor, *ex officio* member representing the Food and Drug Administration (FDA) was unable to attend; Dr. Wellington Sun attended on his behalf.
- ❑ Dr. Bruce Gellin, Director, National Vaccine Program Office (NVPO) was unable to attend; Dr. Mark Grabowsky, NVPO Deputy Director, attended on his behalf.
- ❑ James Cheek, MD, MPH, liaison for Indian Health Services (IHS) was unable to attend; Amy Groom, MPH, Director, IHS National Immunization Program attended on his behalf.

Liaison Representatives

- ❑ Dr. Joanne Langley has concluded her term as the chair of Canadian National Advisory Committee on Immunization (NACI), and Dr. Bryna Warshawsky is the new ACIP liaison representative for NACI.
- ❑ Dr. Mark Netoskie, liaison representative for America's Health Insurance Plans (AHIP) was unable to attend; Dr. Richard Doskey, Regional Medical Officer for Humana/New Orleans, attended on his behalf.

To avoid disruptions during the meeting, those present were instructed to conduct all business not directly related to discussions of ACIP in the hall and to turn off all cell phones or place them in the vibrate mode. 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.

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. In certain circumstances, a formal comment period may be scheduled during the deliberations of a specific agenda item rather than at the

end of the day in order to be considered before a vote is taken. Those who planned to make public comments were instructed to visit the registration desk in the rear of the room to have Stephanie Thomas record their name and provide information on 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, 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 deliberations or 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.

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: www.cdc.gov/vaccines/recs/acip/

Nominations: <http://www.cdc.gov/vaccines/recs/acip/req-nominate.htm>

Applications for ACIP membership are due no later than November 18, 2011 for the term beginning July 2012. Interested parties were encouraged to complete an application and submit it by the deadline.

The following information was shared pertaining to ACIP:

Next ACIP Meeting: Tuesday and Wednesday October 25-26, 2011

Registration Deadlines: Non-US Citizens June 3, 2011 / US Citizens Monday October 10, 2011

Vaccine Safety: www.cdc.gov/vaccinesafety/

Immunization Schedules:

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

Childhood Vaccine Scheduler (interactive):

<http://www.cdc.gov/vaccines/recs/scheduler/catchup.htm>

Adult Vaccine Scheduler (interactive):

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

Vaccine Toolkit:

<http://www.cdc.gov/vaccines/spec-grps/hcp/conversations.htm>

Dr. Pickering noted that at every meeting, an update is provided on the status of ACIP recommendations. Since the last meeting there has been one ACIP statement published in the *Morbidity and Mortality Weekly Report (MMWR)*:

- Policy Note: Japanese Encephalitis Booster Dose; Publication date: 5/26/2011; Vol 60(20):661-663

All ACIP recommendations published since 01-01-11 are reported in the following table:

ACIP Recommendations Published since 01-01-11		
Topic	Publication Date	MMWR Reference
Policy Note: Japanese Encephalitis Booster Dose	05/26/11	Vol 60(20):661-663
2011 Child/Adolescent Immunization Schedule (0 through 18 years)	02/11/2011	Vol 60(05):1-4
2011 Adult Immunization Schedule (≥19 years)	02/04/2011	Vol 60(04):1-4
General Recommendations on Immunization	01/28/2011	Vol 60(RR2):1-61
Policy Note: Meningococcal Conjugate Vaccines	01/28/2011	Vol 60(03):72-76
Antiviral Agents – Influenza	01/21/2011	Vol 60(RR1):1-28
Policy Note: Tdap Vaccine	01/14/2011	Vol 60(01):13-15

<http://www.cdc.gov/vaccines/recs/acip/>

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The following conflicts of interest were declared:

- Dr. Tamera Coyne-Beasley: Research support from pharmaceutical companies is made to her university
- Dr. Janet Englund: Research support to her university from MedImmune, Novartis, Adamas, and Chimerix
- Dr. Wendy Keitel: Research support is made to her institution from Novartis
- Dr. Cody Meissner: Payments are made to Tufts University Medical Center by MedImmune, Pfizer, and Roche for participation in multi-center clinical trials
- Ms. Sara Rosenbaum: Research support to her university
- The remainder of the ACIP members declared no conflicts

Dr. Baker lamented that June was a sad time of year, given that there were five retiring members:

- ❑ Dr. Lance Chilton, Associate Professor, University of New Mexico
- ❑ Dr. Paul Cieslak, Medical Director, Oregon Immunization Program, Oregon Public Health Division
- ❑ Dr. Janet Englund, Professor, Department of Pediatrics Seattle Children's Hospital
- ❑ Dr. Franklyn Judson, Professor of Medicine, University of Colorado
- ❑ Dr. Jon Temte, Professor of Family Medicine, University of Wisconsin School of Medicine and Public Health has been reappointed until June 30, 2015

Dr. Baker called each retiring member forth, presented them with a certificate and an engraved plaque, and thanked them for their service. Retiring members offered the following comments:

Dr. Chilton said that he had very much appreciated being on this committee. He quipped that before he joined ACIP, he thought that ACIP decisions were handed down on an engraved stone to Larry Pickering on a mountain top. He now knows that is not how decisions are handed down. He acknowledged the great deal of work that occurs during ACIP meeting, as well as in the work groups, and very much appreciated the chance to be involved in both components of the work.

Dr. Cieslak said that it had been a privilege to serve on this committee, and that it had been like drinking data from a fire hydrant. He expressed his appreciation to Drs. Pickering and Baker, as well as the CDC staffers who make the deliberations possible. It has been an honor to be associated with his colleagues on this committee.

Dr. Judson said it had been a real pleasure to serve on ACIP, and that he thought as a deliberative body, ACIP serves the country well, and the broader public health community globally.

Dr. Janet Englund said it had been a pleasure and an honor to serve on this committee. She said she thought they needed to acknowledge the unsung heroes, who are the CDC staffers who have worked harder than ever over the past few years.

Session Introduction

Paul R. Cieslak, MD
Advisory Committee on Immunization Practices
Chair, Zoster Working Group

Dr. Cieslak introduced the Herpes Zoster Vaccine session, which included presentations on the following topic areas:

- Overview of Zoster Work Group (WG) deliberations regarding herpes zoster vaccine in adults 50–59 years of age
- Merck vaccine supply status and projections
- Licensure of zoster vaccine among adults 50–59 and detailed review of considerations of the WG

With regard to background, Dr. Cieslak reminded everyone that the FDA licensed Zostavax® for adults ≥60 in May 2006. In October 2006, ACIP recommended Zostavax® for adults ≥60. In 2010, Merck completed the Zostavax® Efficacy & Safety Trial (“ZEST”) in persons aged 50–59. In March 2011, the FDA extended the indications for Zostavax® to adults aged 50–59.

The Zoster Work Group’s terms of reference were to review new data regarding use of zoster vaccine among persons 50–59 years of age, consider revision of ACIP recommendations and review zoster vaccine post-licensure data. Regarding the methods, approach, and activities, the Zoster WG has engaged in 14 conference calls and net-conferences since September 2010. They reviewed published and unpublished data pertaining to the epidemiology and natural history of zoster; zoster vaccine safety, immunogenicity, and efficacy data in persons 50 and older; programmatic issues, including financing, storage and handling; manufacturing, supply, and marketing information; and economic analyses.

The WG does not propose revision of existing recommendations regarding zoster vaccine. The rationale for this conclusion is that there is insufficient evidence regarding duration of vaccine protection to vaccinate well before the peak of zoster incidence. Perhaps paramount in the minds of many members of the WG was that it might be inappropriate to expand recommendations while zoster vaccine remains in short supply. If the limited supply of vaccine is used at ages during which zoster incidence is low, overall zoster incidence may increase. The decision of the WG is not intended to prejudice future deliberations.

The next steps for the Zoster Working Group are to assess new data and address relevant issues regarding a variety of issues, including Zostavax® in persons taking corticosteroids, duration of immunity, Zostavax® in persons with HIV infection, inactivated OKA-VZV in marrow transplant recipients, and other issues that arise. The membership of the working group will be adjusted as appropriate, and Dr. Jeffrey Duchin will serve as the new chair of this working group upon Dr. Cieslak's departure.

Introductory Remarks: Merck Vaccine Supply Status and Projections

Dr. Eddy Bresnitz
Merck & Company, Inc.

Dr. Bresnitz expressed his gratitude for the opportunity to make a few introductory comments. Last summer, Merck requested that CDC reconstitute the Zoster WG that was disbanded in 2006 subsequent to making the current recommendations. He offered Merck's appreciation for CDC's willingness to consider making a recommendation in the 50 to 59 year old age group to help prevent herpes zoster and its complications.

As Dr. Cieslak noted, one of the reasons for the WG's decision not to vote on a recommendation change at this time regarded uncertainty about whether the vaccine supply would meet the increased demand generated among persons 50 through 59 years of age. Although Dr. Bresnitz explained that Merck is confident about its ability to meet projected increased demand, based upon experience and market research, Merck certainly respects the decision of the WG and CDC to postpone a vote and to emphasize vaccination of the eligible population 60 and older.

Dr. Bresnitz pointed out that while Dr. Robinson's upcoming presentation was intended to help the ACIP membership understand why Merck is optimistic about its ability to meet expected demand of zoster vaccine, it is important to note that addressing the supply constraints is necessary, but not sufficient to improve herpes zoster vaccine coverage in the US among the eligible population. There have been great improvements in adult vaccination coverage over the last decade, but the vaccination uptake has plateaued in this population for a variety of reasons. One reason is that the culture and enterprise for adult vaccination needs strengthening at all levels, which was highlighted in a report that was recently voted on by the National Vaccine Advisory Committee (NVAC). That report reflects improved uptake of adult vaccines, but also reflects on the fact that there are many factors other than vaccine supply that impact uptake.

Merck looks forward to working collaboratively with CDC, ACIP, and other stakeholders to improve uptake of herpes zoster and other vaccines. The decision by the WG to postpone the vote begs the question: For how long? Dr. Bresnitz noted that as they listened to the presentations that followed his, Merck would like ACIP and CDC to consider the establishment of criteria or milestones, with input from Merck that would trigger reconsideration of a vote and a potential recommendation for the 50 to 59 year old population at some future point. Specifying such criteria or milestones could create a common platform for establishing a joint move forward to making this important vaccine available to all eligible US people over the age of 50, as well as globally to people who can benefit from the vaccine as Merck builds its supplies and inventory.

Supply Update on Varicella Containing Vaccines

**James Robinson, Vice President
Vaccines Product & Technical Operations
Merck Manufacturing Division**

Mr. Robinson indicated that he is responsible for vaccine manufacturing at Merck. His specific responsibilities are the long-term production strategy for Merck's vaccines, as well as technical support of manufacturing. He has been with Merck for 15 months, and has spent the majority of his time working on this particular topic in order to improve this supply issue. Prior to joining Merck, he had 25 years of experience in vaccine manufacturing and development in the industry, including running the nation's only influenza manufacturing facility for 9 of those years.

The Zostavax® story begins somewhat before the licensure of Zostavax® in 2006. Varivax®, the varicella vaccine for chicken pox, was licensed in 1995. The bulk manufacturing process to support that product is the same process that supports all other products in this product line. The 1995 licensure of Varivax® was followed by licensure of ProQuad® (MMRV) in 2005 and the Zostavax® (Shingles) licensure in 2006. Each product has been licensed in both a frozen and a refrigerated formulation. All six products are manufactured from the same vaccine bulk, and different products require different amounts of bulk. To put in context one of the challenges, the manufacturing of the refrigerated formulation of Zostavax® requires 12 equivalent doses of Varivax®. Zostavax® frozen requires 8 equivalent doses of Varivax®. Obviously, a decision must be made about what to make. Merck decided to prioritize the Varivax® formulation. However, manufacture of Zostavax® is more challenging than manufacture of Varivax®, and a percentage of batches do not have the potency for Zostavax® vaccine. A number of efforts are underway to improve this issue, and some progress has already been shown with the most recent results.

While manufacturing vaccines is always complex, Dr. Robinson has never experienced a vaccine manufacturing process more complex than that needed to prepare bulk for the varicella vaccine product line. Varicella is an intercellular virus that grows on an attached cell line. In the manufacturing of a single batch of bulk, there are more than 25,000 individual manufacturing steps. The steps are completed in customized robotic systems in Grade A space to make sure the product has the appropriate quality. The capital, complexity of managing and maintaining that system, and cycle times are extensive. Improvements being made today will not be seen for approximately a year with respect to products reaching the marketplace. Improvements observed over the last 7 months were the result of work that was done roughly 12 to 18 months ago. Merck is already making the 2012 supply of varicella-containing products, and the 2011 supply is already complete in the bulk form and is in various stages of analytical testing, form fill, and release.

Regarding variability of potency in the process, from a virology standpoint, it is not a highly variable process. However, from the standpoint of how Merck's vaccines are designed, it is a sometimes a challenge to make the higher potency products. If there is any sustained period of time that there are no high potency batches, the ability to make Zostavax® is diminished. However, Merck is always able to and has successfully supplied Varivax® for the pediatric population in recent years. Merck is committed to meeting that market first; however, they continue to focus on ensuring that the company can meet all demands for all markets for these products.

Over the last three years, Merck has produced from 1.7 to 2 million doses of Zostavax® vaccine per year in addition to Varivax® and with varying amounts of ProQuad® each year. Merck takes orders on a first in first out (FIFO) basis, and does not have preferred buying groups. They have been able to supply this product consistently at that level, although not consistently to meet the overall demand for this product in the marketplace. Since December 2010, approximately 2 million doses of Zostavax® have been distributed to over 38,000 unique customers across all customer types, and covering all 50 states plus the District of Columbia. In the last 7 months, that is more than any prior 12 month period since the product was launched. They expect to deliver another 2 million doses in 2011, doubling any previous year's supply of Zostavax® vaccine. Merck expects to continue to increase that with increases of more than 25% in 2012. With new facilities coming online, the opportunity to increase is expected, not in terms of percentage, but in terms of fold increases in supply. Again, these near-term improvements are based on work that was done last year.

Merck is executing a comprehensive strategy for reliable and ample supply. Whereas the process itself and the biology is variable, there are many things that organizations can do to reduce other variability, such as logistics variability, managing cold chain, and the process overall. Merck has increased diligence in these areas and has been able to produce some significantly better results over the past 12 months. The comprehensive strategy focuses on reliability in terms of work flow optimization and standardization, potency in terms of process enhancements, and capacity in terms of new facilities. Merck has invested over \$1 billion over the last few years in new infrastructure for vaccines. The lion's share has been allocated to building its varicella-based product supply, including a \$750 million investment in Durham, North Carolina focused on manufacturing new bulk as well as sterile form filled vials of live viral vaccines. Meeting customer and patient demand across Merck's portfolio of varicella-containing vaccines is a key priority for Merck. Merck's goal is to stay off of CDC's supply shortage list, and to work together with the agency to bring more products to more people.

In summary, live virus manufacturing is inherently complex. Varivax® will continue to be prioritized over other varicella-containing vaccines. The 2011 performance for supply of Zostavax® has materially improved versus prior years, with additional improvement expected in 2012 and beyond. A comprehensive strategy is being executed to deliver a reliable and ample supply of all varicella-containing vaccines. Merck is committed to meeting customer and patient demand across its portfolio of varicella-containing vaccines, and to working closely with ACIP and the working group to manage recommendations moving forward. Merck welcomes any opportunities to present to ACIP regarding its supply situation.

Update: Zoster Vaccine for Adults 50-59 Years of Age

**Rafael Harpaz, MD MPH, CDC Lead, Zoster Working Group
National Center for Immunizations and Respiratory Diseases
Centers for Disease Control and Prevention**

Dr. Harpaz pointed out that Dr. Cieslak set the stage for his presentation by reporting the decision of the WG that it is not appropriate to consider changing the current ACIP recommendations for zoster vaccination of adults age 60 years and older. Given that zoster vaccine is now licensed and available for persons 50 to 59 years, the WG felt that it was very important to present their conclusions to ACIP and to be very transparent about how the WG arrived at its conclusion. .

In terms of the current status of herpes zoster vaccine (HZV) licensure and recommendations, as a reminder, the current zoster vaccine is for adults aged ≥ 60 years without any specified contraindications. This includes persons over 80, who are frail, with chronic illnesses. The vaccine is not intended for treating herpes zoster. It is recommended regardless of whether a patient reports a history of shingles. It is not necessary to screen for varicella history or to check varicella titers. Immunosuppression is a contraindication for HZV, and it is not recommended for persons who previously received varicella vaccine. The FDA initially licensed the vaccine for adults age 60 and older in May 2006, and extended it to adults ages 50 to 59 years in March 2011. This was based on the demonstrated efficacy and safety in a Phase 3 clinical trial, Zostavax® Efficacy and Safety Trial (ZEST), and related data.

In terms of the background of herpes zoster and post-herpetic neuralgia (PHN), important clinical manifestations of zoster are that it causes an acute, self-limited pain syndrome that can be disabling. It can cause acute ophthalmic involvement as well. The complications are of varying frequency and severity and include, most importantly, chronic pain or PHN. This pain is very difficult to control and can result in interference with activities of daily living; depression and its sequelae (e.g., isolation and occasional suicides); and many complications from the medications, particularly for the elderly population that is so afflicted by the disease. Chronic visual impairment can occur, there can be skin scarring or changes in pigmentation, secondary bacterial infections may occur, or there could be neurologic complications (e.g., meningitis, palsies, stroke syndromes).

With regard to the economic burden of herpes zoster, there are direct medical and non-medical costs such as outpatient visits, emergency department visits, and / or hospitalizations; specialist referrals and consultations; laboratory tests and imaging / x-ray studies; and medications and therapeutic procedures. Indirect costs may include absenteeism and reduced productivity (also called presenteeism); productivity losses associated with deaths; care giving by family who help with activities of daily living; and / or pain and suffering. Most of the total herpes zoster disease burden, the predominance of which is pain and suffering, is borne by the individuals themselves. Pain and suffering are not usually even considered in most economic analyses of vaccine preventable diseases, and pain and suffering are very hard to measure.

Regarding the impact of age on burden of herpes zoster, virtually all adults are latently infected varicella zoster virus. Data from the National Health and Nutrition Examination Survey (NHANES) study published by Paul Kilgore about eight years ago show that the seroprevalence among the non-institutionalized population increases by age. According to these data, by age 40, approximately 100% of the population is seropositive and thus at risk of herpes zoster [Kilgore, PE, et al. J Med Virol, 2003; 70:S111-118]. These results have been confirmed in subsequent NHANES data, and are also supported by the very few cases of varicella (e.g., chicken pox) reported amongst older adults in the US.

The burden of herpes zoster increases sharply after age 50 years. Not only does the incidence of herpes zoster itself increase with age, but also among persons who experience zoster the following increase as well: the proportion of herpes zoster with non-pain complications (e.g., ophthalmic, neurologic, and skin complications); the proportion of persons with zoster who are hospitalized (with the length of stay and cost increasing as well); the proportion of herpes zoster associated with death, although for persons who are immunocompetent those numbers are quite small so they need to be validated; interference with activities of daily living (ADLs); and the proportion of herpes zoster with acute pain and progression to PHN. In terms of PHN, severity and duration of pain, inability to tolerate pain, duration / risk of prolonged pain increase with age as well. Even amongst persons who have PHN of a particular severity and particular

duration, age impacts the vulnerability, resilience, ability to access care, ability to tolerate pain medications. These factors are very hard to measure and have not been fully measured. Dr. Harpaz would argue that these are particularly important for the oldest old. The only exception to the relationship of increasing age to increasing burden of zoster is work loss and loss of work-associated productivity, since the portion of persons who are retired clearly increases with age.

Data that support these assertions show that almost every aspect of the burden of zoster disease increases strikingly with age, more than just as a function of the risk of zoster or even the risk of PHN, that themselves are exponential. Data published four years ago by Barbara Yawn regarding zoster incidence in the general population of Olmsted County from 1996-2001 illustrate the increase of zoster as age increases [Yawn BP, et al. *Mayo Clin Proc*, 2007; 82:1341-9]. Data based on administrative claims data from the MarketScan databases show the impact of increasing age on the risk of zoster [MarketScan administrative claims data, Insinga et al., *J Gen Intern Med*. 2005, 20:748-53]. The percentage of zoster patients with non-pain complications are shown in Yawn's Olmsted County data. These complications include skin, neurologic, and other ocular complications [Yawn et al., *Mayo Clin Proc*. 2007; 82:1341-9]. Data from the United Kingdom (UK) reflect the portion of persons with zoster who are hospitalized by age. These data show that even among a subset of persons with zoster who are hospitalized, the length of stay increases with age [Van Hoek et al. *Vaccine* 2009, 27:1454-67]. Data from Connecticut pertaining to the rate of zoster-associated hospitalizations in the general population by age capture both the increase of zoster by age in the population, as well as the risk that those cases will progress to be hospitalized, which increases by age. These rates increase many fold from the age of 50 to 75, with 67% of HZ hospitalizations in persons >65 years of age [Lin F, Hadler JL. *J Infect Dis* 181(2000):1897-905].

Turning to the risk of PHN, Yawn's data from Olmsted County show that the risk of zoster progressing to PHN defined as pain lasting at least 90 days increase 4-fold from patients age 50 to 59 to patients over age 80 years. The same data expressed as an incidence of PHN in the general population rather than the proportion of zoster progressing to PHN illustrate that the rate increases many fold from the age of 50 to the age of 70 or 80 [Yawn, *Mayo Clin Proc*. 2007; 82:1341-9]. Data from the UK regarding the proportion of PHN of moderate to severe pain by age show that even when controlling for PHN of a given duration, the severity of pain increases with age [Gauthier A, et al. *Epidemiol Infect*. 2009, 137:38-47], while data from the Shingles Prevention Study show how zoster impacts the activities of daily living as a function of age [Schmader K et al. *J Am Geriatr Soc*, 2010, 9:1634]. The only exception to the rule that every aspect of zoster grows worse with age is illustrated by data from the Bureau of Labor Statistics that show a decline in the portion of the total population in the workforce by age. Because of retirement, the impact of zoster and its complications on work loss decline with age as does the reduced productivity of persons who are at work with remaining zoster- or PHN- pain [<http://www.bls.gov/cps/wlf-table1-2005.pdf>].

To summarize, not only is the entire adult US population infected with varicella and thus at risk of HZ the rest of their lives, but the burden of HZ disease actually increases greatly in the latter half of life, decade by decade. This is a very different pattern from most other vaccine preventable diseases for which the peak risk period is self-limited or declines to low levels in the latter half of life, decade by decade. The only exceptions might be influenza, for which a vaccine is given each year, and perhaps pneumococcal disease.

With respect to the vaccine, the Shingles Prevention Study (SPS) by Oxman and others focused on adults ≥ 60 years of age and enrolled over 38,500 subjects in 22 US sites with mean follow up of 3.1 years. The vaccine efficacy for preventing HZ was 51.3%, while the vaccine efficacy for preventing PHN was 66.5%. This suggests that in addition to preventing zoster, the zoster that did occur among vaccinees (e.g., vaccine failures) was milder than the zoster that occurred in the unvaccinated controls. The zoster among vaccinees was also less likely to progress to PHN, referred to as an incremental effect. There was also a trend for zoster among vaccinees to cause less interference with activities of daily living. Importantly, the incremental effect has been observed only in adults ≥ 70 years of age, at least in a convincing manner.

During the February 2011 ACIP meeting, Dr. Hung Fu Tseng presented data published in the *Journal of the American Medical Association (JAMA)* based on observations of 75,800 adults ≥ 60 years of age in a large health maintenance organization (HMO) who had received vaccine as a part of routine clinical practice. He demonstrated that the field effectiveness of the vaccine was 55%, which is very similar to the SPS trial, and that the vaccine was more effective at preventing hospitalization associated with zoster (65%). The clinical trial and observational data differed, however, in an important way. The Oxman study showed that the vaccine efficacy for preventing zoster declined with age, but the Tseng study showed no such decline. These disparate results are explained on the basis of the fact that case finding between the two studies differed. It suggests that for persons 60 years of age and older, vaccine efficacy is stable by age for more severe and clinically meaningful disease picked up in a clinical setting than was observed in an observational study where there was aggressive case finding. In that setting, vaccine efficacy was more likely to decline with age for those milder cases that were seen in that context.

Also during the February 2011 ACIP meeting, results were presented regarding the ZEST clinical trial in subjects 50-59 [Schmader IDSA 2010]. The ZEST study included 22,400 subjects in multiple US and ex-US sites, with a mean follow-up 1.3 years. The vaccine's effectiveness at preventing HZ was 69.8%. Vaccine effectiveness at preventing PHN was not studied in the ZEST study because patients are only followed for 21 days. However, there was no difference in HZ severity-by-duration score by vaccine status (i.e., no evidence that HZ in vaccinees was milder in this age group).

Safety of the vaccine has been assessed in SPS, ZEST, a large phase 4 trial, and two large observational studies, and safety has been monitored by the Vaccine Adverse Event Reporting System (VAERS). There is little suggestion to date of severe adverse events regardless of age. Conversely, local injection-site reactions appear to be very common and that risk declines with increasing age at vaccination.

The combined data from ZEST of persons 50 to 59 years of age and from the SPS in persons 60 years and older show a striking decline in vaccine efficacy by age. These two studies were conducted in different settings with somewhat different methods, which is a very important caveat [ZEST (Schmader IDSA 2010) and SPS (Oxman NEJM 2005, 352:2271-84)]. These data stand in marked contrast with data from the observational studies in Southern California by Tseng et al, which shows that the vaccine performance is really quite stable by age [Tseng et al. JAMA 2011, 305:160-166]. As mentioned, one explanation for this is that vaccine efficacy against clinically meaningful disease is better retained with increasing age. Data from the SPS were used to evaluate vaccinated and unvaccinated persons in the study who developed zoster to determine whether they also developed PHN. There was an incremental effect in preventing PHN amongst vaccinees 70 years of age and older, although the numbers were small so the

confidence limits were pretty wide, No such effect was noted for persons age 60 to 69 years [Oxman, ACIP, Oct. 24, 2006].

In summary, the burden of zoster increases with age, and the performance of the zoster vaccine as a function of age is quite complex, with relative preservation of protection as a function of age for more severe disease and less for milder disease. In this context, if one is deciding upon a policy to vaccinate at the age of 50 to 59 rather than the later age, the duration of protection is quite important. The SPS lasted 5 years from 1999 to 2004, with a mean duration of follow-up of 3.1 years. The subset of subjects from that study was subsequently enrolled into an extension study called the Short Term Persistence Study (STPS), the purpose of which was to collect data on longer-term vaccine efficacy. These data clearly show that the zoster vaccine protects for 3 to 4 years, and the data are consistent with the possibility that it might protect for years longer as well. However, given the unique epidemiology of zoster with its burden of disease increasing over time over decades, the unanswered question is: Will the vaccine protect 15 years or 30 years when it really counts? The Long Term Persistence Study (LTPS) will extend the results of the STPS by several years, the results of which are anticipated within the year. The LTPS, however, uses historic controls. Most of the controls dropped out or became vaccinees themselves. Given that the incidence of zoster in the general population is changing, it requires sophisticated adjustments and it will be difficult to interpret the results. Immunogenicity is not especially helpful because there are no good serologic or cell-mediated immunity (CMI) correlates. There will be follow-up observational studies that will be important in time.

Data on durability of protection from the SPS combined with the STPS show that after a decline in vaccine efficacy during the first year, which seems to be a consistent finding in all of the studies, the efficacy appears to be relatively stable during the subsequent 3 years. Beyond that, it is really difficult to know whether vaccine efficacy is waning by year 7, much less to predict how well the vaccine will work years later. It is important to note the very wide confidence limits after year 3 or 4. Related data from the same study assess the efficacy of preventing PHN defined as 90 days of zoster pain or more. These PHN results are very unstable because the numbers are quite small, but it can certainly be said that all of the point estimates are greater than zero, so the vaccine is offering protection. However, it is not possible to say much about waning up to 7 years or beyond [Schmader, IDSA 2008].

According to the Social Security Administration (SSA), persons in the 50 to 59 year age group are expected to live 30 years [<http://www.ssa.gov/oact/STATS/table4c6.html>]. The epidemiology of zoster during those 30 years thus becomes very relevant, and we would want the vaccine to last that long..

The question with which the WG had to grapple was: Should zoster vaccine be recommended for person 50 to 59 years of age? Applying the Yawn data to a cohort of persons exactly 50 years of age and following them for 7 years highlights the very limited extent to which those data on durability inform the issue at hand when compared to the timeframe of interest [Yawn et al. Mayo Clin Proc. 2007; 82:1341-9]. This emphasizes the challenge of extrapolating 7 years of imprecise data for decades to where most of the burden of occurs.

Even if zoster vaccine protects indefinitely with no waning at all, giving the vaccine to a person a long time before the burden of disease is highest is economically inefficient. It is analogous to taking out a mortgage on a retirement home at the age of 50 and only using it sporadically until age 75 years. Those dollars could be used otherwise, working in other ways. Economists call this concept discounting, and the conventional discount value used in the US for economic

studies is 3% per year. If one gave a hypothetical vaccine with lifelong protection 10 years before it was needed to prevent the corresponding disease, the cost of the hypothetical vaccine would be increased by about 30%.

The WG heard several presentations on economic analyses of zoster vaccine in adults age 50 to 59 years from manufacturers and CDC. The ACIP guidelines regarding economic analyses require that these be fully peer-reviewed by CDC economists before presentation to the ACIP. In light of the working group's decisions on this vaccine, those peer reviews were not completed and, therefore, are not being presented during this session. However, Dr. Harpaz presented published data on related issues to illustrate some of the points regarding the impact of age and duration of protection on the cost-effectiveness of zoster vaccine.

Among adults \geq age 60 years, the cost-effectiveness of zoster vaccine is less favorable at the youngest and oldest ages of that range. They form a J-shaped curve. It is less favorable at younger ages due to the lower burden of zoster. Protection is likely to wane by time zoster vaccine recipient reaches older ages when the burden of disease is high. Even assuming lifelong protection, outlay for the vaccine at an earlier age while the disease burden is low is economically inefficient. In terms of older ages, the cost-effectiveness is less favorable because of the decline in vaccine efficacy at older ages, and due to death in the elderly before the vaccine benefit accrues. The J-shaped curve is progressively more acute assuming shorter-lived vaccine duration of protection; whereas, it is flatter if longer vaccine protection is assumed.

Regarding the impact of age at zoster vaccination on its cost-effectiveness as compared to no vaccine policy at all, data from Canada were presented, assuming 15 years of waning protection. The data show that the cost-effectiveness becomes more favorable with increasing age from 60 to 70 years, but then begins to become less favorable in a very steep manner due to the reduced initial vaccine efficacy and the issue pertaining to persons dying before the vaccine benefit accrues [Najafzadeh, *Pharmacoeconomics* 2009; 27:991-1004]. Similar data from the US show cost-effectiveness of the zoster vaccine at various ages 60 and greater compared to no recommendation. In this analysis, the investigator assumed that the vaccine does not wane at all through life, so there is very little curvature to the J. Just the same, there is a slight increase in the favorability of vaccinating at the age of 70 to 74, presumably due to discounting [Pellissier JM, et al. *Vaccine* 2007, 25:8326-37].

Data from the UK address the same question using various assumptions regarding vaccine effectiveness against PHN. Once again, the cost-effectiveness becomes more favorable if instead of vaccinating at age 60, vaccination is given at age 65, depending upon the assumptions [AJ van Hoek et al / *Vaccine* 27 (2009) 1454-1467]. The UK used these data to recommend the vaccine for persons 70 years of age, with a catch-up program for persons 70 to 79. This is understood to be the current policy; however, the vaccine is not available at all in the UK at this time. In data addressing the same question for the US that assume the vaccine lasts only 10 years, the J-shaped curve is very prominent. The favorability of the vaccine increases with age to age 70 years, and then declines dramatically at older ages according to these data [Rothberg, et al., *Clinical Infectious Diseases* 2007, 44:1280]. Looking at the Rothberg data from the same paper in 2007 in a somewhat different way, the duration of protection is highlighted in terms of the way it influences the cost-effectiveness of different age recommendations for the reasons noted earlier. The most favorable cost-effectiveness across the range of duration of protection is vaccinating at age 70 years. In terms of the impact of duration of vaccine efficacy on cost-effectiveness, for 60-year old patients cost per QALY begins at around \$300,000 with a very short duration of 4 years of protection, thus being extremely

unfavorable, and then plummets at 18 years to under \$50,000 per QALY, a more favorable level.

In terms of programmatic considerations, zoster vaccine is the most expensive adult vaccine at approximately \$161 per unit dose and about \$151 for a 10-pack. Regardless, it is about 4 times the cost of pneumococcal vaccine and 10 to 20 times the cost of the various influenza vaccines. This leads to barriers to patients as well as to providers who have very high up-front inventory costs. The US formulation of Zostavax® must be stored at freezer temperature ($\leq 5^{\circ}$ F), a barrier for many providers in terms of stocking the vaccine. Medicare Part D financing is a barrier for many persons age ≥ 65 year, given that the reimbursement is very complex and typically involves high up-front or non-reimbursable costs. In addition, there are generic barriers to adult vaccination, including competing priorities for the provider in terms of chronic disease management and acute care needs; fragmentation of care for seniors, many of whom have multiple primary care doctors or specialist providers and no one knows who is accountable for handling the vaccines; lack of institutionalized well adult visits; and lack of a counterpart to school entry laws with a gatekeeping function in seniors. One bright spot is the growing role of pharmacies. Zoster vaccine can be administered in pharmacies in 45 states, including 35 states on a walk-in basis. This is remarkable in that it means pharmacies can provide a means to rapidly increase uptake, depending upon the level of promotion, interest, and vaccine supply.

There have been recurring supply problems for Zostavax® and other OKA-VZV containing vaccines such as ProQuad®. Several episodes over the past few years have been caused by a series of independent problems. Since licensure, there has not been a single full year during which Zostavax® has been unthreatened by disruptions or delays. Regarding the current status of the OKA-VZV vaccines, Zostavax® backorders are currently being filled, but the situation remains dynamic. ProQuad® is not currently available. Varivax® is prioritized, so the supply has never been directly affected over these years. Merck has been hopeful about future supply, but was reassuring during the prior disruptions and upon the initial launch of Zostavax®. A letter from the manufacturer dated July 2008 distributed just a few weeks after the ACIP recommendations for the zoster vaccine were published, stated that the reasons for shipping delays for Zostavax® were multi-faceted and noted that the demand for the vaccine increased due to increasing publicity and awareness, and that demand for varicella vaccine that relies on the same vaccine bulk material also increased to unprecedented levels driven by the ACIP recommendation for a second varicella vaccine dose.

The potential impacts that these disruptions have on vaccine uptake are that they frustrate providers who must answer for lack of availability, potentially leading them to stop offering zoster vaccine. Patients may never return to be vaccinated, which leads to missed opportunities. Also, in a setting of short supply, there is not going to be much provider- or patient-level marketing and promotion, so providers and patients may be unfamiliar and uncomfortable with the vaccine. Finally, disruptions hinder public-sector activities and goal setting regarding zoster vaccine, including those for CDC's own program. CDC had planned a number of activities to promote zoster vaccine, but cancelled them in light of the supply situation.

There are a number of considerations regarding expanding recommendations to adults age 50-59 years before sustainable supplies are assured. In 2009, the most recent year for which National Health Interview Survey (NHIS) data are available, zoster vaccine uptake in adults ≥ 60 years was just 10%. This may be somewhat higher currently. That means about 90% of adults ≥ 60 years remain to be vaccinated. CDC projects that there will be approximately 93 million adults ≥ 60 years during this decade. Not all of these will be eligible for vaccine, but 40% uptake

by adults ≥ 60 years would require approximately 3.7 million doses per year throughout the decade. That compares to the approximately 7 million doses that were administered during the first 3 to 4 years based on the NHIS data. If the recommendations are expanded to adults age 50 to 59 years, the corresponding numbers of adults ≥ 50 years would be about 140 million total, which would mean about 5.6 million doses would be needed per year to reach 40% of that target.

There are other implications to expanding the recommendations to adults age 50 to 59 years before sustainable supplies are assured. First, it can jeopardize the credibility of all of the players in the vaccine enterprise, public and private. Also in the setting of limited supplies, expanding the recommendation can lead to the diversion of vaccine to persons 50 to 59 years of age instead of to persons 60 years of age and older. This could occur due to differential promotion, differential patient interest, or differential barriers to access (e.g., Medicare Part D [ages 65+] vs. private insurance [ages 50-64]). This would result in a distorted policy that might reduce, rather than increase, disease prevention.

Assuming that 1 million doses of zoster are given to persons 50 versus 60 years of age in 2011 and zoster outcomes are followed through 2015; and that there is no waning of initial vaccine effectiveness; and that there is no incremental effect at preventing PHN among vaccine failures for either age; the anticipated results of excess cases would be as follows:

- 1,838 acute herpes zoster cases
- 960 PHN cases (pain ≥ 90 days)
- 1,107 PHN cases (pain 30-89 days)
- 321 herpes zoster cases with non-pain complications
- 16,412 herpes zoster-associated outpatient visits
- 323 herpes zoster -associated hospitalizations
- 2,490 herpes zoster-associated hospital days

For ACIP recommended programs, CDC is ultimately responsible for assuring that they work effectively and correctly. ACIP has never adopted an expansion of a vaccination program in the midst of a supply shortage. In fact, there were extensive discussions at CDC over the past year regarding whether the Zoster WG should be attempting to identify risk groups and prioritize allocation of the vaccine. In summary, it is hard to make the case to address an expansion in recommendations of the vaccine to new age groups before sustainable supplies are assured, especially if it might result in more, not less, disease.

Based on consideration of these issues, the Zoster WG agreed that it was not appropriate for ACIP to address a change in the zoster vaccine recommendations in the current context. The basis of this conclusion varied among the different members of the working group, but most members felt that the supply issues alone made for a compelling reason. Others were also concerned about the lack of evidence on durability of protection, although that was not quite as universal.

In terms of next steps, CDC will prepare a Notice-To-Readers, which will alert public and providers about change in Zostavax® indication; report the results of the June 2011 ACIP meeting; emphasize the importance of current recommendations that persons ≥ 60 years of age be routinely offered zoster vaccine; and will point interested persons to CDC websites for more guidance. CDC will revise its HZ/HZV websites accordingly. The Zoster Working Group recognized that some providers or patients may wish to use licensed Zostavax® at ages 50 to 59 years, and suggested that CDC provide limited technical guidance for such un-

recommended use based on the principles in current ACIP recommendations for persons age 60 and older.

Discussion Points

Dr. Baker pointed out that one of the limitations has been the requirement for a freezer for this vaccine, which many providers do not have. With that in mind, she wondered whether the refrigerated formulation was anticipated to be available in the future.

Dr. Robinson responded that the refrigerated formulation requires 50% more bulk, so there would be fewer doses available if this formulation is prioritized. The frozen formulation is currently prioritized in order to have more doses available. As the supply expands, more doses of the refrigerated formulation can be made available.

Dr. Judson thought there had been some publications to suggest that the field was getting closer to identifying CMI correlates.

Dr. Harpaz responded that two correlates have been used in the SPS and other studies. One is the fold rise of antibody levels, and the other is using various measures of CMI. Both are weakly correlated with protection, but they do not meet the test of being predictive.

Dr. Chilton said that as a pediatrician, he appreciated the emphasis on getting varicella vaccine distributed and as a senior citizen, he is glad to have his Zostavax®. His hospital requires all hospital employees, especially those who have contact with children, to be immunized against varicella unless they can prove they previously had varicella. He wondered why ACIP was not recommending Zostavax® for those who previously had varicella vaccine. In addition, he wondered whether anyone was studying the booster dose for those who had the vaccine at age 60 years and are turning 70.

Regarding the question about why the vaccine is not recommended for those who have previously had varicella vaccine, Dr. Harpaz replied that most individuals receiving the vaccine will not be aging to 50 years of age for decades, so it is still an academic point. To date, the data have shown that persons who are infected with the OKA strain, i.e., vaccinated with the attenuated varicella vaccine, are at much lower risk of zoster than persons who had the wild-type disease. That is very reassuring, and CDC continues to monitor the data closely. A conundrum would occur if we needed to consider giving an OKA based vaccine to someone to protect them from activation of that very same previously-administered attenuated virus.

Regarding the question about whether a booster dose is being studied, Dr. Bresnitz responded that Merck has begun a booster study that was initiated a few months ago. This study is limited to a couple of the centers that were involved in the SPS. On average, these patients are about 10 years older than when they were first vaccinated. This is an immunogenicity and safety study, the results of which will not be available for several years.

Dr. Jenkins inquired as to whether private insurers are covering Zostavax®.

Dr. Harpaz replied that surveys have shown that private insurance companies covering about 90% of persons 60 years of age and older are offering the vaccine with first dollar coverage.

Dr. Bresnitz added that in the 65 years of age and older population, most will have Medicare Part D. For those 60 to 64 years of age, coverage depends upon their benefits. Over 90% of those privately insured or insured through Medicare Part D will have coverage under whatever plan they have. That coverage will depend upon their benefits, co-pays, co-insurance, dollar limits, et cetera. He did not believe that first dollar coverage applied to the Medicare population. A number of private insurance companies have already approved coverage for individuals in the 50 to 59 years of age population. Of those who have insurance, about 35% are now covered for vaccination if they are between the ages of 50 to 59.

Dr. Rosenbaum pointed out that an increasing paradox for ACIP with the implementation of the Patient Protection and Affordable Care Act (PPACA) is that virtually all public and private insurers other than Medicare will have first dollar coverage with no co-payment for all ACIP recommended immunizations. Under Medicare, vaccines are covered as Part D outpatient prescription drug benefits rather than as a Part B ancillary service. Medicare Part B will pay for the administration of the vaccine, but beneficiaries covered through Part D are subject to a \$250 deductible and cost sharing. Because it is not an in-office service the problem of stocking and supply is magnified. There is going to be an increasing situation in which routine use of some vaccines is particularly compelling for the elderly, those with disabilities, et cetera. However, these individuals will have the most difficulty getting financial access to the vaccine. This is recurring, disturbing, and perverse outcome of PPACA. ACIP should take this into consideration when tackling the larger questions of immunization policy.

Dr. Temte pointed out that as an adult practitioner, he is forced into cost-effective services for his patients. He is amazed at how many of his patients over 65 years of age know about Zostavax®, how many want it, and how many refuse it when they understand the out-of-pocket costs. He is very good about providing Zostavax® for those patients ages 60 through 64 and 364 days who still have private insurance. However, this comes to a halt once their Medicare goes into effect. Less than 5% of his patients on Medicare accept this vaccine. This is a case in which social policy does not match the science.

Dr. Bresnitz added that there is a provision under PPACA for the Government Accounting Office (GAO) to assess the issue of vaccine coverage in the Medicare population, although he was not sure whether it focused only on Zostavax®. A report should soon be published on this.

Dr. Marcy noted that an article was published by Harpaz et al in the *Annals of Internal Medicine* that showed that the major barrier of adults getting zoster vaccine was financial. He thought it was important to note that only 2% to 7% of the eligible population has received the vaccine. It is too expensive, which is a very simple answer to this complex situation.

Dr. Poland emphasized that supply issues make the complex cost issue even more difficult. He thought it was a good idea to put in place a planned mechanism to assess this situation in the future. He thought providing the vaccine at an age prior to the highest burden made sense. This is routinely done in the provision of pediatric vaccines, often decades before children are at risk. Among adult practitioners, increasingly more preventive measures are coalescing around the age of 50 when mammograms, colonoscopies, and other preventive measures are considered. Pediatrics established routine preventive visits and provisions of vaccines within that context, which drives the routine vaccine schedule, similarly and in parallel for age 50 years for adults. He also supported strong consideration of giving guidance of either suggested or recommended use in specific individuals for which the benefits might be clearer (e.g., immunosuppressed, chronic diseases, under age 60 years with a previous zoster episode). A

publication of the January 2011 proceedings of the Mayo Clinic showed a surprisingly high rate of recurrence—higher than what anyone was taught in formal training.

Dr. Harpaz agreed that the study regarding recurrence was eye-opening for many people. The risk of recurrence reported was similar to the risk of an initial episode. In terms of consideration of vaccinating those under the age of 60 based on increased risk, there is no evidence that there is a higher risk in this age group. Immunocompromised individuals are of significant importance to consider, and the working group discussed this issue several years ago in terms of going below the recommended age group for certain subgroups. In theory, it is unknown whether protection against zoster would be retained if one became immunocompromised after vaccination. The only empirical evidence is that there was a group of individuals in the SPS who became immunocompromised and were followed prospectively. The zoster vaccine did not protect that group once they became immunocompromised. In the final analysis, more evidence is needed with regard to this issue. His program is very interested in this issue, and would like to assess it using observational data and so forth.

Dr. Bresnitz pointed out that the vaccine cannot be used in those who are already immunocompromised, but Merck has launched a study using an inactivated vaccine in a transplant patient and is about to launch a study in tumor malignancy patients.

Dr. Harpaz noted that there is also an on-going study in people anticipating kidney transplants.

Dr. Judson emphasized the importance of knowing whether immunosuppression degrades normally durable natural immunity before making a recommendation.

Varicella

**Stephanie Bialek, MD MPH, Herpes Virus Team Lead
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National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention**

Dr. Bialek presented an update on the implementation and impact of the routine 2-dose varicella vaccination program for children. ACIP made a change from a routine 1-dose to a 2-dose varicella vaccination program for children in June 2006, with the first dose administered at age 12 to 15 months and the second dose administered at age 4 to 6 years. The rationale for this change was that outbreaks occurring in highly vaccinated school populations placed a significant resource burden on state health departments. There is also incomplete protection after 1 dose, and improved disease control is anticipated with a 2-dose program. The second dose is expected to provide protection to the 15% to 20% of children who do not respond to the first dose. The risk of varicella is 3-fold lower in 2-dose vaccinees compared to 1-dose vaccinees.

There are a number of challenges to understanding the extent of implementation of a 2-dose varicella vaccination program among 4- to 12-year olds. There are no single national estimates of 2-dose coverage among 4- to 12-year old children. The National Immunization Survey (NIS) describes 1-dose coverage among children 19 through 35 months of age, and the NIS-Teen describes 2-dose coverage among 13 through 17 year olds. Dr. Bialek used a variety of sources to describe uptake among 4- to 12-year old children, including the number of doses

distributed, adoption of school entry requirements, the Kindergarten Survey, and coverage estimates from varicella surveillance sites.

In terms of the number of doses of varicella vaccine distributed in the US from 2005 through 2009, there was a dramatic 2.6-fold increase in doses distributed in 2007 compared to 2006. The number of doses distributed has stayed at that level or higher since [Biologics Surveillance Data, 2005-2009]. Data from 2000-2010 pertaining to varicella vaccine doses administered by age group from the Varicella Active Surveillance Project in Antelope Valley, California show a dramatic increase in the number of doses administered to 3- to 5-year olds, 6- to 9-year olds, and 10-to 12-year olds. This suggests that there was increased catch-up vaccination as well as well after the second dose recommendation.

In terms of the varicella vaccination requirements for school entry in September 2007, a year after the recommendation was made, 4 states required 2 doses, 41 states required 1 dose, and 6 states had no requirements. In the most recent school year, 2010, the number of states that required 2 doses for school entry at some point had increased to 30 and only 2 states had no school entry requirements. In terms of the estimated 2-dose coverage among children in kindergarten for the 2009-2010 school year, coverage estimated by program grantees ranged from 85% to 100%. Idaho, Nevada, and Pennsylvania collect information on 2-dose coverage among kindergartener students, but they do not have statewide 2-dose school entry requirements. Coverage among these three states is somewhat lower (63%, 77%, and 79% respectively), although it is still substantial considering there is no school requirement [MMWR June 3, 2011 Vol. 60/No. 21]. It is important to note that these data are collected in a variety of ways at the state level, and reflect a varying number of schools that have been surveyed, as well as doses that have actually been validated. But, they do offer a picture of what is occurring, at least among kindergarten students.

Minnesota is one of the states in which CDC is conducting active surveillance for varicella outbreaks in 79 schools. The highest 2-dose coverage is among kindergarteners in these schools and among 7th graders, the two grades for which there is a school entry requirement in Minnesota. There has been a fair amount of 2-dose uptake among other grade levels that are not directly affected by the school entry requirement. There is fairly high 2-dose coverage among 1st and 2nd graders. However, 2-dose coverage remains fairly low among 3rd - 6th graders, which highlights the role of catch-up vaccination. In the Varicella Active Surveillance Project in Antelope Valley, California in 2009, where there are no varicella vaccine school entry requirements, kindergarten 2-dose coverage was 84% among kindergarten students and 96% among 5 year olds enrolled in a large managed care organization.

The National Immunization Survey among teens is one of the only sources of data available for monitoring varicella vaccination coverage among adolescents. From the NIS-Teen, a history of varicella disease is becoming less common among adolescents, reported by only 66% of 13-17 year olds in 2007. One dose varicella vaccination coverage among teens without a history of varicella increased from 66% in 2006 to 76% in 2007. Two-dose coverage among teens without a history of varicella remains low in the first year since the ACIP recommendation, with only 19% of teens having received a second dose [MMWR Aug 20, 2010 Vol 59 No. 32]. More work is needed to ensure that catch-up with a second dose is fully implemented among adolescents. In addition, mechanisms are needed for monitoring vaccination coverage among older adolescents, including college students.

With respect to varicella vaccine safety, post-licensure safety monitoring of varicella vaccine reflecting 16 years of use and over 65 million doses is reassuring. Serious adverse events continue to be rare. Understanding adverse events following varicella vaccination requires varicella zoster virus (VZV) strain identification as there is no way clinically to determine whether a potential vaccine-related adverse event is due to or wild-type VZV or vaccine strain VZV. Laboratory capacity to perform VZV strain identification remains critical to monitoring potential adverse events following vaccination with this live virus vaccine.

Shortly after the 2-dose program was recommended, severe local injection site reactions were reported after administration of the second dose of varicella vaccine. These resolved without complications, and are not commonly reported. [Walter PIDJ 2009]. While this does not seem to be a major problem with the second dose program, it is continually being assessed through the Vaccine Adverse Event Reporting System (VAERS).

The strengths of VAERS are that this system can rapidly detect signals, can detect rare adverse events, and generates hypotheses for further study. VAERS data are available to the public via the internet at <http://vaers.hhs.gov/index>. VAERS also has well described limitations in that it cannot assess causality as it lacks information on unvaccinated comparison groups, has reporting biases (e.g., underreporting, differential reporting, stimulated reporting) and inconsistent data quality and completeness. Based on crude reporting rates for all U.S. VAERS reports after any dose of single antigen varicella vaccine from 2005 through 2009, the total reporting rates for all events have been fairly stable. It appears that there has been a decline in the last few years of serious adverse events. In summary, the FDA has not identified any new safety signals through routine surveillance for varicella vaccine since 2006 when the second dose was recommended for all children. Adverse events most frequently reported to VAERS are those expected from previous experience with the use of varicella vaccine (e.g., injection site erythema, swelling, and warmth). An analysis of reports to VAERS since the second dose recommendation is currently underway.

With regard to varicella incidence and outbreaks during the routine 2-dose varicella vaccination program, since 2006 when the second dose was recommended, a 78% decline has been observed in the two varicella active surveillance project sites; these declines have been seen in all age groups. The declines are especially noted in the age groups for which the second dose was recommended: 1 to 4 year olds and 5 to 9 year olds [Varicella Active Surveillance Project 2000-2010; 2010 data preliminary]. There has been a 98% decline in varicella incidence overall since the introduction of varicella vaccination in 1995. The proportion of total cases which have occurred in vaccinated individuals has been approximately 60%. While 2-dose cases have been observed, this seems to have been at a fairly stable rate. There are similar data from other states. Varicella incidence declined 50% from 2005 to 2008 in Connecticut, with declines especially noted in 1- to 14-year olds [Kattan JID 2011]. In New Hampshire, varicella incidence declined 60% from 2006 to 2010, with greater than 70% declines among 5- to 14-year olds [Daly, Abstract presented at CSTE 2011].

With respect to outbreaks, the best longitudinal data come from the Varicella Active Surveillance Project in Antelope Valley, California (1995-2009). In the 2006-2009 period, a total of 21 outbreaks were reported. This was in contrast to 42 outbreaks from 1999-2001, 46 outbreaks from 2002-2005 prior to the second dose recommendation, and in comparison to 236 shortly after the vaccination program was implemented. In the two most recent periods, the median number of cases and outbreaks has been fairly stable as have the duration of the outbreaks.

Data on varicella outbreaks are available for a number of states. Connecticut reported 42 outbreaks from 2005-2006, with a median size of 14 cases; and 2 outbreaks from 2008-2009, with a median size of 5 cases [Kattan JID 2011]. Six state and local health departments are funded by CDC to conduct varicella outbreak surveillance in schools. The overall picture from these projects is that very few outbreaks are being observed in these sites. Dr. Bialek shared data from three of these sites. New York City conducted surveillance in 120-330 schools and reported 1 outbreak in a non-participating school during the 2009-10 school year. Minnesota conducted surveillance in 80 schools statewide and reported 15 outbreaks from non-participating schools. West Virginia conducted surveillance in all public schools statewide and reported 19 outbreaks (n=167 cases). A case-control study is being conducted in West Virginia to assess 2-dose vaccine efficacy.

At the time the 2-dose policy was recommended in the United States, a single vaccine efficacy study had been published. Kuter et al in PIDJ in 2004 showed a 98% 2-dose vaccine effectiveness. The three estimates that have been published since then have ranged from 88% to 98%.

In summary, the routine 2-dose varicella vaccination program for children has been fairly extensively implemented. Thirty states have 2-dose varicella vaccination school entry requirements, and in those states, 2-dose coverage among children in kindergarten was reported as 85% or higher. Fairly robust uptake has also been observed in sites that do not have 2-dose coverage, though coverage in these states lags somewhat behind coverage reported in those states with school entry requirements. In terms of impact, varicella incidence has declined in all age groups coincident with implementation of routine 2-dose varicella vaccination program for children. The greatest declines have been observed among children aged 5-14 years. Outbreaks also appear to be less common than they were during the 1-dose vaccination program.

Regarding future directions, it is clear that there is still room to more fully implement the routine second dose of varicella vaccine for the recommended age groups, and there is also work to do with catch-up vaccination for older children and adolescents. Additional studies are anticipated to better define incremental effectiveness of one versus two doses of varicella vaccine. The scarcity of varicella outbreaks has limited opportunities to investigate vaccine effectiveness, which speaks to the success of the program. Continued laboratory surveillance to monitor varicella vaccine adverse events associated with this live virus vaccine remains important, as is continued surveillance to monitor the long-term impact of routine 2-dose varicella vaccination on the epidemiology of varicella.

Discussion Points

Dr. Baker pointed out how nice it was to hear a wonderful public health success story. One of her motivations for Zostavax® is that she no longer sees varicella with complications in her hospital.

Dr. Hahn (CSTE) mentioned that although Idaho was shown as one of the two states with no requirements, earlier in the year, they passed a 2-dose requirement kindergarten entry requirement.

Dr. Whitley-Williams (NMA) wondered whether there was a correlation between the sites where the outbreaks occurred and the level of coverage.

Dr. Bialek replied that while this is an area of great interest, they do not have enough data to assess the correlation. The sites that were funded to conduct varicella surveillance are a fairly even mix of sites that have a 2-dose school entry requirement and sites that do not. While kindergarten coverage appears to be higher in states with a 2-dose school entry requirement, overall coverage in schools appears to be fairly similar across all of the sites regardless of school entry requirement at this point in the early phases of the program. It is not possible to attribute a difference in outbreak rates by coverage at this point. As noted, having so few outbreaks has made this difficult to evaluate.

In terms of the age distribution in the outbreaks, Dr. Schaffner (NFID) wondered whether there was a shift to the older age groups.

Dr. Bialek responded that a subtle shift has been noted in the active surveillance sites in that there has been an increase in median age of outbreaks from 8 to 9. Outbreaks are still occurring in elementary and middle schools. Given the small numbers found in the surveillance projects, it is difficult to definitively determine whether there has been an age shift. A majority of the outbreaks are being seen in middle school children, although they are still common among elementary students. CDC recently investigated an outbreak in Texas that was exclusively among elementary school students.

Dr. Marcy wondered whether anyone had followed up on outbreaks to determine whether they could be traced to a single medical group or single provider. There are numerous ways to handle this vaccine, which is very fragile.

Dr. Bialek said her understanding was that this had been assessed in several previous outbreaks, but there has never been a situation identified in which there was a single provider who was the source of vaccination in children in whom there was breakthrough disease.

Dr. Seward added that early on in the 1-dose program this was assessed extensively, but states tired of looking because they could not find anything. In response to Dr. Schaffner's question, Dr. Seward reported that age of infection is increasing, especially in unvaccinated persons. However, the incidence by age has dramatically declined in all age groups. There has not been an increase in incidence in any older age groups. People get confused with proportions versus incidence. It is important to keep in mind that incidence has dramatically declined in all age groups.

Dr. Meissner agreed that this is another example of the remarkable success of a recommendation and guidance from CDC in terms of controlling another infectious disease. There was a great deal of discussion about adoption of the initial varicella vaccine, and there was a lot of reluctance to accept the recommendation for a second dose of the vaccine. He remembered that many people felt initially that the recommendation should have begun with 2 doses. It was the perseverance of many people at CDC, including Dr. Seward, who brought about this accomplishment.

Dr. Baker offered gratitude to former ACIP members for helping with that effort.

Dr. Seward indicated that there would be presentations during future ACIP meetings regarding the impact of the varicella vaccination program in preventing varicella-related deaths. A 97% decline in varicella deaths in children is reported on in a paper by Dr. Mona Marin that will soon be published in Pediatrics. In addition, future presentations to ACIP could also include updates

on the safety and effectiveness of varicella vaccine for preventing both varicella and herpes virus zoster in HIV-positive children.

Ms. Stinchfield (NAPNAP) reported that Children's Hospital in Minnesota sees about one chicken pox case per month. These are primarily picked up through their coding and records review, meaning that they were not even sick enough to be tested, and as a result these cases were not picked up through lab surveillance. These children were evaluated clinically, diagnosed, and sent home. Having an in-patient in the hospital with severe chicken pox is highly rare, although it used to be very common. They are also not seeing severe illness in outbreaks. This speaks to herd immunity.

Meningococcal Vaccine

Introduction

H. Cody Meissner, MD Advisory Committee on Immunization Practices

Dr. Meissner reported that in the January 18, 2011 *MMWR*, two new recommendations were published for the use of meningococcal conjugate vaccine, including guidance for routine vaccination of adolescents as well as a booster dose. In addition, guidance was offered for a 2-dose primary series administered 2 months apart for persons 2 through 55 years of age at increased risk of infection due to persistent complement component deficiency or functional or anatomic asplenia. Other persons at increased risks, such as microbiologists or travelers to an endemic area, were recommended to receive a single primary dose. An *MMWR* statement is being prepared that discusses the FDA approval in January 2011 of Menveo® (MenACWY-CRM) in children 2 through 10 years of age. This statement also provides guidance regarding the interchangeability of the two MCV4 vaccines. This statement will note that either of the two MCV4 vaccines may be used in people 2 through 55 years of age and are preferred to quadrivalent meningococcal polysaccharide vaccine. Routine use of MCV4 in children 2 through 10 years of age is not recommended.

The last *MMRW* report on prevention and control of meningococcal disease was published in May 2005. An updated supplement is being prepared and will include all recommendations for the use of the meningococcal vaccines. In April 2010, the FDA approved the use of MCV4-D Menactra® in children as young as 9 months of age. Prior to this, no meningococcal vaccine was licensed in children less than 24 months of age. Approval for this age group was based on the results from trials that evaluated the safety and immunogenicity of the vaccine in children who received a 2-dose series with a 3-month interval beginning at 9 months of age. During this session, the working group proposed expanding the age range for vaccination of certain children at increased risk from 2 through 10 years to 9 months through 10 years. It is anticipated that the number of children 9 through 23 months who will qualify for this indication will be small. Routine use of the vaccine in children 9 months through 23 months will not be recommended. Within the next year, FDA approval for two infant quadrivalent meningococcal conjugate vaccines is anticipated. These two vaccines would be administered in a 4-dose series at 2, 4, 6, 12 through 15 months of age. The working group is continuing to consider the issues surrounding routine infant and toddler vaccination. A discussion of the role of infant meningococcal vaccine is anticipated during the next ACIP meeting in October 2011.

During this session, presentations were offered regarding immunogenicity and safety of Menactra® in children aged 9 through 23 months; recommendations for children aged 9 through 23 months at increased risk for meningococcal disease; and an update on MenA conjugate vaccination campaign in Burkina Faso, Mali, Niger—three contiguous countries in West Africa.

Menactra® Indication for a Two-Dose Series in 9- and 12-Month Olds

David R. Johnson, MD, MPH
Senior Director, Global Medical Affairs
Sanofi Pasteur

Dr. Johnson reported that there is enormous variation throughout the world in terms of the serogroups that cause invasive meningococcal disease, and residents of the US have global contacts. A current example is a cluster of W135 cases in Southeast Florida from Argentina and Brazil presumably. In the US, serogroups vary over time. Serogroup A was predominant in the first half of the 20th Century. There is no clear explanation regarding why serogroup A seemed to disappear, and there probably will not be a good explanation for its return if indeed it does return. From 1990-2008, serogroup C decreased and then increased. Serogroup B decreased and Y increased. W135 remained more or less constant. Clearly, it is important to focus on all of these serogroups. In terms of the number of deaths due to vaccine-preventable invasive pneumococcal disease from 1998-2007, deaths in children at age 1 year, 2 through 4 years of age, and 5 through 9 years of age are similar to deaths in children less than 1 year of age. Case fatality rates during this time period for all age groups were 16.3% for serogroup W-135, 14.7% for serogroup C, and 12.0% for serogroup Y [Cohn AC, et al. *Clin Infect Dis*. 2010;50(1):184-191].

A number of years ago, the US Public Health Service (USPHS) asked vaccine manufacturers to develop quadrivalent vaccines. Indeed, these quadrivalent vaccines have become the standard of care since the 1980s. Menactra® is used worldwide and nearly 40 million doses have been distributed in the last 6 years since its first licensure. Sanofi Pasteur sought to extend the age indication for Menactra® down to 9 months of age to address an unmet medical need in this age group; provide the broad protection of a quadrivalent vaccine; provide clinical benefits similar to those of a 2-4-6 + booster schedule but with half the doses; and avoid issues associated with the increasingly crowded vaccination schedule at 2, 4, and 6 months of age.

The clinical development program included one Phase II study and three Phase III studies to support license extension of Menactra® down to 9 months of age. These included the following:

- ❑ Phase II: MTA26 (vaccination schedule), safety and immunogenicity of 1 and 2 dose schedules of Menactra®
- ❑ Phase III: 1) MTA44 (safety and immunogenicity), safety and immune response to a 9+12 schedule of Menactra® given alone or concomitantly with either MMRV or PCV7 at 12 months; 2) MTA37 (safety and immunogenicity), safety and immune response to MMRV or PCV7 when given with or without Menactra® at 12 months; and 3) MTA48 (safety), safety of Menactra® given concomitantly with MMRV + PCV7 + HepA compared to MMRV + PCV7 + HepA administered without Menactra®

In the Phase II study, three groups were given 2 doses of Menactra® at 9 and 12 months of age, 9 and 15 months of age, or 12 months and 15 months of age. The three control groups in this study received either a single dose of Menactra® at age 15 months or 18 months, or the

polysaccharide quadrivalent vaccine Menomune® at age 3 to 5 years. Blood samples were taken after each dose to assess the immune responses. Serum bactericidal assay antibody titers using human complement (SBA-HC) $\geq 1:4$ are considered by many to be protective. In the study, the more conservative threshold of $\geq 1:8$ was utilized. After a single dose of Menactra®, responses for A and C serogroups were consistent across the age range of 9 months to 18 months. There were increases across this increasing age range for serogroups Y and W135. After 2 doses of Menactra® given to groups 1, 2, and 3 in this study, the antibody responses were high and comparable across all of the 2-dose schedules. About 3 years later, 60 of the children who had received 2 doses of Menactra® in MTA26 were given a booster dose of Menactra®, and their responses were compared to those from age-matched children receiving their first dose. Pre-vaccination seroprotection rates were higher in children who were previously primed with Menactra® and the post-vaccination titers were substantially higher, showing a very strong booster response in those who were previously primed. Comparing these data from Menactra® with those from several studies in the UK that have assessed persistence and boosting in children who received varying numbers of doses of meningococcal conjugate serogroup C vaccine, the antibody persistence following infant doses of MCC vaccines was similar to the persistence following infant / toddler doses of Menactra®. After a booster dose given in the second year of life, two years later these titers return to their pre-booster baseline. This suggests that Menactra® gives comparable responses in this age group to the MCC vaccines that are used in Europe, and that regardless of the infant schedule, preschool boosting is necessary if on-going protection is desired.

In the Phase III studies, participants received Menactra® alone, Menactra® with concomitant vaccines, or concomitant vaccines alone. Sanofi Pasteur has safety data from over 3200 participants in these three studies, and immunogenicity data from about half of them. In MTA44, participants received Menactra® at 9 and 12 months of age without or with MMRV or PCV7. A high proportion of the participants in this study achieved SBA titers $\geq 1:8$ against each serogroup, and this seemed to be unaffected by co-administration of MMRV or PCV7. MTA37 had a very similar design, but with a control group who received MMRV and PCV7 alone at 12 months of age. Seroprotection rates in this study were consistently high after the second dose. The measles, mumps, rubella, and varicella seroprotection rates seem to be unaffected by co-administration with Menactra® compared to co-administration of MMRV and PCV7. The geometric mean antibody concentrations to some of the pneumococcal serotypes were decreased with co-administration of PCV7 and Menactra® compared with PCV7 and MMRV. Opsonophagocytic assays (OPA) were conducted, and the results were quite consistent with the geometric mean titer (GMT) results with the enzyme-linked immunosorbent assay (ELISA) geometric mean concentrations (GMCs). However, the proportion of participants who had OPA titers $\geq 1:8$, which is the conservative estimate of pneumococcal protection, was essentially 100% for all 7 serogroups. The reverse cumulative distribution curves emphasize that the OPA titers were substantially greater than 1:8 and that these were much greater than 1:4, which is often used as a threshold for pneumococcal protection.

In summary of the immunogenicity data, Menactra® induced protective levels of meningococcal responses in infants and induced protective levels of meningococcal responses when co-administered with MMRV or PCV7. Protective levels of MMRV responses were achieved when given with Menactra®, as were protective levels of PCV7 responses achieved when given with Menactra®.

With respect to safety, the objectives were to describe safety profile of Menactra® given at 9 and 12 months of age, and to assess the safety profile of Menactra® given with or without other recommended vaccines at 12 months of age. The Phase III safety study assessed Menactra®

given alone at 9 and 12 months, Menactra® given concomitantly, and concomitant vaccines given with each other. From this study, there are data from over 3200 subjects. In terms of immediately adverse events, no difference was observed by treatment group. Solicited injection site reactions were collected for 7 days. In terms of tenderness, injection site reactions were slightly higher when Menactra® given with MMRV or PCV7, but no higher than when the concomitant vaccines are given with each other. The same was true with erythema at the injection site. Rates of injection site swelling across the different study groups were consistently quite low. Systemic reactions were collected for days 0 through 7 after vaccination. When Menactra® is given alone, fever is quite infrequent. When given concomitantly with other vaccines, fever is no more frequent than when other vaccines are given by themselves. Unsolicited adverse events were similar if Menactra® was administered alone or with concomitant vaccines. Medically significant adverse events were followed from Day 30 to 6 months following vaccination, with 2% to 4% medically significant adverse events reported across all of the treatment groups. There was no difference between the groups. The same can be said for serious adverse events at 2% to 3% and no difference from group to group.

In summary of the safety data, Menactra® was safe when administered alone to infants as young as 9 months of age, and when administered concomitantly with MMRV, PCV7, or HepA at 12 months of age. Safety profiles of MMRV, PCV7, and HepA vaccines were comparable when administered with or without Menactra® at 12 months of age. The overall conclusions from these clinical studies are that Menactra® induced immune responses predictive of protection when 2 doses were administered 3 months apart to infants as young as 9 months of age. Menactra® was safe when administered to infants as young as 9 months of age, whether given alone or with concomitant vaccines.

In terms of indication and usage, Menactra® vaccine is currently indicated for active immunization to prevent invasive meningococcal disease caused by *N meningitidis* serogroups A, C, Y and W-135. Menactra® is approved for use in individuals 9 months through 55 years of age. With respect to the infant indication, for the primary schedule Menactra® is given as a 2-dose series at 9 and 12 months of age. For the catch-up schedule, in children up to 23 months of age, Menactra® is given as a 2-dose series 3 months apart. Nearly 40 million doses of Menactra® have been distributed worldwide. This quadrivalent vaccine is indicated for individuals 9 months through 55 years of age. The 2-dose infant schedule is designed to prevent meningococcal disease with half the number of doses that would be required if started at 2 months of age, and it avoids the already crowded immunization schedule.

Sanofi Pasteur recognizes that the current epidemiology of meningococcal disease in the US does not support a universal infant recommendation. However, if and when that epidemiology changes, they strongly believe that Menactra® vaccine's 2-dose infant indication is the best approach for infant immunization in the US because it provides the broad protection of a quadrivalent vaccine early in life; it is expected to provide substantial reductions in morbidity and mortality; it requires only half the number of doses of a 2-4-6 plus booster schedule; and it avoids disruptions of, or interference with, the infant 2-4-6 schedule.

Recommendation for Infants at Increased Risk for Meningococcal Disease

**Amanda Cohn, MD
CDR, US Public Health Service
Advisory Committee on Immunization Practices**

Dr. Cohn discussed ACIP's recommendations for MCV4-D, Menactra®, as a two-dose primary series for children aged 9 through 23 months of age at increased risk for meningococcal. As noted, MCV4-D as a two-dose primary series for children aged 9 through 23 months of age was approved by FDA in April 2011. This is the first meningococcal vaccine licensed for children aged less than 24 months. However, two infant vaccines with 2-, 4-, 6-, and 12-month schedules are likely to be licensed within a year. The working group is currently weighing the pros and cons of routine infant immunization, including MCV4-D. This information will be presented to ACIP during the October 2011 meeting.

The goal of this session was to extend the high-risk recommendations for 2 through 10 years and 19 through 55 years down to age 9 months of life. There are no prior ACIP recommendations for vaccinating high risk infants aged less than 24 months. The ACIP working group recognizes that all infants aged less than 1 year have higher rates of disease compared to other age groups; however, the focus of this session's recommendation was to focus on specific groups with medical conditions or exposure risks that put them at elevated risk above the general population. These recommendations would mirror the 2- through 10-year old recommendations for children at increased risk for meningococcal disease. There are likely less than 5000 persons in this age group who would fall into these high-risk groups annually.

In terms of defining high-risk children ages 9 through 23 months, there are four groups of infants considered to be at increased risk. The first group is children with complement component deficiencies. Complement component deficiencies generally present later in life and are not recognized by 2 years of life; however, a child may have a family history or some other reason of known history of complement component deficiency that would indicated for vaccination. The second group of children is comprised of children with functional or anatomic asplenia, including infants with sickle cell disease. Approximately 1500 infants are born each year in the US who have sickle cell disease who would be included. Infants who are in a defined risk group for a community or institutional outbreak would also be included. These are very rare in the US and occur infrequently, but should be included in the new recommendations. Also included are infants traveling to an area where meningococcal disease is epidemic or highly endemic, such as those infants who are traveling with their families to the Hajj or who are living in the Meningitis Belt in Sub-Saharan Africa.

In terms of immunogenicity of MCV4-D in persons aged 9 through 23 months, MCV4-D has demonstrated immune response after second dose of Menactra® at 9 and 12 months. Dose 1 is modestly immunogenic for serogroups A and C, but not very immunogenic for serogroups Y and W-135, although it was highly immunogenic for all groups following the second dose. Most children do not have protective antibody levels 3 years after the second dose. For serogroups C and Y, less than 20% of infants have protective antibody levels. However, there was a strong response after the booster dose as demonstrated previously.

Regarding the data that showed co-administration with PCV7, pneumococcal IgG GMCs lower when co-administered with MCV4-D at 12 months. Serotypes 4, 6b, and 18c did not meet statistical criteria for non-inferiority, but the absolute values were lower for all serotypes. While detectable functional antibody was present for 99% to 100% of persons who had an OPA

activity of $\geq 1:8$, the OPA geometric mean titers support the conclusions of the IgG ELISA data showing reduced overall absolute values of titers. No data are available on co-administration with PCV13, which is the vaccine that would currently be co-administered in children receiving meningococcal vaccine in this age group. The clinical significance of lower titers is not yet understood.

With respect to the safety of MCV4-D in children ages 9 through 23 months of age, pre-licensure safety data met non-inferiority criteria at 9 and 12 months. The safety profile is comparable to other vaccines given at 12 months. However, post-licensure safety surveillance will be continued for children through age 23 months since all of these data were generated among children vaccinated at ages 9 and 12 months.

There are some issues that are important to point out in terms of extending the high risk recommendations down to 9 months of age. First, there would be inconsistency in the interval for infants compared to older children who are recommended for a 2-dose primary series. Therefore, infants aged 9 through 23 months would be recommended for a 2-dose primary series 3 months apart, or as persons older than 2 years are currently recommended for a 2-dose primary series spaced 2 months apart. ACIP is considering ways to simplify this recommendation in the full ACIP statement. For this session, it was proposed that the licensed indication be kept for 2 doses 2 months apart in 9 through 23 month old infants. In terms of the timing of booster dose after a 2-dose primary series for persons who remain at increased risk for meningococcal disease, while it is preferable to have the same booster dose interval for younger and older children, the available data indicate that the booster is needed 3 years after vaccination for young children remaining at increased risk. Therefore, a 3-year interval after the 2-dose primary series for young children and a 5-year interval for older children who are vaccinated were proposed.

Pertaining to co-administration with PCV13, the interference demonstrated with PCV7 may be clinically relevant for children with asplenia or sickle cell disease. The reason for the greater concern for these children is because they are at increased risk for pneumococcal disease in general. They may also have reduced response to the vaccination. Multiple visits for vaccines in this special population may be feasible because they may have more medical visits anyway, so it may be easier to separate the doses for this specific group of children as opposed to the general population. While there is not a great understanding of the clinical significance of lower absolute GMT titers, it is believed that an abundance of caution should be taken for children with asplenia or sickle cell disease with respect to co-administration. It is really the serotypes that are in PCV13 but not in PCV7 that children with asplenia or sickle cell disease are at increased risk for at this time, because transmission of the serotypes in PCV7 are very low. This recommendation is really based on an inference from PCV7 to PCV13. The options for policy would be to recommend that PCV13 and MCV4 be administered at least 30 days apart for children with asplenia or sickle cell disease. The recommendation could continue to be made to vaccinate children with asplenia at age 2 years and not extend down to age 9 months for this group to avoid the issue of co-administration; however, that would reduce flexibility for providers. It would be preferable to allow providers to start giving meningococcal conjugate vaccine at age 9 months for this group when there would not be a co-administered vaccine, and then to allow one vaccine to be given at 12 months. Or, there could be no recommendation to administer these vaccines separately.

In terms of the proposed language for the vote, the background section would include information about immunogenicity, duration of protection, and co-administration. In the section outlining high-risk groups for persons aged 2 through 10 years and 19 through 55 years,

language would be included for children aged 9 through 23 months at increased risk for meningococcal disease to receive a 2-dose series of MCV4-D, 3 months apart. Additional recommendations underneath these would address special considerations. The first would be that children requiring protection prior to travel may receive Dose 2 as early as 2 months after Dose 1 to ensure that they receive 2 doses prior to travel. The second point would be that in children with functional or anatomic asplenia, MCV4-D and PCV13 should be administered at least 30 days apart when feasible. The third point is that a 2-dose series is required for any child whose first dose was received prior to their second birthday. This is really a clarification point. If a child receives MCV4-D at 18 months but does not return to the office until after 2 years of age, they would still need the second dose. The fourth point is that those who remain at increased risk for meningococcal disease should receive a booster dose 3 years after the primary series.

Points for discussion and vote were recapped as follows:

- Children aged 9 through 23 months at increased risk for meningococcal disease should receive a 2 dose series of MCV4-D, 3 months apart.
- Children requiring protection prior to travel may receive Dose 2 as early as 2 months after Dose 1.
- In children with functional or anatomic asplenia, MCV4-D and PCV13 should be administered at least 30 days apart when feasible.
- A two-dose series is required for any child whose first dose was received prior to their second birthday.
- Those who remain at increased risk for meningococcal disease should receive a booster dose 3 years after the primary series.

Discussion Points

Regarding co-administration with other vaccines, Dr. Sawyer pointed out that many providers give diphtheria, tetanus, and pertussis (DTaP) vaccine as young as 12 months of age. Since MCV4-D and PCV are conjugated to diphtheria, he wondered whether any information was available on co-administration with DTaP regarding the immunogenicity of both vaccines and safety as the diphtheria protein is added up.

Dr. Coyne-Beasley noticed that immunogenicity and safety data were available for hepatitis A, and was interested in knowing whether there were immunogenicity and safety data for hepatitis B or for varicella, which can also be given at 12 months of age.

Dr. Johnson responded that studies have not been completed with concomitant administration of Menactra® and DTaP vaccines. No studies have been conducted with hepatitis B vaccine, nor are any anticipated.

Dr. Keitel inquired as to whether there were any data showing GMCs of antibodies against the meningococcal serogroups and the effects of co-administration. Threshold titers were shown rather than absolute titers. While threshold titers may be high across the board at a certain point after vaccination, a year later, if the GMC was much lower, it could fall to a low threshold faster.

Dr. Johnson responded that they do not measure GMC. They may measure GMT of the SBA antibodies. He thought they had shared those data with the working group.

Dr. Cohn added that the working group had seen GMC data for the functional antibodies, but not co-administered with other vaccines. The GMCs have not been directly compared when co-administered versus not co-administered, but they were very high after the second dose when not co-administered.

Dr. Baker inquired as to whether post-immunization was defined as 28 days.

Dr. Johnson responded that it was in that range.

Dr. Judson inquired as to whether the proposed immunologic mechanism of interference was related to the conjugate.

Dr. Cohn did not believe that the mechanism of interference was known, but there will be data from other meningococcal conjugate vaccines and their co-administration with PCV7 as well, which will help to understand whether it is the conjugate or type of vaccine versus a meningococcal polysaccharide issue.

Dr. Keitel wondered whether, if levels continue to decline to pre-immunization levels 3 years after vaccine, there was a proposal to administer boosters every 2 to 3 years.

Dr. Cohn indicated that currently the recommendations for older children who remain at increased risk for meningococcal disease are to vaccinate every 5 years with meningococcal conjugate vaccine. The way the recommendations would be stated is if a child's last vaccine was received prior to age 6 years it would be 3 years, and if was received after age 7 years or older it would be 5 years after the previous dose.

Dr. Baker asked whether Dr. Johnson had data in this age group for sickle cell disease specifically and if not, whether any would be forthcoming.

Dr. Johnson responded that they do not have these data, or specific plans to study this in children with sickle cell disease. However, there are on-going studies in children with HIV infection.

Dr. Cieslak requested clarification regarding whether there were immunogenicity data on the specific group of children to whom the proposed recommendation would apply, and incidence in children in this age group with these specific diseases.

Dr. Cohn replied that she could not provide the incidence of disease among children in this age group because it is so rare. The incidence of meningococcal disease is so low that even if a child's risk is 10 times greater, it is still highly unlikely that a case of meningococcal disease will be observed in a child with sickle cell disease in a year. To put this into perspective, assessing 10 years of Active Bacterial Core Surveillance (ABCs), in 10% of the US population there were only 2 cases of meningococcal disease in persons with sickle cell disease in any age group. Many children have penicillin prophylaxis, so it is difficult to compare whether those rates would be different pre- or post-penicillin prophylaxis. The risk was determined a while ago, but the actual number of cases and incidence is very low. Even if risk among children with sickle cell disease is high, the incidence would still be very low considering the low population numbers. Unlike children with complement component deficiency who have a risk of thousands greater

than the general population, this risk is greater but not significant enough to see an increase in cases.

Dr. Judson asked whether there were data for the booster dose at 3 years, and if so, whether it was what would be predicted or if there were any homologous interference with subsequent doses.

Dr. Johnson responded that these data showed that children who had been primed with two doses in the MTA26 study had very good responses. Essentially, 100% of them had SBA titers greater than or equal to 1:8.

Dr. Duchin asked whether there was anything about the specific pneumococcal serotypes that achieved lower titers with co-administration that would allow one to predict what serotypes, if any, would also have interference with PCV13. He wondered if the additional serotypes were causing a greater proportion of disease, whether there was a biological reason to expect that, what the plans were to monitor and detect this, and if the manufacturers planned any studies using PCV13.

Dr. Cohn responded that this would be hard to predict. While it is inferred given that it is the same type of vaccine, there are no data to demonstrate whether this is the case. It is the additional six serotypes. In terms of plans to monitor, because the numbers of very small ($n \sim 2000$ children per year), there is no consensus that this is going to be a population level problem. The rationale for separating the vaccine from others is because there are plenty of indications of adverse events, especially in children with asplenia or sickle cell disease.

Dr. Johnson added that at this point, there are no plans to conduct studies using PCV13.

Dr. Meissner emphasized that a major concern in children 9 months through 23 months of age who are asplenic or have sickle cell disease is pneumococcal disease. The risk for meningococcal disease is so low that it is difficult to quantify. Since there are no data for MCV4-D and the 13-valent pneumococcal vaccine, it is not clear whether the recommendation is arbitrary since it is not based on solid information. The real issue to keep in mind is not to jeopardize protection against pneumococcal disease in these high risk children.

Dr. Baker pointed out that what also is not known is the biologic meaning of the blunting.

Dr. Coyne-Beasley noted that they had not heard a lot of information about the cost or cost-effectiveness of this strategy, and wondered whether there were additional data about this.

Dr. Cohn responded that cost-effectiveness data would be presented for different options for routine immunization, but analyses have not been done for these select high risk groups because these recommendations for these groups have been longstanding. This is not so much a public health recommendation as it is a patient-specific one.

Dr. Baker stressed that with 2,000 subjects out of a cohort of over 4 million, this type of study could never be done accurately.

As a specialist caring for these children, Dr. Englund sees 50 a year in her regional tertiary care clinic that covers children for 2000 miles. Even without recommendations, they struggle with how to protect children who have complement deficiency that is usually proven by a first time

episode of pneumococcal vaccine. Although the numbers are small, she strongly urged her colleagues to consider a recommendation for this limited population.

Dr. Temte wondered how many of the approximately 2000 children receive most of their care in a specialty setting where a relatively complex recommendation is more easily implemented. Of concern is that children with sickle cell disease may not have the benefit of receiving care in a specialty center and may have these recommendations applied to them in a chaotic primary care setting instead.

Dr. Englund responded that the subspecialty geographic settings in which she has worked (e.g., Midwest, South, and West Coast) have clinics where these children are seen about once per year for routine check-ups, even though their primary care is delivered by their primary care physicians. Many of these children are vaccinated according to routine schedules. Approximately 70% of the asplenic children in her state have already received their Prevnar® by the age of 6 months, so she is less concerned about the concomitant Prevnar® issues.

Dr. Baker pointed out that the degree of complexity could be reduced through communication between the primary care physician and the specialist.

Dr. Judson said he was comfortable with the extrapolation to PCV-13, given that the two vaccines are made by the same manufacturer using the same method, and PCV-13 has all 7 components of the PCV-7. However, he thought that the interval of 30 days was arbitrary. The last time he reviewed the data 20 years ago or so the IgG half-life was 28 or 30 days. The only other information that bears on this is for maternal antibody and live virus vaccines. Measles vaccines were first delayed by 6 months, then 9 months, and finally by 12 or 15 months. Even if there is passive antibody titer every 30 days, there is likely to be an interference problem well beyond 30 days.

Dr. Baker noted that the half-life for total IgG is three weeks, but vaccine-induced antibodies vary such that the half-life for antibody to pertussis toxin is 36 days, but may be longer for one of the other pertussis antigens. Three weeks is a best guess, but the biologic meaning remains unknown.

Dr. Keitel emphasized that while this is a nice discussion, the mechanism of interference is unknown and may have nothing to do with anything.

Ms. Rosenbaum pointed out that she had noticed that there are times when ACIP makes a routine recommendation because there is evidence of risk, and sometimes they make a recommendation tied essentially to discretionary exercise of clinical judgment. She requested an explanation of the significance of the difference, and expressed great concern about payers over-riding health evidence.

Dr. Baker responded that routine recommendations are influenced heavily by burden of disease and the epidemiology change and the amount of vaccine coverage. Even with a quadrivalent meningococcal vaccine, serogroup Group B disease is not being addressed for this particular bacteria. In terms of cost-effectiveness, with tiny populations like this where epidemiologically there is increased risk, there has to be a lot of discretion. For example, in 2005 when the adolescent meningococcal quadrivalent recommendation was made, in addition to those with asplenia or sickle cell, at its discretion, because there was no data for HIV-infected people, ACIP recommended that HIV-infected adolescents receive this vaccine because of the potential

perceived risk. ACIP is not just a rubber stamp for FDA licensing requirements where immunogenicity and safety are documented. This is very complicated.

Dr. Cohn added that the cost of the vaccine for this small number of children is minimal in terms of the overall cost of their care. For children who are traveling, the cost is part of the parents' choice to travel and part of travel expenses.

Ms. Rosenbaum said she was hearing that the real difference between a discretionary and a routine recommendation for certain risks has to do with the amount of economic analysis that can be done, in addition to the clinical analysis, so ACIP is fairly confident that within an economic framework a routine recommendation can be made.

Dr. Cohn indicated that the number of children at risk is substantially smaller than for pneumococcal vaccine and asthma. There are hundreds of children with complement component deficiencies. With a prevalence of a risk of 5% or 10%, it is more of a routine recommendation for high risk groups as opposed to these types of targeted recommendations.

Dr. Pickering pointed out that it is not only burden of disease, but also severity of disease. Children with these underlying immune deficiencies do not do very well, and they do not do very well rapidly. Pneumococcal disease clearly is the major disease seen in children with asplenia and gamma globulin anemia. If this vaccine is given, does it really interfere with the pneumococcal response enough to cause concern? That overrides the cost-effectiveness issue.

Ms. Rosenbaum clarified that the reason she was pressing in this case had nothing to do with the recommendation per se as much as it had been a challenge for her in the context of zoster vaccine. That is, if it is known that there are certain health risks in the under 60 years of age population, why is ACIP not recommending routine vaccination when certain health risks are present. She has reviewed ACIP's patterns around this question and finds that often she cannot assess a pattern. That is why she wanted to know why they sometimes recommend discretionary and sometime routine with certain health risks. Routine with health risks sends a much more powerful message to payers than a discretionary message.

Dr. Baker clarified that this is a routine recommendation in a high risk population. She then requested that Dr. Brady summarize the AAP's Committee on Infectious Disease's opinion about this issue.

Dr. Brady (AAP) supported the fact that they do not want to do anything that would potentially impact the burden of pneumococcal disease, particularly the asplenic and sickle cell patients. The issue with meningococcal disease, given the low burden of disease, has been discussed in all of their conversations. He suggested that if ACIP voted on the proposed recommendation, that they make sure to recommend that the pneumococcal conjugate vaccine is given prior to meningococcal and not make that a choice if they are going to be separated by 30 days to avoid the potential impact on the pneumococcal vaccine. Since the mechanism of immunological interference is unknown, it is unclear whether it lingers for some period of time. If it did, it would be very disappointing to find out if the booster dose of meningococcal vaccine was adversely affected by a 9-month dose of meningococcal vaccine. He wondered whether it would be reasonable to either postpone this vote until there was information regarding whether a dose of PCV13 given after the meningococcal vaccine has any impact on the pneumococcal vaccine. Those with complement component deficiency are easier because in those patients *Neisseria meningitidis* disease represents the risk. In the sickle cell and asplenic patients, it is

pneumococcal disease that is the larger risk. The other option would be to consider removing sickle cell and asplenia from this recommendation and include the ones where the advantage of giving meningococcal is seen. The numbers are small, but the population of complement deficient patients is rarely diagnosed at less than 2 years of age. It is important not to impact pneumococcal disease in the sickle cell patients.

Dr. Foster (APhA) said he remembered years ago there was a discussion of 28 days versus one month versus 30 days, and everything was decided at that point to be 28 days. It might be easier and less confusing to make it 28 days,

Dr. Baker noted that in terms of 2- and 3-month intervals, multiples of 28 becomes somewhat difficult.

Dr. Duchin requested clarification regarding whether they could assume that children vaccinated at age 12 months who received both vaccines and experienced interference were all receiving a fourth dose of PCV7.

Dr. Cohn replied that this would have been their fourth dose of PCV7. While the response may be lower, they are likely protected. This is more likely to be a long-term protection issue for these children as opposed to immediate protection in terms of interference.

Dr. Baker pointed out that postponing the vote would probably cause a delay of a year, and no studies are planned.

Dr. Brewer (ANA) inquired as to whether these recommendations would need to be revisited as new vaccines come on-line that have different schedules and numbers of doses.

Dr. Cohn responded that they would be revisiting these recommendations in the context of routine recommendations.

Regarding the distinction between this and the zoster discussion, Dr. Schaffner (NFID) pointed out that in this circumstance, everyone was convinced that both pneumococcal and meningococcal vaccine will provide protection to these children. The question regards how to do it. In contrast, the two populations raised earlier in the morning in terms of zoster included those who have previously had zoster but were younger than age 60 and those individuals about to undergo immunosuppression. It is entirely unknown whether the vaccine will provide protection.

Dr. Whitley-Williams (AMA) shared the same concerns expressed by Dr. Brady, and expressed her hope that through interagency efforts there would be a push to monitor the children being immunized with hemoglobinopathies. This opportunity will be lost once they are immunized with the MCV4-D. CDC and the manufacturer should make sure that study is done. She also noted that she received several calls from local pediatricians when the licensure was extended for administering the meningococcal conjugate vaccine as early as 9 months of age. The feedback from the calls was concern that this would be a routine recommendation. She felt the news media had caused confusion, as well as concern among pediatricians that they would have to administer meningococcal conjugate vaccine routinely as early as 9 months of age. She emphasized the importance of focusing on at risk children.

Dr. Baker agreed that it is a very important communication issue, depending upon the results of the vote.

Dr. Halsey (Johns Hopkins) commented on the most likely biological mechanism for the interference. This was well-documented when tetanus was used as the conjugate protein for *Haemophilus influenzae* b (Hib) and pneumococcal conjugate vaccines and given simultaneously with DTP. If that is true, it was dose-related. Ron Dagan and Juhani Eskola clearly described this, and other studies confirmed it. If this is true, it is likely to be exacerbated by giving the PCV13 and simultaneously with DTaP. Ron Dagan has told Dr. Halsey that he had suggestive data for possible carrier suppression with the CRM protein carrier. He urged the committee to contact Dr. Dagan for this information, although it may not be conclusive. Certainly, the studies need to be done to determine whether that is the mechanism. It is doable and there may be some data available from existing studies.

To address Dr. Whitley-Williams question and concern, Philip Hosbach (sanofi pasteur) indicated that there is a 2- to 10-year old recommendation for high risk children that doctors have previously followed. The vaccine is not overused, nor does the company promote outside that recommendation. He suspected the same would be true for this recommendation as long as it is clearly communicated.

Dr. Baker called for public comment.

Echo Bennett (National Meningitis Association): Hello. My name is Echo Bennett and I am here today because my son, Gavin, contracted meningococcal disease as a baby. I will never forget the day this disease changed our lives forever. Gavin woke up that morning with a slight fever and refused to eat. I called the local health clinic, and they assured me he probably had the flu. But, it wasn't the flu. It was much, much worse. Only 18 hours after his symptoms began, my healthy, happy, 6-month old son was placed in an induced coma and put on life support. I was told he was diagnosed with meningococemia, yet I was unaware of what the even was. Gavin was so small and so sick, and there was nothing I could do for him. He was given a 10% chance of survival, but despite the odds, Gavin survived, but not without a price. The *Neisseria* group C bacteria severely damaged his little arms, legs, and face, and he showed signs of heart and lung disease. He had to undergo a dozen surgeries in his 9 weeks of hospitalization, including muscle flapping, skin grafting with donor sites, a tracheotomy, colostomy, and major facial reconstruction. Doctors were able to save his limbs from amputation, but the scars covering his body are a constant reminder of his battle with meningococcal disease. This was a little over two years ago, but we are still feeling the effects today. Gavin has since undergone 6 more surgeries, and has countless ahead of him. His health is constantly a concern for his doctors to prevent any further effects throughout his lifetime. When Gavin became ill, he was transferred to three different hospitals before receiving the treatment that would ultimately save his life. This is not an easy disease to diagnose or treat, yet it's simple to prevent. There are many other families who have been affected terrible by this disease, whose children suffered as infants and now have lifelong debilitating effects or those whose children who, tragically, did not survive. I am here to speak for all of them, for Lisa Nailman and her daughter Sara, for Molly Dejordan and her son Kenton, for Chrissie Bickham and her daughter Jaily, for Everchris Davis and her son Terrance. These are just a few of the Moms on Meningitis (MOMs) who could not be here today. If you were to ask any of us, we would tell you to do whatever you can to keep your children safe, healthy, and happy. Educate yourselves and vaccinate your kids. We would have done anything to help our kids at this point in time. So, I'm here to tell you that we strongly support the recommendation for meningococcal vaccination for infants, with the recommendation having a 30-day time period between receiving pneumococcal vaccination and starting meningococcal vaccinations. On behalf of the National Meningitis Association Moms on Meningitis, thank you for your consideration and time today.

Frankie Millie (Meningitis Angels): I'm Frankie Millie, the Founder and National Director of Meningitis Angels. Today is the 13th anniversary of my only child's death, so I stand here in his memory and in honor of all of the Meningitis Angels across the country. I want to thank this committee for their dedication to this issue. I am totally confused at this point, and there have been some great valid concerns raised here today with this recommendation. So, what I'm going to say to this committee today is probably going to kind of freak you all out, but I think that this committee, being who you are, need to make the best recommendation on this particular issue that you know to make, and I would ask you that if you decide to recommend this vaccine, or even do a permissive, that you vote "Yes" for VFC coverage as well, because if you're going to make a recommendation, then you need to make it available to these kids. At lot of these children who are high risk already are probably VFC kids, so I'm going to sit back here and just pray for you guys to make the right decision. Thanks.

Dr. Cohn recapped that she thought the decision regarded whether to include asplenia and sickle cell children in this recommendation, and take Dr. Brady's advice and recommend that the booster dose of PCV13 be given at least 30 days prior, or even 90 days prior, to the second dose of MCV4. That would be Option 1 versus removing the sickle cell and asplenia children from this group and not protecting them against meningococcal disease until they are age 2 years of life to ensure that they are receiving adequate pneumococcal protection. Children with HIV are included in the VFC resolution. It is a permissive recommendation for older age groups, so the resolution for these children would be extended down to 9 months of age.

Motion

Dr. Sawyer made a motion to accept the recommendation as stated, with the exclusion of the anatomic asplenia and sickle cell groups who would be dealt with subsequently, and that the other high risk groups be maintained (e.g., travelers to endemic areas, families moving to endemic areas, and those with complement component deficiencies). Dr. Meissner seconded the motion. The motion carried with 13 affirmative votes, 1 negative vote, and 1 abstention.

Dr. Cohn indicated that the second issue would be that two proposals could be made. ACIP could vote to recommend the vaccine down to 9 months for children with sickle cell disease and/or asplenia, with the caveat that they receive the 4-dose pneumococcal booster dose (PCV13) prior to the second dose of meningococcal conjugate vaccine (Menactra®). Or, a recommendation could be made not to include children with functional or anatomical asplenia in this recommendation.

Dr. Coyne-Beasley wondered whether this should be done before the first dose of Menactra® given at 9 months. While they were saying second dose, even one dose could cause interference.

Dr. Cohn responded that that technically would be 3 months prior.

To clarify, Dr. Baker reminded everyone that there is no routine vaccination recommended at 9 months of age, so this would move to 12 months. Practitioners would need to know if they were doing catch-up because something was delayed to make sure that they administer four doses of PCV13.

Dr. Englund expressed concern with simultaneous administration, which she thought should be included. Some children might have two doses to catch up.

Dr. Cohn noted that the original language stated that they should be administered at least 30 days apart, which suggests that they should not be co-administered.

Dr. Englund believes that it is interference, although there are no data. Two huge populations that are perhaps underappreciated are cardiac patients and heterotaxia patients.

Ms. Ehresmann requested clarification regarding whether only non-simultaneous and at least 30 days was to be included, or if the recommendation was to complete the series with at least 30 days and not simultaneously.

Dr. Baker clarified that non-concomitant is the important issue, because that is where there is data for on interference.

Dr. Cohn added that the language could state “do not co-administer” and then determine whether it should be 30 days or 90 days, and the guidance or background section could explain that pneumococcal vaccination should take priority over meningococcal vaccination for children with asplenia.

Dr. Keitel noted that based on the data ACIP was provided, there is evidence that pneumococcal conjugate vaccine given with PCV results in more antibody titers, but she wondered what happened when pneumococcal vaccine alone was compared to pneumococcal vaccine with MMR.

Dr. Cohn responded that there are no data about this.

Dr. Sawyer made a motion to recommend the meningococcal conjugate vaccine as stated on the screen for patients with functional or anatomic asplenia, and that specific language should be included that the vaccine not be co-administered with pneumococcal conjugate vaccine. The priority should be to complete the primary pneumococcal conjugate vaccine series or booster at least 30 days before administering the meningococcal conjugate vaccine. Dr. Meissner seconded the motion, at which time further discussion ensued.

Dr. Judson remained concerned that the key science behind these recommendations. If the mechanism is antibody against the conjugate that somehow renders the vaccine less immunogenic or less able to be processed, the greatest problem would not be with co-administration. It would be the related issue of administering live viruses at the same time or at some longer interval afterwards. He does not feel confident that co-administration is the problem. If this is antibody mediated, it may be far more complicated.

Dr. Keitel agreed. In the circumstances in which carrier suppression has been documented, it had nothing to do with simultaneous administration of vaccines. It had to do with antibody present in the serum at the time. Therefore, there is no basis for concluding that a 30-day interval would be adequate.

Dr. Baker noted that the data show that there is not a problem with MMR, so she thought that in terms of live virus vaccines they could be assured that there was no problem with co-administration.

Dr. Judson clarified that he was saying that by analogy, the interference between live virus vaccines probably was an antibody, and that it was better to give them together than to separate them by the week or month where there might be interferon interference.

Dr. Duchin was not sure that people would be able to interpret what was intended by the sentence "priority should be given to PCV13." It was not clear whether the intent was to complete the series or that the series should be initiated before the MCV series. He suggested making the language more specific.

Dr. Sawyer thought this could be clarified by stating that if a pneumococcal conjugate vaccine was due it should be given first, with the 30-day interval.

Dr. Meissner reminded everyone that the burden of disease for *Neisseria meningitidis* in this population is miniscule; whereas, the benefit of protection from invasive pneumococcal disease in these children is without question.

Dr. Plotkin emphasized that there is extensive literature on epitopic carrier suppression and enhancement. This phenomenon is not unusual at all. The control interval has been usually been a month or so in studies identifying epitopic suppression.

Dr. Baker requested that Dr. Cohn work on the language, and that they return after lunch to vote on the revised language.

Upon the meeting reconvening following the lunch break, Dr. Sawyer indicated that after speaking with his colleagues and realizing how recently the pneumococcal suppression data became available, he preferred to withdraw his motion to allow the working group more time to carefully evaluate the potential impact of meningococcal vaccine suppression in children, especially those with asplenia. Dr. Meissner withdrew his second of the motion as well.

Dr. Baker concluded that this issue would appear on a future ACIP agenda when more information is available to present.

Vaccines for Children (VFC) Program Vote

Lance E. Rodewald, MD
Director, Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Rodewald reminded everyone that ACIP is the sole authority for the VFC formulary, and if there is a change in the indicated age, group, or number of doses, there must be a VFC resolution such that the VFC program is consistent with ACIP recommendations. The purpose of this resolution was to update the eligible groups for meningococcal vaccination to include children 9 through 23 months of age at increased risk of meningococcal disease and to update the intervals for booster doses, and Dr. Rodewald noted that the language would be edited to match the vote.

The original wording for eligible groups was as follows:

- Children aged 2 through 10 years who are at increased risk for meningococcal disease, including
 - children who have complement deficiencies (C3, properidin, factor D, and late component deficiencies);
 - children who have anatomic or functional asplenia;
 - children with HIV infection;
 - travelers to or residents of countries in which meningococcal disease is hyperendemic or epidemic;
 - children who are who are part of an outbreak of a vaccine-preventable serogroup.
- All children aged 11 through 18 years

The revised wording will read as follows:

- Children aged 9 months through 10 years who are at increased risk for meningococcal disease, including
 - children who have complement deficiencies (C3, properidin, factor D, and late component deficiencies);
 - children with HIV infection;
 - travelers to or residents of countries in which meningococcal disease is hyperendemic or epidemic;
 - children who are who are part of an outbreak of a vaccine-preventable serogroup.
- All children aged 11 through 18 years

This is the new table, with the proviso that it must be revised to match the recommendation and break this down into two different age groups:

Age	Subgroup	Primary Vaccination	Booster Dose
9 through 23 months of age	Children with complement deficiencies; functional or anatomic asplenia;	Two doses of MCV4, three months apart	If first dose received at age 9 months through 6 years and remain at increased risk for meningococcal disease, should receive an additional dose of MCV4 three years after primary vaccination. Boosters should be repeated every five years thereafter.
	Children with HIV, if another indication for vaccination exists	Two doses of MCV4, three months apart	
	All others in this age group recommended for vaccination (travelers to the Meningitis Belt, etc)	Two doses of MCV4 , three months apart (infants receiving the vaccine prior to travel can receive the doses as early as two months apart)	

The recommended schedule intervals for 9 through 23 months of age are reflected in the following table, which again will be revised to match the recommendation:

Age	Subgroup	Primary Vaccination	Booster Dose
2 through 18 years of age, with high risk conditions (2)	Children with complement deficiencies; functional or anatomic asplenia	Two doses of MCV4 , two months apart	If first dose received at age 9 months through 6 years and remain at increased risk for meningococcal disease, should receive an additional dose of MCV4 three years after primary vaccination. Boosters should be repeated every five years thereafter.
	Children with HIV, if another indication for vaccination exists	Two doses of MCV4 , two months apart	
	All others in this age group recommended for vaccination (travelers to the Meningitis Belt, etc)	Single dose of MCV4	If first dose received at age 7 years or older and remain at increased risk for meningococcal disease, should receive an additional dose of MCV4 five years after primary vaccination. Boosters should be repeated every five years thereafter.

The recommended schedule intervals for all other children 11 through 18 years of age will remain the same:

Age	Primary Vaccination	Booster Dose
All other children 11-18 years of age	Routine vaccination with MCV4 at ages 11 through 12 years	If vaccinated at age 11 through 12 years, should receive a one-time booster dose at age 16 years
		If vaccinated at age 13 through 15 years, should receive a one-time booster dose at age 16 through 18 years

The following table notes were revised to correct the omission of the polysaccharide vaccine. This just needed to be included and was not something that ACIP voted on as a committee.

Table Notes

- (1) At the time of this resolution, there are currently two licensed MCV4 products. One product, Menactra ®, is manufactured by sanofi pasteur and is licensed for use in persons aged 9 months through 55 years of age. The second product, Menveo ®, is manufactured by Novartis Vaccines and Diagnostics, Inc. and is licensed for use in persons aged 2 through 55 years of age. A meningococcal polysaccharide vaccine is also available. This product is licensed for use in persons 2 years of age and older and may be used when meningococcal conjugate vaccine is unavailable or contraindicated.
- (2) Includes children who have complement deficiencies (C3, properidin, factor D, and late component deficiencies), anatomic or functional asplenia, and children with HIV infection; travelers to or residents of countries in which meningococcal disease is hyperendemic or epidemic; and children who are who are part of a community outbreak of a vaccine-preventable serogroup.

There are no changes to the recommended dosage and contraindications / precautions, which read as follows:

Recommended dosage

- Refer to product package inserts.

Contraindications and Precautions

- Contraindications and Precautions can be found in the package inserts available at <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833>

The statement regarding the update based on published documents will be included, and will be modified to parallel the recommendation:

[If an ACIP recommendation regarding meningococcal 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.]

Motion

Dr. Chilton made a motion to accept the VFC resolution as amended. Dr. Cieslak seconded the motion. The motion carried with 15 affirmative votes, 0 negative vote, and 0 abstentions.

MenAfriVac™ (Meningococcal A Conjugate Vaccine) Introduction in Burkina Faso

Thomas Clark, MD, MPH
Epidemiology Team Lead, Meningitis and Vaccine Preventable Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Clark presented information to help frame CDC’s work in vaccine preventable diseases in a global context, and to share some early good news pertaining to the implementation of MenAfriVac™ in Sub-Saharan Africa. The “Meningitis Belt” of Sub-Saharan Africa extends from Senegal in the West to Ethiopia in the East. It is a region that is at extremely high risk for epidemic meningitis, with predominantly serogroup A meningococcal disease. Across the “Meningitis Belt” there are some 430 million people at risk. Roughly 25 countries are susceptible to outbreaks, but 7 countries are classically described in the “Meningitis Belt,” including Mali, Burkina Faso, Niger, Nigeria, Chad, Sudan, and Ethiopia.

Meningitis epidemics are linked to climate. The climate of this region is characterized by two seasons, the monsoons and high humidity in what would be the US’s summer and prevailing winds from the Sahara in what would be the US’s winter, bringing with them dust and dry air. These coincide with meningitis epidemics. Outbreaks of meningitis disease within the region are really local, so within given districts and villages, attack rates can be as high as 1000 per

100,000 or more, so 1% of the population can be affected. Across the belt, there are thousands or tens of thousands of cases each year, as has been the case for 100 years. Intermittently, in 8- to 12-year cycles, there are explosive epidemics across the region. The most recent occurred in 1996 with 200,000 reported cases [WHO/AFR, October 2006]. Somewhat different from pneumococcal and *Haemophilus influenzae* type b disease, the incidence of meningococcal disease in the region extends well into the third decade of life, so there is a larger population at risk and the prevention strategy, therefore, is different [Campagne et al. Bull World Health Organ 1999;77(6):499-508],

It was clear after the 1996 outbreak that reactive vaccination with polysaccharide vaccines was an unacceptable strategy, and not a good preventive strategy for epidemic meningitis. So there was an appeal by the Ministers of Health in the region to develop a conjugate vaccine, a better vaccine, for the region. In 2001, the Meningitis Vaccine Project was founded through a grant from the Gates Foundation. This project was a collaboration between PATH and WHO resulting in a consortium of manufacturers manufacturing a serogroup A conjugate vaccine. SynCo BioPartners in Amsterdam made the polysaccharide (NmA PS), Statens Serum Institute in Denmark made the tetanus toxoid (TT) carrier protein, an FDA-developed conjugation method was utilized, and the Serum Institute of India manufactured the vaccine. The contracted price that was agreed upon for this vaccine is \$0.40 per dose.

The pre-licensure trials were quite dramatic, with substantially higher titers among older children and adults in Africa than the polysaccharide comparison vaccine. There were equally impressive responses, 20-fold higher titers, among 12- to 23-month old children in Africa than the polysaccharide comparison vaccines. Most importantly, there was evidence of a booster response in 12- to 23-month old children, so behaving like a conjugate vaccine.

The vaccine was licensed late in 2009 and prequalified through WHO in June 2010. That set the "wheels in motion" for a sub-national implementation for adverse events surveillance beginning in September 2010 in Mali, Burkina Faso, and Niger. The implementation strategy for the vaccine was 3-fold. It is rapidly inducing herd immunity by large scale mass vaccination campaigns targeting people 1 to 29 years of age in the affected countries (> 90% vaccine coverage achieved), and then protecting new birth cohorts with intermittent catch-up campaigns or incorporation into the EPI schedule. The EPI dosing and schedule have yet to be worked out and licensed. An important part of this is the overlap. There are other serogroups that can cause disease and outbreaks in the region, so on-going surveillance and epidemic response are important in the event of a W125 outbreak, for example.

This is the first time that a vaccine like this has been developed in this way for Africa, and the first time this sort of strategy has been applied to a regional problem. Therefore, the approach to evaluation is comprehensive for the impact of this vaccine, including monitoring of adverse events, coverage surveys, operational research, impact on epidemics (surveillance), impact on carriage (herd immunity), vaccine effectiveness, immunology of vaccine failures, molecular epidemiology, and duration of protection. There is a 5-year plan to understand the duration of protection of this vaccine, which is the important question.

In Burkina Faso, Mali, and Niger, 20 million doses were given last year. The entire country of Burkina Faso was vaccinated in 10 days, with 12 million doses given and administrative coverage of over 100%. Among the adverse events, there were very low rates of expected typical reactions. There were also very few severe adverse events, none of which were determined to be unusually causally related to the vaccine [WHO, SRWG meeting, 3/5/11].

In terms of attack rates by district in Burkina Faso in the heart of the “Meningitis Belt,” each year numerous districts cross the epidemic threshold of 15 cases per 100,000 over a 2-week period. 2009 is acknowledged to be a quiet year, but 3 districts still cross the epidemic threshold and numerous districts cross the alert threshold. In contrast, only 2 districts reached the epidemic threshold in Burkina Faso. These are thresholds to mount vaccination campaigns. Usually the epidemic threshold is 100 cases per 100,000 and no districts met that threshold this year. In 2011, the trajectory of reported cases of meningitis by clinical definition is much lower than any year recently [Meningitis Weekly Bulletin, Week 19, 2011. WHO Inter-Country Support Team]. Among 2665 suspect cases to date, 1437 have been tested by culture +/- PCR, and there have been 4 confirmed serogroup A cases in the country. This is an unprecedented occurrence of disease. Usually about 20% of cases have laboratory confirmation; however, this year 80% of cases have confirmation. In terms of occurrence related to case confirmation, unlike most years with an appreciable serogroup A burden of disease, predominantly pneumococcal with very little meningococcal serogroup A disease are being observed this year [Meningitis Weekly Bulletin, 2004-10. WHO Inter-Country Support Team; Reunion du Comite National de Gestion des Epidemies, 2011 (weeks 1-22), DLM Burkina Faso].

This is compelling and very good news from the first country in the region to implement this vaccine. Mali and Niger are on track to vaccinate the rest of the country this year, and Nigeria, Chad, and Cameroon will begin vaccinating later this year. Within the next couple of years, the other couple of high risk countries will be finished. The hope is that within 10 years the goal of ending epidemic meningitis in Sub-Saharan Africa will be achieved. This translates to prevention of 123,000 deaths; prevention of permanent disability in 287,000 children and adults; savings of approximately \$99.7 million in direct medical costs; and elimination of epidemic meningitis as a public health concern in Africa.

CDC’s Division of Bacterial Diseases, Immunization Safety, and Global Immunization had a role in technical support for the development and implementation of the vaccine and now the evaluation, but are clearly just players in a much larger collaboration.

Discussion Points

Dr. Schaffner (NFID) called attention to and recognized Dr. Mark LaForce, who is an Epidemic Intelligence Service (EIS) alumnus and is the individual who orchestrated this extraordinary public health achievement.

Dr. Meissner inquired as to whether there were plans to use this vaccine in Asia where there is a lot of serogroup A disease.

Dr. Clark responded that there is a contracted supply for the “Meningitis Belt” of tens of millions of doses per year. The implementation strategy matches the supply. In the future, they will be able to sell the vaccine to anyplace which wishes to purchase it, and there is a development plan for a 5-valent conjugate vaccine with the same technology so there is CWY and also serogroup X, which has been a recently described cause of epidemics in Africa.

MMR Vaccine Working Group Update

Introduction

**Jonathan Temte, MD, PhD,
University of Wisconsin
Chair, ACIP MMR Work Group**

Dr. Temte introduced the Measles, Mumps, Rubella (MMR) Vaccine Working Group, ACIP's newest working group. ACIP recommendations for the use of MMR vaccine are >10 years old, and there have been several changes since 1998. ACIP shortened its recommendations for avoiding pregnancy after vaccination from 3 months to 28 days in 2001. In 2006, ACIP updated recommendations for mumps vaccination. ACIP also updated recommendations for healthcare personnel. Monovalent vaccines are no longer available, although MMRV is available. Measles and rubella were declared eliminated in the US; however, mumps outbreaks have occasionally occurred among highly vaccinated populations.

The MMR Vaccine WG's terms of reference are to review the epidemiology of measles, mumps, rubella, and CRS; review existing statements pertaining to MMR vaccine; review new data on the MMR vaccine; consider safety and immunogenicity among persons with HIV; consider a third dose for mumps outbreak control; and revise / update existing recommendations into a single document. The WG has engaged in two teleconference thus far. The MMR Vaccine WG's proposed schedule of activities is as follows:

Dates	Topic
June – August 2011	Measles vaccination policy
September – November 2011	Mumps vaccination policy
December 2011 – January 2012	Rubella vaccination policy
February – April 2012	Policy related to all 3 diseases
May – June 2012	Draft updated MMR vaccine recommendations

Dr. Temte shared the list of WG members, indicating that Huong McLean is serving as the CDC lead. He also shared a copy of the minutes from the first ACIP meeting May 25-26, 1964. A statement was included reading, "From the status of studies reported recently at a meeting on rubella at the Division of Biologics Standards, it would appear that the development of practicable rubella vaccines may not be anticipated for some years." In fact, 40 years after that statement, rubella was declared eliminated.

2011 US Measles Epidemiology Update

Huong McLean, PhD, MPH

Division of Viral Diseases

National Center for Immunization and Respiratory Diseases

Centers for Disease Control and Prevention

Dr. McLean reported that since measles was declared eliminated in 2000, approximately 50 to 60 cases are observed annually. As of June 17, 2011, there have been 156 measles cases reported in the US since January 2011. This is the most cases reported in the US since 1996 when there were 508 cases. From 1997 to 2001, the cumulative number of cases by month of rash onset has increased each month. For 2002 to 2010, excluding 2008, the curve leveled off in June and July and there are very few cases in the second half of the year. The year 2008 was very similar to the post-elimination years, except at a higher magnitude. Record numbers were reached in 2011, and it is unclear whether this will level off or if cases will continue.

Of the 156 cases reported as of June 17, 2011, 89% were in US residents. There were 12 outbreaks, defined as a chain of transmission of three or more cases. The median outbreak size was 4, with a range from 3 to 21 cases. Most outbreaks have been contained early, with the exception of Minnesota which had 21 cases. The outbreaks were limited in part because of the timely and resource-intensive response of local health departments. The median age was 16 years, with a range of 3 months to 84 years. Of those, 85% were unvaccinated or had unknown status, 70% were unvaccinated, 30% had an unknown or undocumented vaccination status, 34% required hospitalization, and 87% were import-associated.

Of the cases, 17% were under 12 months of age, which is normally too young for vaccination, and 4% were 12 to 15 months of age. Of note, 46% (n=12) of those 6 to 15 months acquired measles while traveling abroad or on an international flight and should have been vaccinated before travel. Most of the cases in adults 20 to 39 years of age had either unvaccinated or undocumented status. Most in the younger age groups were unvaccinated. Almost half of the adults 20 years of age and older had unknown vaccine status. Among US residents who were known to be unvaccinated, 32 (70%) of children / adolescents had religious or personal exemption to vaccination. There were 11 (24%) missed opportunities of those who were eligible but were not vaccinated. Among adults, 7 (44%) had a philosophical objection to vaccinations and were born before 1957.

Among the 53 hospitalizations, 52 (98%) were unvaccinated or had unknown vaccination status and 1 (2%) had received 1 dose. The individual who had received 1 dose was hospitalized for observation only. Complications included 9 (17%) cases of pneumonia. There was no encephalitis or deaths. Overall hospitalization was 34%, with the highest rate among those under 5 years of age: 44% <12 months, 48% 1 through 4 years, 16% 5 through 19 years, and 32% ≥20 years.

There have been importations from all regions. Known sources of importation are reflected in the following table:

WHO Region	Total no. of cases	Countries	Genotype identified
African	2	Kenya (1), Nigeria (1)	B3 (2)
Eastern Mediterranean	2	Pakistan (1), Jordan (1)	D4 (1)
European	25	France (12) , Italy (4), Poland (1), Romania (1), Spain (1), United Kingdom (4), France/United Kingdom*(1), France/Italy/Spain/Germany *(1)	D4 (11), G3 (1)
Americas	1	Dominican Republic†(1)	D4 (1)
South-East Asia	16	India (15) , Indonesia (1)	D8 (5), D4 (1)
Western Pacific	7	China (2), Philippines (4), Philippines/Vietnam/Singapore/Malaysia*(1)	H1 (1), D9 (2)

As noted, 70% of US importations are among US residents traveling abroad. To put this into perspective, Dr. McLean reviewed measles cases in Europe from January through May 2011. As of May 12, there have been greater than 10,000 cases from 18 countries. Outbreaks are ongoing in France, Spain, and Belgium. In France, there have been 12 encephalitis cases and 6 measles-related deaths

http://www.invs.sante.fr/surveillance/rougeole/Point_rougeole_200511.pdf].

To summarize, there has been an increased number of cases. This is the highest number of cases since 1996 (n=156). This is in large part due to a number of importations, particularly countries visited by US travelers. Despite these outbreaks and importations, spread has been limited due to the high 2-dose vaccination coverage and rapid control efforts in the US. Of the importations, 70% have been among US residents traveling abroad. It is important to increase awareness of measles and vaccination among travelers.

CDC response efforts have included a collaborative effort of the CDC laboratory, which has been assisting in testing and retesting as needed through the Division of Viral Diseases with epidemiology and laboratory services. This division has consulted with health departments on response measures as needed. Communication activities include *MMWR* updates, interviews with the media, and other efforts (e.g., websites, provider education, travel education).

Discussion Points

Dr. Schaffner (NFID) pointed out that their neighbors in this hemisphere were responsible for almost no importations, because they have done such a good job eliminating measles through immunization. It is now time to ask Europe why they do not immunize their children.

Dr. Cieslak said he was impressed by the lack of cases from Japan, which used to be a major exporter of measles to the US. He requested comments on the measles picture in Japan.

Hajime Kamiya (National Institute of Infectious Diseases, Tokyo) replied that Japan is in the fourth year of a catch-up campaign. The number of cases is currently down to about 300 per year, which is about 3 per 100,000.

Dr. Plotkin indicated that the problem in Europe is that they do not mandate vaccination against measles, rubella, or mumps. He thought the US government could complain to the European Union about this situation. His French friends in medicine and vaccines are frustrated and unhappy, but the French government is doing little about it.

Dr. Baker indicated that the case of measles they saw in February was an imported case in a child who left the country at 11 or 12 months of age who had not been vaccinated. She said she was astonished by the very high rate of hospitalization, but that she suspected that a lot of those children are being admitted with a diagnosis of Kawasaki Disease. Measles is difficult to differentiate, especially for those who have never seen a case. She wondered whether they had or would have any information on admitting diagnosis. Her patient had bacterial pneumonia as a complication of measles, which was completely missed for two days. They were fortunate that the child was in a private room and was sick enough that he did not go outside of the room, resulting in pretty good infection control. She believes that one problem with spread is not knowing the diagnosis.

Dr. McLean responded that they do not typically collect admitting diagnoses unless states provide it. There were a couple of cases that were misdiagnosed.

Ms. Stinchfield (NAPNAP) reported that Children's Hospital of Minnesota saw 12 of the 14 children who were hospitalized there. Very seasoned infectious disease physicians thought they were dealing with Kawasaki Disease until the sibling presented and looked similar. Other children presented in March with otitis media, fever and a lot of gastrointestinal symptoms and still no rash. In retrospect, it is easy to judge, but when in the middle of it and the first case presents, it does look like similar illnesses. The message for everyone, seasoned clinicians or people who have never seen measles, think measles if there are characteristic diagnostic criteria and international travel.

A participant indicated that 20 years ago, he was at the St. Paul, Minnesota Health Department when there was a small outbreak of measles at a small college. Students from there had traveled to Disney World in Orlando. As the state epidemiologist, he had to quarantine those children and other primary contacts. He was curious about college students coming to the US from the UK, Asia, et cetera who do not have current immunizations. He thought immunizations should be up to date when freshman are admitted to college.

Dr. Baker pointed out that US college students need to be up to date as well before traveling outside the US.

Dr. Turner (ACHA) reported that there is variability among states in terms of college pre-entrance requirements. Where he is in Virginia, students entering college are required to have a cadre of immunizations proven with a clinician's signature in order to be admitted. There were four cases of measles in Charlottesville this spring. He checked their records and found that they had virtually 100% compliance among their 24,000 students. Conversely, California only requires evidence of a hepatitis B vaccine upon college entry. They assume that since they have good primary and secondary school entry requirements, all college students are appropriately vaccinated. They do not take into account that 20% to 25% of students are international, nor do they consider importation associated with international travel.

Dr. Greg Wallace (CDC) pointed out that sometimes exchange students are younger than college age. He emphasized that 70% of the US's direct importations are actually the result of unvaccinated US residents traveling abroad. This is an area in which a direct impact can be made.

Dr. Moore (AIM) reported that a lesson learned in Tennessee is that there are those who were born in the late 1960s and early 1970s who missed out on the 2-dose MMR recommendation. She was born in the early 1970s and received her second dose before she went to Vanderbilt University as an undergraduate in 1999. Two of Tennessee's cases were in their 40s who may have received inactivated vaccine and thought themselves to be vaccinated. They had no idea that they were unprotected until they returned from Europe with the disease. Tennessee has been focusing efforts on vaccination this group as well.

Pertussis

Introduction

Dr. Mark Sawyer Chair, ACIP Pertussis Vaccine Working Group

Dr. Sawyer reported that the Pertussis Vaccine Working Group was given the not so small task of reviewing existing statements on infants and young children (1997), adolescent (2006), adults (2006), and pregnant and postpartum women and their infants (2008) and consolidating these into a single statement. They were also charged with reviewing new data on Tdap, including effectiveness of ACIP recommendations, the interval between Td booster and Tdap, the use of Tdap in adults ages 65 years and older, vaccination of health-care personnel and need for post-exposure prophylaxis, pregnant and breastfeeding women in terms of Tdap use and cocooning strategies, and revaccination. In addition, this WG will review the updated epidemiology of tetanus and diphtheria.

Current ACIP recommendations for use of Tdap vaccine during pregnancy are as follows:

- ❑ During pregnancy
 - ACIP recommends administration of Td for booster protection against tetanus and diphtheria in pregnant women. However, health-care providers may choose to administer Tdap instead of Td during pregnancy to add protection against pertussis in special situations.

- ❑ Postpartum
 - Tdap is recommended as soon as feasible in the immediate postpartum period to protect the women from pertussis and reduce the risk for exposing their infants to pertussis.

- ❑ Cocooning
 - Adults who have or who anticipate having close contact with an infant age <12 months (e.g., parents, grandparents, child-care providers, and HCP) should receive a single dose of Tdap.

Some data were presented to ACIP during the February 2011 meeting. The reason the WG continues to pursue this issue is because they feel that the existing language is inadequate and is not sufficiently protecting infants from pertussis. Additional information requested by ACIP in February included safety of Tdap in mother and fetus, the effect of maternal vaccination on infant immune response to primary DTaP, and cost of a maternal Tdap vaccination program.

This session addressed the following topics:

- ❑ Safety of Tdap in pregnant women and infants
- ❑ Decision and cost effectiveness analysis
- ❑ Pertussis maternal immunization study (interim data)
- ❑ Cocooning
- ❑ Timing of maternal vaccination (pregnancy or postpartum)
- ❑ ACIP recommendations for vote
- ❑ Emergence of pertussis in children aged 7 through 10 years and early evaluation of DTaP effectiveness

Based on reported pertussis incidence by age group from 1990 to 2009, infants have substantially higher rates of disease and the largest burden of death compared to other age groups. Many cannot be vaccinated and require other strategies for prevention of pertussis. The WG members felt that current strategies to prevent infant deaths are insufficient [CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System]. A breakdown by age groups of reported pertussis-related deaths over the past 30 years shows that the great majority of deaths occur in infants 0 through 1 month of age, before they are eligible to receive the first dose of DTaP. This does not include the 2010 California outbreak during which 10 deaths occurred in infants less than 2 months of age [Vitek CR, *et al.* *Pediatr Infect Dis J* 2003; 22(7): 628-34; and National Notifiable Diseases Surveillance System, CDC, 2009]. Several studies have provided evidence that of known sources of transmission, household members were primarily responsible for transmission of pertussis to infants. More specifically, parents were the most commonly identified source of pertussis [Wendelboe AM, *et al.* *Transmission of *Bordetella pertussis* to Young Infants.* *Pediatr Infect Dis J* 2007;26: 293–299; Bisgard KM, *et al.* *Infant pertussis: who was the source?* *Pediatr Infect Dis J* 2004; 23(11):985-989].

The WG has been meeting on this topic for 6 to 8 months, and has gone through an evolution of thinking about the process. Almost everyone on the working group believes that the scale needs to be changed, which currently favors immunization postpartum versus during pregnancy. The majority opinion of the working group is that the scale needs to be balanced to have immunization during pregnancy at least on an equal footing with postpartum immunization. There is a significant minority opinion on the WG that immunization during pregnancy should be favored based on current knowledge about the safety and efficacy of such an approach. Next steps include revision of the pertussis vaccines statement and consolidation of all of the recommendations, continued review of the use of Tdap vaccine in persons age 65 years and older, and the need for a Tdap revaccination.

Safety of Maternal Vaccination for Mother and Infant

Sonja A Rasmussen, MD, MS
Centers for Disease Control and Prevention

With regard to background, Dr. Rasmussen pointed out that pregnant women are traditionally excluded from pre-marketing clinical trials for ethical reasons. Pre-marketing animal studies are performed, but do not always predict the experience of humans. Thus, there is little information available to guide use during pregnancy at the time a new medication or vaccine is marketed. Most available information about the effects of medication and vaccine use in human pregnancy comes from observation of exposures post-marketing. The goal is to determine whether benefits of the medication or vaccine exceed the potential risks of teratogenicity.

A teratogen is an agent that acts during pregnancy to irreversibly alter growth, structure, or function of the developing embryo or fetus. Recognized teratogens include infections, medications, nutritional factors, lifestyle factors, environmental exposures, and maternal conditions. Potential adverse outcomes following exposures during pregnancy include spontaneous abortion, fetal death, preterm birth, small for gestational age (SGA) / intrauterine growth restriction (IUGR), birth defects, developmental disabilities (e.g., vision or hearing impairment, intellectual disability, autism), and cancer in offspring.

The teratogenicity of an agent depends upon the nature of the agent, dose, route of administration, gestational timing, other concurrent exposures, and the genetic susceptibility of the mother and embryo or fetus. Time periods of teratogenesis are shown in the following table:

Time Period	Gestational Weeks	Examples of Teratogenic Effects
Preimplantation (fertilization to implantation)	0–2 weeks	Spontaneous abortion or recovery (“all or nothing”)
Embryonic	2–9 weeks	Structural birth defects
Fetal	9 weeks–delivery	Intrauterine growth restriction Intellectual disability Fetal death

Typically, inactivated viral vaccines, bacterial vaccines, and toxoids are considered safe during pregnancy. Live and / or live-attenuated virus vaccines are contraindicated during pregnancy because of theoretical risk of transmission of the virus to fetus. However, no evidence has demonstrated an increased risk to mother or fetus from any currently available live vaccines (e.g., mumps, measles, rubella, varicella) [Reviewed in Gruslin et al., J Obstet Gynaecol Can 30:1149-54, 2008].

Vaccines currently recommended during pregnancy include influenza vaccine, which protects pregnant women and infants ≤ 6 months of age. ACIP recommends trivalent inactivated vaccine for all women who are or will be pregnant during the influenza season. Tetanus toxoid vaccine protects infants born to women in developing countries from neonatal tetanus from neonatal tetanus where primary immunization has not occurred. WHO recommends 2 doses in first and 1 in each subsequent pregnancy. There is no evidence to demonstrate an increased risk to mother or fetus.

VAERS is the spontaneous reporting system co-administered by FDA and CDC. The strengths of this passive surveillance system include rapid signal detection, ability to detect rare adverse events, generation of hypotheses, encouragement of reports from healthcare providers and acceptance of reports from patients and others, and availability of data to the public. The limitations of the system are reporting bias (e.g., underreporting, stimulated reporting), inconsistent data quality and completeness, it is not designed to assess whether a vaccine caused an adverse event (AE), and it lacks an unvaccinated comparison group.

VAERS data from January 1, 2005 – June 30, 2010 showed that 129 (1.2%) of 10,350 US reports to VAERS after Tdap vaccines involved pregnant women. Of the 129 reports, 4.7% (6) were classified as “serious.” There were no maternal deaths [CDC/ISO unpublished data]. The most commonly reported pregnancy-specific AEs include 21 (16.3%) spontaneous abortions; 5 (3.9%) gestational diabetes; 2 (1.6%) each of stillbirths, oligohydramnios, ectopic pregnancy, threatened abortion, and sub-chorionic hemorrhage; and 1 (0.8%) each of gestational toxemia, preterm delivery, chorioamnionitis, prolonged labor, and congenital anomaly (gastroschisis). The most commonly reported non-pregnancy-specific AEs include 7 (5.4%) injection site reactions. No unexpected patterns or unusual events have been observed.

Pregnancy registries have been established by sanofi pasteur for Adacel® (Tdap) and GlaxoSmithKline (GSK) for Boostrix®. There were 49 Tdap exposures from the Phase IV clinical trials, and one baby with a birth defect. Of the 49, 34 (69%) had no AEs, 10 (20%) had serious AEs (gestational diabetes, threatened labor, spontaneous abortion, preeclampsia, syncope/hypotension/bradycardia, pregnancy-induced hypertension, tuberculin test positive), and 3 (6.1%) had non-serious AEs. There were 47 (96%) with known pregnancy outcomes, including 44 live births with 1 unrelated congenital anomaly (hydronephrosis diagnosed prenatally pre-vaccination), 2 spontaneous abortions, and 1 elective abortion. The registry cases are divided into prospectively and retrospectively reported cases. For the retrospective cases, there is information about infant outcome at the time of the report. For the prospective cases, there are no data about the outcome. Of 480 prospective spontaneous reports, 263 (55%) had no AEs, 27 (6%) had serious AEs (spontaneous abortion, gestational diabetes, preterm labor, tubal rupture, preeclampsia, syncope/headache, ovarian cancer, labor complication NOS), and 31 had non-serious AEs. There were 119 (25%) with known pregnancy outcomes, including 101 live births (no congenital anomalies), 2 elective abortions, and 16 spontaneous abortions. Of 10 retrospective spontaneous reports, 7 (70%) had no AEs, 2 (20%) had serious AEs (2 spontaneous abortions), and 1 had non-serious AEs. For all 10 there was a known pregnancy outcome, including 8 live births (1 with patent foramen ovale and peripheral

pulmonic stenosis), and 2 spontaneous abortions. Peripheral pulmonic stenosis is commonly seen in newborns and is not considered a major birth defect. Data are not yet available from GSK's Boostrix® pregnancy registry.

Other issues that may be of potential concern are thimerosal, fever, and hyperthermia. No scientific evidence exists that thimerosal-containing vaccines are a cause of adverse events among children born to women who received vaccine during pregnancy. Neither Adacel® nor Boostrix® contain thimerosal or mercury. Fever appears to occur infrequently in less than 5%. Fever does have the possibility of adverse outcomes during pregnancy, but most of those adverse outcomes are in the first trimester. Hyperthermia from fever or hot tub use during the first trimester has been associated with certain birth defects, most commonly neural tube defects. A meta-analysis by Moretti et al (2005) suggests a 2-fold risk of neural tube defects with maternal fever during first trimester. Antipyretics appear to attenuate the association. Maternal infection, inflammation, and fever noted at admission for delivery have been associated with an increased risk of cerebral palsy, but it is unclear whether this is related to fever or to underlying infection.

In conclusion, killed vaccines are believed to be safe during pregnancy; however, it is difficult if not impossible to prove the safety of medication or vaccine use during pregnancy. A very large sample size is required to detect rare adverse events, and most studies are too small to rule out a small to moderate increased risk. In addition, exposures during pregnancy can cause a wide range of effects, including problems with development and risk for cancer. It is necessary to weigh the benefits with potential risks. Current data suggest that potential risks, if any, are likely to be small.

Tdap Vaccination to Prevent Pertussis in Infants: A Decision and Cost-Effectiveness Analysis

**Garrett R. Beeler Asay, PhD, MA
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Dr. Asay reminded everyone that the impetus for this study was that during the February 2011 ACIP meeting, interest was expressed in understanding the cost-effectiveness of vaccination during pregnancy with Tdap as compared to cocooning and postpartum vaccination. The objectives of the study were to analyze the cost-effectiveness of alternative Tdap interventions in preventing infant pertussis and to assess the pregnancy dose, postpartum dose, postpartum + Tdap administered to the father, and postpartum + Tdap administered to the father + Tdap administered to grandparents.

In terms of pertussis incidence among infants less than 12 months of age based on data from 2001-2009, the highest rates of disease occurs during the first 2 months of life. As DTaP doses are added, incidence declines. With regard to hospitalizations and deaths as a percentage of total cases, the highest percentage of hospitalizations and deaths occurred in the first two months of life [CDC, National Pertussis Surveillance System and Supplemental Pertussis Surveillance System (2010)].

The current ACIP recommendation to protect infants with Tdap is through cocooning by administering a Tdap booster for unvaccinated household members and caregivers of newborn infants¹. This was found to be cost-effective in one study from Netherlands²; however, there are no studies on cost-effectiveness in the US [¹ Bisgard et al. 2004; Murphy et al. 2008; Van Rie

and Hethcote 2004; Wendelboe et al. 2007; ² Westra et al. 2010]. An alternative strategy would be to move the postpartum dose to earlier during pregnancy, preferably in the third trimester. This would have two potential benefits. The first would be to protect the infant against transmission from the mother similar to postpartum, and the second would be a likely benefit of direct immunity to the infant through maternal antibodies [Healy et al 2004; Van Savage et al 1990; Gall et. Al. 2011; Leuridan, et al. 2008; Shakib et al 2010]. Both of these strategies would have the same program cost because only one dose would be administered.

A potential cost is that transplacental antibody may interfere with active antibody production following primary DTaP dose, which is known as “blunting.” There is mixed evidence for blunting from acellular vaccine [Belloni (2003); Englund et al (1995); Halasa (2008); Van Savage (1990); Wood (2010)]. Because this is an issue, an increase in risk of disease during the second and third month of the infant’s life is included rather than modeling the change in efficacy. While a benefit may be achieved by potentially lowering disease in the first few months, people seem to be concerned about what may occur later with additional doses.

In terms of the methods of analyses, it was assumed that mothers were vaccinated in the third trimester of pregnancy and that there would be full efficacy of the vaccine when the baby is born. Then the increase in risk of disease during the second and third month would be included to model “blunting.” For the postpartum dose, a 2-week delay in booster immune response in the mother was assumed. For additional cocooning doses, a best-case scenario was assumed for the doses given prior to the birth of the infant so that they are fully protected. All vaccine cost were assumed to be the same for all Tdap doses at \$37.55 per dose¹ + a \$20 administrative cost² [¹ CDC 2011a; ² Caro 2005]. A simulated birth cohort model was used with about 4,131,019 (2009 birth cohort size) infants followed for one year¹. Monthly incidence, hospitalization, and death rate were included. The societal costs perspective was included for infants only. The reason the benefits to adults from receipt of this vaccine were not modeled is because this strategy is primarily used to prevent infant disease. The analytic horizon was comprised of direct disease costs totaled over the first year of life. For life years lost, the 2009 average life expectancy of 77.9 years² was used [¹ Hamilton 2010; ² US Census Bureau 2011].

In terms of the model structure, the base case is DTaP alone. Each of the strategies will be compared to DTaP alone. Then there are the pregnancy dose, postpartum dose, and postpartum plus cocooning doses. The outcomes include outpatient disease, severe respiratory disease, neurologic disease, and death. The model tree is repeated each month of the cohort, for a total of 12 months (incidence varies by age), and outcomes are repeated for cocooning and base case.

Regarding general model inputs, 72% coverage was assumed for all doses because the investigators wanted to model the effect of a fully implemented program. Tdap efficacy of 85% was assumed. For incidences, hospitalizations, and deaths, the mean 2000-2007 incidence was used from national surveillance data. This is a period of time for which cocooning was not fully implemented or recommended. A 15% under-reporting rate and a 3% discount rate were assumed. For intervention model inputs, it was assumed that maternal antibodies were 60% efficacious and that they would last for two months. A 10% increase in the risk of disease was assumed in months 2 and 3 due to blunting. Based on the literature, transmission from the mother was assumed to be 35%, from the father 15%, and the grandparent 6%. Medical and non-medical costs were included for each outcome. The medical costs included outpatient visit (\$110), inpatient respiratory illness (\$7,323), inpatient neurologic illness (\$7,032), and death (\$15,808). The non-medical costs included outpatient visit (\$47), inpatient respiratory illness (\$487), inpatient neurologic illness (\$745), and death (\$735). The QALYs were 0.85 for

outpatient visits, 0.58 for inpatient respiratory illnesses, 0.51 for inpatient neurologic illness, and 0 for deaths [Lee et al. 2007 and Lee et al. 2005]. The public health response cost used was \$2,162 (minimum \$1,081; maximum \$3,243).

In terms of the results, when the postpartum dose is added to the base case (DTaP), the graph shifts down over several months. The shift is not even. In the first month it is somewhat smaller because the mother is not fully protected when the baby is born. By the second month, the mother has the full booster response to the vaccine. Further out in months, incidence decreases and the benefit to vaccination decreases as well. Regarding the pregnancy dose compared to the postpartum dose, impact is lower in the first two months because the dose was given earlier so the mother has more protection when the baby is born, and also due to the transplacentally transferred antibodies. In the second month, the line is somewhat above the pregnancy dose due to the increase in risk of disease from blunting. However, it is still below the base case because by vaccinating the mother, the risk of disease was lowered for all age groups. That overrides the blunting effect for these assumptions. The addition of cocooning doses shifts the line down again, as it does when the grandparent is added. The shifts become smaller with each addition because the mother is the greatest identified source of transmission, so the greatest benefit comes from vaccinating the mother. The pregnancy dose has lower cases in the first few months when infants have the highest rates of deaths and hospitalizations.

Regarding the mean percentage of reductions from the base case for all interventions, pregnancy is predicted to have a 33% reduction in cases, which is higher than the other interventions. This is similar with hospitalizations (38%), and more so with deaths (49%). The program costs are the same for pregnancy and postpartum (\$171 million) because only the timing was changed—no doses were added. As doses are added for fathers and grandparents, the program costs increase to \$342 million and \$513 million, respectively.

Based on this model, the program cost per QALY to save one year of perfect life for an infant with the pregnancy scenario is \$415,442. With the postpartum scenario it is \$1,174,143. By adding the father, the cost per QALY rises to \$2,154,170 and by adding the grandparent the cost rises to \$5,418,427. Therefore, according to the model, vaccination during pregnancy is the most cost-effective method.

Many sensitivity analyses were done, although Dr. Asay shared only one during this session. Assuming a worst case scenario of a 50% increase in risk of disease in months 2 and 3 and 20% efficacy of maternal antibodies, compared to the base case the second and third months are above the base case, but in the first two months there are lower rates of disease. Compared to the postpartum dose, vaccine administration during pregnancy has a greater reduction in deaths; however, hospitalizations and cases have a greater reduction when vaccine is administered postpartum. In terms of overall cost per QALY saved, vaccine administration during pregnancy is more cost-effective than postpartum administration.

In conclusion, two factors drive pregnancy cost-effectiveness. The first is when the mother is fully protected at birth for a given vaccine efficacy because the dose was given earlier, and second there is maternal antibody transfer to infant, giving the infant some form of direct protection in the first few months. In the worst-case scenario with 50% risk of disease in months 2 and 3, the pregnancy dose was still found to be more cost-effective. Additional cocooning doses are predicted to be less cost-effective because they are preventing less disease.

The limitations of the model are that only infant disease was measured. The benefits to adult from being vaccinated were not assessed. The model also did not measure the vaccine recipient's time away from work or transportation cost. This is a static model. If a fully dynamic model had been utilized, the cost-effectiveness results would be somewhat better, but the ranking among interventions would not change. Finally, there is no clinical trial to evaluate efficacy maternal antibodies in infants or blunting.

Pertussis Maternal Immunization Study

Dr. Jennifer L. Liang
ACIP Pertussis Vaccine Working Group

Dr. Liang reported that during the previous week's WG call, interim data were presented from Stage 1 of the Pertussis Maternal Immunization Study, and Dr. Scott Halpern was kind enough to permit her to present these data on his behalf during this session. The study is sponsored by Dalhousie University. It is a double-blinded randomized clinical trial using Td or Tdap. The Tdap product used is Adacel®. This is a large trial that plans to enroll 440 pregnant women in two stages. Enrollment for Stage 1 is complete. The final infant visit and interim analyses on safety and immunogenicity were completed and presented to the Data Safety Monitoring Board the previous week. Stage 2 enrollment will commence in August or September 2011 and trial completion should occur in December 2012.

The analysis of the two groups was blinded and included 48 infants whose mothers received either Td or Tdap during their late third trimester. For one group, there was evidence of lower geometric mean antibody levels one month after third DTaP dose. Therefore, antibody levels were analyzed at 0, 2, 4, 6 months. At birth and 2 months, elevated antibody titers were observed in the same group that had lower levels at the third DTaP. For both groups, there was an increase in antibody from 6 to 7 months indicating a response to the third DTaP dose. For both groups, antibody levels were comparable at 4 to 6 months. The Data Safety Monitoring Board recommended continuation of the study with Stage 2. The working group reviewed the interim data and concluded that the data are reassuring, and are consistent with published literature and assumptions made in the decision analysis presented by Dr. Asay.

Does "Cocooning" Work to Prevent Pertussis in Infants?

Dr. Jennifer L. Liang
ACIP Pertussis Vaccine Working Group

Dr. Liang reminded everyone that since 2005, ACIP has recommended cocooning as a strategy to protect infants from pertussis. Dr. Asay presented results from a model comparing the effectiveness of Tdap given either during pregnancy or during postpartum and cocooning to prevent infant pertussis. But in the real world, does cocooning work to prevent pertussis in infants? The WG group has heard about two examples of successful cocooning programs, one at the local level at Ben Taub General Hospital in Houston, Texas and another at the state level in 18 birthing hospitals in Nevada. In Nevada, either all birthing hospitals are either actively cocooning or beginning a cocooning program. Important success factors for these programs are having a champion for the cause, having donated healthcare provider time, and providing free Tdap to mothers and their families.

A number of challenges continue to impact the implementation of cocooning programs. Even after 5 years, cocooning is still a relatively new immunization platform with little infrastructure to ensure effective implementation. In addition, pertussis awareness varies. Two populations require vaccinations, including postpartum women and their families. Postpartum vaccination is not typically administered in the setting of new immunization providers. There are also reimbursement issues [Healy CM, et al. Pertussis immunization in a high-risk postpartum population. *Vaccine*. 2009 Sep 18;27(41):5599-602].

Thus, 5 years later, cocooning is not working at a national level. Most cocooning programs achieve moderate postpartum coverage among mothers, and have very limited success in vaccinating fathers or other family members. There is poor uptake of Tdap even when made available at no cost to birthing hospitals. At this time, there are no demonstrations of program sustainability or scaling-up of cocooning programs. Examples of not fully successful examples include Jefferson County, New York. During the increase in pertussis incidence, the state made Tdap available to birthing hospitals in Jefferson County, but uptake was poor. In California, during the 2010 epidemic, free Tdap was made available to birthing hospitals for a limited time. Not all birthing hospitals accepted the free vaccine to implement a cocooning program because of the work it would require, and not having the ability to sustain the program once free vaccine was no longer available. California is currently surveying the birthing hospitals that did implement a cocooning program to determine how many of them have been able to sustain their programs through alternative funding for Tdap.

Limited data are available regarding the effectiveness of cocooning, and have assessed only the maternal postpartum dose. One ecological study found no impact of only maternal postpartum Tdap on infant disease.¹ In one state, pertussis incidence in infants born at hospitals with a postpartum Tdap policy was lower compared to hospitals without a postpartum Tdap policy, suggesting that vaccinating new mothers may reduce transmission of pertussis from mothers to infants.² [¹Castagnini L, *et al.* Impact of maternal postpartum Tdap vaccination on pertussis illness in young infants. IDSA, Vancouver Canada. Presented on October 23, 2010; ²Winter K, *et al.* Effectiveness of postpartum Tdap vaccination in California hospitals. CSTE, Portland Oregon. Presented June 2010].

The WG unanimously concluded that while they would recommend cocooning all contacts of infants who are not current on Tdap, cocooning is an insufficient national strategy to prevent pertussis morbidity and mortality in newborn infants. This led the WG to ask the question: to prevent neonatal pertussis, should the timing of the mother's Tdap vaccination change from postpartum to during pregnancy?

Discussion Points

Dr. Baker indicated that the data that was presented as an abstract form was in press at *Clinical Infectious Disease*. This was a comparison of a cocooning hospital that is a public hospital where patients are primarily Hispanic. The highest number of deaths occur in Hispanic infants. The vaccine, 7-day a week nursing, and faculty time are free. Families are being immunized, not just the mother. Dr. Castagnini's data pertained just to women, and in a 17-month period of time there was no impact on prevention of pertussis disease as defined clinically and by positive PCR plus clinical manifestations. This has been extended to the families in the hospital before the mother is discharged. The nurses educate the mother and find out how many family contacts, and 50% of fathers and 96% of women are given Tdap at a cost of at least \$1 million per year. When the program ends in December, the hospital will end the program because

there no reimbursement for them for this program. Cocooning everybody is very difficult to implement.

Dr. Judson asked whether “cocooning” as term every caught on so that patients and their families understood what it meant.

Dr. Baker replied that this is a medically uninsured, under-served population. English is usually a second language, so the nurses are bilingual. The patients and their families had no clue. Part of this was education in an appropriate language, but these were obviously accepting parents who wanted their families protected. One thing that made the program very difficult was the pandemic, because the hospital would not let any family member visit the mother, including the father. The father was permitted in during delivery, but was not allowed back in until he returned to pick up the baby.

Dr. Coyne-Beasley expressed her appreciation for the presentations, especially Dr. Asay’s very clear description of the cost-effectiveness analyses.

Dr. Cieslak noted that they usually think in terms of incremental costs, and it struck him that the \$171 million might be tallying the cost of vaccinating these women. However, there is already a recommendation to vaccinate these women. The only difference regards when to vaccinate versus adding any vaccine costs.

Dr. Asay responded that this was correct, but in abiding by the standards used for cost-effectiveness, the cost of the dose has to be included because this is a program that would hopefully be fully implemented. It is true that the current recommendation is that these women should be vaccinated at some time point. Just moving the postpartum dose back could have no change in program costs.

Dr. Baker pointed out that in their program, women know whether they received a shot or not at some time. They have no clue what the shot was. For those that can be determined, it was usually influenza vaccine.

Ms. Rosenbaum pointed out that ironically, because of the way many public and private insurers pay for maternity care, this could actually cut the cost because what could happen is that it will be treated as part of the global fee and no incremental payment will be made; whereas, before there may have been some cases in which providers were paid extra postpartum, although even that is unreliable. This is the problem with anything that is pregnancy-related. The tendency on the part of insurers of all kinds to pay for specific procedures that fall within their general concept of pregnancy-related is pretty low. However, if something is not called “pregnancy-related” it will not be recognized as a standard of care and there will not be an argument for building it into the global fee. She underscored the notion that at worst, this is a wash in terms of the cost.

Dr. Marcy inquired as to whether blunting pertained only to pertussis or if it also included tetanus and diphtheria antibody levels. He also requested clarification about what they meant by “blunting” and what level is no longer offering clinical efficacy. Although he was unclear what was even meant by “blunting,” it seemed to be the variable upon which this discussion was based.

Dr. Liang replied that the concerns about blunting were raised with regard to whether maternal antibodies would interfere with the infant’s primary immune response for primary DTaP doses.

The correlates of protection are not well-understood. The clinical implications of lower response to primary DTaP series are unknown. Because it was a concern in 2005 when the original recommendation was made, they were trying to address this with the current data available and within the model, what the impact would be.

Dr. Asay added that diphtheria and tetanus were not modeled. Regarding blunting, by vaccinating the mother, a dose is being added to the schedule. This will lower the overall risk of disease for every age group. If efficacy is falling, at the same time the risk of disease is also falling.

Dr. Judson requested confirmation that blunting is a concept, there is no definition, and there are no true correlates to reduce efficacy.

Dr. Liang confirmed that this was correct.

Dr. Clark pointed out that most of the literature pertains to diminished response to the primary series for pertussis antigens. Analogous is that there are some data on a birth dose of acellular pertussis vaccine. There has some diminished response to diphtheria antibody, but all children reach protective titers, so there is a correlate of protection. The blunting question really regards diminished response to the primary series, because of the presence of maternal antibodies. The data from Scott Halpern's study were reassuring that there is a response in all children. However, the correlate of protection does not exist so the clinical efficacy is not known. This is why a modest hypothetical increase in disease occurrence was built in, assuming that this would be the only impact.

Dr. Marcy indicated that Joe St. John was administering neonatal whole cell pertussis immunization in the late 1960s. He wondered whether neonatal birth immunization as is done with Hepatitis B might be the ultimate answer if there was great concern about blunting.

Dr. Baker noted that the study Dr. Clark quoted pertained to acellular pertussis vaccine alone that was conducted in Switzerland. When Kathy Edwards's group in Nashville assessed currently available vaccine in neonates, it did not work. There would have to be some sort of acellular pertussis vaccine alone product if they were going to back up to the neonate.

Regarding sustainability of cocooning, Dr. Temte indicated that anecdotally in his experience family practice does a terrible job of cocooning. Technology has made this worse, because with the electronic medical record (EMR) everything he does requires a lot of excess time. For him to immunize his patient in the room is pretty simple. To immunize his patient and her husband, who is also a patient, requires him to open another window, log this in, and go through an incredible series of steps to order a vaccine. He wondered whether Dr. Campos-Outcalt heard similar issues, and how many pregnant patients' other family members obstetricians would be able to provide vaccines for. Hospitals will not do this because they cannot afford the administration costs.

Dr. Campos-Outcalt (AAFP) agreed that cocooning is very hard to sustain because there are a number of administrative issues. When his daughter-in-law was pregnant, he sent his wife to her internist, not a family physician, for a vaccine. She received her influenza vaccine, but when she returned he asked about Tdap and she said it was not even discussed. This is a frequently overlooked vaccine for adults regardless.

Dr. Gall (ACOG) responded that an obstetrician will see a pregnant woman 8 to 15 times during her pregnancy. It takes a lot of time to talk about vaccines like influenza, Hepatitis A, and Tdap to get her up to speed. Tdap has been given during pregnancy and have published data about this. However, it is unknown who is with the patient (e.g., husband, boyfriend, or someone else). The grandparents rarely attend a visit with the mother. It is unknown who else is in the household constellation who needs the vaccine, and there is no way to finance those other people.

Dr. Baker stressed that the key is finding out who is in the household and who will be around the baby during the first year or even first 6 months of life. This is potentially a huge number of contacts. They have on-going funding from private foundations, et cetera. She thinks that even with 50% of the fathers and 96% of the mothers, they may not observe an effect from cocooning. Again, this hospital has 4000 to 5000 deliveries per year, and the cost of the program is more than \$1 million per year. In many states, it is a law that someone has to be a patient for a hospital nurse to administer a vaccine. They have to have two nurses, hired by the children's hospital, to do this work. To say it is complicated and expensive is an understatement. This is all because pregnant women are orphans in terms of medications and vaccines.

Dr. Englund said that cocooning has never been proven to work. A prospective, multi-site, international study in 2007, up to one-third of all cases were outside the home. Although it is known that the mother and father are responsible for well over half or even up to two-thirds of the cases and that the other one-third are casual contacts. Cocooning is doomed to fail, and it is not scientifically proven. Maternal immunization offers the opportunity to protect against the most important risk factor and the baby with one cheap vaccination.

Dr. Baker pointed out that hospitals pay for MMR postpartum immunization with no problem. It is a matter of convincing Medicaid to include this tiny cost.

Dr. Duchin agreed with all of the observations that were made about the difficulty of cocooning, but he sees that as typical of risk-based vaccination recommendations, which have traditionally been very difficult and have not been very successful. With Hepatitis A and B, there were very low coverage rates before moving to a broader recommendation. Pneumococcal vaccine was challenging as well. Trying to single out certain risk groups within a larger population has always been difficult, and cocooning is especially difficult, but it is not that unique to this population.

Dr. Baker reminded everyone that they have already recommended that all adolescents and adults be given Tdap vaccination, but adults are not given this vaccine. The amount of medical capture time for a pregnant woman makes the implementation of that recommendation potentially doable.

Dr. Chilton noted that 2 of New Mexico's 38 birthing hospitals are using a cocooning strategy, and they are seeing only about two-thirds of mothers immunized and far less than this in the one other contact allowed in these hospitals. They have fewer resources than Dr. Baker described in her hospital. With no dedicated resources, it may be difficult to sustain any efforts.

According to the data presented, Dr. Cieslak pointed out that there has been an average of about 18 infant deaths per year from pertussis over the past decade. Given that there are about 4 million births per year, this is less than 1 in 200,000 infants. One could make the argument that they should be considering whether vaccinating pregnant women not likely to cause more

than 1 in 200,000 miscarriages or spontaneous abortions. What concerns him even more is that when this many pregnant women are vaccinated, a certain number of them are going to have miscarriages, stillbirths, preeclampsia, et cetera and they are going to blame the vaccine for it. Consideration needs to be given to the potential impact on vaccine programs from a recommendation like this.

Dr. Baker indicated that there would be presentation regarding timing in pregnancy. Most serious adverse events associated with pregnancy occur early. If women are being vaccinated during the third trimester, there will not be a congenital anomaly. The baby is just growing. She deferred this comment to the next discussion.

Dr. Gall (ACOG) pointed out that everyone in the US has at least one or two early ultrasounds. There is an anatomy scan at 18 to 20 weeks, and there may be an early scan for diagnosis at 8 to 14 weeks. If the vaccine is positioned at 18 to 20 weeks or after ultrasound, it would be known whether the baby had pre-existing issues.

Dr. Baker noted that vaccine and administration costs are much less than ultrasound, not that she is against ultrasound.

Timing of Maternal Tdap Vaccination: During Pregnancy or Postpartum?

Dr. Jennifer L. Liang ACIP Pertussis Vaccine Working Group

Dr. Liang indicated that in the end, the WG decided that given that Tdap coverage among adults is very low and that most pregnant women would be eligible for Tdap, the real issue to discuss would be the timing of when an unvaccinated pregnant woman should be vaccinated (e.g., during pregnancy or postpartum). Over the course of 8 months, the WG weighed the facts and experiences of others to reach a number of conclusions. Dr. Liang explained how each conclusion was reached.

First, the WG concluded that postpartum vaccination is a suboptimal national strategy to prevent infant pertussis morbidity and mortality. Five years after ACIP's recommendation for cocooning, there is no widespread implementation. It is difficult for all close contacts of newborns to be vaccinated. There is poor uptake of Tdap when made available to birthing hospitals, and no demonstration of program sustainability.

Second, the WG concluded that vaccinating pregnant women during the late second or third trimester is acceptably safe for both mother and fetus. As Dr. Rasmussen presented, Td and TT have been used extensively in pregnant women. No evidence indicates administering either vaccine during pregnancy are teratogenic. Data and expert opinion support that Tdap is acceptably safe to both a pregnant woman and the unborn fetus. And finally, the WG recommends Tdap during the third or late second trimester to minimize concerns about adverse fetal effects associated with Tdap vaccine.

Third, the programmatic cost of vaccinating with Tdap during pregnancy or postpartum is the same. There is already a recommendation in place for postpartum Tdap vaccination. The model presented by Dr. Asay shows that by changing the timing of maternal Tdap vaccination from postpartum to during pregnancy, the programmatic costs and the number of Tdap doses would be the same. But, administering Tdap during pregnancy would prevent more infant

cases, hospitalizations, and deaths. Based on the model, for every scenario, the impact of vaccinating during pregnancy is favorable.

Fourth, the WG concluded that there are not sufficient concerns about blunting of an infant's immune response to primary DTaP series to not recommend maternal vaccination during pregnancy. Transplacental antibodies may interfere with infant's active antibody production following primary DTaP. The degree of interference to infant's immune response is not yet known, but is short-lived. The clinical importance is not clear. The benefits of protection outweigh risk of less protection later in infancy. Current on-going studies will not answer clinical significance.

Fifth, the WG concluded that late second or third trimester maternal vaccination may prevent infant pertussis during the same pregnancy. Vaccinating a pregnant woman with Tdap will provide protection against pertussis to the mother herself. For the infant, transplacental transfer of maternal antibodies may provide protection against pertussis in early life. Again, the effectiveness of preventing infant pertussis is not yet known.

Dr. Liang reminded everyone that in his opening remarks, Dr. Sawyer conveyed the WG conclusions on the timing of Tdap vaccination. After 8 months of discussion, the WG does not believe that postpartum Tdap as part of the cocooning program should be the preferred national strategy to prevent pertussis in neonates. The majority of WG members supported language which put Tdap during pregnancy or Tdap postpartum on equal footing. A minority of WG members supported language which gave preference to Tdap during pregnancy. Both of these options were presented to ACIP for consideration and vote as follows:

General Recommendation Proposed Language for Maternal Tdap Vaccination:

Option 1

Women's healthcare providers should implement a maternal Tdap vaccination program for women who have not previously received Tdap. Healthcare providers should either administer Tdap during the third or late second trimester* or immediately postpartum.

*After 20 weeks gestation

Option 2

Women's healthcare providers should implement a maternal Tdap vaccination program for women who have not previously received Tdap. Healthcare providers should administer Tdap preferably during the third or late second trimester*. Alternatively, they would administer Tdap immediately postpartum.

*After 20 weeks gestation

Discussion Points

Regarding the small number of deaths, Dr. Baker pointed out that the babies do not just die within 24 to 48 hours after hospitalization. They have one to three weeks of extracorporeal membrane oxygenation (ECMO). To be placed on ECMO in her hospital, on day one it's nearly a half a million dollars. She does not think that they should be measuring costs of a baby's death, but it is not just a quick death. A tremendous amount of medical resources are required for those infants.

Dr. Clark (SME) agreed, and pointed out that there are numerous reasons pertussis is missed as a diagnosis. Especially in infants, pertussis is under-recognized and under-reported. The absence of cough is a major reason, but the lack of apnea as a presentation in the case definition misses cases and deaths that occur before two weeks of cough. Several cases in California were confirmed as pertussis, but they were not reported because of the case definition.

Dr. Judson pointed out that pregnancy is a state of mild immunosuppression. He wondered if anything practical was done in terms of outcome, efficacy, antibody titers, et cetera.

Dr. Liang responded that at this time, there are no data.

Dr. Baker emphasized that when clinical trials are not permitted in pregnant women it is very difficult to answer this question. Dr. Halpern's study will assess pre- and post-immunization during pregnancy. His window begins at 26 weeks. There will be maternal and infant sera information. The NIH trial will also have this information. There will not be a large number of subjects. The immune suppression that Dr. Baker has observed relates to tolerance to the fetus rather than immune suppression to vaccine response.

Dr. Judson stressed that not only is acellular pertussis being administered, but also diphtheria and tetanus are being administered. The schedules for immunization should not be identical based on duration of protection and antibody. He wondered whether there was any concern about this. When he began working in medicine, tetanus and diphtheria were administered anytime anyone was cut and / or presented in an emergency department for anything. Ten years after that, papers were being published on the dangers of over-immunization with tetanus, and that optimal spacing was 10 years in most cases. Now there seemed to be a concept that there is no danger in over-immunizing. He wondered whether this had been shown adequately.

Dr. Baker replied that there are data on Td from Dr. Halpern in children that show that a 2-year interval is no problem, and shorter than a 2-year interval was based on risk / benefit balancing. She has occasionally inadvertently immunized adults with Tdap in as short as 6 weeks with no problems.

Dr. Clark (SME) added that this did not involve very much additional antigen. Effectively, transmission of toxigenic *Corynebacterium diphtheriae* has been eliminated, so there is really very little exposure anymore. There is minimum occurrence of tetanus disease, and the current schedule and strategy are responsible for that. Thus, he did not believe they were talking about dramatic changes that would cause concern one way or the other.

Dr. Gall (ACOG) indicated that in his study that was recently published, Tdap was used so there were data on response to tetanus and diphtheria antigens. They responded nicely, so there was no blunting between the pertussis antigen and the tetanus and diphtheria. The responses were not astronomical, but they were very reasonable.

Dr. Marcy thought the toxicity studies were from a famous destroyer study, where those in the Navy were receiving tetanus shots annually. Administering an annual vaccine has gone out of practice. He wondered what the interval should be for women who have not previously received Tdap. It is known that pertussis antibody levels, whatever that means, fall off after about 5 years. If antibodies are given cross-placentally to the fetus, they are already being diluted to

some extent, so he thought it was important to include the interval. Women who have not received Tdap within a certain period of time should receive it again.

Dr. Baker responded that the problem is that they don't have this information, although they will be hearing about it in future meetings.

Dr. Marcy said that if they were going to base everything they were going to vote on upon information, they would not be voting.

Dr. Baker said that what is different for those who are not young babies is that pertussis immunization provides cell-mediated as well as humoral immunity. However, babies do not have cell-mediated immunity. They have only maternal antibody or their own antibody that they make after their primary series.

Dr. Liang clarified that the phrase of "not previously received Tdap" is also to address the fact that Tdap is currently licensed and recommended for only one time use. The recommendation is geared toward women who have never received Tdap.

Dr. Coyne-Beasley pointed out that the statement was made during the presentations that the programmatic costs of Tdap vaccine during pregnancy or postpartum are equal; however, if administered during pregnancy the vaccine prevents more infant cases, hospitalizations, and deaths. The presentation also indicated that in every scenario, vaccination during pregnancy is favorable. She was trying to understand the context of that comment within a recommendation that did not favor immunization during pregnancy versus postpartum.

Dr. Baker responded that a significant minority of the WG thought that should be favored, but a significant majority believed otherwise.

Dr. Sawyer reported that the feeling of those on the WG who held the majority opinion was that there is a lack of data on blunting, and that some data specifically addressing that issue will be forthcoming in the next one to two years. Therefore, they believed that it was premature to make a recommendation strongly in favor of immunization during pregnancy.

Given that it could affect the VFC vote, Ms. Rosenbaum requested clarification regarding whether they were saying that vaccinating the mother is important not only because protects the baby from her transmitting illness, but also because it stimulates the creation of antibodies within the infant. That is, when the baby is born it would have antibodies in its system that it would not have otherwise.

Dr. Baker clarified that an adolescent or adult pregnant woman will benefit because she will make antibodies to protect her against pertussis herself. The side benefit is to hopefully transfer protective antibodies to the baby. The influenza model is a good example. This is a very bad disease in a pregnant woman, so she is immunized. The benefit for the baby is substantial in terms of febrile respiratory disease.

Dr. Duchin was impressed by the presentation making a strong argument for vaccination during the latter stages of pregnancy, and the WG not favoring that opinion versus weighing them equally. He requested further information about the data that would be forthcoming that might make it less desirable to recommend vaccination during pregnancy at this time. It was not clear to him exactly how to weigh that in consideration of the two options proposed.

Regarding the working group discussions about Option 1 versus Option 2, Dr. Liang clarified that Option 1 gives equal weight to Tdap immunization during pregnancy or postpartum. Those who supported this language did not feel that there was sufficient evidence to justify preference of one versus the other. Cocooning has yet to be proven effective, and it is known that infants are born with maternal antibodies. However, the effectiveness of those antibodies has also not yet been proven. Due to those concerns and the concerns about blunting, many of the WG members felt that there was insufficient data to justify the preference of during pregnancy versus postpartum immunization.

Dr. Duchin inquired as to whether any studies were underway that would offer additional data about the effectiveness of maternal antibody transfer to the infant.

Dr. Liang replied that she did not know of any studies underway to address this issue. It would likely take a large number of pregnant women to be vaccinated and infants to be followed up in order to understand the significance of maternal antibody transfer. This information may never be available.

Dr. Baker reminded everyone that Tdap is a booster vaccination. It was licensed and subsequently recommended by ACIP on the basis of serologic bridging, not on the basis of an efficacy trial. Although there is no protective correlate, it was licensed because the antibody concentrations in Tdap-immunized adolescents and adults were similar to the efficacy studies performed in young infants. Thus, there is some information.

Dr. Sawyer added that the information the WG is looking forward to is specific data from two small studies that will illuminate the exact degree of blunting. The preliminary data the working group heard the previous week was encouraging that although there may be some blunting, it is a relatively mild effect. Those are the only additional data that will be forthcoming.

Dr. Baker clarified that the preliminary data pertained only to first versus third dose, so the additional data will address a lot more points to understand the degree of blunting after the first and second doses. It is known that the first dose primes, but does not protect.

Dr. Duchin noted that the modeling addressed that to some degree by still favoring prevention of disease in the first month or two regardless of what occurs with blunting.

Dr. Keitel pointed out that efficacy of acellular pertussis vaccine in adults for prevention of pertussis has been demonstrated. Joel Ward was the senior author.

Dr. Temte stressed that potential adverse birth outcomes is an important issue. There are very limited data to evaluate that effect. He wondered whether the WG discussed prospective planning to monitor for potential adverse fetal outcomes.

Dr. Liang replied that the WG did not have specific discussions on follow-up, but she would assume CDC would do so.

Dr. Baker added that there are two pregnancy registries that have been active all along. Most people in the registries were immunized during the first trimester.

Dr. Jenkins pointed out that a natural number of spontaneous abortions would occur, and that it would be important to assess the outcomes to determine the context.

Dr. Hahn (CSTE) noted that prenatal vaccination falls to the obstetric provider for the most part, while postpartum falls into the hospital setting. This means two different groups need to be aware of this, and balancing them equally is a reminder that this is a shared responsibility. Hospitals need to be put on notice that they need to check whether women received Tdap during pregnancy.

Dr. Chilton did not believe that in general those who care for pregnant women have done very well at immunizing pregnant women, and that if there was an additional reason for them to do so, it might also strengthen the recommendation to administer influenza vaccination during pregnancy as well.

Dr. Baker noted that obstetrical care providers did a really great job last season with influenza vaccinations compared to previous seasons.

Dr. Moore (AIM) pointed out that from a program management perspective, she would not agree that this is a programmatically equivalent process. Programs consider lines of defense to protect the neonate. The first line of defense is pre-conception immunization, the second is the three months during the third trimester when they are in the clinic a lot, and the last line of defense is postpartum immunization. The last line of defense provides the least amount of protection for the infant, as shown in the presentations, so they do not consider these lines of defense to be equivalent. There's a major difference in having 3 months versus 3 days to vaccinate a woman. Programmatically, a better job can be done with a preference on vaccinating unvaccinated women during the third trimester. If two groups are responsible, each will assume the other handled it. It is necessary for people to take ownership at each point in the process up to the time the baby is delivered.

Dr. Gall (ACOG) felt that if Option 1 was selected, nothing would be done. This is basically the same inertia that will keep people doing what they are already doing. There will be no driving force. Option 2 says that it is preferable to vaccinate during pregnancy, but cocooning is also an option for those who do not wish to vaccinate. He thought cocooning should be removed as it is not working, and it was unclear to him why they kept "beating a dead horse."

Dr. Campos-Outcalt (AAFP) noted that while they were all reassured about the safety of the vaccine, many of their patients will not be. Even though it is given in the second or third trimester, which is unlikely to lead to any adverse events, the number of potential claims from people who think the vaccine has harmed their baby during that time is unknown and could be significant. He thought because the vaccine is given to children, these claims would be submitted to the Vaccine Compensation Program, which should help with that problem.

Dr. Duchin wondered what was known about the acceptability of the strategy of vaccinating mothers during pregnancy, and how likely it is that this recommendation would be adopted.

Dr. Baker replied that it is not the mothers who won't accept vaccination, it is the doctors. If recommended by an obstetrician, acceptance rates are over 90%. Her program has nursing providing education, and there are postpartum orders from the doctors. Her population is a highly vaccine accepting women of Hispanic ethnicity. She believes a medical platform will be easier from a programmatic point of view.

Regarding insurance coverage of obstetrical care and deliveries, Dr. Doskey (AHIP) noted that a number of individual policies are still sold in the US that do not include obstetrical coverage. Everything associated with those admissions are denied, including vaccination.

Dr. Baker replied that fortunately, that represents a relatively small number of people in the population base. However, undocumented immigrants receive paid hospital care immediately upon delivery and their Medicaid eligibility is taken care of for the mother and baby. This is a reverse situation where the poor and disadvantaged have an advantage.

Dr. Doskey (AHIP) stressed that the portion of the population with individual policies is expected to grow as the exchanges come into play over time.

Ms. Rosenbaum added that coverage for maternity care is a mandatory essential benefit, and hopefully all women in the individual market eventually will be covered.

Dr. Baker pointed out that issues that will occur years from now were not ACIP's concern during this meeting.

Dr. Brewer (ANA) indicated that ANA has an affiliate relationship with the American College of Nurse Midwives, and they speak in favor of Option 2.

Dr. Temte asked ACOG and AAFP representatives to comment on whether their organizations would endorse a recommendation for immunization of pregnant women if ACIP were to vote for this.

Dr. Gall (ACOG) felt that ACOG would endorse such a recommendation. He tried to get ACOG to include pregnancy in 2009 in their recommendations; however, ACOG insisted on following ACIP's decision at that time.

Dr. Campos-Outcalt (AAFP) responded that AAFP places a high value on harmonization of vaccine records, and would probably endorse such a recommendation.

Dr. Baker indicated that in 2008, AAP recommended vaccination of pregnant women before the document was published.

Phil Hosbach (sanofi pasteur) suggested being careful about the wording in the recommendation so as not to denigrate the cocooning strategy. While it is a difficult strategy, many moms have been successful in getting their husbands immunized. It is better to cocoon, so they do not want women to give up on getting those around her immunized. Wanting to protect the baby will motivate more people to get immunized.

Dr. Baker responded that the WG is committed to cocooning. She reminded everyone that at least 10% to 11% of babies are born pre-term in this country, and it is unknown what level of maternal antibody would be protective in those babies. She thought cocooning was very much should be a continued recommendation regardless of the option selected.

Dr. Sawyer confirmed that this was correct.

Motion: General Recommendation for Maternal Tdap Vaccination

Ms. Ehresmann made a motion to accept Option 2. Dr. Coyne-Beasley seconded the motion. The motion carried with 14 affirmative votes, 1 negative vote, and 0 abstentions.

Dr. Liang indicated that to address ACIP's concerns about cocooning, the proposed recommendation for cocooning does not differ from what has previously been accepted by ACIP, and mirror the language that ACIP accepted with regard to the use of Tdap. The proposed language is more of a harmonization to combine the adolescent and adult recommendations. The proposed language for cocooning and for special situations read as follows:

Cocooning

Adolescents and adults who have or anticipate having close contact with an infant aged less than 12 months (e.g., parents, siblings, grandparents, child-care providers and healthcare providers) should receive a single dose of Tdap to protect against pertussis if they have not previously received Tdap. Ideally, these adolescents and adults should receive Tdap at least 2 weeks before beginning close contact with the infant.

Special Situation Proposed Language: Pregnant Women Due for Tetanus Booster

If a tetanus and diphtheria booster vaccination is indicated during pregnancy for a woman who has previously not received Tdap (i.e., wound management, more than 10 years since previous Td), then healthcare providers should administer Tdap preferably during the third or late second trimester*.

*After 20 weeks gestation

Special Situation Proposed Language: Unknown or Incomplete Tetanus Vaccination

- To ensure protection against maternal and neonatal tetanus, pregnant women who never have been vaccinated against tetanus should receive three vaccinations containing tetanus and reduced diphtheria toxoids during pregnancy.

- The recommended schedule is 0, 4 weeks, and 6-12 months. Tdap should replace 1 dose of Td, preferably during the third or late second trimester* of pregnancy.

*After 20 weeks gestation

Discussion Points

Dr. Chilton pointed out that pediatricians do see pregnant women when they present at 13, 14, 15, et cetera. He wondered whether a woman who has a wound in the first trimester should receive a tetanus-containing vaccine at that time. He was not sure this was clear.

Dr. Liang replied that the working group presented the specific language to vaccinate during the third or late second trimester to remove some of the concern about safety. Based on the safety data available, there has not been any indication of negative infant outcomes for women vaccinated in the first trimester.

Dr. Gall (ACOG) indicated that he would give Tdap to a woman who was injured in the first trimester. The study for which data are becoming available includes women who were given Tdap at various times during pregnancy. There will be data on the antibody levels at the time of delivery for the mothers and babies, so they will know whether there is any difference in their responses.

Dr. Baker emphasized that anything done during the first trimester is dangerous in terms of coincidental adverse events, and it is very difficult to assign cause. Her greater concern in terms of pertussis is that there is enough antibody to protect the baby. The half-life for pertussis and tetanus-specific antibodies is slightly longer than 30 days. The first reason for administration during the third or late second trimester is to avoid safety concerns pertaining to spontaneous abortion, congenital anomalies, et cetera. The second reason is that there are not enough data on the amount of antibody going to the baby. Since hospitals typically do not have Tdap, she suggested modifying the language to say that "If a woman is not in the late second or third trimester and sustains a tetanus-prone wound, she should receive TD and Tdap should be given after that."

Dr. Englund pointed out that whatever they do will drive policy, and it would be inappropriate to require a pregnancy test before administering Tdap. Tdap is given widely in the healthcare system for exposures.

Dr. Baker agreed, pointing out that if there is a tetanus-prone wound handled by a pediatrician, they will do whatever they will do. However, it is handled by an emergency department, Tdap often is not stockpiled there other than perhaps in children's hospitals.

It was Dr. Keitel's understanding was that the cocooning language was focused on addressing immunization of potential older contacts, predominantly after the baby is born. She wondered if they could build into the statement that a strategy should be implemented as soon as it is known that a woman is pregnant. That would give more time to ensure that other family members are immunized and protected before the baby is born. That reinforces the concept that a pregnant woman should be given Tdap.

Dr. Baker said she thought the WG wanted to emphasize that it should be at least two weeks before the beginning of close contact.

Dr. Marcy reminded everyone that the closest correlative study pertained to pertussis toxin titers, which fall off quickly. He thought they were kidding themselves to think that a woman who received Tdap in 2006 would still be giving protection to the infant. However, there is no recommendation for a booster.

Dr. Baker reminded them that hopefully they would have an answer to that question in October. She clarified that they were not voting on a new dose because they did not have the data on duration of protection. They were voting on people who have not received Tdap.

Dr. Duchin wondered whether they should include language advising healthcare providers on what to do when the pregnant woman has an unknown vaccine status. The option on which they voted was to vaccinate women who had not previously received Tdap, and he thought it would help to include a sentence about how to handle women of unknown vaccine status.

Dr. Baker responded that it could be similar to what is done for infants of unknown vaccine status, which is to immunize them if unsure.

Dr. Liang clarified that the general recommendation stated that any adult with an unknown Tdap status should receive Tdap.

Dr. Duchin thought this should be included in the pertussis part of the discussion, not just the diphtheria and tetanus discussion.

Dr. Keitel wondered what the implication of the cocooning strategy recommendation would be for the VFC.

Dr. Rodewald replied that VFC coverage stops with the 19th birthday, and it covers only the direct vaccinee. Passive vaccination is not part of the VFC program. It specifically excludes passive immunization for RSV immunoprophylaxis because it is not a vaccine—it is a passive immunization.

Regarding the question of claims, Geoffrey Evans (HRSA) reported that to date there have been very few claims that alleged injury in a fetus. The best answer so far is that the law is mixed. It is not yet known whether a claim can go through successfully on that allegation. It has gotten to the point where the medical merits have received a decision in terms of whether the vaccine recipient can be viewed in terms of the fetus versus the individual who receives the vaccine. Currently, the answer is not clear.

Dr. Pickering inquired as to whether this program covers all ages through adults.

Geoffrey Evans (HRSA) responded that it does as long as the vaccine is recommended for routine use in children. Any recipient, no matter what age, can file a claim or have a claim filed on their behalf.

Dr. Judson said that for healthy pregnancies, the only time women are seen for sure in the third trimester will be just before delivery.

Dr. Baker said that this was no longer common.

Dr. Gall (ACOG) clarified that the third trimester begins at 28 weeks, so 28 to 40 weeks constitutes the third trimester, 13 to 28 the second trimester, and 1 to 13 weeks the first trimester. Women are seen every 4 weeks until about 28 weeks, at which time they are seen in 3 weeks, followed by every 2 weeks, and in the last month every week, so there are 8 to 13 visits.

Dr. Judson requested clarification about whether the vaccine would be given right around delivery, even though that would be considered the third trimester.

Dr. Baker said she thought there were very good data on the percent of number of obstetrical visits in the US. Women certainly present in the third trimester. Even in her extremely disadvantaged population, no women have presented at delivery having had no prenatal care. They have immunized 18,000 people. At least two weeks would be required for sufficient maternal antibody levels to be available for transport to the fetus.

Dr. Judson wondered whether they would immunize at the delivery visit if a woman slipped through.

Dr. Baker responded that this would be postpartum.

Dr. Cieslak emphasized that wound management is typically a “do it now” situation, but the language indicates a preference for the late second or third trimester. He thought this could cause someone to wait another three months before giving a booster.

Dr. Baker noted that this language could be improved for clarity.

Dr. Clark (SME) said that wound management was a separate issue and the recommendation would be to administer Tdap.

Motion: Cocooning and Special Situation Language

Ms. Ehresmann made a motion to accept the Cocooning and Special Situation Language that aligns with Option 2. Dr. Temte seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions.

VFC Resolution Update:
Vaccines to Prevent Diphtheria, Tetanus, and Pertussis

Lance E. Rodewald, MD
Director, Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevent

Dr. Rodewald reminded everyone that and ACIP vote is required if there are changes to the ages, groups, or doses of a vaccine. The purpose of this resolution was to revise the previous resolution to incorporate new recommendations regarding the vaccination of pregnant adolescents. Eligible groups continue to be children and adolescents aged 6 weeks through 18 years. There were no changes in the recommended schedule or intervals. Only Table Note #7 was changed to mirror the vote for Option 2:

(7) Option #2 Adolescents who are pregnant and have not previously received Tdap should receive Tdap preferably during the third or late second trimester (after 20 weeks gestation). Alternatively, Tdap can be administered immediately postpartum.

Discussion Points

It seemed to Ms. Rosenbaum that there was a plausible argument in terms of immunization of a pregnant woman, whether it is this vaccine or influenza, regardless of her age if it is the immunization of a Medicaid-eligible child. It is Medicaid-eligible children who are covered under the VFC program. Under the Medicaid statute, an infant who is born to a woman who is enrolled in Medicaid is automatically enrolled in Medicaid. There is no separate application process because the only feasible way to immunize the infant effectively is to do so in utero. This is a rare instance in which it would be within the confines of the statute to define an infant prior to birth as a Medicaid-eligible child. Children up to age 21 are entitled to all age-appropriate immunizations. Pregnant women would be entitled to all appropriate immunizations regardless because they are entitled to pregnancy-related care. The significance of the VFC issue in this context is the provisions of free vaccine to obstetrical practices, which would immeasurably increase the likelihood of an immunization being provided, as well as reaching certain un-insured or under-insured children. Ms. Rosenbaum proposed that CDC enter into a formal discussion with CMS about the feasibility in the case of infectious diseases, for infants who are born enrolled in the program, to be treated as Medicaid-eligible children for purposes of VFC. She thought this would have an extraordinary effect of being able to do much more to actively engage obstetrical practices in what ACIP recommends as the standard of practice.

Dr. Pickering thought that with this suggestion, they should engage in a discussion with the university attorney regarding this issue.

Dr. Rodewald agreed that it would be beneficial to have a discussion with CMS, and that in this case there is passive rather than active immunization of the child.

Ms. Rosenbaum added that from a clinical point of view, the issue of active versus passive has a meaning. From a legal point of view, it may have very limited meaning. That is, the most efficient way to immunize the child is to do so in utero, and that makes the child a Medicaid-eligible child.

Dr. Wharton acknowledged that this discussion would be initiated internally.

Motion: VFC Resolution

Dr. Chilton made a motion to accept the VFC Resolution. Dr. Coyne-Beasley seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions.

Emergence of Pertussis in Children Aged 7 through 10 Years and Early Evaluation of DTaP Effectiveness

**Lara Misegades, PhD, MS, EIS Officer
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention**

Dr. Misegades discussed the emergence of pertussis in 7- to 10-year olds and presented interim results from two evaluations of DTaP effectiveness. Based on data from 1922 to 2010, since the introduction of whole cell pertussis vaccine in the late 1940s, the number of reported pertussis cases has fallen dramatically. However, pertussis continues to be endemic. The last large increase in reported cases occurred in 2004 and 2005. The data for 2010 is not yet finalized, but the number of cases are expected to surpass the number of cases in 2005 [CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System and 1922-1949, passive reports to the Public Health Service].

Based on data regarding reported pertussis incidence by age group from 1990 through 2010, infants still have substantially higher rates of disease compared to other age groups. However, disease rates among 7- to 10-year olds have been increasing since 2005 [CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System *2010 data are provisional]. Beginning in 2005, an increase was observed among 7-year olds. This group is the first birth cohort who have largely received acellular vaccine for all 5 pertussis doses. With each successive year, a stare step picture of disease has essentially emerged among this birth cohort, although the case count scale differs by year. In 2009, the case count dropped at age 11, which is consistent with the recommendation for Tdap. This trend also holds for the later birth cohorts. Given these data, it was important to more closely asses DTaP effectiveness and duration of protection.

Previous clinical trial estimates of DTaP efficacy vary widely depending upon the case definition, the vaccine type, the schedule, and the trial design. Estimates from trials using the WHO case definition vary from 59% to 93%, and one previous study assessing the US 5-dose schedule estimated short-term effectiveness at greater than 95% for 4 to 5 doses up to 59 months of age, or just shy of 5 years of age. CDC is currently conducting two evaluations of DTaP effectiveness and duration of protection. The first is a case-control estimate using provider verified immunization and conducted in collaboration with the California Department of Public Health (CDPH). The second is a multi-state registry-based assessment. Dr. Misegades briefly described the methods and interim results from these two assessments. California reported an increase in the number of pertussis cases as early as February 2010. The state declared an epidemic on June 18, 2010 and by the end of 2010, more than 8000 cases had been reported. As of September 2010, there was a high burden of disease in California in the 7- to 10-year old age group despite high vaccine coverage. This is reflective of the national data and provided an opportunity to evaluate the pertussis vaccine program [California Department of Public Health, Immunization Branch].

The primary objectives of the CDPH / CDC Pertussis VE Assessment were to estimate the overall effectiveness of DTaP following the complete childhood series, and determine the duration of protection by assessing vaccine effectiveness at specific time points post-vaccination. Counties with either a high incidence or high case counts were invited to participate. Health Officers from the following 15 counties agreed to participate in the assessment: Alameda, Del Norte, El Dorado, Fresno, Madera, Marin, Merced, Orange, Riverside, San Diego, San Luis Obispo, Santa Cruz, Santa Clara, Sonoma, and Stanislaus.

The study included cases and controls who were 4- to 10-years of age at illness onset or enrollment from the 15 participating counties. Three unmatched controls per case were selected from the same providers reporting the cases. All vaccine history information for both cases and controls was collected through in-person visits to provider offices. Logistic regression was used to calculate vaccine effectiveness, accounting for clustering by county and provider.

All confirmed, probable, and suspect cases were included in the analysis aged 4 to 10 years, based on the CDPH case definition. This is a modified CDPH definition, which includes a suspect case category for PCR-confirmed cases with a cough of any duration and Epi-Link cases with a cough of any duration plus one other symptom. Last December, data collection teams had completed approximately 3800 abstraction forms and data on an additional 500 people have recently been received. Information on both cases and controls is being linked to pertussis surveillance and immunization registry and manufacturer lot data in order to exclude children who were pertussis cases in previous years, and also to help verify and assess the completeness of the vaccine date and brand information. Dr. Misegades presented interim results from this study that did not yet include the recently received data.

The range of recommended ages for the fifth DTaP dose is 4 to 6 years. To get a sense of when cases and controls were receiving the fifth dose, the distribution of age at fifth dose was assessed. In this assessment, both cases and controls in California received the fifth dose earlier in the range, with 65% of cases and 68% of controls receiving it at 4 years of age. With regard to interim vaccine effectiveness results, the vaccine effectiveness estimate for 5 doses compared to no doses across all ages was 85.9% with a 95% confidence interval of 75.6% to 91.9%. The recommended childhood vaccination schedule for pertussis allows for a fourth dose only schedule if the fourth dose is received after the fourth birthday. The preliminary vaccine effectiveness estimate for the fourth dose received after age 4 compared to zero doses across all ages is 80.4%. Regarding the time since fifth dose analysis estimate using unvaccinated as the reference category, the estimated vaccine effectiveness is 94.5% among children who are less than one year out from their fifth DTaP dose. There is a modest decrease in effectiveness for each year after this. For example, two years after the fifth dose, vaccine effectiveness is estimated to be 90.8% and by the time children are 5 or more years out from their last DTaP dose, the estimated vaccine effectiveness is 69.1%.

The next steps for the California assessment are to link the data with both registry and manufacturer data, and assess the completeness of the vaccine data and brand information. Additional analyses will also be done to assess the potential impact of case definition, vaccine product, and incomplete vaccination records on the vaccine effectiveness estimates.

CDC is also assessing waning of immunity in the 5 years post-DTaP dose through a registry-based evaluation of incidence rates and risk of pertussis. EIS Officer, Sara Tartof, is leading this evaluation. Although this is a multi-state assessment, the results presented during this session were based on data from Minnesota. DTaP information from Minnesota's immunization registry was linked to pertussis surveillance information for the 1998-2003 Minnesota birth cohorts. Only children who received all 5 DTaP doses, with their fifth dose between the ages of 4 and 6 years of age, were included in the analysis. The total linked cohort size is approximately 200,000 with 353 confirmed and probable pertussis cases. Cumulative incidence and rate ratios were calculated for each year following the fifth DTaP dose up to five years out. Individuals aged out of the analysis at age 10, and rate ratios were calculated using the one year post-vaccination group as the reference. Adjustments were made for repeated measures correlation structures. Both incidence proportion and risk increased with increasing time since

the fifth DTaP dose. At 5 years out, the risk of disease is about 4 times higher than the risk in the year immediately following the fifth dose.

To summarize, preliminary California results suggest that short-term vaccine effectiveness estimates are consistent with pre-licensure estimates, and there continues to be additional evidence that the vaccine protects well against a range of clinical presentations captured by the pertussis case definition. It was not possible to estimate vaccine effectiveness through the Minnesota assessment due to the lack of a clearly defined unvaccinated group in the immunization registry, but the increased risk with increasing time since fifth dose support the California findings. These results suggest that waning of immunity is occurring prior to the adolescent Tdap booster. Moving forward with these analyses, consideration will be given to whether this is the primary factor driving the current disease burden and trends among 7- to 10-year olds and whether any interventions or policy changes might be needed.

Discussion Points

Dr. Judson noted that the epidemiology of pertussis has always been problematic. When assessing a relatively small group in a specific age group, often the answer pertains to diagnostic bias. Over the decades, Colorado has almost always had one of the highest rates of pertussis. There are many pertussis pediatric infectious disease experts, a large children's hospital in central Denver, and a state laboratory with high capacity for pertussis tests in Colorado. Therefore, whenever few patients are reported in the newspaper or through *MMWR*, index suspicious increases and anyone with a cough in the suspect group will receive a diagnostic test and many people are pulled in who are not really clinically pertussis.

Dr. Misegades responded that the various case definitions will be assessed to determine how those may impact estimates. A preliminary assessment restricted to confirmed only, all children who meet the clinical case definition, does not appreciably change the vaccine effectiveness estimate.

Dr. Baker requested clarification regarding whether the investigators were using "cough for two weeks" for the definition in this age group.

Dr. Misegades confirmed that they are using "cough for two weeks."

Dr. Plotkin (Vaccine Consultant) mentioned that based on the Swedish data from the acellular pertussis trial conducted in the 1990s, it appears that efficacy is waning following acellular pertussis. Interestingly, the data suggest that immunity is holding up better in the whole cell group. That is something for ACIP to think about in the future.

Dr. Baker concluded that ACIP is every interested in the duration of protection of DTaP and Tdap.

Vaccine Supply Update

Dr. Lance Rodewald
Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Rodewald reported Merck is not currently distributing its adult hepatitis B vaccine. The dialysis formulation is available, and the adult formulation is anticipated to be available in the third or fourth quarter of 2011. Production and supply of GSK's adult hepatitis B vaccine and hepatitis A/hepatitis B combination vaccine currently are sufficient to meet demand for routine adult usage of adult Hepatitis B vaccine. Merck anticipates availability of its adult hepatitis A vaccine some time in 2012. Production and supply of GSK's adult hepatitis A vaccine and hepatitis A/hepatitis B combination vaccine currently are sufficient to meet demand for routine adult use of adult Hepatitis A vaccine.

DTaP-IPV (Kinrix®) is currently unavailable in both syringe and vial presentations. Re-supply is expected in July 2011. MMRV (ProQuad®) will not be available for the remainder of 2011. Merck is committed to returning ProQuad to the market. Details regarding timing and availability will be provided at a later date. Merck has adequate supplies of M-M-R II® and VARIVAX® to meet current demand. Since December, Merck has released zoster vaccine doses in all months except February. Customer wait times for orders are approximately 2 to 3 months. Merck expects to continue to release doses of ZOSTAVAX® regularly for the balance of 2011, but as inventory is building and demand remains strong, backorders may persist.

With regard to supply constraints Cervarix vials will be discontinued as of September 2011. Pre-filled syringes will continue to be available.

CDC's vaccine supply / shortage webpage is available at: <http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm>.

Human Papillomavirus Vaccines

Introduction

Dr. Janet Englund
Chair, ACIP HPV Working Group

Dr. Englund reminded everyone that in October 2009, FDA licensed the quadrivalent HPV vaccine for males 9 through 26 years of age for prevention of genital warts. ACIP stated that HPV vaccine may be given to males 9 through 26 years of age for prevention of genital warts, but did not include the vaccine in the routine immunization schedule for males. ACIP voted to include HPV vaccine for eligible males in the Vaccine For Children program. In December 2010, the FDA included the indication for prevention of anal cancer in females and males. Subsequent to this, the HPV Working Group (WG) has discussed what additional recommendations may need to be made for HPV vaccine.

Dr. Englund reviewed the presentations to be given during this session related to HPV vaccine for males and investigations of the long-term effectiveness of the quadrivalent HPV vaccine. While this session was designed to prepare ACIP for an upcoming vote, there were no votes on this topic during the June 2011 ACIP meeting.

Background

Lauri Markowitz, MD

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

Dr. Markowitz reminded the committee that there are two HPV vaccines licensed for use in the US. The quadrivalent vaccine was licensed in June 2006 for females and ACIP recommended routine use in females 11 or 12 years of age and catch-up through 26 years of age. In 2009, the bivalent vaccine was licensed for use in females and ACIP revised recommendations to state that either vaccine would be used for routine vaccination of females. In 2009, the quadrivalent vaccine was licensed for use in males based on data showing efficacy against genital warts and ACIP provided guidance that the vaccine may be used in the licensed age range. Both vaccines are included in VFC for females and the quadrivalent vaccine for males. As mentioned earlier, as of December 2010, quadrivalent vaccine has an indication for prevention of anal cancers.

Since February 2010, ACIP has continued to review data related to HPV vaccine for males. In October 2010, ACIP reviewed quadrivalent vaccine safety and heard data presented from the VSD rapid cycle analysis for females, and reviewed vaccine efficacy data in males, HPV vaccination program and coverage in females, provider acceptability, and cost-effectiveness. In February 2011, ACIP reviewed the epidemiology of HPV-associated cancers in the US, and heard a presentation on anal infection and anal cancer. Additional cost-effectiveness analyses were also presented.

As reported during the February 2011 meeting, there are about 7000 HPV 16/18 associated cancers in males diagnosed annually in the U.S, including about 1400 HPV 16/18 associated anal cancers. During the last ACIP meeting, information was reviewed about the epidemiology and natural history of anal infection and cancers. Of note, among the cancers in males, the majority of HPV-associated cancers are cancers of the oropharynx. Because of this and because of requests from members of the committee, Dr. Markowitz indicated that oropharynx cancers were to be discussed during this session. There is no FDA licensed indication for prevention of oropharynx cancers for the quadrivalent HPV vaccine. ACIP needs to consider how they will handle outcomes for which there is no indication. This will be discussed again in future GRADE presentations.

With regard to vaccine efficacy in males, there are data for prevention of HPV vaccine-type related genital warts and AIN2/3. The genital wart efficacy data comes from a study in heterosexual males and men who have sex with men (MSM). A smaller study in MSM provided data on efficacy against anal pre-cancer lesions. In females, several larger efficacy studies were conducted, including two Phase 3 trials called Future I and Future II as well as a Phase 2 study. These have been combined in several analyses to assess efficacy for major endpoints. These studies have found high efficacy for prevention of cervical pre-cancers, vulvar and vaginal pre-cancers, and genital warts in females.

Based on data from these studies, quadrivalent HPV vaccine has an indication for prevention of the following diseases caused by HPV types 6, 11, 16, and 18: cervical cancer, vulvar cancer, vaginal cancer, anal cancer in males and females, genital warts in males and females, cervical adenocarcinoma in situ (AIS), cervical intraepithelial neoplasia (CIN) grades 1 – 3, vulvar intraepithelial neoplasia (VIN) grades 2 and 3, and vaginal intraepithelial neoplasia (VaIN) grades 2 and 3. There are no data on efficacy against oropharyngeal cancer, penile cancer, or RRP, nor are any studies in progress. From the quadrivalent vaccine studies in females, there has been no evidence of waning protection, although some vaccinees have lost detectable antibody.

Follow-up data available are through 5 years from the Phase 2 study. Dr. Markowitz indicated that during this session, some data would be shared from the post licensure studies being conducted by the manufacturer. There are multiple monitoring efforts on-going in the US, including those to assess cervical and other cancers through cancer registries, HPV typing has been initiated in several sites, CIN monitoring with HPV typing of lesions in sentinel projects, genital warts through network of STD clinics, and type-specific HPV prevalence in NHANES and looking at types in routine Pap specimens.

As has been presented in the past to ACIP, coverage is increasing in females, but is still low. In 2009, 44% of females age 13-17 years had initiated vaccine nationally; 27% had received all three doses. This summer, National Immunization Survey (NIS)-Teen data will be available from 2010 and will include coverage in males and females as well as data on bivalent vaccine uptake. Although there are no NIS-Teen data on uptake in males yet, there are data from other sources. The Immunization Information Sentinel Sites are funded to enhance and analyze data routinely collected in the sentinel areas. In males ages 13 to 17 years, vaccination increased throughout 2010 (year after quadrivalent vaccine licensed for use in males) , but coverage was just over 4% in the highest site [Courtesy of K Cullen, CDC]. Dr. Markowitz also showed data from the 8 managed care organizations (MCOs) that participate in the Vaccine Safety Datalink; since the beginning of 2010 through May 2011 the number of doses administered increased from 0 to over 700 doses per week for males. By comparison, females doses in the MCOs were about 7 times higher per week in May 2011 [Vaccine Safety Datalink Courtesy of E Weintraub, CDC].

The WG is continuing to review new data related to HPV vaccines, epidemiology, HPV-associated cancers, and vaccination program issues. The working WG is focusing on considerations for recommendations for males; there is increasing support for routine use of vaccine in males.

Quadrivalent HPV Vaccine: Evidence for Durability of Protection

Alfred J. Saah, MD, MPH
Merck Research Laboratories

Dr. Saah presented results of two long-term follow-up studies, as well as serological data on a new assay that Merck developed to address the issue of apparent HPV type 18 seronegativity, which is really an assay-specific phenomenon more than having any basis in reality.

The current data on duration of protection results from a Phase II study P007, which has 5-year data, as well as a Phase II study in which the monovalent vaccine was assessed during the initial proof of concept. There are 9 years of follow-up data from monovalent HPV 16 vaccine. Also with P007, Merck was able to demonstrate that a challenge dose of vaccine demonstrated

immune memory. For the longer-term studies, Merck has assessed young women 16 to 26 years of age in the Nordic Long-Term Follow-Up Study. This study is being conducted in four Nordic countries (Denmark, Iceland, Norway and Sweden), and will follow approximately 5400 women for 10 years after the end of the study—14 years for women who were vaccinated in the base study. There also will be effectiveness data from a long-term extension study of Gardasil® in adolescents vaccinated from the ages of 9 to 15.

During this session, Dr. Saah presented information from the 6-year report from the Nordic Long-term follow-up study. The 8-year report will be available the second or third quarter of 2012 and will include a good deal more follow-up data. The data presented during this session represented a mean of 6 years from the beginning of the study, known as Future II or Protocol 015. The benefit of this population is that it acts as a sentinel cohort. The population was vaccinated approximately 3 to 4 years before the vaccine was licensed, so if there are breakthrough episodes of disease, they can be identified early.

Cohort 1 is the cohort that was vaccinated at baseline that is comprised of approximately 2700 women who will contribute approximately 14 years of follow-up after vaccination by the end-of-study. Cohort 2 is a group of 2100 women who were vaccinated at the end of the study who received placebo. Another group of approximately 600 women who elected not to be vaccinated at the end of the base study. They self-selected and are being followed, but no data are available on this population to date. The primary endpoint is HPV 16/18-related CIN 2 or worse. This endpoint was selected because such lesions are routinely biopsied. This is a registry-based surveillance system, so the investigators are able to obtain the biopsies by identifying women who have had Pap tests and subsequent biopsies or loop electrosurgical excision procedures (LEEP). These biopsy blocks are retrieved and submitted to the laboratory that has done all of the HPV PCR work throughout the base study. There is no placebo control group. The statistical methodology being used in this study is a controlled chart method, which is a method borrowed from manufacturing to set the parameters and determine whether the numbers of cases observed exceed the parameters set. It was estimated that efficacy would be maintained above 90%, and there are a certain number of cases that would be expected if vaccine efficacy fell below that level. The secondary endpoints include CIN 2 or worse related to HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 or 59 and CIN (any grade), AIS, cervical cancer, vulvar cancer or vaginal cancer related to HPV 6, 11, 16 or 18. This is an interesting group because vulvar and vaginal lesions are not routinely biopsied unless surgery is considered. The safety endpoints include deaths, cancers, hospitalizations and other safety outcomes that the investigators are able to assess in various patient registries.

With regard to the primary endpoint analysis for the per protocol population, individuals received three doses of vaccine and had baseline seronegativity and were PCR negative at the end of the vaccination series. Of the 1000 women who had subsequent follow-up during the first two years of follow-up after the end of the base study, there were no cases of HPV 16/18-related CIN 2/3. If this population were not vaccinated, over the course of the 6 years from the base of the study, 23 cases of HPV 16/18-related CIN 2/3 would have been expected. In just this period alone of two years, 6 cases would have been expected. In any event, because the N is relatively low, these are women who just left a study of 4 years duration for cervical cancer and other lesions, there is not statistical significance to say that women are actually protected through 6 years. However, those data will be available in the next analysis. The number of person-years needs to be in the neighborhood of 2500 to 2800 for the statistical power and capability to be able to say with confidence that efficacy exists through a certain period. Certainly, trend data indicate that there are no breakthrough disease endpoints.

Assessment of the lesions due to the other vaccine types was determined to try to address the question of cross-protection or replacement. The particular population is the one that is naïve to the relevant type by PCR at baseline. For the 4 HPV types in the quadrivalent vaccine, this requires serological negativity at baseline in addition to being negative by PCR to the relevant type. There were 3 cases of HPV 31/33/35/39/45/51/52/56/58/59-related CIN 2/3 or worse in this population. Of these, 1 was HPV 31-related, 1 was HPV 33-related, and 2 were HPV 52-related. This is more or less what would be expected over this period of two years following the end of Future II. Postulating that 16/18 account for about half the cases, approximately 6 cases of CIN 2/3 would be expected due to HPV 31/33/35/39/45/51/52/56/58/59.

In terms of safety, Cohorts 1 and 2 were both assessed. There were two deaths, one of which was associated with "crashing a motor vehicle with undetermined intent", and the other of which was "intentional self-harm by jumping from a high place." Pregnancy was the most common new medical event. New medical events occurred in approximately one-fourth of the study subjects. Approximately 75% of the subjects had no new medical events during the first two years following the end of the study. There were 11 musculoskeletal disorders, including systemic lupus erythematosus and arthropathy. Other musculoskeletal disorders tended to include back aches, pubic symphysis instability, or other issues that may have been associated with pregnancy or regular arthritis. There was also one incident of anaphylactic shock. Dr. Saah clarified that he offered information about Cohorts 1 and 2 not for purposes of comparison, but rather for the purpose of completeness.

In summary of the Nordic Long-Term Follow-up Study, basically a trend of continued protection has been shown in women who were vaccinated a mean of 6 years previously. This demonstrates that the vaccine is generally safe and is well-tolerated for a mean of 6 years following vaccination.

Protocol 018 was conducted to assess safety and immune response in adolescents. This study included 1781 boys and girls who were randomized 2:1 to vaccine or saline placebo. The primary group being followed from the base study had to achieve month 42. At this point, the investigators are able to follow the individuals who have agreed to the study out to month 72, at which time they receive either a Pap test or swabs if they either reach the age of 16 and/or are sexually active. The same is being done with boys in terms of sampling, looking more for persistent infection. The catch-up group is also being studied. Interestingly, the serology results from month 7 to month 72, the percent positive for types 6/11/16 are all high. Type 18 goes to 74%, which is higher than the proportions typically observed in the older populations of women because these were individuals vaccinated in the neighborhood of 9 to 15 years of age. Nevertheless, it is substantially lower than the others. This is what Dr. Saah meant earlier when he mentioned that it was an assay-dependent issue. Similar results were found in both sexes.

Another interesting finding was how quickly young adolescents become infected. Comparing the mean ages of the 12 to 15 year olds, when the catch-up group of nearly 500 were eligible for vaccination at the end of the study, they achieved a rather impressive rate of seropositivity to some of the HPV types. For HPV 6, they went from 7/1000 to 9%. For HPV 16, they went from 7/1000 to 11%. For HPV 18, they went from 3/1000 to 6%. This is over the course of a mean of three years. The age range for the early vaccination was 9 to 16 years, which moved to 11 to 18. The message here is clearly toward vaccinating youngsters before they become sexually active.

The primary effectiveness endpoint for females was a combined incidence of vaccine type persistent infection and disease, including CIN and AIS, VIN and VaIN, genital warts, or cervical/vaginal/vulvar cancer. Dr. Saah shared data for all subjects who received at least one dose of vaccine and had at least one follow-up visit for effectiveness regardless of baseline sexual history, PCR status, or serostatus. These were adolescents who were largely not sexually active at the time that they were vaccinated. There were 157 individuals who were assessed for persistent infection and Pap testing. There are approximately 50 more young women who had only external genital exams for genital warts and did not have swabs or a Pap specimen taken. There was no CIN of any grade or genital warts related to any of the vaccine types observed in the follow-ups.

In summary, the vaccination of adolescents prior to sexual debut provides durable protection from persistent HPV 6/11/16/18 infection and disease through 6 years post-vaccination. Anti-HPV 6/11/16/18 antibody responses to the quadrivalent vaccine among preadolescents and adolescents generally persist for 6 years post-vaccination. No breakthrough cases of persistent infection or disease related to vaccine HPV types 6/11/16/18 were observed. Safety is similar to that observed in clinical program. The quadrivalent is generally well-tolerated over the long-term. These data underscore the importance of early vaccination.

Regarding assay concordance, questions were raised regarding the durability of protection given the “seronegativity” seen in the cLIA, particularly for HPV type 18. Data from clinical trials show continued efficacy for HPV 18 endpoints regardless of cLIA serostatus. Clinical long-term follow-up data shown here demonstrate durable protection, and there are no efficacy differences seen across a wide range of GMT levels, including those with the lowest GMTs. There clearly was an issue, which was the selection of a monoclonal antibody for the cLIA. The cLIA is a competitive Luminex immunoassay (cLIA). For types 6/11/16/18, a monoclonal antibody was identified against a single neutralizing type. For type 16, the early investigators were fortunate because it was both an immunodominant type as well as a highly specific epitope that was a major neutralizing site. For type 18, an antibody was selected that identified type 18 for its specificity. It was, unfortunately, less immunodominant. There were neutralizing antibodies present, but because this was a competitive assay, the only antibody being measured was the one that could compete off the monoclonal antibody. Therefore, Merck assessed the cLIA and a new assay, a total IgG Luminex immunoassay (IgG) that measures all of the antibodies against a particular virus-like particle, as well as the pseudovirion-based neutralization assay (PBNA). The PBNA tends to be the gold standard against which either the cLIA, ELISA, or total IgG assay are measured in order to identify correlation so that the easier assay can be used in the future. A secondary goal of the study was to potentially broaden the number of serological assays with high correlation to neutralizing antibody available for HPV type-specific antibody detection in human sera. Comparisons among assays were restricted to HPV types 16 and 18.

In terms of study design, for each HPV type, samples were selected to provide comparable representation from different populations, bleed intervals, and range of responses in the cLIA with 648 samples selected for HPV 16, 623 samples selected for HPV 18, and samples selected from 3 clinical studies of the vaccine (e.g., P011, P019, and P020). These samples were specifically selected at baseline, month 7, and month 24 in all three of these studies to deliberately stress the system. Some were selected at or near the cutoff in baseline, and others were selected based on the high and low systems. These are not population data or what would be expected to be observed in a large group of individuals who were vaccinated 4 to 5 years ago. Such studies are being conducted, but this was done for purposes of validating the assay.

There was a very high degree of correlation between the various assays. For both HPV 16 and HPV 18, over all samples tested, the cLIA and IgG assays were strongly associated with each other and the PBNA. The correlation coefficient for all samples combined ranged between 0.92 and 0.95 across the 3 assays and 2 HPV types. The strong agreement among the 3 assays was consistent across protocols and PD3 bleed intervals. The majority of correlations fell between 0.85 and 0.95. The association among assays was weaker for baseline samples than for post-dose 3 (PD3) samples, which was attributed to baseline sample proximity to the LLOQ of the assays. The difference in positivity rate between the cLIA and IgG assays for HPV 16 and HPV 18 was investigated. Serostatus outcomes were compared for IgG and PBNA (based on cLIA serostatus outcome). Approximately 80% of the PD3 samples seronegative in the cLIA for HPV 16 or HPV 18 had neutralizing antibodies at or above the level of serostatus cutoff in the IgG assay: 22/28 for HPV 16 and 97/122 for HPV 18. Regarding the comparison between PBNA and IgG for cLIA-positive samples (HPV 16/18), for HPV 16, 478/478 (100%) of the PD3 cLIA-positive samples also tested positive in the IgG and PBNA assays. For HPV 18, 402/407 (99%) of the PD3 cLIA-positive samples also tested positive in the IgG and PBNA assays.

Regarding the conclusions and clinical implications, the cLIA and the IgG assays correlate well with the PBNA. IgG seropositivity correlates with neutralizing antibodies in the PBNA. PD3 cLIA-negative sera show positivity in IgG assay and PBNA. Such findings corroborate the high clinical efficacy against disease in cLIA-seronegative subjects. The IgG assay measures a wide array of antibodies against HPV and will be important in long-term serological evaluation of clinical vaccination programs. Evidence of durability continues to accumulate, with 5 years of data from Phase II, and 6 years from Phase III LTFU in 16-26 year-old women and 9-15 year-old adolescents. A high proportion of post-dose 3 cLIA-negative sera show concurrent positivity in IgG assay and PBNA.

HPV-Associated Oropharyngeal Cancer

Aimée R. Kreimer, PhD

Investigator

Infections & Immunoepidemiology Branch

Division of Cancer Epidemiology and Genetics NCI, NIH

Dr. Kreimer reminded everyone that more than 120 HPV types have been identified, with about 40 of which infect the mucosal surfaces of the genital track. These are grouped as either non-carcinogenic as they are unable to induce neoplastic transformation or about 15 carcinogenic types. The most important type is HPV16 as it is the most prevalent and carcinogenic. She also briefly reviewed the anatomy of the head neck, which is grouped into three sub-sites when thinking of head and neck cancer etiology, the oral cavity, oropharynx, and larynx. It is specifically the oropharynx that is the HPV-related sub-site of the head and neck. The oropharynx includes the base of tongue, tonsils, posterior pharyngeal wall, soft palate, and uvula; therefore, she referred to these terms interchangeably and most often as tonsillar cancer or oropharyngeal cancer. It is interesting to note that the oropharynx shares a common feature with the cervix in that it has this cancer-susceptible transformation zone, which is a junction where two epithelial cell-types meet. This provides a biologic rationale why HPV infection may cause some cancers at this site.

In 2005 and 2009, experts met at the International Agency for Research on Cancer (IARC) to review the carcinogenicity of HPV infection. They concluded that HPV type 16 has sufficient evidence in humans that it causes cancers of the cervix, vulva, vagina, penis, anus, oral cavity, and oropharynx. They then went on to say that there is limited evidence in humans that it causes cancers of the larynx [Lancet Oncology 2009; 10: 321]. The importance of this topic is highlighted by the fact that the incidence of oropharyngeal cancer is actually increasing. It has been documented from cancer registries that over the past 20 years, oropharyngeal cancers overall have been increasing [Presented at 2011 ASCO Annual Meeting, Chaturvedi AK et al]. In fact, this trend has been reported in developed countries around the world, including British Columbia¹, the Netherlands², Sweden³, the United Kingdom⁴, and Australia⁵. Note that in developing countries, this phenomenon of increasing oropharyngeal cancer has not been documented [¹Auluck A. Cancer 2010; 116:2635, ²Braakhuis BJ. Oral Oncol 2009;45:e85, ³Hammarstedt L. Acta Otolaryng 2007; 127:988, ⁴Conway DI. Oral Oncol 2006; 42:586, ⁵Hong AM. Vaccine 2010;28:3269].

Since it is known that in many developed countries use of tobacco and alcohol, which are the main risk factors for head and neck cancer, overall have been on the decline, it raises the question: What explains these increasing trends in oropharyngeal cancer? In recently presented data at the ASCO annual meeting in 2011, Dr. Chaturvedi and colleagues presented data from their testing of oropharyngeal tumor specimens from the cancer registries of Hawaii, Iowa, and Los Angeles from this time period. This was done with multiple assays. HPV DNA positivity was quite low at 16% being HPV DNA-positive in the earlier time periods. However, this increased such that approximately 75% of tumors occurring over the most recent decade are HPV DNA positive. As a note, to account for possible degradation of tumors over time, cervical tumors were tested as well, for which it is known that HPV is a necessary cause, and the HPV positivity for the oropharyngeal tumors were adjusted accordingly. This confirmed that, in fact, tumor degradation was not present with regard to HPV positivity. Now that it is understood that it is really the HPV positivity that is explaining the rising incidence of oropharyngeal cancer, investigators went on in the cancer registries to assess the rates of incidence for the HPV positive oropharyngeal cancers compared to HPV negative. Remembering that oropharyngeal cancer overall is increasing over calendar time, when the investigators stratified this by HPV positive versus HPV negative oropharyngeal tumors, the HPV positive have more than doubled over the past 16 years; whereas, incidence for the HPV negative tumors has declined by about half. Because of this important finding, the authors went on to project what the incidence rates of these tumors will look like over the next several decades. They contrasted this to the observed and projected trends for cervical cancers. Observed data were available through 2008, and from 2008 on rates were projected based on current trends. These data reflect a continued decline of cervical cancer; however, at an important timepoint in 2010 (a projection because data are not yet available) there will actually be the same incidence of cervical cancer and oropharyngeal cancer in men. Projecting out to about 2020, the rates of cervical cancer will cross the rates of oropharyngeal cancer overall [Presented at 2011 ASCO Annual Meeting, Chaturvedi AK et al].

Only one prospective study to date has evaluated the question of HPV and head and neck cancers. The reason a prospective study is so important is because it addresses one of the key criteria of causality, that exposure precedes disease. In a Nordic cancer study that links to a serum biobank, investigators studied the association between HPV and head and neck cancer. In terms of all head and neck cancer combined, when the odds of seropositive patients were compared to the odds of seronegative patients, HPV 16 (a marker for exposure) seropositive patients had a 2-fold increased risk of head and neck cancer overall. These serum samples were collected on average about 9.5 years before cancer diagnosis, showing that exposure to

HPV infection preceded disease. The authors went on to stratify by different anatomic sites in the head and neck. Anatomic sites typically considered not to be associated with HPV infection such as the oral cavity had weak associations that did not attain statistical significance. For laryngeal cancer, there was a border line statistically significant finding with a modest odds ratio. However, for cancers of the oropharynx, despite having few numbers of cases, a 14-fold increased risk was observed of oropharyngeal cancer associated with HPV 16 L1 seropositivity [Mork et al. *N Engl J Med* 2001; 344:1125].

An important case-control study evaluated 100 oropharyngeal case patients and 200 age and gender matched controls was conducted in Baltimore, Maryland. The investigators assessed several aspects of the association of HPV infection and oropharyngeal cancer. The association between HPV biomarkers and oropharyngeal cancer was assessed. HPV 16 L1 serologic status (a marker of exposure) increased the odds of oropharyngeal cancers significantly. In the assessment of oral HPV 16 infection measured in oral rinse samples, again very high odds ratios were observed, which suggested that if someone had an oral HPV 16 infection, they were at increased risk of oropharyngeal cancer. An assessment of HPV 16 E6 or E7 serologic status, a different type of serologic marker considered to be a marker of an HPV-associated cancer, also found a very high odds for increased oropharyngeal cancer. Sexual behaviors were also assessed, and it was noted that sexual behaviors that would typically put a woman at risk for cervical cancer (e.g., lifetime number of vaginal sexual partners, a young age at first intercourse) increased the odds of having either an oropharyngeal cancer and an HPV16 positive oropharyngeal cancer. Also observed was that having a high number of lifetime oral sexual partners increased the odds of oropharyngeal cancer. These data combined are taken to mean that sexual behavior is a risk factor for oropharyngeal cancer, which is probably marking transmission of HPV infection to the oral region. Also evaluated were the effects of whether tobacco and alcohol in conjunction with HPV infection further increased the odds of oropharyngeal cancer. Tobacco use alone, alcohol use alone, and tobacco and alcohol use combined were assessed. This was stratified by the HPV 16 L1 seronegative individuals, so this was a case-control comparison, and then by HPV 16 L1 seropositives. Amongst seronegative individuals, the interaction of alcohol and tobacco use combined was as expected. However, among HPV seropositives, there was no evidence of interaction. The investigators interpreted this to mean that there are really two pathways to getting to an oropharyngeal cancer, one induced by tobacco and alcohol and one by HPV infection [D'Souza et al *NEJM* 2008; 356:1944].

It is now starting to be understood that HPV positive head and neck cancers actually have a distinct risk factor profile to those of the HPV negative. A study by Gillison et al evaluated tobacco, alcohol, dentition, oral sex, and marijuana use in a dose response relationship. Tobacco was assessed by number of pack years, alcohol by number of drink years, dentition by number of teeth lost, oral sex by lifetime number of oral sex partners, and marijuana by number of joint years. Comparing HPV positive head and neck cancers to controls, there was no observed association with tobacco use, alcohol consumption, or dentition. However, there was a dose response trend in terms of oral sex: increasing numbers of oral sex partners increased the odds of HPV-associated head and neck cancer. For the HPV negative cancers, the classic risk factors for head and neck cancer were observed (e.g., increasing tobacco use, increasing alcohol, and teeth loss) [Gillison ML et al. *J. Natl. Cancer Inst.* 2008 100:407-420].

In terms of building the evidence that HPV-positive oropharyngeal cancers have distinct pathologic, molecular, and clinical features, from a pathologic perspective, they have a basaloid histopathology and are typically poorly differentiated. From a molecular perspective, viral integration and expression of the viral oncogenes E6 and E7 inactivate p53 and pRb, which is responsible for tumorigenesis. Fewer TP53 mutations were observed. From a clinical perspective, HPV positive head and neck cancers are typically diagnosed at a later stage and commonly have nodal metastases. Despite these cancers presenting at an advanced stage, it has been observed that HPV positive head and neck cancers actually have a survival advantage. In a randomized controlled trial assessing different modes of radiotherapy, tumors were tested for HPV DNA at the time of randomization. At three years, about 86% of those with HPV positive tumors were still alive compared to those with HPV negative tumors at 57% [Ang KK et al *New Eng J Med* 2010; 363:24]. At this point, it is believed that HPV tumor status is a prognostic factor for survival. This is a key point in understanding that throughout the continuum of disease, HPV-positive oropharyngeal cancers are a distinct disease entity compared to the HPV negative tumors.

Certain individuals are at a clear increased risk of oropharyngeal cancer. This includes persons with AIDS¹ whose standardized incidence rate compared to that for the general population is 1.6 (95%CI = 1.2 to 2.1). Husbands of women with cervical cancer² have a 3-fold increased risk of tonsillar cancer. In fact, in the literature, a few cases of concurrent HPV-positive tonsillar carcinomas in couples (n=3)³ have been observed. Also at increased risk are individuals who had anogenital squamous cell carcinoma (cervical, vulvar/vaginal, or anal)⁴ have about a 5-fold increased risk for tonsillar cancer [¹Chaturvedi A *JNCI* 2010; ²Hemminki K *Eur J Cancer Prevention* 2001; ³Andrews E *J Infect Dis* 2009; ⁴Frisch M *Lancet* 1999].

With respect to oral HPV infection in people without cancer, a systematic review of the literature pooled all studies published to date to assess oral HPV infection and categorized the data as either positive for oral HPV16, carcinogenic oral HPV or overall oral HPV infection. For HPV 16, it was found that 1.3% of the individuals had an oral HPV 16 infection. HPV16 infection at anogenital sites is usually much higher than this (although genital HPV infection is closely linked to age at sexual initiation) Oral HPV infection of any type was observed in 4.5% of individuals; at anogenital sites, overall HPV prevalence is often much higher (i.e.: an order magnitude--~45%--for cervical, penile, or anal infection) [Kreimer AR et al. *Sex Transm Dis* 2010; 37:386].

Because HPV prevalence is so low, it complicates looking forward in time at HPV infection. However, a few small studies have assessed oral HPV incidence. In a study in Finland of healthy men and women in an obstetrics clinic¹, there was a very low incidence of 3%. To contrast the 3% with what is typically observed at the cervix among women of childbearing age, there would be an incidence of closer to 20%, again showing that oral infection is a much more rare event compared to cervical infection³ In another study, oral HPV incidence rate was lower among HIV negative (10%) women compared to HIV positive women (30%) in the US². [¹Rintala M et al. *J Clin Virol* 2006; 35:89; ²D'Souza A et al. *Int J Cancer* 2007; 121:143; ³Winer RL et al. *Am J Epidemiol* 2003; 157:218].

Only two studies have focused on oral HPV persistence measured at 6 months (e.g., a type-specific oral HPV infection being at one point in time and when looked for 6 months later having the same time present in the oral specimen). One study assessed over 1600 men¹ with an outcome of any HPV type. There were 56 baseline infections to follow prospectively. At 6 months, 61% persisted. The Finland study assessed carcinogenic HPV for persistence in 460 women, among whom there were 59 baseline infections. Of those, 100% persisted. This broad range conveys the paucity of data on this topic. Cervical HPV persistence, which has been

better characterized, is typically around 70% after a 6-month time period³ [¹Kreimer AR. 2010 International IPV Meeting, July 2010; ²Rintala M et al. J Clin Virol 2006; 35:89; ³Winer RL Cancer Epidemiol Biomarkers Prev 2011; 20:699].

Regarding age-specific oral HPV prevalence, a study in 3 countries of over 1500 men assessed increasing age categories and oral HPV prevalence. A non-significant increase was observed in oral HPV prevalence across age categories. This is starkly different from what is observed at the cervix where there is a very high prevalence soon after sexual debut that decreases as a woman ages. Thus, very different patterns are being observed in terms of the natural history of the HPV infections at the two anatomic sites (the oral region vs the anogenital region) [Kreimer AR, Cancer Epidemiol Biomarkers Prev 2011; 20:172].

As expected, the risk factors for oral HPV infection include lifetime and recent numbers of sexual partners, oral sexual behaviors, deep mouth kissing, current tobacco use, and immunosuppression induced by HIV infection.

Important research questions remain and include the following:

- Is persistent oral HPV infection a risk factor for oropharyngeal cancer and, if so, what is the time between persistent oral HPV infection and oropharyngeal cancer?
- Does a precancerous state exist for oropharyngeal cancer?
- Does HPV cause cancers in the head and neck beyond the oropharynx?
- Will prophylactic HPV vaccines protect against HPV in the oral region, and thereby protect against a subset of these cancers?

In summary, HPV 16 causes a subset of head and neck cancers, predominantly in the oropharynx. Molecular, epidemiological, and clinical evidence suggest these tumors are distinct from HPV-negative head and neck cancers. Oral HPV 16 is rare in healthy people, although the natural history of the infection is not well-studied. Oropharyngeal cancer is increasing in the US and other countries due to HPV infection. Direct evidence showing the HPV vaccine protects against oral HPV infection is lacking.

HPV Vaccine Cost-effectiveness Updates and Review

Harrell Chesson, PhD

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During this session, Dr. Chesson addressed the use of QALYs to assess vaccine cost-effectiveness; HPV vaccine cost-effectiveness; and responses to ACIP queries from the February ACIP meeting pertaining to catch-up of males through age 26 years, details of QALYs gained by male vaccination, and the impact of duration of protection assumptions.

Dr. Chesson explained that cost-effectiveness of vaccines is often assessed in terms of cost per QALY gained by vaccination. QALYs are useful in evaluating vaccines because they take into account gains in quality and length of life. Health outcomes included in recent cost-effectiveness models of HPV vaccination include genital warts, CIN, cervical cancer, vaginal and vulvar cancer, anal cancer, oropharyngeal cancer, penile cancer, and RRP. The potential vaccine impact on these outcomes is assessed in terms of QALYs. There is evidence of vaccine efficacy for genital warts, CIN, cervical cancer, vaginal and vulvar cancer, and anal cancer. These are often referred to as the indicated outcomes; however, in the model

sometimes all of the outcomes are included—even those without evidence of efficacy to determine how the cost-effectiveness estimates change depending on the outcomes included.

Regarding cost-effectiveness thresholds in the US, there is no consensus on the appropriate cost-per-QALY threshold for determining cost-effectiveness of public health interventions. Likewise, there is no ACIP-established threshold for determining vaccine cost-effectiveness. A threshold of \$50,000 to \$100,000 or even \$150,000 is often cited; however, this has often been described as arbitrary and lacking empirical or theoretical justification [See Grosse (2008), Weinstein (2008), and Weinstein et al. (2010)]. Another way to think about cost-per-QALY thresholds is to look at cost per-QALY estimates for existing vaccines in the US. The following table on the left shows the cost per-QALY gained by childhood vaccines in the US. The first 5 vaccines listed have been found to be cost-saving; that is, they pay for themselves. The final two vaccines, while not cost-saving, still have attractive cost per-QALY estimates of about \$10,000. The table on the right shows the cost per-QALY gained by adolescent vaccines in the US. HPV vaccine ranks favorably among other vaccines. As shown in the bottom rows, some adolescent vaccines have cost per-QALY estimates of over \$100,000:

Cost per QALY gained by childhood vaccines in the US		
Vaccine	Cost per QALY gained (compared to no vaccine)	Source
DTaP	<\$0 (cost-saving)	Ekwueme (2000); Zhou (2006)
Hib	<\$0 (cost-saving)	Zhou (2006); Coon (1985)
MMR	<\$0 (cost-saving)	Zhou (2004, 2006); White (1985)
Polio	<\$0 (cost-saving)	Zhou (2006); Thompson (2006)
Varicella	<\$0 (cost-saving)	Zhou (2004, 2006); Prebid (1985)
Influenza (LAIV)	≈ \$10,000	Prosser (2006)
Hepatitis A	≈ \$10,000 to \$30,000	Dai (1999); Reih (2007)

QALY, quality-adjusted life year; DTaP, Diphtheria and tetanus toxoids and acellular pertussis; Hib, Haemophilus influenzae type b; MMR, Measles, mumps, and rubella; LAIV, live, attenuated influenza vaccine.

Updated to 2009 US dollars and rounded. This table shows a collection of point estimates; the ranges shown for hepatitis A reflect base case results of two studies. For each vaccine, the actual range of plausible cost-effectiveness estimates varies (not shown). See the sensitivity analyses in the source studies.

Cost per QALY gained by adolescent vaccines in the US		
Vaccine	Target group	Cost per QALY gained (compared to no vaccination)
Hepatitis B	College freshmen	<\$0 (cost-saving) to ≈ \$10,000
Hepatitis A	College freshmen	<\$0 (cost-saving) to ≈ \$15,000
HPV	12-year-old girls	≈ \$3,000 to \$45,000
Influenza	12- to 17-year-olds, high risk	≈ \$10,000
Tdap	All 11-year-olds	≈ \$25,000
Influenza	12- to 17-year-olds, healthy	≈ \$140,000
Meningococcal	2-dose, all 11 & 16-year-olds	≈ \$160,000

Source: Ortega-Sanchez et al. Pediatrics (2008), except HPV and Meningococcal (see notes).

Tdap, Tetanus and diphtheria toxoids and acellular pertussis; influenza estimates are for inactivated vaccine. For HPV, the lower and upper bound estimates (Eliava (2007) and Kim (2006), respectively) were published after the cutoff date for inclusion in the Ortega-Sanchez review. Estimate for Meningococcal was presented by Ortega-Sanchez, October 2010 ACIP. All estimates updated to 2009 US dollars and rounded. This table shows a collection of point estimates; the range shown for HPV reflects base case results of two studies, and the ranges shown for hepatitis A & B reflect base case results from two perspectives. For each vaccine, the actual range of plausible cost-effectiveness estimates varies (not shown). For more details, see the sensitivity analyses in the source studies.

With regard to some of the key points presented at previous ACIP meetings, it is known that routine vaccination of 12 year old girls is a cost-effective use of public health resources in the US. These findings are consistent across a wide range of models, conditioned only that the vaccine provides sufficient duration of protection. However, there is more uncertainty in cost-effectiveness estimates for vaccination of adult women and vaccination of males.

The cost-effectiveness of male vaccination depends on vaccine coverage of females, at least in the models that take into account herd immunity (or indirect effects) of vaccination. The most favorable scenario for male vaccination is when coverage of females is low. Many models suggest that male vaccination is not likely to be cost-effective when female coverage is high. With higher female coverage, there is less impact of male vaccination on disease in females. More males are protected indirectly through female vaccination.

The cost-effectiveness of HPV vaccination depends on the health outcomes included in the analyses. The most favorable scenario for vaccination is when all potential health outcomes are included. Vaccine costs are also an important factor in affordability and cost-effectiveness of male vaccination. With lower vaccine costs, male vaccinations are more likely to be cost-effective over a wide range of scenarios (e.g., higher female coverage).

HPV vaccination of MSM appears cost-effective, at least in the first and only study to address this issue. In that study in 2010, Dr. Kim found cost per QALY estimates of less than \$50,000 for MSM over a range of assumptions about age at vaccination and prior exposure to HPV. Additional data are needed to assess this in more detail, such as type-specific HPV acquisition by age among MSM [Kim JJ. Lancet Infect Dis. 2010;10:845-52. MSM: Men who have sex with men. QALY: quality-adjusted life year].

Accounting for recent trends in cancer incidence does not have major impact on male vaccination cost-effectiveness, because the impact of accounting for decreasing trends in some cancers (e.g., cervical) is offset by the impact of accounting for increasing trends in other cancers (e.g., oropharyngeal, anal). Possible exceptions are if recent trends are assumed to continue for 50 to 100 years before leveling off, or if future annual changes in cancer incidence are assumed to be greater than in recent years.

Routine vaccination of males in the US could be cost-effective, particularly if coverage of females is low ($\leq 50\%$), and the two most recent studies that have addressed this issue found cost per-QALY estimates of \$24,000 to \$62,000. [\$24,000 per QALY is from Merck model (Elbasha & Dasbach, 2010) with effective coverage (all 3 doses) by age 18 of $\approx 40\%$ and $\approx 25\%$ for females and males, respectively. \$62,000 per QALY is from Kim et al. (2009) with 50% 3-dose coverage of girls and boys by age 12].

However, routine male HPV vaccination might not be cost-effective, even if coverage of females is low. This is true in certain scenarios when key assumptions are varied, when male vaccination is compared to a strategy of increased female coverage, and if males vaccinated have mostly vaccinated partners.

To summarize the available cost per-QALY estimates for male vaccination, the studies were grouped according to the outcomes that were included in the analysis. For any given study, the cost per-QALY gained by vaccination increases as female coverage increases. However, the degree to which this increase occurs differs across the studies. For the higher coverage scenarios, there is less agreement across the studies; whereas, in lower coverage scenarios, the models tend to be in more agreement. How the cost per-QALY gained changes depending upon what health outcomes are included in the analyses is shown in the following table of the Chesson study:

Estimated cost per QALY gained including different outcomes
(Chesson et al. model)

HPV disease included	Lower coverage scenario 30% 3-dose coverage at age 12 50% 3-dose coverage by age 28		Higher coverage scenario 50% 3-dose coverage at age 12 70% 3-dose coverage by age 28	
	Female (Ages 12-28)	Male (Age 12)	Female (Ages 12-28)	Male (Age 12)
Cervical disease only	\$21,300	\$121,700	\$23,700	\$253,900
+ vulvar and vaginal cancer	\$19,800	\$113,700	\$21,800	\$237,300
+ genital warts	\$15,200	\$84,400	\$18,900	\$187,500
+ anal cancer	\$12,200	\$68,200	\$13,600	\$134,800
+ RRP	\$10,900	\$68,500	\$12,300	\$132,400
+ oropharyngeal	\$7,300	\$41,800	\$8,300	\$81,800
+ penile cancer	\$7,200	\$41,400	\$8,200	\$80,900

QALY: quality-adjusted life year. RRP: recurrent respiratory papillomatosis. Cost-effectiveness ratios for female-only vaccination are as compared to no vaccination (screening only). Cost-effectiveness ratios for male vaccination show the incremental cost per QALY gained by adding vaccination of 12-year-old boys to the female-only vaccination strategy. With coverage of 12-year-old boys assumed to be the same as coverage of 12-year-old girls. Cost-effectiveness ratios include all diseases in the preceding rows (if applicable).

As shown, the cost per-QALY gained changes depending upon what health outcomes are included in the analysis. Two coverage scenarios were included, a lower 3-dose coverage scenario in which there was 30% coverage of girls by 12 years of age and 50% coverage by age 26, and a higher 3-dose coverage of 50% by age 12 and 70% by age 26. Including only cervical outcomes, the cost per-QALY gained by male vaccination is over \$100,000 per-QALY. As increasingly more potential health outcomes are included in the analysis, the cost per-QALY gained by male vaccination decreases until it reaches approximately \$40,000 in the lower coverage scenario and approximately \$80,000 in the higher coverage scenario when including all health outcomes. The first four outcomes listed are those for which there is evidence of vaccine efficacy. When limiting the analysis to those indicated outcomes only, the cost per-QALY gained is about \$70,000 in the lower coverage scenario and about \$130,000 in the higher coverage scenario.

The published studies typically report cost-effectiveness of adding male vaccination to female-only vaccination, but another strategy to reduce HPV burden in both sexes is to increase vaccine coverage of females. An important public policy question to ask is: What is the cost-effectiveness of male vaccination compared to a strategy of increased vaccine coverage of females? Chesson et al assessed this in their model and found that the incremental cost per-QALY of male vaccination when including all outcomes was over \$100,000 when compared to a strategy of increased female coverage. In contrast, when the usual approach was used of comparing male vaccination to the status quo female coverage, the cost per-QALY gained by male vaccination was in the \$25,000 range. In this example, the strategy of increased vaccine coverage of females could incur costs of over \$350 per additional woman vaccinated, above and beyond the cost of vaccination, and still be as cost effective as male vaccination.

Dr. Chesson presented new information in response to the questions raised during the February 2011 meeting. The first request was for additional information regarding the cost-effectiveness of male catch-up vaccination. The following table shows the lower coverage and higher coverage scenarios used in the previous example. The top row shows the cost per-QALY gained by female only vaccination, the next row shows the cost per-QALY gained by adding 12-year old boys to a vaccination program, and the bottom three rows show what happens when male vaccination is expanded to include 18-year olds, 21-year olds, and 26-year olds. The cost per-QALY gained really increases when moving beyond age 21 in the model at over \$400,000 in the lower coverage scenario when including only the indicated outcomes, and well above \$150,000 when including all outcomes:

Cost-effectiveness of male catch-up vaccination
(Chesson et al. model)

Cost per QALY gained

Vaccine strategy	Lower coverage scenario 30% 3-dose coverage at age 12 50% 3-dose coverage by age 26		Higher coverage scenario 50% 3-dose coverage at age 12 70% 3-dose coverage by age 26	
	Indicated outcomes only	All outcomes included	Indicated outcomes only	All outcomes included
Females aged 12 to 26	\$12,200	\$7,200	\$13,800	\$8,200
+ 12 year old males	\$68,200	\$41,400	\$134,800	\$80,900
+ males aged 13 to 18	\$117,700	\$87,900	\$185,200	\$102,800
+ males aged 19 to 21	\$207,300	\$102,900	\$244,300	\$117,000
+ males aged 22 to 26	\$424,300	\$177,800	\$458,300	\$185,800

Indicated outcomes include cervical outcomes, vaginal, vulvar, and anal cancers, and genital warts. All outcomes include indicated outcomes plus oropharyngeal cancer, penile cancer, and recurrent respiratory papillomatosis. The same coverage rates were applied to males and females (although coverage by age 26 will be lower in males than females in scenarios where male vaccination is not extended through age 26 years).

While Dr. Chesson did not show the Merck model results, he pointed out that there are two key differences in their results and the Chesson model. First, the Merck model found that vaccination of males up to the age of 18 was more cost-effective than vaccinating 12-year old boys only. They also found that the cost per-QALY did not increase as much when going to age 26. It was about \$50,000 when including all outcomes and about \$100,000 when including the indicated outcomes only.

During the previous ACIP meeting, the members also requested more information about what diseases account for the gains in QALYs. It is known that additional health benefits accrue when females are vaccinated and when males are added to the female-only vaccination program. The models assess these health gains in terms of QALYs. The members requested information regarding what health outcomes account for most of the QALYs gained. The following table shows the percent of QALY benefit attributable to HPV disease prevented. For both female only vaccination and the incremental benefit of male vaccination, cervical outcomes and oropharyngeal cancer accounted for over 70% of the QALYs gained. However, for male vaccination, oropharyngeal cancer accounted for practically the same amount of QALYs as cervical cancer:

**Percent of QALY benefit attributable to HPV disease prevented
(Chesson et al. model)**

All outcomes

HPV disease	Percent of benefit attributable	
	Female-only vaccination	Male vaccination (incremental gain in QALYs when male vaccination is added to female vaccination)
Cervical	57%	37%
Oropharyngeal	21%	36%
Anal	10%	12%
Genital warts	7%	11%
Vulvar	3%	2%
Vaginal	1%	1%
RRP	1%	<1%
Penile	<1%	1%

QALY: quality-adjusted life year. RRP: recurrent respiratory papillomatosis. Vaccination strategies (both sexes as well as female-only) include ages 9 to 26 years.

Another way to look at this is to limit this analysis just to the outcomes for which there is evidence of vaccine efficacy. When doing so, cervical cancer is still the greatest contributor to the number of QALYs gained for both female only vaccination (73%) and male vaccination (59%). However, anal cancer (13% female; 19% male) and genital warts (9% female; 18% male) have a much greater impact on the QALYs gained for male vaccination than for female only vaccination.

Another question posed during the last meeting pertained to the impact of duration of vaccine protection assumptions. With reasonable certainty, it can be said that assuming a shorter duration of vaccine protection would make female-only vaccination less cost-effective. However, a shorter duration of vaccine protection could make male vaccination less cost-effective because of the reduced impact on vaccinated males [Kim BMJ (2009)]. It also could have the counterintuitive results of making male vaccination appear more cost-effective, given that the reduced impact on vaccinated females could leave a greater HPV burden to be averted by male vaccination even with a shorter duration of protection [Jit BMJ (2008)].

In conclusion, male vaccination in the US is potentially not cost-effective, particularly at high female coverage levels. Even at current female coverage levels, male vaccination may not be cost-effective, particularly when compared to a strategy of increased female coverage or if males vaccinated have mostly vaccinated partners. However, male vaccination is potentially cost-effective, particularly at current female coverage levels. All available models suggest that there are potentially favorable cost-per-QALY estimates when female coverage is $\leq 50\%$. Also, with a lower vaccine cost, male vaccination is much more likely to be cost-effective across a wide range of scenarios.

Policy Considerations: HPV Vaccine for Males

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Dr. Dunne reviewed policy considerations for HPV vaccine for males. Quadrivalent HPV vaccine is licensed for males 9-26 years. In October 2009, ACIP provided guidance that the vaccine may be used in males 9-26 years for prevention of genital warts. Since that time, a variety of data has been presented, as highlighted at the beginning of this session. The quadrivalent HPV vaccine has been demonstrated to prevent genital warts and anal cancers in males, and had an indication for prevention of these two outcomes.

In terms of estimated HPV and HPV 16/18 associated cancers for men and women, as noted, there are about 7000 HPV 16/18 cancers in men. The majority of these cancers are cancers of the oropharynx. There are no clinical trial data demonstrating efficacy for prevention of oropharynx cancers, or for prevention of penile cancers [National Program of Cancer Registries and SEER, covering 83% coverage of US population; Gillison ML, et al. Cancer 2008].

Over the last few years, the ACIP HPV WG has been deliberating on HPV vaccine for males, and an important consideration has been cost-effectiveness. As shown by Dr. Chesson, the cost-effectiveness of male vaccination appears favorable in the scenario of lower vaccine coverage. As vaccine coverage in females increases, cost-effectiveness of male vaccination becomes less favorable.

The male HPV vaccine recommendation options that have been discussed and brought before the committee, include retaining existing guidance for males 9-26 years (or permissive recommendations), or recommending routine use of 11- or 12-year old boys. In addition, the ACIP HPV WG has considered vaccine options for men who have sex with men. There is a greater burden of HPV-associated outcomes including genital warts, anal pre-cancers and cancers in MSM. The Kim model, as highlighted in Dr. Chesson's, presentation demonstrated a favorable cost per-QALY of vaccinating MSM through age 26 years [Kim JJ. Lancet ID 2010;845-52]. Most ACIP HPV Working Group members favor a strategy of routine vaccination of all males at an age at which they are likely to have the greatest benefit (e.g., 11 or 12 years) rather than an approach targeting MSM. The benefits of HPV vaccine to MSM would be emphasized and included in any male vaccine recommendation.

If vaccine was recommended for routine use, catch-up vaccination needs to be considered. The WG has discussed different vaccination options. As presented by Dr. Chesson, cost-effectiveness models demonstrate less favorable cost per-QALY with increasing age. For all scenarios, the cost per-QALY gained by male vaccination increases with age at vaccination. For this and other reasons, the ACIP HPV Working Group has focused on two options for catch-up: catch-up through age 21 and catch-up through age 26 years.

There are different advantages of catch-up vaccination through age 26 years, or through age 21 years. Licensure of the vaccine is to age 26, so a catch-up recommendation through age 26 years may create less confusion about implementation. Also, this recommendation would be harmonized with the female vaccine recommendations. Finally, a recommendation through age 26 years would broadly capture all men through age 26 years, including MSM seeking care. The advantages of catch-up vaccination through age 21 years, are that this would focus the program on the younger age group. This recommendation may be a better use of health care resources, given that the cost-effectiveness data demonstrate a higher cost per-QALY with increasing age. Finally, a recommendation through age 21 years would focus limited resources on those with the greatest benefit, but would still capture youth from high school and through college who may benefit from vaccination.

For either of these considerations, it is important to note that male vaccine implementation in the 22-26 year olds would likely be less than in the younger group, similar to what has been observed for females. Given limited doses delivered in that age group, the overall costs of the program, regardless of the recommendations for catch-up, may be minimal. Another point to consider regarding catch-up vaccination is harmonization with the female recommendations. If male catch-up vaccination was through age 21 years, it may be advantageous to harmonize female catch-up to age 21 years as well, which would be a change in the recommendations. An advantage of this is that programs would focus on the age groups in which there would be the greatest benefit.

The Kim / Goldie model demonstrates the cost-effectiveness of vaccination of females through age 26 years. For males, the cost per-QALY of female vaccination increases with increasing age, and the highest cost per-QALY occurs in the oldest age group [Kim JJ, Goldie SJ. *N Engl J Med* 2008;359:821-832].

As has been presented, most WG members support routine vaccination of males, particularly with a lower HPV vaccine cost. Opinions about catch-up recommendations vary. A few WG members support no catch-up, or catch-up through age 18 years. Some WG members support catch-up through age 21 years, and some WG support catch-up through age 26 years. Over the ensuing months, additional discussions of these options will take place. It is important to note that most WG members support harmonization of female and male recommendations regardless of the catch-up considerations. The next steps of the ACIP HPV Working Group are to discuss recommendation options, and present to ACIP an update on HPV vaccine safety, 2010 vaccine coverage estimates from NIS, Grades of Recommendation Assessment, Development and Evaluation (GRADE) evidence for HPV vaccine in males, and HPV vaccine recommendation options.

In conclusion, Dr. Dunne posed the following questions regarding HPV vaccine recommendations for males:

- What are the opinions of the committee on vaccine recommendations for males?
- What are the opinions of the committee on vaccine catch-up options?
- What additional information is needed for these considerations, if any?

Discussion Points

In terms of what additional information may be needed, Dr. Temte commented on the properties of cost-effective analysis for a program that comes from compartmentalizing the whole program. A recommendation was made for the “low hanging fruit,” which was the girls and now there is a much “higher fruit,” which is the boys. Anytime those are assessed independently, the result will be very negative in terms of cost-effectiveness. He wondered what would occur if an assessment was made of a male and female harmonized schedule in comparison with a base case of doing nothing in terms of the cost-effectiveness of an HPV program for adolescents.

Dr. Chesson replied that this could be done for the next ACIP meeting. Some of these analyses have been done already. However, anytime some of the options are ignored (such as female-only vaccination), the cost-effectiveness of the end result (such as male and female vaccination) will be overestimated.

Dr. Sawyer requested clarification on the conditions that are or are not included in the cost-effectiveness models. He understood the rationale for eliminating the conditions for which there is no evidence that HPV causes the cancer, but it was not clear why they were focusing on cervical cancer only rather than considering all things that could be prevented and are known to be caused by HPV.

Dr. Dunne responded that she thought there were just different perspectives of the WG members in terms of the value of all outcomes that could be preventable and the indicated outcomes. That was why they showed indicated outcomes and all outcomes.

Dr. Sawyer pointed out that they do not do this for a lot of other illnesses. Pneumococcus causes pneumonia and meningitis, but they do not dissect the different illnesses it causes and decide which are the most worth preventing.

Dr. Baker pointed out that the problem is that there are efficacy data for some anatomical sites but not others. However, she thought considering all outcomes was very helpful.

Dr. Marcy expressed concern about the slide that stated “next ACIP meetings” plural. He thought there should be a vote during the October 2011 meeting. No further information is needed for these considerations. He felt there were already ample data, and pointed out that

Dr. Chesson was beginning to reshow slides he had shown a year previously.

Dr. Baker thought the plan to update female uptake would be helpful in terms of that discussion.

While he knew it was unrealistic to think that there would be any data forthcoming regarding the vaccine and oropharyngeal malignancies, Dr. Meissner wondered whether everyone agreed that it was biologically plausible that the vaccine would have the same beneficial impact on oropharyngeal disease.

Dr. Markowitz replied that there are no efficacy studies, but there may be data from some studies assessing the infection.

Dr. Kreimer added that she is involved in the Costa Rica Vaccine Trial which is a publicly funded NIH vaccine trial evaluating the vaccine efficacy of the GSK vaccine. The primary aim was to assess infection at the cervix, but anal and oral specimen collection was added to that at the final randomized study visit. Because oral HPV infections are quite rare, the sample size will be limited, but they will be able to provide some proof of principle data over the next several months assessing just prevalence of oral HPV 16/18 infection in a vaccinated compared to an unvaccinated arm. She stressed that because the study was not powered to assess oral, there will likely be inadequate power to reach a strong conclusion. Because this was implemented at the final study visit, oral persistence of infection will not be assessed. This is simply a one-time measure of oral HPV infection.

Dr. Duchin wondered whether there were any data that assess the antibody levels in the tissues of the oropharynx comparable to the data presented in the early stages of HPV vaccine development regarding the cervix, and whether the pathophysiology of the development of the cancer was similar. He also thanked the working group for being so responsive to the ACIP membership's questions.

Dr. Kreimer responded that it was uncertain whether the pathophysiology of the cancers is similar, because in terms of the natural history of cancer, it is unclear whether it has a pre-cancerous state. It is known that there is infection leading to cancer, but there is still a "black box" in the middle.

Dr. Wharton wondered whether anatomically oropharyngeal cancers started whether they initiated in the transition zone, or whether this was known.

Dr. Kreimer replied that she would say that is where they initiate because the tonsillar crypts has exposed epithelium.

Dr. Keitel wondered whether the age of diagnosis of people with HPV positive oropharyngeal cancer the same as the age of diagnosis of HPV negative oropharyngeal cancer. She also wondered whether the oropharynx can be sampled, or whether there was anything inhibiting the detection of DNA.

Dr. Kreimer responded that there is a difference in age of earlier diagnosis for the HPV-associated cancers by a couple of years. It is significant that the HPV-positive cancers are diagnosed at an earlier age. Measurement of oral HPV in the oral region is actually quite complicated because it is difficult to directly sample the tonsils due to the gag reflex. The investigators have worked to optimize specimen collection and processing for oral HPV DNA analysis

Dr. Baker noted that the recommendation for collection of culture specimens for Group A streptococcal pharyngitis is based on good studies, but this recommendation is hardly ever followed. It is quite difficult to collect a good sample because of the gag reflex in children, even with three people holding them down.

In terms of risk factors, Dr. Keitel pointed out that marijuana use was not discussed at length. She requested insight into why that might be an independent risk factor.

Dr. Kreimer replied that in the graph contrasting HPV positive and HPV negative head and neck cancers, in HPV positives there is a dose response trend with marijuana use. These data were adjusted for sexual behaviors; however, there could still be residual confounding due to sexual behaviors. Researchers are following up on this hypothesis and investigating this topic currently.

Dr. Englund reported that the WG members and CDC have tried very hard to provide the ACIP membership with answers to their questions, but have also offered continuous feedback to stimulate everyone's memory about how far things have come since the vaccine was licensed over 5 years ago. They want to have institutional memory within ACIP and to understand the progress that has been made, and that opinions have changed.

Dr. Markowitz thanked Dr. Englund, who was rotating off as the HPV Vaccine Working Group chair. She has been a great chair and provided sound advice and guidance as the group dealt with many difficult issues over the last few years.

Dr. Baker congratulated the WG and those at CDC for being very responsive to the ACIP membership's questions the last couple of meetings.

Dr. Sawyer said one of the figures that was presented that stuck with him was that HPV cancers in males account for 7000 cases per year compared to 14,000 in women. Half as much is not a trivial number, so he thought rather than continuing to try to decide whether males should be immunized, they should call the question.

Dr. Schaffner (NFID) felt that institutional memory was about to be diluted and new members will join. If there is going to be a vote during the October ACIP meeting, he wondered if any plans were being considered to bring the new members up to date on some of these very "pregnant" issues.

Dr. Markowitz replied that they will plan to summarize all critical data that have been presented during past meetings.

Dr. Pickering added that when there are new members, CDC conducts orientation sessions with them before their first meeting to bring them up to speed on all issues. A couple of new members have been involved either as liaisons or members of working groups, so they are current on the issues.

Day 1 Public Comments

No public comments were offered on the first day of the June 2011 meeting.

June 23, 2011

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Wharton reported that during the March 2011 Immunization Conference, CDC presented an updated economic analysis of the return on investment of childhood immunizations. This analysis was last done in 2005. Given that a number of new vaccines have been added to the immunization program since that time, it was important to update it. The new model adds information for pneumococcal conjugate 7-valent vaccine, hepatitis A, rotavirus, and the second dose of varicella vaccine to the series of vaccines given through age 6 years. It also includes updated healthcare costs, vaccine prices, vaccine coverage, and annual births to 2009 figures. The bottom line of this new analysis was that the return on investment for vaccination of children born in one year in the US through age 6, according to the ACIP recommended childhood immunization schedule, is 20 million illnesses prevented; 42,000 premature deaths averted; \$13.6 billion in medical costs saved; \$59 billion total savings; an average of \$3 medical savings for every \$1 spent; and an average of \$10.2 total medical and societal savings for every dollar spent.

Regarding the Vaccine Toolkit, on June 9, 2011 there was a special issue of *Health Affairs*, which was presented with a special issue on *Vaccines and Immunization*. That issue included an article by CDC and HHS staff on parental acceptance and vaccine concerns. There have been other recent publications in this area as well. The way CDC views this issue is that in the US, reinforcing the skills of clinicians to help them better address parental concerns is a key approach to improving vaccine acceptance and sustaining high immunization coverage. NCIRD has worked with the American Academy of Pediatrics (AAP) and other key partners, including FDA and NIH, to develop a set of updated health communication tools to improve provider care and interactions related to immunizations. These materials grew out of formative research conducted with parents in several parts of the country, as well as in-depth interviews with doctors and nurses. New materials have been developed to address a variety of issues. The materials available so far are on the website at the Vaccine Toolkit URL, and other materials are still being developed. CDC is very excited about this, and hope that they will be useful for the people who have to have these conversations every day in the office.

Centers for Medicare and Medicaid (CMS)

Linda Murphy reported that CMS has worked on an interim upgrade for the administration fees, which are making their way through clearances. The hope is to have the information published in July 2011. They are still working on the larger regulations. Once published, she will distribute a notice to ensure that ACIP members are aware of it.

Department of Defense (DoD)

Jesse Geibe offered DoD's gratitude for the support provided by CDC and ACIP during the development process of adenovirus vaccine that DoD will begin administering in the near future, particularly with the development of the vaccine information statement.

Department of Veterans Affairs (DVA)

Dr. Kinsinger reported that about half of the DVA clinical facilities ordered high dose influenza vaccine this year totally about 173,000 doses. They do not have records on how many of those doses were actually used, but the sites were surveyed and it was determined that there was a lot of variability. Some sites used the vaccine a lot, while other sites were confused and uncertain as to when and for whom high dose vaccine should be administered. More guidance about using high dose influenza vaccine would be very helpful as those data become available. They noticed a decrease in uptake of influenza vaccine by healthcare professionals this year, although DVA is not quite sure why and wondered whether others had noticed a similar trend. There is some concern about the side effects from the H1N1 vaccine, so there may be some residual uncertainty about influenza vaccine among DVA healthcare professionals. They hope to put a system in place in the fall that will allow them to track uptake very easily.

Food & Drug Administration (FDA)

Dr. Wellington Sun provided a synopsis of the vaccines that have been licensed by FDA since the February 2011 meeting. The adenovirus vaccine for ages 17 to 50 years for the military, a FluZone® intradermal formulation, Menactra® supplement for 9 months to 23 months, and Zostavax® were approved. Regarding interference amongst bacterial vaccines, FDA also approved the change in prescribing information for Menactra® and Boostrix® based on a study conducted about co-administration. Basically, there appears to be some interference from an antibody standpoint between Menactra® and Boostrix® in the pertussis assays. It is not clear what this means. There is no correlate of protection, but that phenomenon was observed in co-administration. He encouraged those interested to read that label.

Health Resources and Services Administration (HRSA)

Dr. Evans reported that a final rule was published on June 22, 2011. Four vaccines have been added to the program since 2004 (e.g., hepatitis A, trivalent influenza, meningococcal, and HPV). When new vaccines are added to the program, they are put in a footnote until final rulemaking is undertaken. Formal rulemaking was undertaken, with the opportunity to add injuries, and these four vaccines will now be listed in separate box categories. No associated injuries were added at this time. In the future, the Institute of Medicine Committee on Vaccines and Adverse Events will be releasing its much anticipated paper, which is approximately 50% longer than in 1991 and 1994. This is why it is taking longer to clear and publish. It is expected that from this report, there may be opportunities to add injuries to some of these vaccines. The report will cover varicella, influenza, both hepatitis vaccines, meningococcal, HPV, DTaP, MMR in various combinations. It will cover 12 vaccines total, and is quite an ambitious effort. This major effort was sponsored in part by CDC. HRSA looks forward to discussing the results of this report during the October ACIP meeting. Perhaps the IOM will be able to present at that time as well.

Indian Health Services (IHS)

Amy Groom reported that approximately 73% of IHS's healthcare personnel had received influenza vaccine, which was about the same as it has been for the past couple of years. While they are happy with this percentage, they believe they can do better and are considering implementing a mandatory influenza vaccination policy as well as other vaccines recommended for healthcare personnel. This policy is currently being review by their Chief Medical Officer. IHS is working to organize a stakeholders meeting with the American Indian community and

providers to assess national vaccine plan implementation issues. A concerted effort is also being made to assess adult vaccination within Indian adult services. There is a vaccination program for children, but adult vaccine coverage is variable. With all of the healthcare reform activities that are ensuring access to adult vaccines for the remainder of the population, they want to better assess what is occurring in IHS health facilities. They will be conducting a survey to determine which facilities are providing the recommended vaccines and what issues there may be. They have had a lot of success with pharmacists providing immunizations at various sites, so a concerted effort is being made to inform pharmacists of the goals pertaining to adult vaccination.

National Institutes of Health (NIH)

Dr. Neshin reported that NIH joined other agencies and organizations in commemorating the 30th anniversary of the first reported cases of AIDS. Dr. Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID), issued a statement that is located on the NIH website. He also co-authored *Thirty Years of HIV and AIDS: Future Challenges and Opportunities* was published in the *Annals of Medicine* [Carl W. Dieffenbach and Anthony S. Fauci, *Ann Intern Med* May 31, 2011 E-345; published ahead of print May 31, 2011]. There is also a slide show on public health advances. The Vaccine Research Center celebrated its anniversary and hosted the anniversary symposium. The objective was to describe the advances in the last 10 years. The speakers were Dr. Collins, Dr. Fauci, and many of the NIAID faculty investigators. NIAID supports studies of new vaccine candidates and licensed vaccines, so there are studies underway in Phase 1 or Phase 2 for candidates for malaria, dengue, et cetera. Studies are also conducted in populations that require protection such as pregnant women. All of the protocols can be reviewed on the website.

National Vaccine Program Office (NVPO)

Dr. Grabowsky thanked everyone for their indulgence, indicating that he was tardy due to engagement of a rehearsal operation exercise earlier in the morning in which they practiced transferring decision-making authority from Washington to Atlanta. The National Vaccine Plan was released in February. NVPO continues to write the implementation plan with some engagement activities. NVPO is well underway in terms of implementing priority areas such as the methodology for identifying vaccines and vaccines.gov has been launched. The Adult Immunization Working Group of the National Vaccine Advisory Committee released its report, and will vote on the safety report of that committee in September 2011. The Interagency Influenza Task Force is a high priority of Dr. Koh.

National Vaccine Advisory Committee (NVAC)

No report.

Discussion Points

Dr. Baker commented that she had reviewed the new health communication tools to improve provider care and interactions related to immunizations and found them to be outstanding. She inquired as to whether the updated report on the impact of vaccines had been or would be published.

Dr. Wharton responded that information was included in an *MMWR* article, which could be provided to ACIP members, and a peer-reviewed publication is being prepared.

General Recommendations: Febrile Seizures

Introduction

Jeff Duchin MD
Chair, General Recommendations Working Group

Dr. Duchin reminded everyone that the vaccine safety monitoring system reflected a small increase in seizures. This was discussed during the February 2011 ACIP meeting. Because of the observation of a potential increase in febrile seizures associated with PCV, CDC leadership asked the General Recommendations Work Group to establish a subgroup to evaluate the problem. The terms of reference for this subgroup were to:

- Review data on the risk for febrile seizures after seasonal trivalent inactivated influenza vaccine (TIV) and pneumococcal conjugate vaccine (PCV13/7) in children aged 6 through 23 months
- Describe what is known about the causes, preventive measures, and clinical significance of febrile seizures
- Present options to ACIP for any action(s) related to the use of these vaccines for the 2011-2012 influenza season
- Describe what is known about incidence of febrile seizures in association with childhood vaccines alone and in combination (including influenza, pneumococcal, pertussis-containing vaccines, MMR, MMR-V)
- Describe whether vaccination against influenza provides protection against febrile seizures
- Provide a framework for determining when vaccine-associated febrile seizures should lead to a change in recommendations for administration of one or more vaccines

Although the analysis of the significance of this observation is on-going, the risk appears to be lower than was initially estimated. During this session, presentations included a clinical review of febrile seizures; review of current data on association of febrile seizures with TIV and PCV; benefits of TIV and PCV (morbidity prevented; potential impact of missed doses); policy options; and communication considerations. The Febrile Seizures Subgroup Work Group concluded that no change in recommendation for simultaneous administration of TIV and PCV is indicated at this time. Additional data collection and analyses are underway, and information for healthcare providers and parents will be developed.

Clinical Aspects of Febrile Seizures

Harry L. Keyserling, MD
Professor of Pediatrics
Emory University School of Medicine

Dr. Keyserling explained that a febrile seizure is defined as a seizure with fever $>38^{\circ}\text{C}$ in children age 6 months through 6 years with no CNS infection, no prior history of epilepsy or afebrile seizures, or metabolic disturbances. Febrile seizures are quite common. Approximately 2% to 5% of children have a lifetime risk of developing febrile seizures. Of these, 97% are simple febrile seizure defined as generalized seizure lasting less than 15 minutes with no recurrence in the following 24-hour period. Complex febrile seizure make up 3% of febrile seizures defined as focal, lasting greater than 15 minutes, and/or recurrent within 24 hours. It is thought that complex febrile seizures are probably related to underlying CNS problems. In terms of the pathophysiology, the mechanism for fever causing a seizure is unknown. The fever can be from any sources (e.g., infection, vaccines, environmental). It is probably not a cytokine phenomenon, but is truly an increase in body temperature. The fever induces an abnormal, sudden, excessive electrical discharge of neurons. It is known that genetic factors are important. Children with febrile seizures have a family history in first degree relatives of 10% to 20%. Many genetic markers have been identified that correlate with febrile seizures.

In terms of the epidemiology, Berg assessed children in what Dr. Keyserling considered the pre-modern vaccine era before MMR and other vaccines from 1960 through 1967. This was a population-based study of an HMO from which 18,000 children were followed. The investigators assessed febrile and non-febrile seizures. Of the seizures, 70% were febrile, in the age group of 12 through 23 years of age about 90% were febrile, and 10% were admitted to the hospital. Regarding underlying cause, syndromic causes not laboratory-confirmed infections, 15% were roseola (some reports indicate that 30% to 40% of children below 20 years of age have roseola as the cause of febrile seizures), about 50% were upper respiratory infections, and about 15% were gastrointestinal disease [van den Berg BJ et al: *Pediatr Res* 1969;3:298-304].

Another important point is that even though during the period of life from 6 to 60 months of age children might have 25 to 50 febrile episodes, recurrences of febrile seizures occur in about 50% of children. Even in children with febrile seizures, the majority of the time febrile illnesses will not induce a febrile seizure and about 40% of the time the fever itself is the first indication to the parents that the child is ill.

Moving to the period from 1997 to 2006, a Vaccine Safety Data Link study showed that acellular pertussis vaccine was not associated with febrile seizures; whereas earlier studies of whole cell pertussis vaccine had shown an association. There was a very similar pattern to the earlier study. The incidence of seizures peaks at about 15 months of age [Huang, W.-T. et al. *Pediatrics* 2010;126:263-269].

An important question regards the sequelae or potential outcomes of simple febrile seizures. There are no significant sequelae for simple febrile seizures. There appears to be no decline in IQ, no developmental disorders, and no behavior disorders associated with febrile seizures. There is an increased risk of epilepsy and risk of recurrence of febrile seizures, and there are some theoretical risks (e.g., injury, aspiration, cardiac arrhythmias). There are approximately 100,000 to 200,000 febrile seizures per year in the US. From one emergency room report, in children in the age range of 12 to 23 months, about 1% of emergency room visits are related to the first simple febrile seizure. There really have not been any reports of significant injury, aspiration, or cardiac arrhythmias, so these could be rare events. It is important to remember that those in this age group are not swimming or driving. Toddlers fall down frequently, so the theoretical risk of having a problem related to physical manifestations of the motor activity from a seizure and loss of consciousness in this age group generally is not large.

Two population-based studies have addressed whether any significant brain damage occurs. The first showed that children with simple febrile seizures have approximately the same risk (1%) of developing epilepsy by the age of 7 years as the general population. Another study showed that children who have had multiple simple febrile seizures, are younger than 12 months at the time of their first febrile seizure episode, and have a family history of epilepsy are at a slightly higher risk (2.4%) of developing epilepsy by 25 years of age. This increase may be a coincidence rather than causal. In terms of risk of recurrent febrile seizure, a child who has one febrile seizure has a 30% chance of having another one, a 20% chance of having two, and about a 5% chance of having 3 seizures.

With regard to what occurs when a child is evaluated for a febrile seizure, the American Academy of Pediatrics (AAP) recently published new recommendations. Basically, the recommendation was to do nothing in terms of laboratory or imaging evaluations and to consider doing a lumbar puncture to evaluate the cerebral spinal fluid if the patient has evidence of CNS infection, or for children less than 12 months of age who have not been immunized with Hib and pneumococcal vaccines. An EEG, electrolytes, complete blood count, and neuroimaging are not recommended. In terms of treatment, continuous or intermittent anticonvulsant therapy is not recommended. While anticonvulsants decrease the risk of recurrence by 80% to 90%, there is significant toxicity. Phenobarbital has been associated with a decreased IQ and behavioral disorders. Therefore, the recommendation is that even though pharmacological intervention works, there is more risk than benefit. Antipyretics offer no benefit.

In terms of additional issues, certainly when a child has a febrile seizure it is stressful to the family, daycare center staff, and anyone else witnessing the event. There are also the costs of medical evaluation. Most of the time the parents bring their child in themselves; however, occasionally an ambulance is needed for which there is a fee, and the cost of an ER visit can vary depending upon the work-up but can be as high as \$2,000 for the evaluation.

Safety Data Update

Jerome I. Tokars, MD, MPH
Immunization Safety Office (ISO)
Division of Healthcare Quality Promotion
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention (CDC)

Dr. Tokars presented updated analyses on febrile seizures following a trivalent inactivated influenza vaccine (TIV) based on data from the VSD. Regarding the methods, data were obtained from 8 managed care organizations within the VSD. Self-controlled analyses compared the number of cases on days 0 to 1, which is the risk interval, to days 14 to 20, which is the control interval. Here, day 0 is the day of vaccination. Febrile seizures are initially identified using automated data seeking the ICD9 code for convulsion (780.3). Chart confirmation ensures febrile seizure. Data come from inpatient and emergency departments, and outpatient data are excluded. Only the first event in 42 days is collected to assist in identifying incident cases.

In February 2011, data were presented to ACIP that the VSD had identified an increased risk of seizures on days 0-1 post-vaccination among children 6 through 59 months of age who received their first dose of TIV. Most had received other vaccines, most commonly 13-valent pneumococcal conjugate vaccine (PCV13). Questions about the risk of febrile seizures after TIV included the following:

- Was the risk in 2010-11 higher than in past influenza seasons?
- What was the role of concomitant vaccines?
- What age groups were affected?
- What is the attributable risk?
- What is the effect of first versus the second dose of TIV?

The attributable risk per 100,000 in 12 through 23 month old children was found to be very high in children who received both TIV and PCV13. There is some evidence of elevated risk in those who received only one or the other of the vaccines, but the confidence interval overlaps with zero, so these are not statistically significant findings and are probably not clinically important. During the February 2011 ACIP meeting, it was reported that the largest excess risk was in 12 through 23 month old children who received a concomitant first dose of TIV and PCV13 (+/- other vaccines). The attributable risk was reported to be 61 (95% CI 13 to 109) per 100,000 vaccinees or approximately 1 excess febrile seizure in 1640 children who received both vaccines. Since that time, additional data for the 2010-2011 influenza season have been received, and a chart review of cases after TIV was completed. There has been an updated calculation of the attributable risk for first dose TIV. For children who received TIV with or without PCV13, chart-confirmed febrile seizure data were used. For children who received PCV13 only, non-chart confirmed data were used with an estimated chart confirmation rate. There are also data on the second dose of TIV. Dr. Tokars emphasized that these are preliminary data.

First dose TIV recipients age 6 through 59 months (N=206,174) from August 2010 through February 2011 included 40,375 (20%) 6-11 month olds; 60,677 (29%) 12-23 month olds; and 105,122 (51%) 24-59 month olds. TIV+PCV13 +/- other vaccines were received by 57,197 (28%) children; TIV+non-PCV13 vaccines were received by 37,364 (18%) children; and TIV only was received by 111,613 (54%) children. The number of cases identified by ICD-9 codes was 32 in the risk interval and 34 in the control interval. Available for chart review were 30 in the risk interval and 31 in the control interval. There were 27 chart-confirmed cases in the risk interval and 26 in the control interval. There were 25 chart-confirmed seizures in the risk interval and 22 in the control interval [Chart confirmation rate for risk interval 25/30 (83%), for control interval 22/31 (71%), for both combined 47/61 (77%)]. The reason that many of these are not confirmed as febrile seizures appears to be because of a lack of documentation, so there are more seizures than can be definitely described as febrile seizures with confidence.

In terms of the characteristics of the TIV recipients with chart-confirmed febrile seizures in the risk interval (N=25), 21 (84%) were diagnosed in the emergency department and 4 (16%) were diagnosed in the inpatient setting. Of the 25 cases, 8 (32%) had a prior history of seizures, 5 (20%) had a family history of seizures, 5 (20%) had a concurrent URI (including 2 otitis media, 1 pharyngitis), 1 (4%) had a concurrent UTI, 17 (68%) received concomitant PCV13, and 17 (68%) received concomitant DTaP. In the data presented in February 2011, slightly more children had received PCV13 than DTaP, while in the updated data 13 received both PCV13 and DTaP. While they have data on PCV13, data have not yet been received on DTaP.

Updated attributable risk estimates of febrile seizures were calculated in 9 categories by age group and receipt of concomitant PCV13. The primary finding is that the highest elevation in attributable risk continues to be in children 12 to 23 months of age who have received both vaccines. The attributable risk is in the range of 42; however, there is also some evidence of an increase in attributable risk in the other age groups who received both vaccines, and some evidence of increased risk in the 12 to 23 month old children who received only TIV or only PCV13. These findings are based on generally low numbers stratified into the 9 categories. In terms of first versus second dose of TIV, the number of children who received TIV+PCV13 +/- other included 5,476 children. This is roughly only one-tenth of the number who received first dose of TIV+PCV13. The number of cases in the risk (n=2) and control (n=3) intervals were small. Because of the small numbers, the estimate of risk of the second dose of TIV is really not feasible.

In response to the questions that were raised about the risk of febrile seizures after TIV, in terms of whether the risk in the 2010-11 season were higher than in past influenza seasons, risk was primarily seen in the 2010-11 season. Regarding the role of concomitant vaccines, risk is highest when TIV given with other vaccines. Concomitant PCV13 versus DTaP were received equally by cases. Data are currently not available to evaluate DTaP. However, PCV13 was new for 2010-11 season, and increased risk of febrile seizures was not found after TIV in prior years when DTaP was used. With respect to the affected age group, there are limited data to define an age group-specific risk. Current analyses show that the highest attributable risk in the 12 through 23 month group and there is some evidence of risk in the 6 through 11 month age range. The updated attributable risk estimate for 12 through 23 month olds when TIV is given concurrently with PCV13 is 42 (95% CI 3,81) per 100,000 or 1 per 2375 vaccinees. The caveats are that the measures are of TIV administered with PCV13 concomitantly versus no vaccine, not versus TIV and PCV given at separate visits. The confidence interval is wide, and focusing on a single point risk estimate may be misleading. In terms of the question regarding the effect of first versus second dose of TIV, the limited number of second dose vaccinees and few cases limit the ability to compare effects.

Further work to address this issue includes an alternate modeling approach to calculate the attributable risk using a larger dataset to estimate the baseline risk; assessing the effect of DTaP; comprehensively studying recommended childhood vaccines and febrile seizures; and continuing to monitor during the 2011-2012 season.

Burden of Disease Information / Next Steps

Andrew Kroger M.D., M.P.H.

**National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention**

Regarding the burden of influenza among children in the US, Dr. Kroger reported that complications include respiratory issues (otitis media, sinusitis, croup, pneumonia—viral and secondary bacterial), musculoskeletal (myositis, rhabdomyelitis), cardiac (myositis, pericarditis), neurologic (seizures, encephalopathy, encephalitis), and exacerbation of chronic conditions (asthma, cardiac failure). Hospitalization rates from influenza vary with season and age group. Estimates from 2003-04 through 2007-2008 in children less than <6 months of age were 9 to 30 per 10,000/year, in children 6-23 months 3 to 11 per 10,000/year, and in children 2-4 years 1 to 4 per 10,000/year. For children <5 years, estimated direct costs were \$40 to \$160 million for hospitalizations and \$60 to \$270 million for emergency department visits. Mortality varies with season, with the highest mortality in the youngest children. In the 2003-2004 season mortality in children < 6 months was 0.88 per 100,000/year, in children 6-11 months 0.59 per 100,000/year, in children 1 year of age 0.77 per 100,000/year, and in children 2 years of age 0.35 per 100,000/year [Dawood F et al. *J Pediatr* 2010; 157(5):808-14; Fairbrother G et al. *Vaccine* 2010;28(31):4913-4919; Bhat et al. *N Engl J Med* 2005;353:2559-2567].

Regarding influenza-associated pediatric deaths by week of death from 2007-2008 through 2010-2011, for the week ending June 11, 2011 FluView showed that influenza mortality like influenza disease follows a seasonal pattern as would be expected. Therefore, seasonality is critical in terms of a vaccination policy.

An association of febrile seizure with influenza, particularly Influenza A, has been noted. Chung et al (Hong Kong) found that influenza A was associated with 17.6% of 923 hospitalized febrile seizures over 5 years. Chiu et al (Hong Kong) showed that in 1997 and 1998, influenza A accounted for 10.8% and 21.7% of febrile seizure admissions, respectively (35% and 44% during periods of peak flu activity). Kwong et al (Hong Kong) found that 19.5% of children admitted with influenza A developed febrile seizures. Van Zeijl et al (Netherlands) noted a positive seasonal correlation between peak influenza activity and febrile seizure presentation. In a retrospective cohort study of children hospitalized with lab-confirmed influenza (LCI) during 4 seasons (2000-2004), Newland et al (Philadelphia) found that of 435 patients 6 months through 4 years of age, 27 (6.2%) had seizures meeting definition of simple febrile seizure [Chiu SS et al. *Pediatrics* 2001;108:1-7; Kwong KL et al. *Pediatr Neurol* 2006;35:395-399; Chung B et al. *Arch Dis Child* 2007;92:589-593; Van Zeijl et al. *J Pediatr* 2004;145:800-805; Newland J et al. *J Pediatr* 2007;150(3):306-310].

2010-2011 ACIP recommendations for influenza vaccination for children aged ≥ 6 months are as follows [MMWR 2010;59:1-62]:

- ❑ Annual vaccination recommended for all persons ≥ 6 months
- ❑ For children 6 months through 8 years receiving seasonal influenza vaccine for the first time, two doses are required to ensure adequate immune response
 - Doses must be administered a minimum of 4 weeks apart
- ❑ Schedule determined to some extent by time of year (vaccine becomes available approximately in September)
 - Optimal protection afforded by administration of both doses early in season

In terms of the US burden of pneumococcal disease following introduction of 7-valent pneumococcal conjugate vaccine, data from a national ambulatory medical care survey showed a drastic reduction in invasive pneumococcal disease. Even at this point, in all age groups there were still 4 million illness episodes. There were 445,000 hospitalizations for community-acquired pneumonia, with $>90\%$ of these hospitalizations occurring among persons ≥ 5 years old, and there were 22,000 deaths. The annual direct costs totaled \$3.7 billion and totaled \$7.7 billion including indirect costs. In children less than 5 years of age there were 1,050,000 illness episodes, a total of 1,132,000 antibiotic courses, and 42,000 hospitalizations [Huang, Vaccine 2011;29:3398-412]. This is relevant because protection of vaccine is relied on for herd immunity and reduction of disease in all age groups.

The 13-valent pneumococcal conjugate vaccine was introduced into the routine schedule in March 2010. This replaced PCV7, which was associated with prevention of 211,000 cases of invasive pneumococcal disease between 2000 and 2007 (Pilishvili JID 2010). The 13-valent vaccine was recommended for all children at 2, 4, 6, and 12-15 months. The relevance of a booster dose in the second year of life is that it confers additional individual protection over primary series, it is likely important for mucosal immunity (pneumonia, otitis), and it is considered important for reducing transmission to other age groups. Most developed country schedules include a booster dose, though some use only 2 doses (“2+1” schedule) in the first year.

Invasive pneumococcal disease is also seasonal. Data from that Active Bacterial Core (ABC) surveillance system from 1998-2008 showed that the percentage of cases is highest in the months of September through April, similar to influenza disease in some respects. Again, there will be somewhat of a window in which vaccination needs to be administered in order to target the vaccination for the prevention of disease. In terms of the importance of vaccinating various age groups, the highest incidence rate is in the age group 12 through 15 months of age (24 cases per 100,000). To wait until 16 to 18 months would involve missing the peak incidence in the earlier age group [CDC, Active Bacterial Core surveillance, unpublished].

The WG realized that it was limited in the amount of safety data available, although safety data are continuing to be received on an on-going basis. The influenza vaccination season will arrive in September as well, and the WG is aware that something must be done about this in terms of having a message about the safety data. Thus, part of the working group’s task was to determine what type of data are available to warrant any kind of changes in the nature of the message. Data are available that assess the risk of febrile seizures with simultaneous vaccination, the amount of simultaneous vaccination with TIV and PCV, and the dose number for the fourth dose of PCV13 (as opposed to 5th dose following a recent 4th dose after first

birthday) and for dose number 1 versus 2 of TIV. Data are needed regarding the risk of febrile seizures with simultaneous versus non-simultaneous vaccination, and for the context of simultaneous vaccination with other vaccines.

Regarding the rate of simultaneous vaccination, National Immunization Survey data were assessed to get a sense of how often simultaneous vaccination occurs. Children age 12 through 23 months who were vaccinated in one influenza season (2008-2009 season) were included in the assessment. The number of children who received PCV and TIV simultaneously totaled 471,296 that season. This is basically a population-based estimate of simultaneous vaccination rate using a 4 million birth cohort equaling 12%. With an attributable risk of (42/100,000) 198 febrile seizures might be expected in a typical season due to simultaneous vaccination. However, an important caveat is that the seasons are not typical. In the 2010-2011 season, for example, there was a specific formulation of TIV and a mix of PCV7 and PCV13. It is difficult to draw long-term conclusions based on current data.

The number needed to vaccinate to prevent one hospitalization from influenza ranges from 1031 to 3050 at 50% vaccine efficacy in children 6 through 23 months of age [Lewis EN, Griffen MR, Szilagyi PG, et. Al. Pediatrics, 2007]. This is an important statistic from the perspective of trying to come up with some type of risk-benefit calculation of simultaneous vaccination. Interpretation of true efficacy can vary. The paper by Lewis et al addresses this. This raises the question: How much risk of influenza infection and invasive pneumococcal disease are we willing to take with delayed vaccination, in order to prevent the occurrence of febrile seizures?

In terms of the potential contribution of other vaccines, there was a past recommendation to select MMR + varicella instead of MMRV for the first dose in children 12 through 47 months based on an attributable risk of febrile seizures of approximately 40/100,000. Current VSD data suggest that other vaccines might have elevated risk as well. Chart-reviewed cases of febrile seizures suggest that simultaneous TIV and DTaP have risks comparable to TIV and PCV13 (number of cases 17). DTaP is not even on the table for messaging due to lack of data.

There have been some attempts in the WG at consensus, and there were later attempts at consensus following the publication of the handouts. The working group WG feels that the issues regarding febrile seizure need to be addressed through messaging; however, this does not necessarily require an ACIP vote. The data are still pending, but some important information can still be placed in messaging, including a statement about the general risk of febrile seizures; information about the benefit of prevention of influenza / invasive pneumococcal disease (burden of disease); information for the provider regarding additional criteria which must be met to make the decision to give simultaneous vaccination or to defer (e.g., children at risk for invasive disease; no family history of febrile seizures; if family history, consideration of antipyretics). There was fairly strong consensus among WG members that if a decision was going to be made to delay one of the doses, delaying of PCV13 is preferable. During the February 2010 ACIP meeting, revisions were made to the General Recommendations on Immunization stating that there is no evidence to suggest that antipyretics should be given prior to or during administering a dose of the vaccine. The question remains: Should antipyretics be given after vaccination before fever occurs? This has been discussed, and there are opinions on both sides of the issue.

Discussion Points

Dr. Keitel inquired as to what form the messaging would take and how it would be presented.

Dr. Kroger replied that a policy note is an option, although that would not have an ACIP recommendation behind it. The thinking is more along the lines of information for the website, and the content for this is being developed. There is also discussion about whether there are specific groups for which a delay might be permissible. Whether the Vaccine Information Statement (VIS) is being discussed in terms of whether this is a suitable medium for dissemination of this type of information. While used by providers, VIS information is intended for parents. There is a long turnaround time to revise a VIS. It can take months to make a revision to a VIS, which is a disadvantage because there is a short turnaround time for the upcoming influenza season. Given that the data are variable and it is unclear what to predict in various seasons based on the different formulations of vaccines and seasonality variance with respect to severity, it is unclear whether a long-term turnaround time for the VIS will be applicable for this influenza season. There is fairly solid certainty that information will be included in the website.

Regarding the association of influenza disease with febrile seizure, Dr. Cieslak asked whether there was a way to estimate the risk of febrile seizure following an actual episode of influenza. That would be one of the easiest ways to address relative risk. While hospitalizations were mentioned, a nice direct comparison of risk of febrile seizures would be an easier message.

Dr. Kroger responded that the data are limited to hospitalizations, but there are data that include risk of hospitalization for influenza and how many of those have had febrile seizures.

Dr. Marcy requested further information regarding why the cohort is 12 to 23 months when most children receive their combination vaccine at 12 to 15 months.

Dr. Tokars clarified that Dr. Marcy was referring to the fact that the data are currently divided into three groups, one of which is 12 through 23 months of age. While the data could be divided into other groups, the question regards whether there is a clear reason for doing that versus what might be referred to as “epidemiologic gerrymandering” because there is a higher relative risk in one group. Certainly, the dose of PCV would be given during that timeframe. It is not clear whether the best way to analyze the data is to hyper-stratify it into smaller and smaller categories. Even if there was a higher relative risk on one category, possible due to small numbers, it is not clear how much credence this could be given. Rather than stratification, another approach is to use a regression analysis that does not cut things into small categories, which is how this was approached.

Dr. Chilton expressed concern about the possibility of recommending the use of acetaminophen to families with a history of febrile seizures, given that as Dr. Keyserling noted, acetaminophen is not successful in preventing febrile seizures and one study indicated that it could decrease response in patients simultaneous given a pneumococcal vaccine and acetaminophen.

Dr. Kroger clarified that Dr. Chilton was referring to the study in *The Lancet* that discussed the effect of antipyretics on the pneumococcal vaccine. Those data were presented to ACIP prior to publication, and Dr. Kroger thought it was after the vote but prior to the publication of the general recommendations. His recollection of the discussion was that one of the challenges of interpreting that paper was interpreting the clinical relevance of the results with respect to pneumococcal conjugate vaccine. The wording was clarified in the general recommendation to

state that there is no evidence to support the use of antipyretics. That change was in part due to the fact that based on the data, antipyretics do not seem to prevent febrile seizures in those who have previously experienced a febrile seizure. More papers are anticipated to be published on the topic of antipyretics. Although he did not know the specific results, Dr. Kroger indicated that they are assessing immunogenicity and antipyretics and it seems to be tipping the other way from the results in the other article.

Dr. Baker reported that Dr. Pickering had shown her an article pertaining to the potential for overdose of acetaminophen, which raised an additional caution for this situation.

Dr. Sawyer expressed concern about focusing on an adverse event from a vaccine without focusing sufficiently on the benefit of the vaccine or the risks of not vaccinating. He called attention to the background materials provided to the ACIP membership that discusses why children fall behind on their vaccine schedule. The primary reason those 9 to 15 months of age fall behind is failure to receive simultaneous vaccination when in their doctor's office. They run the risk of contributing to this issue by suggesting that simultaneous vaccination might be problematic. Careful consideration must be given to the balance in communication and emphasizing the risk of not being vaccinated.

In terms of messaging, Dr. Baker inquired as to the plans of partner organizations with respect to separate communication efforts from or communication efforts in collaboration with CDC on this matter.

Dr. Brady (AAP) replied that given the current information, it is reasonable not to make any major changes either in communication or otherwise since there is insufficient information to make a strong statement. If by some chance there is a change, AAP could utilize a number of methods to inform the pediatric community (e.g., blasts, briefs, on line, et cetera). He concurred that the worst course of action would be to send a message that would suggest that delaying vaccination is a better strategy than preventing disease. It is already difficult to ensure that children are vaccinated on time, and the risk of disease is worse than the risk of febrile seizure.

Dr. Baker emphasized that the risk of disease is much greater than the risk of any adverse events based upon the data.

Dr. Campos-Outcalt (AAFP) concurred that any communications should address relative risks, putting the risk of febrile seizure in context with disease.

Dr. Englund agreed and thought that for ACIP to recommend that providers discuss febrile seizures during a visit would be harmful to the process. If such a recommendation were to be made, it should be done on the day the child is born since the risk of febrile seizure is a common childhood event and the vast majority are not associated with vaccines.

Dr. Temte thought much had been made about sometimes over-responding to signals. He acknowledged their wonderful colleagues at the VSD who are establishing a great deal of expertise in responding to potentially harmful signals. The question regards whether to couple the assessments of an exposure and the potential outcome with a concomitant evaluation of febrile seizures within the VSD in terms of harms versus benefits. Some of the discussion pertaining to influenza regarded the fact that influenza alone could cause febrile seizures. Perhaps immunization to prevent influenza could prevent febrile seizures. In retrospect, it is a wash or actually a benefit.

Dr. Judson agreed with the general sentiment that had been expressed, and thought the issue of antipyretics to be subsidiary. He thinks that it is important to distinguish between anti-inflammatory and non-anti-inflammatory antipyretics, because there is a theoretical possibility that anything that reduces inflammation can also reduce the beneficial inflammatory immune response to the vaccine versus the acetaminophen.

Dr. Duchin pointed out that as they got involved in the subject of long-term issues pertaining to febrile seizures and vaccines, it would be extremely beneficial to hear the results of studies on febrile seizures. CDC has several networks in place that would be appropriate to assess this type of problem.

Dr. Jenkins noted that while she did not know the general procedure for development of informational materials involving lay audiences, she thought it was important to strike the right balance in terms of protection versus risk. She suggested that parents could offer beneficial feedback.

Dr. Pickering thanked those in the Immunization Safety Office (ISO) for their hard work regarding this activity. This has been a phenomenal gathering of data. Regarding Dr. Tokar's slide #11 titled "Characteristics of TIV Recipients with Chart Confirmed Febrile Seizures in the Risk Interval," the table indicates that 5 children had URIs and 1 child had a UTI, which is 6 children or 25%. He wondered what the consideration was for excluding children with these confounders from the analyses. Clearly, they could have fever due to the underlying medical condition, and exclusion could change the findings.

Dr. Tokars responded that these are children in the risk interval, so there could also be children in the control interval who have these diseases as well. In fact, these are the febrile seizures that would be due to URI and not vaccine. This would be referred to as non-differential misclassification, which would bias the results toward the null. It is possible that if these were excluded, there would be higher risk. One reason for not doing this is that there has been difficulty obtaining data on certain information regardless of whether a child had fever. If people continue to be excluded, there will be such a small set of data, the investigators will not be able to say anything about the issue. That is the trade-off.

Dr. Paradiso (Pfizer) pointed out that the group under consideration received TIV with or without PCV because those were the signals assessed. If 75% of the children also had DTaP and 90% had one other vaccine, it was not clear how those would be teased out. He suspected that if they considered TIV+DTaP and 75% of the children had DTaP, it would result in the same answer as TIV administered with other concomitant vaccines. He wondered how that would be taken into consideration with multiple vaccinations.

Dr. Tokars responded that the current data do not include children who received DTaP and not PCV13 or TIV. When those data are received, it may be possible to unravel some of this. However, if most of the children received all three vaccines simultaneously, it becomes an unanswerable question. They really cannot speculate beyond what the data show. Vaccines other than these three are down the list in terms of frequency, so it does not appear that they belong in the mix in terms of figuring out what is occurring.

Dr. Duchin pointed out that in past years when children received TIV, DTaP, and PCV7, this risk was not observed. Circumstantial evidence has changed. In addition to the formulation of the influenza vaccination is the addition of PVC13.

Dr. Coyne-Beasley noted that in terms of crafting the messaging, there will be people who present with low-grade fever or children with no contraindications merely because the media influences them not to acquire the vaccine.

Dr. Tan (AMA) supported many of the statements regarding balancing of the message. He reminded everyone that this all began because of the reports of febrile seizure in Australia. He congratulated the VSD for its ability to respond and provide data, and for reassuring everyone that the US has a system that works.

Hepatitis B Vaccines

Introduction

Mark Sawyer, MD
Chair, Hepatitis Working Group

Dr. Sawyer reported that the Hepatitis Working Group continues to discuss the issue of Hepatitis B vaccination in persons with diabetes, and wanted to determine whether the ACIP membership received adequate information to prepare them for a potential vote on this topic during the October 2011 meeting.

The WG discussion in 2009 about this term of reference was initiated because of continuing outbreaks of hepatitis B among adults with diabetes. In recent years, these outbreaks have been identified among older adult residents of long-term care facilities, particularly assisted living facilities. Outbreaks were tied to lapses in infection control practice, primarily during assisted blood glucose monitoring. Lapses during other care practices also might contribute. Patient-to-patient transmission has been the major mode of transmission. A person with chronic hepatitis B infection is the source of the virus for others, through lapses in infection control. Residents of these facilities are usually older adults, and they suffer substantial morbidity and high fatality rates from acute hepatitis B. They also may have high rates of chronic infection, which contributes to a reservoir for further transmission. Outbreaks have continued, despite infection control guidance for long-term care facilities since 2005.

The WG has had extensive discussions covering a wide range of topics since 2009. Presentations have been given on this topic at 5 ACIP meetings, and to the Healthcare Infection Control Practices Advisory Committee (HICPAC). A number of CDC/FDA/CMS initiatives have been undertaken during this time to provide additional infection control guidance, to alert the patients and the public about these concerns, and to encourage development of improved diabetes care devices, and updated patient guidance has been posted on the CDC and American Diabetes Association (ADA) websites.

This session included updates on incidence of acute hepatitis B by diabetes status and age, economic analyses of a program for vaccinating adults with diabetes, and proposed recommendations from the Hepatitis Working Group.

Update of Hepatitis B Incidence Among Persons with Diabetes

Meredith Reilly, MPH

Division of Viral Hepatitis

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

Centers for Disease Control and Prevention

Ms. Reilly presented an update on the estimated incidence of acute hepatitis B among adults with and without diabetes. The updated analysis included additional diabetes data provided by the Emerging Infections Program (EIP) sites following the February ACIP meeting. Before presenting the updated estimates, Ms. Reilly briefly reviewed the methods used to estimate annual acute hepatitis B incidence. The numerator consisted of confirmed acute hepatitis B cases from four EIP sites in 2009 and 2010. Cases in persons less than 23 years were excluded because vaccination coverage is likely high among this age group. In the analysis presented in February, 31% of cases had unknown or missing diabetes status and these cases were excluded from that analysis. To address the cases with missing diabetes data, the EIP sites were asked to attempt to determine the diabetes status of these cases. Over the past several months, the analysis was updated with new data that resulted from the EIP sites' efforts. The proportion of cases with unknown diabetes information decreased from 31% to 18% by early June 2011. As suggested by ACIP in February, the remaining cases with unknown diabetes status were classified as "persons without diabetes." The denominator was determined using 2009 state based Behavioral Risk Factor Surveillance System (BRFSS) data along with the New York City (NYC) Community Health Survey for self-reported diabetes status among adults 23 years or older.

During 2009 to 2010, 331 reported acute hepatitis B cases aged 23 years or older were reported in the four EIP sites. Of these, 49 (14.8%) had a diabetes diagnosis, 282 (85.2%) of cases had either no documented diagnosis of diabetes or no diabetes information, 224 (67.7%) cases or 2/3 of these were documented as "no diabetes," and there was no diabetes information for 58 cases (17.5%).

Data on the number and percent of acute hepatitis B cases by age group and diabetes status highlight differences in diabetes prevalence among acute hepatitis B cases between younger and older age groups. Of acute hepatitis B cases, 12.6% of those 23 to 59 years of age had been diagnosed with diabetes, and 26.4% of those aged 60 years and older had been diagnosed with diabetes. Comparing these figures to the general population across the four EIP sites, 5% of adults aged 23 to 59 years, and 18% of adults aged 60 years and older, had been diagnosed with diabetes. Overall, the EIP case report data indicated that approximately 15% of acute hepatitis B cases had been diagnosed with diabetes, higher than the 8% estimated diabetes prevalence among the general population of the four EIP sites.

The overall incidence of acute hepatitis B among adults with diabetes was 2.1 per 100,000 compared with 1.1 per 100,000 for adults without diabetes. The rate ratio of 1.9 was statistically significant. For adults aged 23 through 59 years of age, the rate ratio comparing acute hepatitis B incidence among adults with diabetes to adults without diabetes was statistically significant at 2.6. For adults aged 60 years and older, the rate ratio was 1.6, but was not statistically significant.

To summarize, additional data on diabetes status resulted in higher incidence estimates and similar rate ratios compared with results presented to ACIP in February 2011. Updated estimates were included in the economic analysis to be presented during this session. Rate ratios of 2.6 for adults aged 23 through 59 years and 1.5 for adults aged 60 years and older were used in the model. Since then, additional data resulted in a slight increase in the rate ratio to 1.6 for adults aged 60 years and older. To strengthen the analysis, additional EIP sites have agreed to evaluate the diabetes status of their acute hepatitis B cases reported during 2009 and 2010. Additional data are expected over the next few months.

Discussion Points

Dr. Keitel asked whether there was any additional information about other behavioral risk factors that could be associated with acquisition of acute hepatitis B.

Dr. Reilly responded that the investigators compared some of the reported risk factors that the sites collect routinely (e.g., two or more sex partners, MSM, sexual contact, IDU, household contact) by diabetes status and did not find any significant differences between the two groups. For most risk factors, the groups without diabetes had a slightly higher rate of reporting those risk factors.

Dr. Pickering inquired as to whether there were any data on the incidence or prevalence of hepatitis C between the two groups.

Dr. Reilly responded that for this study, hepatitis C was not assessed.

Dr. Cieslak noted that hepatitis C is usually asymptomatic and surveillance for it is abysmal.

Cost-Effectiveness of Hepatitis B Vaccination Among Persons with Diabetes

Thomas J. Hoerger, PhD
Public Health Economics Program
RTI International

Dr. Hoerger indicated that the study question was relatively simple: What is the cost-effectiveness of hepatitis B vaccination among adults aged 20 through 59 years with diabetes in the United States? The perspective taken for this study was to assess the direct medical costs (e.g., the cost of vaccination minus the costs averted by vaccination), and will also examine QALY adjusted life years gained.

The main intervention strategy is the use of hepatitis B vaccine in adults aged 20 through 59 with diagnosed diabetes, which potentially includes up to 8.4 million persons. The reason the study focused on those aged 20 through 59 is because there is evidence of declining vaccine efficacy, especially after age 60, and because the preliminary analyses showed that there are very high cost-effectiveness ratios at higher age groups. Also examined was the alternative strategy of vaccinating all adults age 20 year and older with diagnosed diabetes, which includes about 17.2 million persons. The difference between this and the main intervention is the addition of vaccinations for individuals 60 and older. The time frame for the intervention is one year, so it was assumed that everyone would take up the vaccine within a year. The analytic horizon to assess the saved medical costs and QALYs gained is the remaining life expectancy

of the target populations. As is recommended for cost-effectiveness studies, a 3% annual rate was used for discounting.

The analytic method was cost-utility analysis (CUA), which is a specific type of cost-effectiveness study. Now it is becoming so common that CUAs and cost-effectiveness analysis are used almost interchangeably. What makes it a CUA is that the changes in QALYs are being assessed as the denominator in the incremental cost-utility ratios (ICURs):

$$\frac{(\text{vaccine cost} + \text{administration cost}) - (\text{cost of illness averted by vaccination})}{\text{Change in QALYs}}$$

Change in QALYs

The summary outcome measure is QALYs gained which accounts for patient utility in a health state and the number of years in the health state. Deaths are accounted for by assigning a utility value of zero in the years when the person is deceased. All costs are in year 2010 dollars.

A decision tree is used in the analysis for acute infections. At the branch that says “susceptible” there is a probability of infection or no infection. Of acute infections, about 30% are symptomatic and 70% are asymptomatic. Of those who have symptomatic disease, about 38% are hospitalized and the rest are not. If they are not hospitalized, they do incur some costs for outpatient care but they recover. Among the hospitalized cases, about 4% are fulminant infections and some of those require liver transplants. Among those who do and do not receive liver transplants, there is a possibility of death. For asymptomatic cases, about 6% will become chronic infections [Acute model structure and parameters based on Zhou et al., 2003 and Kim et al., 2006].

In terms of transitions after chronic infection, chronic hepatitis is important because it can lead to compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), and liver transplantations and death. Probabilities are included in the model for all of these complications. This model is run to calculate how many people have these various complications [Chronic model structure and parameters based on Zhou et al., 2003 and Kim et al., 2006].

One of the key factors in this analysis is the incidence among adults with diabetes by age group. One of the primary factors is that account is taken of the hepatitis B incidence ratio among persons with diabetes versus those without diabetes. EIP sites’ hepatitis B incidence ratio for diabetes was 2.6 until age 60 at which time it is 1.5. The calculated incidence per 100,000 diabetes increases until around age 35 to 39 and then begins to decline based on these numbers from the surveillance. It is also important to account in the analysis for the fact that those cases are only coming from individuals who are susceptible, so also taken into account is the fact that some people already have been naturally infected with hepatitis B infection and some individuals have already been vaccinated.

For the incidence among susceptible adults with diabetes, existing vaccine coverage is taken into account and is relatively high for younger age groups and declines as individuals become older. Also taken into account is the prevalence of previous HBV infection based on individuals who have diabetes. Again, the incidence rates are higher among the relatively younger age groups. Vaccination program inputs include 10% coverage with a 3-dose series, a private vaccine price per dose of \$52.50, a CDC vaccine price per dose of \$28.00, administration costs per dose of \$14.42, lifetime duration of protection, and no adverse events since the vaccine is generally considered to be very safe. The uptake rate of 10% is based on indirect evidence about what might occur if there is a recommendation that these groups be vaccinated; there are three pieces of indirect information. One of these is the difference in vaccination rates between people who are currently recommended for vaccination and those who are not currently recommended to receive vaccination. A second piece is estimates from manufacturers of the increase in demand that would occur if people with diabetes were recommended for care, and the third is based on the uptake rate for DTaP vaccination. The analysis can be viewed as a one-time catch-up program with all susceptible adults with diagnosed diabetes offered vaccination and a 10% take-up rate. Vaccine efficacy estimates are based on a CDC review of vaccine efficacy studies in adults and persons with diabetes. There is certainly evidence from this review that efficacy rates fall as age rises, especially after age 65.

The cost inputs for the various complications include the following:

Variable	Cost
Outpatient costs for symptomatic	\$402
Hospitalization for non-fulminant	\$12,034
Hospitalization for fulminant	\$19,481
Chronic hepatitis	\$1,824
Inactive carrier	\$402
Compensated cirrhosis	\$7,402
Decompensated cirrhosis	\$46,864
Hepatocellular carcinoma (HCC)	\$40,334
Liver transplantation (1st yr)	\$378,229
Liver transplantation (subsequent yr)	\$36,725

The Health Utility Index is based on a product of baseline value for persons with diabetes and utilities for hepatitis states and is as follows:

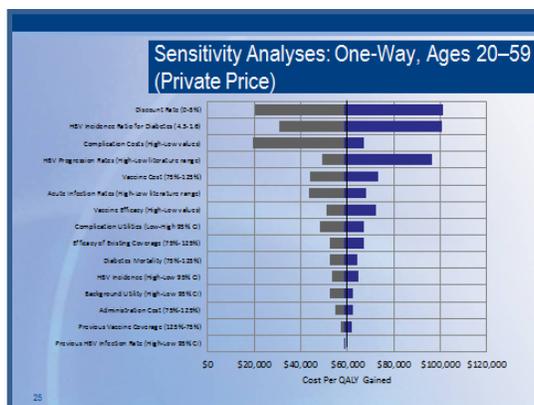
Susceptible / Immune	0.75
Inactive carrier	0.74
Chronic hepatitis	0.71
Compensated cirrhosis	0.62
Decompensated cirrhosis	0.41
HCC	0.37
Liver transplantation	0.65

Another assumption made is that there is no cost for visits incurred either by patients or physicians because these vaccination will be administered during visits for diabetes-related care. There are relatively frequent visits for persons with diabetes, so vaccinations can simply be added on to those visits. Also incorporated in the model are background diabetes mortality rates [Kim et al., 2006]. The relative risk of death for persons with diabetes is approximately 2 for most age groups [Geiss et al., 1995; Gregg et al., 2007; 2011 Diabetes Fact Sheet], but it is lower for age groups 75 and older [McBean et al., 2004]. This may be important because many deaths occur in these age groups. In terms of one-way sensitivity analyses, low and high clinically relevant values based on the literature are used. For probabilistic sensitivity analyses, input values are drawn from all distributions simultaneously, 1000 draws are run, and 95% credible intervals are calculated.

In terms of the results, the main analysis focuses on vaccinating persons aged 20 through 59, but also assessed are cases prevented by vaccinating those 60 and older. For example, vaccinating 10% of persons 20 through 59 years will prevent 5071 acute infections over the course of these persons' remaining lifetimes. Of these, about 1521 would be symptomatic, leading to prevention of 555 hospitalizations, 23 fulminant cases, 9 transplants, and 16 fulminant deaths. Given that about 6% of acute cases lead to chronic infection, about 304 chronic cases will be prevented and corresponding complications including 175 cases of cirrhosis, 67 cases of decompensated cirrhosis, 40 HCCs, 6 transplants, and 141 deaths. For the age group 60 and above, the numbers are much lower.

Turning to cost utility results with a 10% take-up rate, the results for the main intervention include \$110,172,395 in program costs; \$22,681,172 in medical costs saved; \$87,491,223 in net cost; 1,489 discounted QALYs saved; and a cost per QALY of \$58,762. The results do mask differences between different age groups. The cost per QALY is about \$6,000 for the youngest age group of 20-29; it is about \$57,000 per QALY for 40 to 49; and \$249,000 per QALY for 50 to 59 years. As noted, the main analysis focuses on the 20 to 59 age groups, but the older age groups are shown to illustrate that the cost-effectiveness ratio really increase in those groups. There are three major factors that drive the result that cost-utility ratios rise with age, including fewer years at risk because life expectancy is shorter, lower hepatitis incidence risk after ages 35-39, and declining vaccine efficacy. Regarding the cost utility of vaccinating those individuals older than 60, for the entire population of 20 and older, the cost-utility ratio is \$159,633 per QALY. In just the oldest age group, this goes up much higher to over \$2 million per QALY.

The following diagram shows the sensitivity analysis. Some related variables are grouped in the diagram, with all variables in the group set to their low values and then to their high values. Effects of individual inputs from the group are generally very small. Ordering in parentheses indicates which value of the input parameter leads to a lower cost-utility ratio and which value leads to a higher cost-utility ratio. For example, high complication cost values lead to lower cost-utility ratios and low complication cost values lead to higher cost-utility ratios. For the discount rate, zero percent leads to the low value and 5% leads to high value. In the case of the hepatitis B incidence ratio for diabetes, it is the high value which is from the 95% confidence interval of 4.3:



To understand how sensitive the results are, low and high clinically relevant parameters are included. In many of these cases, for example in the case of complication costs, all of the low values and all of the high values were grouped together to come up with this calculation.

Again, for the probabilistic sensitivity analysis, input parameters were drawn from appropriate distributions and the model was run 1000 times. The 95% percent credible interval is based on the 2.5 and 97.5 percentile values for each output variable. Note that the median, 2.5 percentile, and 97.5 percentile results for different variables may not come from the same model run (e.g., the 2.5 percentile value for QALYs saved may come from a different model run than the 2.5 percentile cost per QALY saved). Especially important is the cost per QALY (\$56,681) for which the probable interval rises from \$18,442 to \$129,082 per QALY. As in most studies, there is uncertainty of the cost-utility ratio.

A number of other analyses were also done. One of these assessed the base case for age 20 through 59 years using the lower CDC price (\$28 per dose) rather than the higher private patient price (\$52.50 per dose). This led to a lower cost per QALY of \$31,000. Unfortunately, the percentage of adults who received hepatitis B vaccine at the CDC price is unknown. The impact of take-up rate on costs, QALYs, and ICUR was assessed for ages 20-59 at the private price. This showed that QALYs gained also rise proportionately with uptake-up rate. As uptake-up rate increases, the cost of the program increases, but the ICUR remains the same because net costs (the numerator in the ICUR) and QALYs gained (the denominator) increase proportionately. In addition, a qualitative analysis was done of the overlap with current recommendations. Some adults aged 20-59 with diabetes are already recommended for vaccination. Of these, 15% have chronic liver disease, severe kidney disease, or high-risk behavior for infection. This rises to 24% if health-care personnel are also included. The impact on cost-utility ratios is uncertain. However, if all persons with diabetes have same incidence and same complication rates cost-utility ratios do not change. Because vaccination rates are

moderately higher in recommended groups, program costs and QALYs gained could decline by less than 24% if these groups are excluded from the analysis.

The main analysis focuses on vaccinating persons with previously diagnosed diabetes. Another analysis projected the cost of vaccinating persons diagnosed with diabetes in the future. This projection requires a number of strong assumptions: (a) age-specific incidence and prevalence rates for diabetes will remain constant in future years; (b) 95% of persons younger than 20 will be vaccinated prior to entering the model; (c) the take-up rate will be 10% in the year that a person is diagnosed with diabetes, and no additional vaccination will occur after the year when diagnosis occurs. Key insights from these analyses are that program costs for vaccinating 10% of incident diagnosed diabetes cases are considerably lower than the one-time, catch-up costs of vaccinating 10% of prevalent diabetes cases in the main analysis. This occurs because there are more prevalent cases than incident cases (8.4 million prevalent cases aged 20-59 vs. 1.2 million incident cases). This accounts for the largest share of the difference. Also, incident cases tend to be younger than prevalent cases, and thus are more likely to have been previously vaccinated. In addition, annual undiscounted program costs are likely to fall in future years as younger cohorts with higher previous vaccination rates age upwards. The cost-utility ratios for individual age groups are the same in this analysis as in the main analysis. Thus, program costs fall in later years because younger cohorts have high rates of previous vaccination. Cost-utility ratios for individual age groups do not change.

There are limitations and possible impacts on incremental ICURs. The analysis is necessarily based on simulation model. Some inputs are uncertain. For example, incidence of hepatitis B may be underrepresented (ICURs ↓), and incidence ratio estimate assumed that cases with unknown diabetes status did not have diabetes (ICURs ↓). Costs do not include public health costs for outbreak control (ICURs ↓). Benefits from reduced transmission or herd immunity are not included (ICURs ↓). The analysis assumes that vaccinations will be provided during regularly scheduled visits for diabetes care (ICURs ↑). The main analysis does not account for lower vaccine cost (CDC price) for immunizations in public sector (ICURs ↓).

In summary, adults with diabetes have higher hepatitis B incidence rates than adults without diabetes. Vaccination provides protection, but efficacy declines with age. The cost-utility ratio for vaccinating adults with diabetes ages 20 through 59 years is \$58,762 per QALY, which is the private price. The cost-utility ratio rises with age. Take-up rate affects program costs and QALYs gained, but does not affect the cost-utility ratio.

Discussion Points

Regarding the assumptions made on the costs, Dr. Keitel requested additional information about screening for susceptibility before vaccination, diagnosis of acute hepatitis, testing for response to vaccination, and on-going screening for HCC and people with chronic hepatitis, liver biopsy for consideration of treatment, and treatment of chronic hepatitis.

Dr. Hoerger replied that almost all of those variables were assessed either in the sensitivity analyses or the costs in the main analysis. The one cost he heard that was not included was testing for susceptibility for hepatitis before vaccination. One sensitivity analysis assessed revaccination for adults, especially in the age group 60 through 69, after vaccination. That had a very small effect on the QALYs gained and had a very high cost-utility ratio.

Regarding the incidence of diabetes, Dr. Duchin thought he heard Dr. Hoerger say that a potential increase in the incidence of diabetes in the future. He wondered whether that was because it was believed that the population who would age and get diabetes is also the population that has been immunized.

Dr. Hoerger responded that this was a question of simplicity in not trying to load up the analyses with somewhat difficult to determine trends in incidence. If he had to bet, he would say that the incidence is going to rise given recent trends in diabetes.

Dr. Duchin's understanding is that diabetes incidence is increasing, and he wondered whether that would significantly change the results of the analysis.

Dr. Hoerger replied that it would increase the cost of the program, but it would also increase the benefits of the program. Those two effects would cancel out in the cost-utility ratios. The cost per QALY gained is not going to be affected as much by the incidence of diabetes.

Regarding the realities of new programs and new costs in the current deficit environment, Dr. Judson pointed out that when something like this is attempted at the state level where programs are often level or trickling down and they cannot deficit spend, nothing is accomplished. When he went before the state legislature to try to sell a universal mandatory school entry immunization for hepatitis B, they required a fiscal note stating what it would cost, what it would accomplish, and who would pay for it. The sensitivity to vaccine costs are being dealt with all of the time with the new hepatitis B vaccine. When their state law was passed, he thought the cost of hepatitis B vaccine in 1994 was \$8. At \$28 dollars, things are clearly not moving in the right direction. Diabetes is a risk marker, not a risk factor. Probably the sole exception is in the long-term care areas where breaches in hospital infection control are occurring.

Ms. Ehresmann commented that as a member of the working group, one of the challenges they are struggling with the issue of cost-effectiveness is the dramatic change that occurs after 60 years of age. While cost-utility is important, by the same token they do not want to suggest that those over 60 years of age are not worth the vaccine.

Dr. Baker suggested that this is an issue that is more broad than hepatitis B immunization.

Dr. Whitley-Williams (NMA) wondered whether the analyses took into account the prevention of secondary infections. While that may be more difficult to assess, it would drive up the benefit in terms of savings in medical costs.

Dr. Hoerger replied that the potential reduction of transmission or herd immunity effects were not taken into consideration.

It was not clear to Dr. Plotkin in the sensitivity analysis whether the vaccine effectiveness variable was based on the upper likely limits of the effectiveness of the current vaccine, or whether consideration was given to the possibility (which is real) of newer vaccines that are more effective in the elderly. That is, does it take into account possible improvement?

Dr. Hoerger responded that the sensitivity analysis was based on the review that assessed existing vaccines, and does not take into account possible improvements.

Next Steps: Proposed Recommendations

Dr. Trudy Murphy

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

Dr. Murphy reported that the ACIP Hepatitis Working Group, after reviewing an extensive body of information, has weighed infection control practice as the major strategy for prevention of hepatitis B and other bloodborne infections among adults with diabetes. While everyone would like to promote infection control, the WG concluded that infection control alone is probably not the solution to preventing most hepatitis B infections in this vulnerable population in the near future, particularly among younger people who have diabetes and may not be in an institution setting where there is oversight and control. Given this, the WG proposed two recommendations for vaccinating adults with diabetes for the full ACIP membership, taking into account the cost-effectiveness analysis.

To review, there are ACIP recommendation categories with the new GRADE system. A Category A recommendation applies to all persons in an age or risk group, and suggests wording such as “recommend,” “recommend against,” “should,” and “should not.” A Category B recommendation is one that encourages individual decision-making based on weighing desirable and undesirable effects. Suggested Category B wording includes words like “may vaccinate,” and “suggest against vaccination.” The working group has begun to frame the recommendation in this format, but had not completed the GRADE formatting before this meeting. Each of the two proposed recommendations would include Category A and B proposed wording. The following represents an overview of the two proposals:

In Option 1, hepatitis B vaccination is recommended for unvaccinated adults with diabetes who are <60 years of age (Category A). Individual clinical decision making is recommended for vaccination among unvaccinated adults with diabetes who are ≥60 years (Category B). In Option 2, hepatitis B vaccination is recommended for unvaccinated adults with diabetes (Category A). Individual decision-making (Category B) is recommended for vaccinating frail elderly adults with diabetes, and for post-vaccination testing, with revaccination for non-responding adults with diabetes who are less likely to respond (e.g., those ≥ 60 years). The actual wording proposed by the working group is as follows:

Option 1: Category A

Recommend

- Hepatitis B vaccination is recommended for unvaccinated adults with diabetes who are <60 years of age. The hepatitis B vaccination series can be safely given to persons of any age, but current hepatitis B vaccines are less efficacious and less cost-effective in older adults. Therefore, the hepatitis B vaccine series should be completed as soon as feasible after diabetes is diagnosed.

Option 1: Category B

Recommend individual clinical decision making

- Decisions to vaccinate adults with diabetes who are ≥60 years of age should incorporate consideration of the particular adult’s likelihood of acquiring hepatitis B virus infection, including the risk posed by an anticipated need for assisted blood-glucose monitoring; the likelihood of experiencing chronic sequelae or other complications if infected; and the decline in immunologic response to hepatitis B vaccine with advancing age.

Option 2: Category A*Recommend*

- Hepatitis B vaccination is recommended for unvaccinated adults with diabetes. The hepatitis B vaccination series should be completed as soon as feasible after diagnosis since vaccine effectiveness declines with advancing age.

Option 2: Category B*Recommend individual clinical decision making*

- Providers are encouraged to use clinical judgment to determine the suitability of hepatitis B vaccination for frail elderly adults with diabetes.

Option 2: Category B*Recommend individual clinical decision making*

- Revaccination with 3 additional doses of hepatitis B vaccine generally increases the proportion of non-responding adults who achieve a protective level of antibody to hepatitis B surface antigen (anti-HBs, $\geq 10\text{mIU/mL}$). For adults in whom a reduced response to the initial series might be expected (e.g., adults ages ≥ 60 years, obesity), revaccination would be medically appropriate. If revaccination is planned when a protective level is not achieved, testing for anti-HBs is recommended 1-2 months after completion of the initial hepatitis B series.*

*MMWR 2006;55 (RR-16):26-29 (Appendix A)

Each option might include additional guidance, such as the following:

Available data do not confirm an advantage to any specific hepatitis B vaccine, dosage or approved schedule for adults with diabetes. No additional hepatitis B vaccination is recommended for adults with diabetes who received a complete series of hepatitis B vaccine at any time in the past.

The majority preference of the working group is Option 1. The rationale is that Option 1 recommends vaccination for age groups achieving the highest rates of protection, that is, up to age 60 years. An advantage of covering adults to age 60 years is that the recommendation includes 68% of adults with new diabetes diagnoses. By contrast, covering adults to age 50 years, but not ages 50 through 59 years, would be more cost-effective, but would include less than 38% of adults with a new diabetes diagnoses. The working group felt that the increased cost for including ages 50 through 59 years could be justified by the larger proportion of adults with diabetes who could be protected. Option 1 was also favored by the working group because, although not encouraging vaccination at ages 60 and older, it does not place a barrier to vaccinating older adults, which might be a consideration in some situations (e.g., an outbreak). Option 1 is silent on revaccination for non-responders, which is done at high cost. The most important reason that WG members moved to favor Option 1 over Option 2 was the considerably lower cost of Option 1, approximately \$58,000 per QALY saved.

A minority of the WG continued to favor Option 2 primarily because it protects more adults with diabetes. Option 2 is simple and it is consistent with other hepatitis B vaccine recommendations, which do not make distinctions by age for who should or should not be vaccinated. Option 2, while recommending vaccination of all adults with diabetes, encourages individual clinical decisions for vaccinating frail elderly adults, who generally have limited life expectancy and may have poor response to vaccination. It also discourages post-vaccination

serology except when revaccination of non-responding adults would be medically appropriate. Option 2 is associated with considerably higher cost at approximately \$159,000 per QALY saved, and this estimate does not include post-vaccination serology or revaccination.

In conclusion, Dr. Murphy indicated that during the October 2011 ACIP meeting, anticipated topics on the matter of hepatitis B include additional incidence data; vaccine efficacy data from older adult residents in institutional (outbreak) settings; information on how a hepatitis B vaccination program for adults with diabetes might be implemented; and GRADE analysis of the strength of evidence for a proposed recommendation. She then invited input on the proposed recommendations.

Discussion Points

Dr. Baker inquired about the WG's plans in terms of the timing of a vote.

Dr. Murphy replied that the WG wants to ensure that the ACIP membership feels that they are ready for a vote. This could be done as early as October 2011. The GRADE analysis has already been completed.

Dr. Marcy did not understand including the decline in immunological response to hepatitis B vaccine with advancing age. There is one immunizer and one elderly person. It was not clear how that relationship would be influenced by a population observation, given that a provider will not know whether a person is in the 30% failure rather than 70% acceptance group.

Dr. Murphy responded that this is a very important question that the working group has spent a great deal of time discussing. Some members of the working group are involved in nursing home administration and geriatrics. They informed the working group that they find it difficult to acquire consent from older adults with dementia, and many LTC residents have a short life expectancy. Some of the wording proposed has been provided by those working group members. An attempt has been made to try to identify the key factors that would result in favoring vaccination or not.

Dr. Marcy did not feel that the proposed wording did this. It offers an excuse not to give the vaccine if a provider wants to save money. He was very concerned about including this.

Dr. Murphy pointed out that this was part of the rationale behind the Option 2 approach. She invited other input about how this might be addressed.

Dr. Cieslak clarified that the cost of the vaccine does not vary by age or anything else. It is three doses at \$58.50 per dose plus some administration fees. Based on the cost-utility analysis and the prices reach millions of dollars per QALY saved, the reason is that at some point, it is very unlikely that some people will benefit from the vaccine because of lesser risk of being exposed to the virus during remaining years of life, risk of progressing to chronic disease, and to a lesser degree, lesser chance of responding to the vaccine.

Dr. Marcy emphasized that he was talking about one individual with a needle and one person with a deltoid—not a population.

Dr. Cieslak stressed that everything done in medicine is based on assessing risk across populations.

Dr. Duchin suggested that there was some language that could bring some clarity to the intent; that is, age is not the only indicator of physiological robustness. Clinicians need to consider the likelihood that the patient would respond to the vaccine as one factor in making a decision. He said he liked Option 1, but it was not clear why it did not include language about the consideration for post-vaccination testing in that option as well. Age is not the only factor that should determine the type of counsel given in the recommendation.

Dr. Murphy replied that the major reason it was not included in Option 1 was the cost of testing plus revaccinating those persons who do not respond. This would be a complete second series.

Dr. Duchin clarified that he was not suggesting that testing be recommended, but that advice be given about when testing would be appropriate post-vaccination. For instance, even patients under the age of 60 can have conditions for which post-vaccination testing might be indicated.

Dr. Meissner inquired as to whether there are data regarding the ability of individuals over 60 to respond to a second series of hepatitis B vaccine.

Dr. Murphy replied that there are limited data, which suggest that individuals over 60 do respond and that overall response may be as high as 80% with three additional doses. However, the data are so limited that it is difficult to have great confidence in them.

To avoid problems that have been observed with respect to insurance coverage regarding recommendations that say “may,” Dr. Doskey (AHIP) recommended that the working group should use more definitive language in the recommendation that is put before the full ACIP membership for a vote.

Dr. Baker said she thought that not only insurance companies, but also physicians have problems interpreting the word “may.”

Dr. Schaffner (NFID) observed that it is recognized that immunizing adults is more elaborate than immunizing children in many ways, and offers more challenges. One of the challenges is that ACIP’s recommendations for adults are too complicated to remember and implement. He strongly endorsed simplicity. If they want diabetics to be immunized, then ACIP should recommend immunizing and should not include a lot of qualifications around that recommendation. Doctors’ decisions in these types of circumstances are difficult, and if they are worrying about which patients might get hepatitis B, they are going to think about sex and drugs. They are not going to think about the issues that brought this to ACIP’s attention. He found it a particular paradox that older patients, especially those who are cared for in nursing homes or other facilities—the very group that brought this to ACIP’s attention—is now not being recommended for vaccination.

Regarding Option 1, Dr. Schmader (AGS) pointed out that providers, particularly those in the nursing home setting and assisted care facilities, are going to need a lot more education about what the risks are and who should or should not receive the vaccine. It would be simpler to state that persons in nursing homes with diabetes should receive the vaccine. Regarding Option 2 and the use of the term “frail elders,” the definition of “frail” is highly debated in the geriatrics literature and that alone would suggest removal of that term. The somewhat accepted term for frailty is “geriatric syndrome,” which is characterized by fatigue, easy exhaustion, muscle weakness, low muscle mass and physical inactivity. Many individuals in nursing homes are not frail. They do not meet that definition and still might benefit from the vaccine. His

suggestion was to remove the word “frail” and include language that would address the concept, which he was happy to discuss off line.

Dr. Fryhofer (ACP) indicated that they care for the majority of individuals who would be excluded if only those under 60 are vaccinated. She agreed that this must be kept simple. Everyone knows what diabetes is, and if it is too complicated, the goal will not be accomplished. Americans are living longer, though not necessarily living better. That means as people grow older, increasingly more Americans are likely to end up in a nursing home situation unable to control excretions; therefore, possibly putting more people at risk if someone is hepatitis B positive. Increasingly more people are going to develop diabetes.

Dr. Baker pointed out that there are many people in their 80s and 90s who are functionally like her 60-year old grandmother was who was less functional because of her cardiac disease.

Dr. Duchin raised the issue that when ACIP makes a recommendation, even in the context of children, the recommendation is usually made for an age cohort with the understanding that that cohort will be protected into the future. In the context of hepatitis B and using a cutoff of 60 years of age, he did not think the intent was that adults would not be protected when they reach nursing home age. The cohort will age up and successive cohorts will be protected. The question regards whether to immunize everyone immediately. For instance, when an age frame is chosen with respect to childhood vaccinations, there is always some discussion about catch-up and whether that is cost-effective.

Dr. Marcy said he thought pediatricians’ goal was to immunize as many of their cohort as possible. The goal of the nursing homes, which are not all “Hyatt Hotels,” is to save as much money as possible. If nursing homes can find an excuse not to immunize, they will use that excuse.

Dr. Duchin emphasized that vaccination should begin younger so that as people age into the nursing home, they are already protected.

Dr. Moore (AIM) supported Option 2 and endorsed simplicity, with the caveat that the individual providers consider the vulnerability of the patient. Programmatically, AIM runs into tremendous difficulty trying to help adult healthcare providers implement recommendations. In addition, one third of people develop diabetes after the age of 60. It is incorrect to think that everyone is aging into the over 60 population protected.

Dr. Baker also said she liked Option 2 for its simplicity.

Dr. Temte wondered for those over the age of 65 who qualify for Medicare whether this would be a Part D or Part B vaccination.

Dr. Linda Murphy (CMS) replied that she did not have information on Medicare because she works strictly with Medicaid. However, she requested that someone email her the question and she would follow-up.

Dr. Chilton pointed out that several years ago in deciding whether he should sign up for long-term care insurance, he determined that information appears to show that his likelihood of being in long-term care for very long is low. This supports Option 1 in that those in nursing home care are unlikely to be there long, and if they are infected with hepatitis B, they are unlikely to have clinical manifestations of that.

Dr. Murphy indicated that the figures differ somewhat for nursing homes and for assisted living facilities where people do have a longer longevity. She did not know whether long-term insurance covers assisted living in terms of longevity of stay. Most of the outbreaks that have occurred in the last five years have been in assisted living facilities, which have the least regulation.

Dr. Cieslak did not believe the WG had any data at all for the population that led to the discussion in the first place on either the incidence of hepatitis B among diabetics in long-term care, or efficacy of the vaccine among diabetics in long-term care.

Dr. Baker inquired as to whether any studies were planned that would address Dr. Cieslak's comments.

Dr. Murphy replied that a limited amount of data would be presented during the October 2011 ACIP meeting regarding long-term care vaccine efficacy among residents in outbreak settings. Based on the provisional data she has reviewed thus far, it aligns with current estimates. She knew of no plans to try to determine incidence in these facilities.

13-Valent Pneumococcal Conjugate Vaccine (PVC13)

Introduction

S. Michael Marcy, MD Chair, Pneumococcal Vaccines Work Group

Dr. Marcy reminded everyone that the 13-valent pneumococcal conjugate vaccine (PCV13) is proposed to be used for prevention of pneumococcal disease (including pneumonia and invasive disease) in adults ≥ 50 years of age, specifically prevention of disease caused by *S. pneumoniae* 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F. Accelerated approval was applied for in December 2010, with a decision anticipated in October 2011. Licensure is to be based on demonstration of non-inferiority of opsonophagocytic assay (OPA) response to PCV13 versus currently licensed 23-valent pneumococcal polysaccharide vaccine (PPSV23).

The Pneumococcal Vaccines Working Group's terms of reference are to:

- Review data on immunogenicity, safety, efficacy, and cost-effectiveness of pneumococcal vaccines in adults
- Determine whether available data for adult PCV13 immunogenicity and cost-effectiveness are sufficient to determine value of vaccination of adults
- Develop a revised statement for use of pneumococcal vaccines if it is determined that a new policy statement including adult PCV13 recommendations is needed; however, policy options for use of PCV13 among adults were not presented during this meeting

Evidence reviewed to date includes immunogenicity and safety results from Pfizer's Phase III studies, and cost-effectiveness and public health impact of different adult pneumococcal vaccination strategies. Evidence to be reviewed during upcoming calls includes updated PCV13 immunogenicity and safety data, and new data on PCV13 immunization for high-risk adults. Evidence that will not be available to ACIP prior to the anticipated licensure includes efficacy of PCV13 against invasive disease, pneumococcal pneumonia, and all-cause pneumonia (Netherlands, results 2012), and indirect effects among adults of PCV13 use in children.

During this session, presentations were delivered on the public health and economic impact of routine PCV13 vaccination of adults ≥ 50 years of age, an update on the epidemiology of pneumococcal disease among adults in the US, and considerations for 13-valent pneumococcal conjugate vaccine use among adults.

Public Health and Economic Impact of PCV13 in US Adults ≥ 50 Years of Age

David Strutton, PhD, MPH
Pfizer, Inc.

Dr. Strutton reported on the public health and economic impact that Pfizer has estimated for Prevnar 13® in adults over the age of 50. Prevnar 13® is the same product currently used in pediatric population (Prevnar®) which was launched approximately 10 to 11 years ago in the US and has had a tremendous impact on public health. Prevnar 13® covers 6 additional pneumococcal serotypes. The analysis presented takes into account impact of Prevnar®. The 23-valent polysaccharide vaccine (PSV23) is currently recommended for all adults older than 65 years of age. About two-thirds of that population has been vaccinated. It is also recommended for adults 18 to 64 years of age at high risk for pneumococcal disease, about a third of whom have been vaccinated. This analysis focuses on an age-based recommendation for all individuals 50 years of age and above. The idea is that Prevnar 13® could be recommended for all adults older than 50 years of age regardless of previous history of vaccination with pneumococcal polysaccharide vaccine.

The study question addressed was the expected public health and economic impact of PCV13 use in US adults age ≥ 50 years. This was evaluated using a microsimulation model depicting risks and costs of invasive pneumococcal disease (IPD) and all-cause non-bacteremic pneumonia (NBP). Clinical outcomes and economic costs were evaluated over a lifetime in US adults age ≥ 50 years under two alternative vaccination strategies: 1) Use of PCV13 in all adults age ≥ 50 years at model entry, and no subsequent revaccination compared to the current recommendation for the polysaccharide vaccine. Revaccination scenarios with Prevnar 13® at 5 or 10 year increments were also examined; and 2) Use of PPSV23 per current ACIP recommendations. Alternative strategies for use of PCV13 and PPSV23, as well as a strategy of no routine vaccination, also were considered.

The clinical outcomes and economic costs were projected over a specified period of interest for alternative vaccination strategies and included expected total cases of IPD and non-bacteremic pneumonia (NBP), total life years, total deaths due to IPD and NBP, total medical care costs for IPD and NBP, total value of morbidity / mortality-related work loss, and total costs of vaccination. In terms of the inputs for the model, baseline rates of IPD were based on 2006 Active Bacterial Core surveillance (ABCs) data (Pfizer Inc., data on file). Serotype coverage for PPSV23 (67%) and PCV13 (45%) were based on 2008 ABCs data. Baseline rates were adjusted to account for the potential indirect effects that Prevnar 13® would have on the

pediatric program. This was done in a manner consistent with the model for the pediatric program. Serotype-specific changes for 6 serotypes unique to Prevnar 13® were assumed to be same as for Prevnar® serotypes. For NBP data from the literature were used for rates of all-cause inpatient NBP based on “confirmed” all-cause hospitalized (non-bacteremic) CAP cases. Rates of all-cause outpatient NBP were based on “presumptive” all-cause ambulatory CAP cases from the literature. Again, rates were adjusted to account for the potential indirect effects of Prevnar 13® pediatric program would have on the rates of both hospitalized and out-patient pneumonia. This was also done in a consistent framework, as was done with the PCV13 pediatric program evaluation for ACIP a couple of years ago.

In terms of effectiveness for invasive pneumococcal disease and pneumonia for the two different vaccines under evaluation, for all data points, data from the literature, input from a series of advisory boards conducted over the past two years, and expert opinion generated from those advisory boards were utilized. For the polysaccharide vaccine, effectiveness against invasive pneumococcal disease would be highest in the youngest, healthiest group in this population. Vaccine effectiveness wanes by time since vaccine receipt, with increasing age, and by risk status.

Vaccine effectiveness data against invasive pneumococcal disease for the conjugate vaccine were primarily based on the PCV7 data in pediatric population. The estimates were used from the clinical trial for Prevnar® and they were adjusted for age, time since vaccine receipt, and risk group using a similar framework as was used for the polysaccharide vaccine. In terms of the decline with time since vaccine receipt, the rate was assumed to be 50% from what was used for the polysaccharide vaccine. It was also assumed that subsequent doses of the conjugate vaccine would be as effective as the first dose after accounting for the time that has passed and any risk changes incurred since the initial vaccination.

Estimates for the immunocompromised patients in the adult population, data were derived from the pediatric program from an analysis of the impact of Prevnar® on HIV positive and HIV negative patients. Vaccine effectiveness was assumed at 91% for the youngest, healthiest cohort in this model. That wanes over time and by age of risk. Based on a study conducted in HIV positive patients in Malawi, 71% effectiveness was used in the youngest age group that is high risk (50-64/High-Risk). The data available are based on this study which showed a 74% efficacy against vaccine type invasive disease with Prevnar® in HIV positive people [French. *N Engl J Med* 2010;362:812-22]. This corroborates the estimates used in the model.

For the polysaccharide vaccine, data were used from the literature on potential effectiveness against pneumonia. All studies that had some level of blinding showed that the polysaccharide vaccine does not work on pneumonia. This assumption is consistent with the model that was presented in February 2011 by Drs. Smith and Zimmerman. For the conjugate vaccine, data were again used from the pediatric program and those were adjusted by age, time, and risk in a similar fashion as was done for invasive pneumococcal disease. For hospitalized pneumonia, effectiveness estimates were started at 25% and were waned over time, age, and risk. Based on the same study from French, the point estimate of effectiveness against all-cause pneumonia in the 50-64/Low-Moderate Risk group is 25%. This suggests that the methodology is reasonable and corroborates the approach used.

The pneumonia effectiveness estimates are critical in this model, and this is a point that drives the difference between the two vaccines. There are no clinical trial data from Prevnar 13® in adults on pneumonia yet, so the best data available were used. There are a number of ways this can be approached. The model presented in February 2011 by Drs. Smith and Zimmerman approached this by trying to estimate the percentage of pneumonia that is pneumococcal, the serotype coverage that would reflect the coverage for Prevnar 13® and an estimate of effectiveness. The model presented during this session by Dr. Strutton approached it in a different fashion by assessing the effectiveness level observed in the pediatric program and in immunocompromised adults to corroborate the levels of effectiveness being assumed. Since this is a critical component of the model and there is no certainty in the estimates used, a number of sensitivity analyses were conducted, including one in which the level of effectiveness was reduced by 50% as a starting point and everything was waned over time from there.

Key parameters used in the model included the following:

- ❑ Population demographics from 2007 US Census and 2006 NHIS [US Census Bureau. Available at: <http://www.census.gov/population/www/projections/popproj.html> [accessed July 15, 2009; and National Center for Health Statistics. 2006 Health Interview Survey]
- ❑ Medical costs of invasive pneumococcal disease and inpatient pneumonia were from the 2005 Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) [Agency for Healthcare Research and Quality. Available at: www.hcup-us.ahrq.gov/nisoverview.jsp [accessed June 22, 2008].
- ❑ Medical costs of outpatient pneumonia were based on unpublished healthcare claims data and published case-finding algorithm for CAP [Colice. *Chest* 2004;125:2140-2145].
- ❑ Price per dose of PCV13 was assumed to be \$108, and price per dose of PPSV23, \$49 [Redbook. Monvale, NJ: Medical Economics, Inc. July 2010].
- ❑ Vaccine administration cost was assumed to be \$17 [RBRVS. Salt Lake City, UT: Ingenix Inc. 2009].
- ❑ Future life years and costs were discounted at 3% per year and were expressed in US dollars for 2009.

In terms of the cost of pneumonia, the investigators feel that these estimates are conservative. For inpatient pneumonia, they do not take into account the effect of re-hospitalization rate, which has been estimated to be 20% within a 30-day period. Also, in terms of work loss productivity, the estimates used are relatively conservative based on a new research project just completed and submitted to IDSA this year. From a societal perspective, these estimates are expected to be relatively conservative.

To account for some of the uncertainties in the model development, a series of sensitivities analyses were conducted. The sensitivity of the expected net impact of PCV13 versus PPSV23 to selected model changes was explored, each in turn. Effectiveness of PPSV23 was assumed to persist for a maximum of 5 years, and alternatively, for 1 year. Herd effects were assumed to be higher by 50% in each year of the modeling horizon. The effectiveness of PCV13 against all-cause pneumonia was assumed to be higher by 20%, and alternatively, lower by 20% and 50%. The cost of vaccination was assumed to be higher by 10% of the cost of patient visits (\$1.88,

based on reimbursement for 5-minute evaluation of established patient). The cost-neutral threshold of effectiveness of PCV13 against all-cause pneumonia was also examined.

With regard to the public health impact estimated that Prevnar 13® would have if transitioning from the current recommendation for the polysaccharide vaccine for those 50-64 years of age at high risk and everyone over ≥65 years to an age-based recommendation for Prevnar® for everyone 50 years of age and older in the US. This model estimates that there would be reductions approaching 19,000 cases of invasive pneumococcal disease; 840,000 cases of inpatient pneumonia; 650,000 cases of outpatient pneumonia; and about 74,000 untimely deaths over the remaining lifetime of the adult population 50 years of age and above. This is based on a one-time vaccination with Prevnar 13®. The economic consequences of that public health impact from a payer perspective, not taking into account lost productivity, absenteeism, or presenteeism, the model estimates that transitioning from the current polysaccharide recommendation to the Prevnar 13® recommendation would result in cost savings of \$6.4 billion over the remainder of the lifetime of this adult population. If lost productivity is taken into account, the economic consequences would be savings of \$11.7 billion dollars for this population. There is a lot of uncertainty in the model, so a probabilistic sensitivity analysis was run in which the simulation of the model was run 100 times. When this model was simulated over a range of estimates for the various inputs, 99 of 100 estimates ended up in the cost saving quadrant.

A couple of scenarios were run for potential revaccination programs, including an every 10-year revaccination program for Prevnar 13®, which would lead to a greater reduction in disease and a substantial reduction in untimely deaths, as well as additional cost savings. From a payer perspective, the cost savings would approach \$10 billion. From a societal perspective, cost savings would approach \$20 billion. When the revaccination program is adjusted down to 5 years, the public health impact continues to rise. Under reasonable assumptions concerning vaccine effectiveness and cost, use of PCV13 in all adults age ≥50 years, in lieu of the current strategy for use of PPSV23, would yield fewer cases of disease and lower overall costs.

There are some limitations to the model. Perhaps the area of greatest uncertainty concerns assumed effectiveness of vaccination with PPSV23 and PCV13 against all-cause pneumonia. Estimates for PPSV23 are based on data from a modeling study that incorporated expert opinion and data from a case-control study, a meta-analysis of relevant trial data, and assumptions in other modeling exercises. Estimates for PCV13 were based on data from trials of PCV7 in children. Effectiveness of PCV13 was assumed to wane at 50% of rate for PPSV23. Another area of parameter uncertainty concerns clinical burden of all-cause pneumonia, as these estimates are based on published data from a single study in a single geographic area.

Discussion Points

Regarding non-bacterial pneumonia, Dr. Baker wondered whether the data on all-cause community-acquired pneumonia (CAP) were from ICD-9 codes or ICD-9 codes plus chart reviews in terms of the number of cases every year. She also wondered what percent was estimated that would be caused by the pneumococcal serotypes in the 13-valent vaccine for inpatient or outpatient CAP.

Dr. Strutton replied that the hospitalized pneumonia estimates were based on ICD-9 codes and a chart review. This is why the one particular dataset was selected for the estimates of burden. The outpatient visits are just presumptive CAP based on coding and no chart review. The previous model shown in February estimated the percent of pneumonia that was pneumococcal

and the serotype coverage; whereas, the model presented during this session approached the effectiveness estimates based on the evidence of the level of effect in the pediatric program, which was corroborated with the HIV positive estimate from French. These were two different approaches, and this is why such a dramatic range was estimated in the analysis.

Regarding the efficacy of Prevnar 13 against non-bacteremic pneumonia, it was not clear to Dr. Cieslak how well pediatric data could be extrapolated to adult populations given the variety of causes of pneumonia. The reduction in HIV infected adults did not appear to be statistically significant, so it is entirely possible that there is zero protection against non-bacteremic pneumonia.

Dr. Strutton clarified that this was a point estimate. The estimates were not totally based on the Malawi data. It was also based on the pediatric program, which would represent patients with an immature immune system and assessed the level of effect of Prevnar® on pneumonia in that population. That was then applied to the adult population beginning with healthy 50 year olds. That was then waned by age, time, and risk. In lower ages, years of immunoscence was estimated at lower levels for a starting place for an effectiveness estimate on pneumonia, and that would wane again over time following the time since receiving the vaccination. The investigators recognize that this is a limitation, which is why they tested such a dramatic range down to cost neutrality, which was a 60% reduction in the preliminary estimate. That was waned again by age, time, and risk.

As a member of the WG, Dr. Duchin found it very difficult to interpret this study because of the scarcity of data on vaccine effectiveness versus non-bacteremic pneumonia and vaccine effectiveness against non-bacteremic pneumonia. Although this was a very interesting exercise, Dr. Duchin found it very difficult to translate this into anything that could lead to action until there are further data on these critical points.

Dr. Turner (ACHA) wondered how recipients of the polysaccharide were handled in the model, and whether they would also receive the conjugate and if this was accounted for in the model. In addition, Prevnar 13 is missing 10 antigens versus the polysaccharide. He wondered if the model accounted for the effect that those residual 10 may cause some disease in the conjugate recipients.

Dr. Strutton responded that it was assumed that receipt of the conjugate vaccine would not be based on previous receipt of polysaccharide. In terms of the 10 residual antigens, serotype coverage was based on the current serotype coverage for the two vaccines, for which the conjugate had a lower serotype coverage because there are less serotypes in that vaccine. For pneumonia, it was based on an all-cause estimate, so it did not take into account the serotype specific effects. They did try to estimate the serotype coverage and the percent that is pneumococcal in terms of pneumonia, which fit within the range of estimates included in the sensitivity analyses.

Dr. Paradiso (Pfizer) indicated that in all of the trials in which they have assessed invasive disease and pneumonia, an impact on invasive disease is observed in the 75% to 100% range depending upon the population being studied. For all-cause pneumonia, a lesser effect is observed because all-cause pneumonia can be many things. The percent of pneumonia that is pneumococcal is never really known; however, the impact can be assessed for all-cause pneumonia. What is reassuring about the data in HIV positive adults is that it looks exactly like the data for children, with 75% effectiveness against invasive disease and about 25% against all-cause pneumonia. Although it did not achieve significance in the model, the pattern is

almost exactly the same. The serotype coverage was 50%, so for PCV7 in the Malawi population, there was 50% serotype coverage and a 25% reduction in disease. This implies that approximately 50% of the pneumonia was pneumococcal. This can be reverse calculated. While the exact number is unknown, the data in children has consistently been between 20% and 40% reductions in all-cause pneumonia. That corresponds to an invasive disease efficacy of approximately 75% to 95%.

Current Epidemiology of Pneumococcal Disease in Adults

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Ms. Pilishvili reminded everyone that the current recommendation for 23-valent pneumococcal polysaccharide vaccine (PPSV23) is for the following groups [MMWR 1997; 46(RR-8):1-24]:

- All adults 65+ years
- Persons 2 to 64 years with:
 - chronic cardiovascular or pulmonary disease
 - functional or anatomic asplenia
 - chronic liver disease or alcoholism
 - cerebrospinal fluid leak
 - diabetes mellitus
 - cochlear implant
 - immunocompromising conditions
- Persons 2 to 64 years old living in high risk settings (long-term care facilities)
- Persons 19 to 64 years who smoke cigarettes (added last year)
- Persons 19 to 64 years with asthma (added last year)

ACIP does not recommend routine revaccination with PPSV23 for persons age 65 years or older. However, for persons who previously received PPSV23 before age 65 for one of the high-risk indications, revaccination is recommended if it has been ≥ 5 years since first PPSV dose. In addition, revaccination with a second dose is recommended for immunocompromised adults and adults with asplenia.

The 7-valent pneumococcal conjugate vaccine used in children since late 2000 has dramatically reduced the incidence of invasive infections in this country in the vaccine target age group, as well as adults of all age groups through herd effects. The herd effect has ranged from 22% to 50% reductions observed in 2010 when compared to pre-vaccine baseline [Moore, IDSA, 2009 & ABCs unpublished data]. The age distribution of pneumococcal disease has changed since PCV7 introduction with children contributing less to the overall disease burden. Despite the large reductions observed among adults due to herd effects, a high burden remains, especially for older adults. Among older adults age 65 and older, there are an estimated 36 cases per 100,000 in the US.

In terms of the serotype-specific changes in the incidence of invasive disease among adults, invasive disease caused by the serotypes in the 7-valent conjugate vaccine formulation has virtually been eliminated. At the same time, there have been increases in all non-PCV7 serotypes. Most of these increases were driven by a single serotype (19A), especially in children, but also in adults. Increases have also been observed in invasive infections that are

caused by serotypes included in the 23-valent formulation (excluding the serotypes in the 7-valent formulation). Increases have occurred in invasive infections that are caused by these serotypes despite long-term availability of the 23-valent vaccine and modest increases in vaccine coverage in recent years [ABCs unpublished data, continuous sites].

Regarding the herd effects of pneumococcal conjugate vaccine (PCV7) on pneumonia among adults in the US, three studies evaluated the impact of PCV7 introduction on adult pneumonia burden. All three studies were conducted using administrative data. Grijalva and colleagues (2007) found small but not statistically significant reductions in the incidence of all-cause and pneumococcal pneumonia in adults 40 to 64 years of age and 65 years of age or older. Up to a 25% reduction, but not statistically significant, was observed in pneumococcal pneumonia hospitalizations. Nelson and colleagues (2008) found no consistent reductions in adults with presumptive hospitalized and presumptive outpatient pneumonia. This is the study that was mentioned earlier in which ICD-9 codes were used to identify cases of pneumonia, followed by validation through chart and chest radiograph reviews. A newer study by Simonsen and colleagues (2011) found different results in which fairly large reductions were observed in pneumococcal pneumonia at 34% and 54% depending upon the age groups, and these were significant. These studies differ in data sources that were utilized, case definitions applied, methods of data analysis, and time points at which vaccine impact was evaluated. In terms of what can be concluded about whether there are herd effects of PCV on non-bacteremic pneumonia, the current studies rely on ICD-9 codes and are subject to limitations.

First, pneumonia cases are subject to misclassification. In addition, the trends are being examined based on administrative datasets, so changes in coding practices, admission criteria, and culturing practices may impact these trends. The key message in assessing whether there are herd effects of conjugate vaccine use on non-bacteremic pneumonia using the current data systems available is that it is difficult to measure the magnitude of the effect given the current data systems. However, based on what is known about the contribution of pneumococcus to non-bacteremic pneumonia, it can be concluded that the herd effect of PCV13 on non-bacteremic pneumococcal pneumonia is biologically plausible.

Adults with chronic and immunocompromising conditions are at highest risk for pneumococcal disease. CDC unpublished data evaluated trends in invasive disease before and after the 7-valent vaccine introduction by race groups and by presence of indications for the 23-valent polysaccharide vaccine. The study observed significant reductions in overall disease for all co-morbid and race groups. The infections caused by 7-valent vaccine serotypes have been virtually eliminated for all co-morbid and race groups. However, increases have been observed in the non-PCV serotypes for all groups and the increases have been most dramatic among blacks with immunocompromising and chronic conditions that are indications for 23-valent vaccine. Similar data for adults age 65 years and older show virtual elimination of the 7-valent vaccine serotypes as causes of invasive disease, but increases in non-vaccine serotypes for this age group were most dramatic among both race groups with indications for the 23-valent vaccine [Muhammad et al. Manuscript in preparation]. Despite large reductions in pneumococcal disease rates observed for all race and co-morbid groups, there are still disparities in disease rates after 9 years of 7-valent vaccine use.

Given the observed changes in pneumococcal disease in adults after 7-valent vaccine introduction, what is the current distribution of serotypes that are causing invasive disease? The 13-valent serotypes cause from 50% to 59% of invasive disease among healthy adults and 38% to 46% of invasive disease among adults with co-morbid conditions. Coverage provided by 13-valent vaccine decreases by age and presence of co-morbid conditions. The additional 11 serotypes that are included in the 23-valent vaccine composition account for anywhere from 20% to 30% of invasive disease.

In summary, large herd effects on invasive pneumococcal disease from PCV7 use in children are still evident among adults. Pneumococcal disease burden remains high among adults 50 years of age or older with an estimated 27,000 IPD cases of invasive pneumococcal disease; 4000 deaths; 374,000 outpatient visits; 194,000 emergency department visits; and 1.4 million hospital days due to pneumonia among adults 65 years or older. Racial disparities in disease burden remain despite dramatic PCV7 herd effects. No population level effects of PPSV23 have been observed on invasive pneumococcal disease or non-bacteremic pneumonia despite increased coverage.

Considerations for PCV13 Use Among Adults, Summary of Immunogenicity and Efficacy, and Cost-Effectiveness Studies

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As noted earlier, it is anticipated that the 13-valent pneumococcal conjugate vaccine (PCV13) for adults will be licensed toward the end of 2011 in the US. The proposed indication is for prevention of pneumococcal disease, including pneumonia and invasive disease, in adults 50 years of age and older for disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. Licensure will be based on demonstration of non-inferiority of OPA response to PCV13 compared to PPV23. A confirmatory trial will be conducted with pneumonia as the primary endpoint, and will be submitted as a post approval supplement. Key factors to consider for PCV13 use among adults include immune response, efficacy, herd effects from pediatric PCV13 program, potentially preventable disease burden, and cost-effectiveness. Key factors to consider for PCV13 use among adults in terms of immune response are whether immunogenicity is non-inferior to the currently licensed vaccine (PPV23), and there are no established serologic correlates of protection for pneumococcal disease in adults.

There are a number of published immunogenicity studies in the US with head-to-head comparisons of a single dose of PCV versus PPSV23, and these studies differ in age groups, prior PPV vaccination, and time points of serology [Goldblatt (2009), De Roux (2008), Dransfield (2009), Scott (2008), Ridda (2009), Miernyk (2009), Feikin (2001), Crum-Cianflone (2010), Penaranda (2010)]. All of these studies conclude that a single dose of the 7-valent vaccine was better or as good as the polysaccharide vaccine. Serotype-specific IgG levels were higher or as high for some serotypes of the 23-valent vaccine. Only one of the studies used the 13-valent vaccine formulation, and the sample size was 15 in each arm. Some of these studies show that for select serotypes, an improvement was observed in response to the conjugate vaccine compared to the polysaccharide vaccine. For example, the Goldblatt study showed that for 3 of the 7 serotypes in common the response was superior, for one of the serotypes (19F) in the 23-valent vaccine the response was superior than the 7-valent, and for the remaining serotypes

there was no difference observed. In the absence of serologic correlates of protection for adults, OPA assumes a greater role since it measures functional antibody responses elicited by vaccine. The De Roux, Dransfield, Scott, and Miernyk studies also evaluated the OPA results and compared the results to the ELISA IgG levels, and the OPAs did not change the conclusions of these studies. Similar results were found in studies that focus on HIV positive adults [Feikin (2001), Crum-Cianflone (2010), Penaranda (2010)]. These studies demonstrate that serotype-specific IgG levels and OPA activity, where it was measured, were similar after a single dose of the 7-valent or polysaccharide vaccine. The Crum-Cianflone study showed that response to PCV for 3 out of 4 serotypes measured at 1 month post-dose was superior for the 7-valent vaccine as compared to the 23-valent vaccine. However, when the response was measured at 6 months post-dose, for all 4 serotypes measured, the response was equivalent for the 7-valent and 23-valent vaccines.

The results of the Phase III immunogenicity studies of PCV13 versus PPV23 were presented to ACIP in February 2011. In summary of these studies, non-inferior immune response post-dose 1 for PCV13 compared to PPSV23 was demonstrated for all common serotypes. In pneumococcal vaccine naive adults, 9 of 13 serotypes showed a statistically greater response. In adults pre-immunized with PPSV23 ≥ 5 years prior, 11 of the 13 serotypes showed a statistically greater response. There was improved response when PCV13 was given as the first dose with sequential vaccination one year apart. When two doses of PCV13 given one year apart were compared to one dose of PPV23 followed by PCV13 one year later, for 10 of 13 serotypes statistically greater response was observed. When PCV13 was given first followed by PPV23 or PPV23 was given first followed by PCV13, 11 of 13 serotypes statistically greater response was observed.

Another factor to consider is the efficacy of conjugate vaccines among adults; however, limited data are available. The only study is the double-blind, placebo-controlled clinical efficacy trial conducted in Malawi among HIV-infected (88%) adolescents and adults who recovered from documented invasive pneumococcal disease (N=496). Two doses of the 7-valent were given in this trial, and the trial demonstrated 75% efficacy against vaccine serotype invasive disease and 25% efficacy against all-cause pneumonia (although not statistically significant). This is a very different population in Africa, so it is unclear whether these results can be extrapolated to the US population. These are the only data pertaining to efficacy against invasive disease among adults.

There are no data on efficacy of the vaccine against non-bacteremic pneumonia; therefore, the direct efficacy of the vaccine in adults is not known. There is an on-going trial in the Netherlands that will provide crucial data on the efficacy against pneumonia. That study involves 85,000 community-dwelling, pneumococcal vaccine naïve adults ≥ 65 years of age. The primary objective is efficacy against the first episode of vaccine serotype community-acquired pneumonia, and the secondary objectives are efficacy against non-bacteremic vaccine type CAP, vaccine type IPD, all pneumococcal CAP, and death. The safety profile will also be assessed. The occurrence of the primary outcome, vaccine type CAP, will be established on three criteria: clinical definition of CAP, chest radiographic interpretation consistent with pneumonia, and determination of pneumococcal serotype. Determination of serotype will rely primarily on culture, but there will be two additional diagnostic techniques used (e.g., PCR and antigen tests that were evaluated prior to inclusion in the study). The results from this study will not be available for the next 1 to 2 years.

Also important to discuss are the potential herd effects of PCV13 and preventable disease burden in adults. Regarding the rank order of IPD serotypes among adults >65 years of age in 2010, the three most common serotypes are 19A, 7F, and 3. These are included in the 13-valent formulation and account for over one-third of invasive infections among adults in this age group. The remaining most common serotypes are either covered by the 23-valent vaccine (22F, 9N, 11A) or they are not covered by any of the vaccine formulations. There is a similar picture in terms of rank order for adults 50 to 64 years old, except that 7F causes more infections [CDC, unpublished, 2010].

Given the data, the question is: will PCV13 use in children reduce disease in adults similar to what was observed with the use of 7-valent vaccine use in the US? PCV7 introduction led to near elimination of vaccine type IPD among adults of all age groups. Carriage and transmission for some PCV13 serotypes is similar to PCV7 serotypes (types 19A, 7F, 6A). Serotype 1 is rarely carried, so it unclear if vaccinating children will reduce type 1 disease. Efficacy of PCV13 may not be similar to PCV7 for some types (types 1 and 3). The key message is that the herd effects of PCV13 are likely to be observed, given the PCV7 experience.

Cost-effectiveness must also be taken into account. Given the high cost of the vaccine and the availability of the two vaccines for adults soon, studies are needed to identify the most cost-effective strategies for vaccinating adults using these two vaccines. One cost-effectiveness analysis was presented by Dr. Strutton during this session. Another model was presented in February 2011 and these data were updated based on incorporation of the comments received from the ACIP membership and working group members. As a reminder, a decision modeling technique was used, which was employed to examine 6 different pneumococcal vaccination strategies with the conjugate vaccine and the 23-valent vaccine. The model followed a hypothetical US cohort of 50 year olds yearly until death. Detailed assumptions and inputs of this model were presented during the February ACIP meeting. As a reminder, the key assumptions included the following:

- ❑ Base case:
 - Assumptions regarding PCV13 effectiveness against IPD and non-bacteremic pneumonia (modified Delphi panel)
 - Herd effects of PCV13 against non-bacteremic pneumonia were modeled based on the point estimates from Grijalva et al
 - Vaccine uptake was modeled based on observed vaccine uptake for the 23-valent vaccine, which is 60.1% adherence for age 65 and older and 33.9% for co-morbidity-based uptake

- ❑ Worst case:
 - Assumed the lowest PCV effectiveness against noninvasive pneumonia (modified Delphi panel)
 - Age-based vaccination uptake = 60.1%, co-morbidity-based uptake = 33.9%

- ❑ Changes since the February ACIP presentation include
 - Real vaccine uptake instead of 100% uptake
 - Assumption of herd effects against non-bacteremic pneumonia

Regarding the public health impact of the vaccine strategies, PPSV strategies prevented more invasive disease than strategies that used only the 13-valent vaccine, while strategies that used 2 scheduled doses of the 13-valent vaccine prevented more non-invasive pneumonia. In the base case sensitivity analysis, results were most sensitive to variations in vaccine effectiveness estimates and herd effects from the pediatric use of the 13-valent vaccine that were assumed for non-invasive pneumonia. With respect to incremental cost-effectiveness analysis results under base case and worse case assumptions, only strategies were included that were not eliminated by strict or extended dominance. Compared to no vaccination, 13-valent vaccine given as a substitute for the 23-valent vaccine using current recommendations cost \$28,900 per QALY gained. 13-valent vaccine given routinely at 50 and 65 years of age cost \$45,100 per QALY gained compared with a strategy of substituting PCV13 in the current recommendation. A strategy of PCV13 given at the ages of 50 and 65, followed by a dose of polysaccharide at the age of 75 years cost \$496,000 per QALY gained. The other two strategies, use of polysaccharide vaccine with current recommendations as well as a dose of the conjugate vaccine given at 50 and followed with a dose of polysaccharide given at the age of 65, were the dominated strategies in the base case and were excluded. In the worst case analysis, the current recommendation strategy with the 23-valent vaccine is no longer dominated and is favored, costing \$34,000 per QALY gained. 13-valent vaccine substituted in the current recommendations costs \$131,000 per QALY gained, and the other strategies had prohibitively high cost-effectiveness ratios.

In terms of the cost-effectiveness analysis summary, the models show that PCV13 in adults could be highly cost-effective. However, both models rely heavily on assumptions about indirect effects of PCV13 on non-bacteremic pneumonia. The current PPSV strategy is favored if PCV13 effectiveness is low against non-bacteremic pneumonia. Results are sensitive to assumptions regarding PCV13 effectiveness against noninvasive pneumonia, PPSV effectiveness against invasive pneumococcal disease, and that herd immunity effects on the likelihood of PCV13-type disease.

In conclusion, PCV13 provides immune responses that are, for some serotypes, greater than for PPV23 in both vaccine naïve and previously immunized adults. However, the clinical relevance is unclear without a correlate of protection. Revaccination with PCV13 does not appear to lead to diminished response. Cost-effectiveness and public health impact estimates of PCV13 strategies rely on assumptions of burden of vaccine-preventable disease after herd immunity impact and efficacy against non-bacteremic pneumonia. Data on efficacy against non-invasive pneumonia and herd effects of pediatric PCV13 use pending completion of those studies. No data are available on duration of protection.

In terms of whether there is a role for PCV13 use among adults, the pros are that there is a large, potentially preventable burden of adult disease. Efficacy against pneumonia in children suggests possible efficacy against non-invasive pneumococcal pneumonia among adults. There is no evidence of population-level prevention with PPV23. The cons are that the potential herd effects of PCV13 use among children may limit the utility of PCV13 among adults. There are no efficacy data against pneumonia, and there are limited data on efficacy against adult invasive pneumococcal disease (PCV7 only).

The next steps are to evaluate relevant new data as they become available, including data from the efficacy trial against pneumonia (CAPITA); the impact of pediatric PCV13 program on disease burden and serotype distribution among adults; and additional immunogenicity data from Phase III studies (adults 18-49 years old, high-risk adults, and long-term persistence of immune response). Consideration will be given to revision of the ACIP recommendations as

these additional data become available, and the evidence will be reviewed to consider PCV13 for high-risk adults.

Discussion Points

Dr. Baker inquired as to when information would be available about the pediatric effects of Prevnar 13®, when data would be available from the Netherlands trial and how long the follow-up is post-immunization to detect pneumonia.

Dr. Pilishvilli responded that the ABCs data are being examined in real-time to assess the pediatric effects on herd immunity. These data are not complete and consistent results have not yet been observed. Based on what has been observed with the 7-valent vaccine, after there is one year of complete data available, there should be some indication of whether there is a herd effect.

Dr. Paradiso (Pfizer) added that recruitment for the pneumonia trial occurred through two influenza seasons, or over two years. Follow-up has been two years after that, and some subjects will be followed for three years. This is a case accrual endpoint, so that data are not analyzed until there are enough cases for all of the endpoints. These data are estimated to be available in about early 2013 for a primary endpoint. Consideration is being given to whether an interim analysis can be done; however, they do not want to jeopardize the endpoint by doing this so they have to be careful.

Dr. Marcy noted that in that week's *Vaccine*, he thought he saw something about 6C, which is beginning to cause more problems in pediatrics and is the fourth leading cause of adult invasive disease.

Dr. Paradiso (Pfizer) replied that the data indicate that 6A, B, and C are related serotypes that are part of the same serogroup. 6B was in the 7-valent vaccine and cross protective antibody can be made against 6A, so by functional activity, killing of 6A is not as good as killing of the homologous strain. Some impact has been seen on 6A even with Prevnar® introduction. It turns out that 6B antibody does not kill 6C. On the other hand, the data that were published showed that the antibody of 6A does, in fact, kill 6C. In vitro, looking at OPA activity, it does look like those two are more closely related and there is potential for cross reactivity. However, there are only in vitro data at this point.

Dr. Cieslak pointed out that the two cost-analyses gave pretty different results, one with cost savings to society across a broad range of assumptions and the other always costing money and sometimes costing a lot of money. He requested an explanation of the differences in the model or inputs that explain the differences in outputs.

Dr. Pilishvilli responded that there is a methodology difference. One model follows a cohort of 50 year olds over a lifetimes; whereas, the other assesses the population of 50 and above. Some of the inputs are also different. The input for efficacy against pneumonia is more conservative, so the estimation in the Pittsburgh model was to calculate the contribution of pneumococcal disease to overall pneumonia and then apply the projected vaccine efficacy and the relative contribution of the serotypes. So, this actually comes up with a much smaller proportion of what the vaccine types of pneumococcal disease will be for all-cause pneumonia. Another difference is that outpatient cases were not included in the Pittsburgh analysis.

Dr. Zimmerman added that one of the major differences in what was presented in February versus what was presented during this session was the difference in the ceiling. For modelers, that is an interesting theoretical perspective: What ceiling should be included in a cost-effectiveness analysis? While 100% is sometimes used in policy circles, it is almost never achieved. Certainly for adult vaccinations, 100% is not achieved. So, 60% was used because that was the time point with the vaccination rate against pneumococcal disease according to the NHIS. The critical issue is the proportion of pneumonia that is due to pneumococcus. That is to say, Pfizer used the generally accepted 30%. CDC is funding research on this topic, which is another critical issue. If it is substantially less, if 15% of pneumonia was attributable to pneumococcus, that will make it much more expensive. If it is closer to 50%, the vaccine will be much more cost-effective. This issue is critical, but will not come from CAPITA because the population is different from that of Northern Europe.

Dr. Judson pointed out that the literature has varied over the years in terms of the extent to which any of the pneumococcal vaccines prevent non-bacteremic pneumococcal pneumonia in the different age groups. A number of those studies were reviewed during this session; however, he was still left lacking a best estimate in terms of the efficacy of PCV7 to prevent non-bacteremic pneumococcal pneumonia.

Dr. Pilishvilli responded that there are no data on the efficacy of the conjugate vaccines against non-bacteremic pneumonia. That is a crucial piece of data that is missing, and is one of the reasons that the working group felt that this is why it is difficult to develop policy options at this time. The assumptions to which Dr. Zimmerman referred are also based on what is known about the contribution of pneumococcus to overall all-cause pneumonia. Based on the literature, this is anywhere from 25% to 30%. The estimates incorporated in the Pittsburgh model assumed, in addition to the contribution of pneumococcal pneumonia that there will not be 100% efficacy against all pneumococcal pneumonia and the contribution of the vaccine types to pneumococcal pneumonia.

Dr. Turner (ACHA) said he was still obsessing over the serotypes that are not included in PCV13 that are included in the polysaccharide. Knowing that if the polysaccharide was given after the conjugate and the shared antigens could be boosted in addition to getting the benefit from the non-shared antigens, he wondered why they did not analyze a model of giving the conjugate at age 50 and the polysaccharide as a booster at age 60 or 65.

Dr. Zimmerman responded that they did analyze this scenario because a priori was exactly that schedule, but it did not come up as either making as much public health impact, or as being cost-effective. It is included in the public health models, but is not included in the cost-effectiveness models because it drops out due to the dominance and extended dominance conventions. To respond to Dr. Judson's earlier question, in the Pittsburgh model, the efficacy among 50 year olds to the conjugate vaccine against vaccine type non-invasive pneumonia started at age 50 at 74% and in 10 years was down to 41%. Those are very midrange, sober estimates and the investigators thought that instead of back-calculating, they simply asked the direct question so that the Delphi panel would not have to back-calculate the percentage of pneumonia and the percentage of serotypes.

Dr. Paradiso clarified that there is no controversy about conjugate vaccine efficacy in any trial that has ever been done in any age group assessing invasive disease or pneumonia. The models of public health impact focus on addressing the current US disease burden after 30 years of using the vaccine in over 65 year olds and high risk groups down to 50, and a serotype coverage after those 30 years of using that vaccine where 65% to 70% of the population has received that vaccine. So, the impact on the serotype distribution of disease has not changed with the use of polysaccharide, as has been seen with the conjugate vaccine. The immunogenicity and immunological mechanisms are very different than with the polysaccharide vaccine. This is observed in terms of not only the response, but also the response to subsequent boosting and the existence of memory. As was mentioned, more data will be shared with the working group over the next months that assess boosting over time and memory responses. It is important to look at the whole picture of trying to address a burden that is very high.

Dr. Grabenstein (Merck) emphasized that assumptions are essential in those models. One meta-analysis showed zero percent efficacy of the polysaccharide vaccine for non-bacteremic pneumonia. There is another meta-analysis that shows that there is 70%. There is an RCT from Japan for non-bacteremic pneumonia showing 60% efficacy. It depends upon which studies go in or out of the meta-analyses. When numbers range from 0% to 70%, the logical approach is to do a sensitivity analysis on the efficacy for the polysaccharide vaccine against pneumonia, which he had not seen in any of the presentations and which he recommended doing.

Influenza

Introduction

Wendy Keitel, MD Advisory Committee on Immunization Practices

Dr. Keitel reported that since the last ACIP meeting, the working group has convened a teleconference approximately every other week as necessary to discuss a number of topics related to several new vaccines in terms of safety, efficacy, and immunogenicity. The WG has also been drafting the guidelines for use of influenza vaccine for the upcoming season. The decision was made this year not to develop an extensive document discussing influenza as well as the guidelines, but instead to provide an abbreviated document that would highlight the strains; the recommendations for the number of doses, particularly in children; and the administration of inactivated influenza vaccination to persons with a history of egg allergy.

During this session, presentations were delivered regarding influenza activity, influenza vaccine distribution and coverage, vaccine effectiveness, Fluzone® High-Dose, Fluzone® Intradermal, and influenza vaccine and egg allergies.

Influenza Vaccine and Egg Allergy

John M Kelso, MD
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Dr. Kelso discussed the issue of administering influenza vaccine to patients who have egg allergies, which has heretofore been a contraindication to immunization. He indicated that he was presenting on behalf of the Clinical Immunization Safety Assessment (CISA) Hypersensitivity Working Group, which consists of 9 allergists/immunologists, 6 CISA principal investigators, fellows, and CDC ISO. This group reviewed egg allergy and influenza vaccine over 9 months or longer to ultimately reach consensus conclusions.

Under consideration is the approach to a patient who has had an immediate-type allergic reaction to the ingestion of eggs, but who has never received the influenza vaccine. If a patient has already had an apparent immediate-type reaction to this or any vaccine, the approach would be very different and would include skin testing with the suspect vaccine and vaccine ingredients. Patients who have IgE-mediated egg allergy have a theoretical risk of anaphylaxis if injected with influenza vaccines containing egg protein. Withholding influenza vaccine from egg-allergic recipients has very real risk, namely the morbidity and mortality associated with the disease. Influenza vaccine contains measurable quantities of egg protein as ovalbumin. The question is: Does this cause systemic reactions when injected into egg-allergic patients?

Seventeen published studies have involved over 2600 egg-allergic subjects getting influenza vaccine without any serious reactions (e.g., no respiratory distress or hypotension), and with only a low rate of minor reactions (e.g., hives, mild wheezing). So, the answer appears to be no. With regard to patients with severe egg allergy, most studies have specifically included patients with histories of severe anaphylaxis ($n > 200$) with egg ingestion, and these patients also tolerate the vaccine. So, even these patients do not appear to be at risk of serious reaction. In terms of whether skin testing with the vaccine will help predict a reaction, in a few studies, vaccine was withheld from patients with positive prick or intradermal skin tests. In the majority of studies where skin testing was done, vaccinated skin test positive subjects had no reactions, or no greater rate of reactions than skin test negative subjects. The rate of reactions is the same whether skin testing is included in the protocol or not. In one very large study conducted at Boston Children's Hospital, for a few years skin testing was part of their protocol for giving influenza vaccine to children and for subsequent years this testing was removed from their protocol. Their overall rate of reaction to the vaccine was very low regardless of whether skin testing was part of the protocol. Thus, skin testing with the vaccine is not helpful. Another cautious approach to this were studies that were conducted early on that divided the dose (10% and if no reaction after 30 minutes 90%) vaccine was administered. In those studies that divide the dose, the vast majority of patients ultimately tolerate the 10+90% vaccine dosing. Studies with single dose also report no serious reactions. These patients ultimately receive the full dose, so dividing the dose appears to be unnecessary.

The reason no serious reactions are being reported appears to relate to the amount of egg protein that is present in the vaccine. What is actually being measured in terms of "egg protein" is ovalbumin, which is one of the protein constituents of eggs. It is the most important allergen, and is the protein to which patients make IgE antibody. Ovalbumin is measured by immunologic assays and is the surrogate for the total egg protein content of the vaccine. In the studies reporting the ovalbumin level, vaccines used have contained as much as 0.7 mcg per 0.5 mL dose without serious reactions, so at least that much is tolerated. That is, the vaccines

available for administration contained up to this much ovalbumin and there were no reactions, so it is known that at least amount is fine. To put this into perspective, the absolute smallest amount of ovalbumin that anyone has ever eaten that caused any sort of objective sign was 130 mcg. Three of the five manufacturers report the maximum amount of ovalbumin in the package insert, and two of the five provide the information on request. The claimed amounts are all below 0.6 mcg per 0.5 mL dose. The measured amounts in independent laboratories are usually much lower than the claimed amounts. The one outlier has been Fluzone®, which is of particular concern because that is the only vaccine approved for children under age 3. Between the 2009-2010 and 2010-2011 vaccines, even the Fluzone® vaccine contains considerably less ovalbumin. There is reason to believe that this will be the case going forward. It is very likely that there is just not enough ovalbumin in the vaccine to cause a reaction. Therefore, the consensus conclusions of CISA were that:

1. Egg allergy of any severity (including anaphylaxis) is not a contraindication to the administration of influenza vaccine, but rather a precaution.
2. Patients who report that they are egg-allergic should be referred to an allergist, where the current status of the patient's egg-allergy (often outgrown) can be assessed by history and skin or blood tests for IgE antibody to egg.
3. Skin testing egg-allergic persons with influenza vaccine prior to administration is not required because of its low sensitivity and specificity in predicting serious reactions to vaccine administration.
4. Dividing the dose of vaccine is also not required because the majority of even severely egg-allergic patients can tolerate the full vaccine dose without severe reaction.
5. Influenza vaccine should be administered to those who are egg-allergic in a setting where anaphylaxis can be recognized and immediately treated should it occur and patients should remain under observation for at least 30 minutes after vaccination.

Administering Influenza Vaccine to Egg Allergic Recipients: A Focused Practice Parameter Update

**Dr. Matthew Greenhawt
University of Michigan Medical School
An Arbor, Michigan**

Dr. Greenhawt reviewed the following practice parameters for administering influenza vaccine to egg allergic recipients:

- Summary Statement 1. Egg allergic patients generally should receive influenza vaccinations because the risks of not vaccinating outweigh the risks of vaccinating.
- Summary Statement 2. Persons with a history of suspected egg allergy who need an influenza vaccination should be evaluated by an allergist/immunologist with expertise in food and vaccine allergy.
- Summary Statement 3. Skin testing (prick and/or intradermal) with the influenza vaccine itself in egg allergic individuals does not reliably identify patients who are at increased risk of reacting to the vaccine because of their egg allergy.
- Summary Statement 4. Administration of influenza vaccines to egg allergic individuals should be performed by clinicians experienced in recognizing and managing anaphylaxis and in a setting equipped to manage potential adverse reactions (including anaphylaxis).
- Summary Statement 5. Egg allergic patients who receive influenza vaccine should be observed for at least 30 minutes after receiving the last dose of vaccine.

- Summary Statement 6. Both the single-dose and 2-dose (10%, 90%) methods are appropriate for administering influenza vaccine to egg allergic individuals.

NIAID Recommendations for the Vaccination of Egg-Allergic Individuals with Seasonal Influenza Vaccines

Matthew J. Fenton, Ph.D.

Chief of the Asthma, Allergy, and Inflammation Branch

On Behalf of the Division of Allergy, Immunology, and Transplantation (DAIT), NIAID, NIH

Dr. Fenton noted that NIAID's recommendations for vaccination of egg-allergic individuals are largely consistent with ACIP draft language. A white paper was prepared in January 2011, which the ACIP membership had an opportunity to review. NIAID recommends administration of seasonal influenza vaccine (TIV) to egg-allergic individuals with a medical history limited to egg protein-induced hives and/or angioedema. Such individuals will not require two-step dosing or skin testing with the vaccine prior to TIV vaccination, but should remain under observation for at least 30 minutes following vaccination. Individuals with a history of anaphylaxis to egg proteins can safely receive the TIV vaccine using a 2-step or multi-step challenge protocol, but the use of very low ovalbumin- (OA-) containing vaccines (preferably <0.1 mcg/ml) is critical. This differs from the presentations by Drs. Kelso and Greenhawt. It is certainly quite possible that this category of high risk patients could receive the single dose of vaccine safely, and it may prove to be unnecessary in almost all cases not to use a multi-step protocol. However, the published data to date really only include just over 200 subjects with a history of anaphylaxis, which NIAID feels that larger studies really be needed to make a less conservative recommendation at this point. At this time, NIAID think the data published to date are very encouraging and hope that additional studies will address this issue. There are virtually no data at this point on TIV vaccination of egg-allergic patients with uncontrolled asthma, and such patients should not receive the vaccine until a further risk assessment has been performed.

NIAID agrees with Drs. Kelso and Greenhawt that skin prick testing with the TIV vaccine should not be relied upon to distinguish between groups that are more versus less at risk of systemic reactions (e.g., Chung et al 2010). Prospective studies are needed to determine if the risk of TIV-induced severe reactions in very young egg-allergic children is different than that in older children, adolescents, or adults. Vaccine manufacturers should be encouraged to make OA content available to the CDC for dissemination and use by health care professionals. This recommendation is made in part to aid in the ease by which these data can be obtained by healthcare professionals. In some cases, the ovalbumin limits are noted by the manufacturer, while in some cases the manufacturer must be contacted. In many cases, the actual lot to lot ovalbumin content can be far more than what is stated as the maximum allowable ovalbumin concentration. A history of reactions to any vaccine represents an additional risk group, but one that is likely to involve sensitivities to vaccine components other than egg proteins. NIAID recommends that individuals with a history of severe reactions to any vaccine should be referred for further risk assessment.

Three additional studies reported subsequent to the NIAID white paper after January 2011 are consistent with the recommendations and the comments made by Drs. Kelso and Greenhawt and include the following:

- ❑ Webb et al performed 285 single-dose vaccinations (OA content of up to 1.4 mcg/ml) in a group that included individuals with a history of severe egg allergy (23%). There were no systemic reactions in any of these vaccinated individuals.
- ❑ Owens et al performed a retrospective chart review of children with egg allergy (64 patients, 96 total vaccinations) who received the TIV (OA content of up to 1.4 mcg/ml) by a two-step protocol. There were no episodes of anaphylaxis and all observed reactions were mild cutaneous symptoms.
- ❑ Howe et al performed both a 5-year retrospective chart review of children (135 patients) who received the TIV (OA content of up to 1 mcg/ml) and a prospective study (69 egg-allergic children and 14 non-egg-allergic children) that included children with a history of anaphylaxis. There were no serious reactions observed in either study. In the prospective study, 12 of 13 patients with a history of anaphylaxis tolerated TIV given as a single dose.

Discussion Points

Dr. Baker requested that Dr. Fenton define “uncontrolled asthma” and expressed concern that the largest risk group of children for influenza complications is comprised of asthmatics, and NIAID was basically stating that these children should not receive influenza vaccine.

Dr. Fenton responded that this referred to a severe group of asthmatics on oral Prednisone and high doses of inhaled steroids who have very poor lung function.

Dr. Kelso responded that there is no definition per se, but those who have poor lung function at the time they are evaluated should not receive the vaccine until they are treated appropriately with steroids and other agents, and their pulmonary functions returns toward the normal range.

Dr. Baker pointed out that someone with pulmonary function of less than 75% would be at the highest risk of having influenza complications.

Kelly Moore (AIM) requested clarification regarding whether the recommendation meant “egg allergic” children with uncontrolled asthma, or just uncontrolled asthma. She also wondered whether “egg allergic” referred only to those with anaphylaxis or a broader category of children with “uncontrolled asthma.”

Dr. Fenton confirmed that the recommendation refers to “egg allergic” children with uncontrolled asthma. The recommendation also refers to a broader group, not just those who are egg allergic with anaphylaxis.

Dr. Baker stressed that the point of the presentation was to tell them that egg allergic children may have completely outgrown their egg allergy or do not have severe reactions. Children with severe asthma are a very high risk group. She also highlighted the fact that the speculation that the risk of being vaccinated and triggering a full-blown anaphylactic episode could be greater than the risk of someone with impaired lung function being susceptible to influenza infection is not backed up by data.

Dr. Marcy suggested using “moderate persistent” or “severe persistent” rather than “uncontrolled” because there are case definitions for those. He also wondered why they would send anyone to an allergist, given the statements that history and skin testing do not matter. He emphasized that language should be included at the outset of the recommendations that providers must be prepared to handle serious reactions.

Dr. Kelso clarified that the recommendation indicates that skin testing with the vaccine to predict whether someone is going to react when it is injected into them is not helpful, because even patients with positive skin tests go on to receive the vaccine uneventfully. That is different from using skin testing to egg with a commercial extract of egg to confirm someone’s current egg allergy. Regarding the case definition, Dr. Kelso thought “uncontrolled” came out of the allergy literature on giving allergy immunotherapy injections. In the case of influenza vaccine, patients are being injected with things that they are known to be allergic to. About .5% to 1% of injections will result in a systemic allergic reaction and anaphylaxis. In that case, someone with fully controlled asthma is more likely to have a bad outcome from an anaphylactic event. In the case of allergy shots, patients are asked about their level of symptoms in terms of their asthma and sometimes a pulmonary function test is administered prior to giving an allergy shot. In the case of influenza vaccine, the same would be true. If someone’s asthma was poorly controlled, and they happen to be unlucky enough to have an anaphylactic event on top of that, they could have a worse event. No patients thus far have had any serious reactions. It still seems to be a reasonable step not to administer the vaccine to someone who may be allergic to ovalbumin. He sympathized with the quandary about definitions, but even the allergy world and the asthma guidelines moved away from “mild, moderate, persistent” to “fully controlled” or well-controlled” asthma, which could easily be discerned by history.

Dr. Marcy inquired as to the protocol: should the skin test be positive to egg?

Dr. Kelso replied that this merely establishes whether the child is egg allergic. Because egg allergy is typically outgrown, the child would be given an egg challenge to confirm this. Once a child has outgrown their egg allergy, giving him / her influenza vaccine would be no different than giving it to any other child.

While she did not have a problem with the idea itself, Dr. Baker expressed concern about placing a recommendation to refer someone to an allergist in the middle of influenza-specific recommendations, given that it is very misleading. Also, if a patient is referred to an allergist at the beginning of influenza season, it may be the middle of influenza season before they are actually able to get an appointment. She suggested a cost-effectiveness study on the benefit of referrals to allergists and pulmonary function tests for asthmatics. If pediatricians or family practitioners know ovalbumin content, this information should be disseminated at the beginning of the influenza season and hopefully the content should be below the threshold. It is difficult enough to vaccinate children without adding more barriers.

Dr. Judson agreed with Dr. Baker. While he thought Dr. Kelso’s presentation was clear, logical, and helpful, he did not think it supported the strong wording. Item 3 stating that “Skin testing egg-allergic persons with influenza vaccine prior to administration is not required . . .” sounds soft versus “not indicated” or “not recommended.” People should not be thinking about getting tested at the time they are ready to receive their influenza vaccine. Item 4 includes a further qualifier in the statement, “Dividing the dose of vaccine is also not universally required . . .” This may deter a physician or healthcare provider who is ready to immunize.

Dr. Kelso agreed, pointing out that these statements came out of the consensus process. His vote was “absolutely not required; don’t need to divide the dose.” The equivocation about whether it is necessary or helpful to divide the dose in certain high risk patients is dealt with the language. He provided the conclusions of CISA, which then has developed actual recommendations for ACIP to consider, which should answer questions about who should be referred to an allergist, dividing the dose, et cetera. This will apply to a very small percentage of patients who might actually be referred, and will leave the vast majority able to be vaccinated without concern about these considerations.

Dr. Keitel pointed out that they had heard three different position statements from three different organizations. The working group wrestled with the language as well. The Influenza WG considers ascertaining whether a person is allergic to eggs to be a separate issue. She suggested reviewing the language the WG developed.

Dr. Grohskopf read the following guidance from the WG pertaining to influenza vaccination of persons with egg allergies:

- Egg allergy may be confirmed by a consistent medical history of adverse reactions to eggs and egg-containing foods, plus a skin and/or blood testing for IgE antibodies to egg proteins.
- Individuals who have experienced less severe reactions to egg (hives only) may receive influenza vaccine with the following additional measures:
 - a) as studies published to date involved use of TIV, TIV rather than LAIV should be used;
 - b) vaccine should be administered by a healthcare provider who is familiar with the subject of egg allergy and who is able to ascertain the ovalbumin content of the vaccine available to him/her;
 - c) vaccine with an ovalbumin content ≤ 0.6 mcg/dose should be used;
 - d) vaccine recipients should be observed for at least 30 minutes for signs of a reaction following administration of each vaccine dose.
- Other measures, such as dividing and administering the vaccine by a two-step approach and skin testing with vaccine are not necessary.
- Persons who may be at higher risk for severe reaction and who should be referred for further risk assessment prior to receipt of influenza vaccine:
 - a) Those who report having had reactions to egg involving such symptoms as angioedema, respiratory distress, lightheadedness, or recurrent emesis;
 - b) Or who required epinephrine or other emergency medical intervention;
 - c) Particularly those which occurred immediately or within a short time following egg exposure (minutes to hours).

Dr. Baker suggested that the egg allergy information should appear at the end, given that this is a recommendation about influenza vaccine. Otherwise, it will be extremely confusing to practicing physicians. Expecting pediatricians or family practitioners to know the egg ovalbumin content is completely unrealistic.

Dr. Sawyer clarified that the Influenza Working Group language does not contain language pertaining to asthma and uncontrolled asthmatics. Given the comments during this session, it seemed that this language should be included. In the rare chance that a vaccine recipient with uncontrolled asthma should have a severe reaction, based on the experience of the allergy group that they are more likely to have a bad outcome, ACIP should not take an extra chance on that.

Dr. Baker emphasized that they are more likely to have a bad outcome from influenza.

Dr. Sawyer clarified that he was not saying they should not be influenza immunized, but was saying that they should be influenza immunized by someone who is an expert in severe allergic reactions.

Dr. Grohskopf responded that such language was included in the recommendation at one time, but the clinical opinion from some WG members that they thought they would be able to judge that. She was not adverse to adding the language back, but requested input from other working group members regarding their opinions.

Dr. Kelso said he was inclined not to include such language in terms of simplification and the small numbers of patients to whom this might apply. However, he was not averse to inclusion of this language if it was necessary to achieve consensus. The wording put forth by the working group regarding referral to an allergist should address the residual concerns about patients with particularly severe allergy and dose division. All current vaccines meet the ovalbumin criteria.

Dr. Baker stressed that language about ovalbumin should be removed.

Dr. Greenhawt indicated that a large portion of immunologists feel that this is very concerning, although he does not particularly agree. Regarding the study that established 1.2 as the safe level, this is a by-product of what happened to be distributed in the last year. This is something they could live with because it is largely moot.

Dr. Temte inquired as to the prevalence of egg allergy in the general population, the prevalence of uncontrolled asthma in egg-allergic patients, and the likelihood he would see one of these patients in the next 40 years.

Dr. Kelso replied that the prevalence of uncontrolled asthma in egg-allergic patients is thought to be, at most, about 1% in children. This is much less common in adults. The vast majority of toddlers who are egg-allergic will no longer be egg-allergic by the time they are school-aged. In children who have food allergies, there would be a higher incidence of asthma in general because atopic diseases tend to coexist. However, the percentage of those children who would also happen to have poorly controlled or uncontrolled asthma would be very small. Moreover, poorly controlled asthma is not a diagnosis, but is a temporary condition. Everyone's asthma can be well-controlled with the appropriate medication regimen.

Dr. Cieslak viewed people as being vaccinated in three settings, including the routine setting of a grocery store, a physician's office capable of handling some reactions, or an allergist's office. He thought it would be most useful for the guidelines to succinctly spell out, based on information a patient is likely to disclose, which of those three paths they should be sent down. He was thinking about standing orders that physicians would be signing in terms of potential reactions.

Dr. Baker indicated that pharmacies in Houston are more likely to have emergency equipment available because they give more immunizations than physicians' offices.

Dr. Greenhawt said the academy probably would not recommend that egg-allergic children go to Walgreen's or CVS. Given the level of evidence and monitoring, it makes the most sense for them to be vaccinated in their doctor's office. Although the risk may not be that great and may not be in excess of the typical patient, this is not the typical patient. These patients need some special forethought.

Dr. Cieslak thought that some patients would state that they have an egg allergy because their mother told them once that they once had a reaction, or some will say they vomited after they were vaccinated or after they had eggs once. It would be nice if they could narrow this down to the smallest group that needs to be sent to an allergist's office.

Dr. Greenhawt thought the academy's position would be that someone who says they are allergic to eggs should be seen by an allergist. Some patients will actually have an allergy and others will not. He sees both types of patients every day. In their guidelines, they did not want to get into the issue of stating where to acquire the vaccine. The goal is to increase access to influenza vaccine in persons who say they are allergic to eggs.

Dr. Keyserling (SHEA) expressed concern about how much variation there is within one manufacturer from lot to lot. He wondered whether ovalbumin content disclosure is a regulatory issue in terms of lot release criteria and if so, whether a statement could be made about not releasing a lot with over 0.7 micrograms.

Dr. Sun (FDA) responded that the amount of ovalbumin is a lot specification. He thought it was in the range of what had been shown, but there is variability between manufacturers as shown in the data.

Dr. Baker pointed out that there is also variability in the recommendations in that one states less than 1.2 and the other less than 0.6 micrograms.

Phil Hosbach (sanofi pasteur) pointed out that manufacturers try to improve the process over time. As they have developed the high dose and interdermal vaccines, sanofi pasteur has had some incremental and process changes over the last couple of years, including equipment changes. Those changes were validated and submitted to and approved by FDA. Ovalbumin is not a release criterion for a final vaccine. However, following some of the changes they have tested some of the lots and these were found to be at a level of 0.1 micrograms per dose or less. Therefore, sanofi pasteur feels that the ovalbumin content has been significantly reduced through that purification process.

Dr. Chilton supported removing ovalbumin content from the discussion if it is no longer an issue. It would be very difficult for him in his practice to evaluate that each time he received a new lot of vaccine. He also preferred not to include anything about "uncontrolled asthma," especially if it is not clearly defined. He has patients who require albuterol two or three times a week and he does not know whether that is poorly controlled or not.

Dr. Keitel pointed out that individuals who can eat eggs are not egg-allergic. There is the separate issue of whether a person is egg-allergic and needs to be evaluated for egg allergies, which needs to be separated from influenza vaccine. In her opinion, if someone has an egg allergy, she would prefer that they received influenza vaccine in a doctor's office. She agreed with moving the statement from the beginning to the end.

In the spirit of keeping things simple, Dr. Jenkins thought it would be useful to devise a set of three or four questions for practitioners to consider to help them determine whether to administer an influenza vaccine to a child, or to refer them to an allergist.

Dr. Baker wondered why the working group used the wording "may receive influenza vaccine" versus "should."

Dr. Brady (AAP) pointed out that since these recommendations pertained to the current season and there was no ovalbumin issue at this time, this should be removed from the recommendation. Language could be included in the text that describes the overall concern about ovalbumin. In addition, people order vaccines late in the year. If there a situation in which ovalbumin content exceeds the threshold, practitioners need to know that before they order. It is too late at this time to address this because people have already placed orders.

Dr. Baker recapped that they had heard some good suggestions, but these were not included in the recommendations presented. The first bullet should be moved to be last, "may" should be "should," and language about ovalbumin should be removed.

Dr. Sawyer said he had not heard a complete answer to his concern about asthmatics. He heard from the NIAID group that children with uncontrolled asthma are at higher risk when they have an anaphylactic reaction for a bad outcome. If there is a population in whom a worse outcome can be predicted if they receive an influenza vaccination, it seemed to him that ACIP should call attention to this in its recommendations.

Dr. Baker requested that Dr. Fenton clarify that this is theoretically possible, but that there are no data to support that children with uncontrolled asthma are likely to experience a worse outcome.

Dr. Greenhawt replied that Dr. Fenton had left, but said that as was stated previously by Dr. Kelso, there are soft data to suggest a worse outcome. It is the feeling that patients with uncontrolled asthma who receive an injection of something to which they are allergic will have a worse outcome.

Dr. Fryhofer (ACP) pointed out that administration of influenza vaccinations to egg-allergic patients is a new frontier, and she felt strongly that the recommendation pertaining ovalbumin should remain in the recommendation. Having the provider go through an extra step is reassuring. They also heard that Fluzone® is the only influenza vaccine recommended for children under 3 years of age, but it has the highest ovalbumin content. ACP has 0.6 micrograms per dose in its recommendations. She thought they should clarify the size of the dose, and leave the numbers in.

Phil Hosbach (sanofi pasteur) clarified that milligrams per dose for the pediatric vaccine is less than 0.1 micrograms per dose.

Dr. Baker thought that 0.6 micrograms or less would simplify the recommendation for busy family practitioners and pediatricians.

Kelly Moore (AIM) expressed confusion about the LAIV being excluded, only because if ovalbumin is the issue with egg allergy, LAIV showed the least ovalbumin of any of the TIVs. She wondered what the thought process was regarding LAIV and children with egg allergy. The risk to children with uncontrolled asthma from influenza is among the highest risk for hospitalization and death. This cannot be overlooked in terms of missed opportunities with the broader group of egg-allergic children as opposed to those with anaphylaxis.

Dr. Keitel responded that LAIV was excluded was that no studies have been conducted with LAIV, and LAIV is administered by an alternative route. It is unknown whether administration via a different route will cause a reaction in patients with reactions to egg protein.

Dr. Englund indicated that the most frequent complaint in pediatric offices is that people think they may have had a reaction to eggs. She thought the first bullet should state that the recommendation does not pertain to subjects who are not egg-allergic. If they eat eggs without incident, they are not egg-allergic and it will not be necessary to consider the rest of the list. She emphasized that busy people do not read the whole statement.

It seemed to Dr. Baker that a statement should be added to the first bullet such as, "Individuals who eat eggs are not egg-allergic." For individuals who have reactions, she suggested stating "individuals who have reactions" rather than "less severe reactions" and then the rest.

Dr. Pickering indicated that the sentence, "These are the final recommendations by ACIP" could be included there so that it would be read immediately before any of this is listed.

Dr. Baker suggested adding the screening questions that Dr. Jenkins requested to the statement.

Ms. Ehresmann noted that this is the only topic for which her agency received a call from an allergist to encourage support for this decision. She has never received a call from anyone else. She thought that there was overriding support for removal of the statement regarding ovalbumin content to make it less complicated. Because it is not an issue for the upcoming season, she proposed removing it.

Dr. Cieslak asked whether the sentence that was moved to the end pertaining to skin or blood testing had anything to do with ACIP's recommendation about whether to administer an influenza vaccination. If not, it should be scratched from the recommendation. Otherwise, the only place he could see that it mattered was for a population of children who were tested and found to be positive who never had a history of a reaction.

Dr. Greenhawt responded that this would represent a significant population .

Dr. Cieslak pointed out that those who are egg-allergic who have never had a reaction also need to be addressed in the recommendation. They should probably go to a doctor.

Dr. Kelso responded that there are certainly children who are sensitized who make IgG antibodies to eggs who are positive by skin tests or blood tests, but whose parents do not know what happens when they eat eggs because they have never had eggs. They were sensitized through a respiratory route, skin contact, breast milk, or some other way. Some of those patients would react if they ingested eggs. In terms of simplifying matters, parents could simply be asked what happens when their child eats eggs. If the parents state that the child eats eggs uneventfully, they are not egg-allergic. If something more severe than hives occurs, further evaluation should be done. Screening for egg allergy can be done reliably by history. He agreed that it is true if an individual provider is not sure for some reason whether a patient is allergic to eggs, there are various mechanisms by which they can figure this out, including blood testing, sending them to an allergist, et cetera.

Dr. Baker requested further input regarding whether to keep the language pertaining to ovalbumin in the recommendation.

Dr. Grohskopf replied that that the quantity had been expressed as either 1.2 mcg per mL or 0.6 mcg per 0.5 mL dose, so it was not really inconsistent, but she will check. There has been a significant amount of discussion regarding ovalbumin. The reasons for keeping it in is because the information is available on some manufacturer package inserts but not all, and there may be variability from season to season and lot to lot. Therefore, it is difficult to make a blanket statement that would cover everyone in every circumstance. Hopefully in the future, the information will be more easily accessible such that the issue could be addressed for the majority of egg-allergic people who only have hives and may be missing out on getting vaccinated. The information can be simplified.

Dr. Brady (AAP) emphasized that this is a recommendation for this year, and there will be another one next year. As most people mentioned, most people look at the recommendations. Ovalbumin is not an issue this year, so perhaps it could be removed from the recommendations but included in the text so that people are aware that it is important but is not an issue this year. If it is included as a recommendation, everyone who has already ordered vaccine is going to be confused and may not immunize someone if they do not know that ovalbumin content.

Dr. Sun (FDA) pointed out that many of the package inserts have already been printed for the current year's influenza vaccine. The package inserts state that egg allergy is a contraindication, so he is not sure how to deal with this issue. However, he did believe that there could be confusion and that further deliberation is required.

Dr. Baker thought it was the same as having an off-label recommendation for compelling reasons. Often practitioners cannot find the package insert much less find a magnifying glass to read it. Therefore, she did not think the package insert would pose a major barrier.

Motion

Ms. Ehresmann made a motion to accept the recommendation as modified based on the discussion and with removal of the ovalbumin statement, and with the understanding that the recommendations pertain to this year and must be re-evaluated each year. Dr. Cieslak seconded the motion. The motion carried with 13 affirmative votes, 0 negative vote, and 1 abstention.

Influenza Activity Update

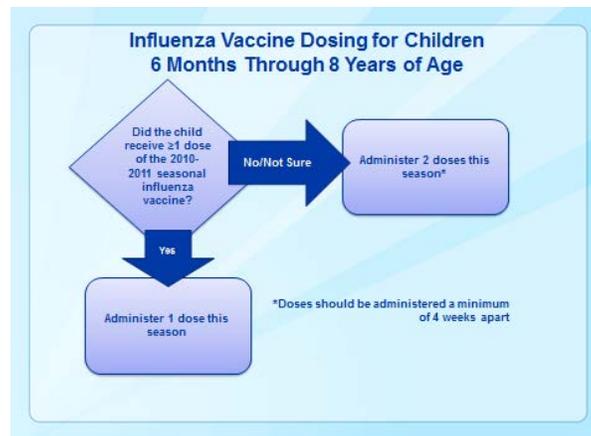
Lisa Grohskopf, MD, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Grohskopf reported that the vaccine virus strains would be the same as those in the 2010-2011 vaccine, and would include the following:

- A/California/7/2009 (H1N1)-like
- A/Perth/16/2009 (H3N2)-like
- B/Brisbane/60/2008-like

A new intradermally-administered TIV, Fluzone Intradermal® manufactured by sanofi pasteur) was licensed in May 2011. This vaccine is indicated for persons aged 18-64 years. It is administered intradermally via a single-dose, prefilled microinjection syringe. Is an alternative to other seasonal vaccines for the indicated age group, and there is no preferential recommendation.

There working group has had some discussion regarding the number of doses for children 6 months through 8 years of age. This is was somewhat complicated in 2009 by the pandemic 2009 H1N1 virus. Children in this age group do not develop full immunity with the initial dose of vaccine in the first season it is administered. In past seasons, 2 doses have been required during the first season a child in this age range receives influenza vaccine. In order to simplify things this year and because the vaccine virus strains for the coming season are the same as for this past season, the algorithm proposed is to ask whether a child received at least one dose of the 2010-2011 seasonal influenza vaccine. If so, one dose should be administered for 2011-2012. If unsure or at least one dose was received, two doses should be administered. This is depicted in the following diagram upon which ACIP members ultimately voted:



Discussion Points

Dr. Keitel proposed that these recommendations be accepted with the caveat that a footnote be included on the algorithm that relates to Option 2 that regards whether a child received an influenza vaccine before 2010 and had the monovalent H1N1. If so, they will only need one dose for 2011-2012. Dr. Jenkins seconded the motion.

Dr. Sawyer wondered why a footnote when there is a different version of the algorithm diagram that includes that scenario and seemed clearer to him than putting them in the footnote.

Dr. Keitel responded that there was a robust discussion about the selection of the option. The simple Option 1 was favored by the majority of the WG members.

Dr. Sawyer emphasized that although the other option was more complicated, it is the reality. He thought placing it in a footnote made it even more difficult. Therefore, he disagreed with the majority opinion of the WG because many children received monovalent H1N1 vaccine and seasonal influenza vaccine in 2009-2010.

Ms. Ehresmann expressed confusion with regard to whether they were voting on the diagram.

Dr. Baker clarified that they were voting on the antigen content and the simple diagram.

Dr. Englund inquired as to what AAP had chosen. If there are different diagrams, there will be confusion.

Dr. Baker said she thought the intent for AAP was to be in concert with ACIP.

Dr. Englund supported the simpler diagram, but thought that adding a footnote, even as a separate diamond above made more sense than the complicated version of the diagram.

Dr. Pickering indicated that Dr. Bernstein from AAP wrote both of these documents. The feeling was that the simpler one would be better, and the two groups try to harmonize whenever possible.

Dr. Sawyer said his concern was that if someone followed the simpler diagram but did not read the footnote, they would make the wrong decision regarding whether a child needs two doses. Complexity or not, that is the situation.

Dr. Baker clarified that they were voting on the antigen content, the simpler diagram, and either a traditional footnote or additional diamond as suggested during the discussion.

Motion

Prior to the discussion, Dr. Keitel proposed that the recommendations be accepted with the caveat that a footnote be included on the algorithm that relates to Option 2 regarding whether a child received an influenza vaccine before 2010 and had the monovalent H1N1. If so, they will only need one dose for 2011-2012. Dr. Jenkins seconded the motion. Following the discussion, Dr. Baker recapped that they were voting on the antigen content, the simpler diagram, and either a traditional footnote or additional diamond as suggested during the discussion. Dr. Judson added that he would include the “minimum of 4 weeks apart” in a box for the two doses. The motion carried with 9 affirmative votes, 3 negative votes, and 1 abstention.

Dr. Baker concluded that they could leave it to the wisdom of the CDC lead staff and WG members to make this as clear and simple and possible to reflect the discussion, working off of the simple diagram.

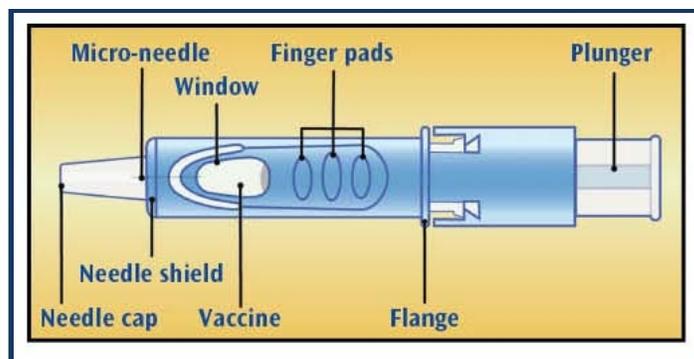
Fluzone Intradermal[®] (Influenza Virus Vaccine)

David R. Johnson, MD, MPH
Senior Director, Global Medical Affairs
sanofi pasteur

Dr. Johnson reminded everyone that ACIP recommends annual influenza immunization for everyone 6 months of age and older. For the first time, ACIP recommendations include healthy adults 19 through 49 years of age. Given that young adults have traditionally been hard to capture with vaccination, strategies for extending the reach of influenza immunization are needed. Fluzone[®] Intradermal is a new vaccine option for adults 18 through 64 years of age. This may contribute to an increase in immunization rates. Influenza vaccination coverage rates are still below national goals, especially among young adults, including those who have high risk conditions. It is hoped that the intradermal vaccine will help to improve this situation.

The presentation of antigen to dendritic cells induces a robust immune response. The vaccine comes in a simple, easy to use microinjection system that results in reduced volume and less antigen. The skin plays a key role in immune function. The intradermal vaccination exploits the skin, the body’s first line of defense in recognizing and eliminating invading organisms. The skin is rich in dendritic and other immune cells. Because of extensive blood vasculature and lymphonic network, the skin facilitates the traffic of these cells as well as antigens in and out of its dermal layer. The dendritic cells are the power house of the skin’s immune potential. It is a highly specialized antigenic cell that can stimulate a robust and long-lasting immune response to viral.

Tapping into the skin’s immune cells has been done for many years; however, this has usually been done through the Mantoux Technique, which can be cumbersome and uncomfortable for patients. Therefore, sanofi pasteur developed a new approach for intradermal delivery. Dr. Johnson instructed ACIP members to open the boxes provided to them that included a sample syringe. Fluzone Intradermal[®] utilizes a novel microinjection device, illustrated in the following diagram:



This single-use glass syringe is prefilled with 0.1mL dose of vaccine. The syringe has a 30-gauge, short-bevel needle permanently affixed to the end of the syringe. The depth of insertion limited to 1.5 mm from the skin's surface. Dr. Johnson described how to utilize the syringe and to demonstrate had the ACIP members inject the vaccine into the orange sponges provided. Following administration, pressing hard on the plunger emits a needle sheath over the needle.

In terms of the attributes of this system, the needle is 90% smaller than needles traditionally used for IM injections, and the short needle reduces the possibility of damage to nerves and blood vessels. The design of the device ensures consistent delivery of the vaccine into the dermal layer regardless of a patient's age, gender, muscle mass, or body-mass index (BMI). The microinjection system is easy to use such that only minimal training is needed. In addition, there is nothing to prepare. The device is essentially ready to go from the box to the injection. Given the size of the needle, it is expected that patients will like being injected with the device even if they have avoided vaccination before because they do not like needles. The integrated needle shield may reduce contamination, injury, and infection in health-care personnel.

When comparing Fluzone Intradermal® vaccine with regular Fluzone®, some of the most striking differences are with respect to the antigen content, the injection volume, and the tiny needle. Fluzone Intradermal® contains 40% less antigen in an 80% smaller dose that is administered through a micro needle. Again, the product is an inactivated influenza virus vaccine indicated for active immunization of persons 18-64 years of age against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. Persons 18-64 years of age should receive a single annual 0.1mL intradermal dose, and the recommended site is over the deltoid. This is an area where people are used to receiving a vaccination, and this area is preferred because here the skin has a uniformity in its thickness and is thick enough to allow reliable deposition of the vaccine into the dermal layer.

The safety and immunogenicity of Fluzone Intradermal® was evaluated in three trials. Dr. Johnson discussed the Pivotal Trial FID31, which was a multi-center, modified, double blind trial to assess the safety and immunogenicity of this product compared to standard Fluzone®. Fluzone Intradermal® induced GMT responses that were very similar to Fluzone® for all three strains. Seroconversion rates were similar, though they were somewhat lower for Fluzone Intradermal® with the B strain. For seroprotection rates, there was hardly any difference for all three strains. In terms of safety, participants were observed for 30 minutes in the clinic after vaccination. Participants recorded solicited injection-site and systemic symptoms on a diary card each day for 7 days following vaccination. Diary cards and unsolicited adverse events were reviewed by study staff during clinic visit 28 days after vaccination. SAEs and healthcare provider contacts were assessed by telephone 6 months after vaccination. As expected, injection site reactions were more common with Fluzone Intradermal® than Fluzone® because

the vaccine is injected just below the skin surface. However, these injection site reactions were generally mild to moderate and resolved within 3 to 7 days. The frequency of pain within the 7 days post-vaccination was similar across the two vaccine groups, and despite the higher frequency of certain injection site reactions, the real-world experience suggests that these reactions are not that bothersome to the recipients of the vaccine. There was no material difference with respect to solicited systemic reactions between the two vaccine groups, which were typically mild to moderate and transient. Rates of immediate, unsolicited, and serious adverse events were similar in the two groups.

While Fluzone Intradermal® was licensed in the US in May 2011, it will not be available until the upcoming season. However, sanofi pasteur has some insight into how intradermal influenza vaccinations perform in the real-world through experience with licensed and used elsewhere (e.g., Intanza® in the Northern Hemisphere and Instivac ID® in the Southern Hemisphere). Satisfaction surveys were conducted in Australia and Argentina. Almost all respondents who received intradermal vaccine reported being either very satisfied or satisfied with their vaccination experience. Minimal pain with the injection, a quick administration process, and feeling reassured by the micro needle were frequently cited reasons for their satisfaction. When intradermal vaccine recipients were asked what they wanted to do next year for influenza vaccination, the vast majority reported that they wanted to receive the intradermal vaccine again. When the Argentinian sample was followed up 7 to 10 days later, they still felt the same way. The survey of Australian providers showed that they had liked their experience with intradermal vaccination. Most preferred administering it over an IM injection, and almost all said that they would definitely or probably recommend it to their patients next year.

In summary, Fluzone Intradermal® vaccine induces a robust immune response in adults 18-64 years of age. Injection-site reactions are more frequent due to administration of influenza antigens into the dermal space, but not bothersome to vaccinees in routine clinical practice. The systemic safety profile, including unsolicited adverse events and severe adverse, is comparable to IM. The real-world experience demonstrates a high level of satisfaction with intradermal vaccination. The microinjection system is well-accepted by patients and providers due to the shorter needle length, smaller gauge, and lower antigen content compared with traditional IM vaccine. The system ensures consistent and accurate delivery of antigen into the dermis, whatever the patient's physical characteristics. There is a simple administration technique that is easy to learn and is intuitive. The needle shielding system enhances safety. Fluzone Intradermal vaccine is an attractive alternative to traditional IM vaccine and may help increase immunization coverage rates among adults®.

Discussion Points

Dr. Meissner noted that the microinjection system looked more complicated than the standard mechanism, and he wondered how much more expensive it is than using a standard needle and syringe.

Phil Hosbach (sanofi pasteur) responded that the price is very similar to prefilled syringes. It is about \$1 to \$2 more because the device is more expensive.

Fluzone High Dose Update

David R. Johnson, MD, MPH
Senior Director, Global Medical Affairs
sanofi pasteur

Dr. Johnson reminded everyone that while older adults comprise only about 15% of the US population, they make up 63% of influenza hospitalizations and account for 90% of influenza-related deaths despite the fact that they have a vaccination coverage rate of nearly 70%. The risk of death and hospitalization from influenza clearly increases with increasing age. For those with high risk conditions, the risk of dying from influenza increases dramatically for older adults as evidenced by multiple studies. As HAI titers increase, the risk of infection decreases. Older adults do not make as much influenza antibody compared to younger adults. This difference in antibody response is likely responsible for influenza vaccine effectiveness being consistently lower in older adults compared to younger persons. With these issues in mind, sanofi pasteur developed Fluzone High Dose®. In many respects, Fluzone High Dose® is just like other currently licensed influenza vaccines. However, Fluzone High Dose® differs in that it contains four times more HA than standard influenza vaccines and it does not contain an adjuvant, antibiotics, gelatin, or preservatives.

Three pre-licensure trials were conducted for Fluzone High Dose® involving thousands of patients. Given that the results were essentially the same across these trials, Dr. Johnson presented information on Pivotal Trial FIM05. FIM05 was a multicenter, randomized, double-blind, controlled Phase III trial of Fluzone High-Dose® vaccine for older adults. The purpose was to compare the immunogenicity and safety of Fluzone High-Dose® vaccine (60mcg HA per strain) with standard-dose Fluzone® vaccine (15mcg HA per strain). This trial was conducted among medically stable persons ≥65 years of age living in the community. There were 3876 subjects randomized to receive vaccine in a 2:1 ratio. Of those, 3851 were included in the immunogenicity analysis. Blood samples were drawn before and 28 days after vaccination, and serum samples were assessed for antibody to each of the 3 vaccine components by HAI testing using standard methods.

As expected, the rates of injection site reactions were higher with the high dose, but these reactions were generally mild to moderate and were transient. For solicited systemic reactions, there was no material difference between the vaccine groups. Rates of immediate, unsolicited and serious adverse events and deaths were similar between the two groups. Two serious adverse events were considered to be vaccine-related, one in each group. Of the reported deaths, none occurred within 28 days of vaccination. Two endpoints were considered to assess superiority of Fluzone High-Dose®: GMT ratios and differences in four-fold rates. Typically, immune response would be considered superior if it was even minimally higher but statistically higher than the other response. However, for Fluzone High-Dose® it was necessary to demonstrate super superiority. That is, the lower bound of the 95% confidence interval for the GMT ratio had to exceed 1.5 instead of just 1. The lower bound of 95% confidence interval for the 4-fold rise rates had to be greater than 10 percentage points and not just greater than 0. Fluzone High-Dose® achieved super superiority for the A strains, and was superior for the B strain if considering the traditional measure but not if the measure established in this protocol was considered. Sub-analyses showed that Fluzone High-Dose® induced robust immune response regardless of age, gender, or cardiopulmonary disease history.

In summary, no important safety differences were observed between Fluzone® and Fluzone High-Dose®. Fluzone High-Dose® was more immunogenic than the standard dose Fluzone® and achieved overall immunogenicity compared to Fluzone®. Based on these results, Fluzone High-Dose® was licensed through FDA's accelerated approval process in December 2009. Of those elderly who were vaccinated last season, about 10% received Fluzone High-Dose® vaccine. It has an established benefit under Medicare Part B, and has its own CPT code.

Regarding the post-approval experience, for the period July 1, 2010 through May 15, 2011, sanofi pasteur's pharmacovigilance department received over 400 reports of adverse events associated with either Fluzone® or Fluzone High-Dose®. About 75% of reports were for Fluzone® and the remainder were for Fluzone High-Dose®. Most reported adverse reactions were non-serious. One possible reason for the higher rate for Fluzone High-Dose® compared to Fluzone® is increased reporting with a new vaccine in a special population. Age-related morbidities may also account for some of the increased adverse events. Further study revealed that nausea, vomiting, and diarrhea were included in the top 10 adverse events observed for Fluzone High-Dose®, but not for regular Fluzone®.

Given this interesting signal, further investigation was done. The rate of nausea, vomiting, and diarrhea was about 13 cases per million doses. In most cases, these were non-serious and usually arose within 24 hours of receiving vaccination. Given the number of lots involved, this did not seem to be a lot-specific or lot-related issue. The investigators then turned to the public VAERS database to better understand this finding. VAERS data also showed an increase in adverse report rates for Fluzone High-Dose® compared to Fluzone®. Overall, the picture from VAERS appeared to be similar to what was observed in the sanofi pasteur safety database. Further investigation revealed that the rate of nausea, vomiting, and diarrhea stabilized at around 50 per million doses. Given the limitations to VAERS and reporting to sanofi pasteur's database, the investigators reviewed an HMO database that covers 14 million persons in the US. Based on these data, regardless of the time after vaccination, the rates for provider visits for nausea, vomiting, and diarrhea were the same for high dose and other influenza vaccines. It remains unknown whether the increase in nausea, vomiting, and diarrhea reports represents a true difference or is a reporting artifact associated with the use of a new vaccine in a special population. Fluzone High-Dose® did not alter the likelihood of patients seeking healthcare with complaints of nausea, vomiting, and diarrhea.

In response to the report of nausea, vomiting, and diarrhea, sanofi pasteur took a number of steps, including a thorough review of the manufacturing process. No quality issues were identified for lots associated with the reports, nor could any aspects unique to the production of Fluzone High-Dose® vaccine be implicated. Fluzone® and Fluzone High-Dose® are both manufactured in the same facility using equivalent licensed processes. Each report of nausea, vomiting, and diarrhea was followed up. This revealed that about 50% of persons experiencing nausea, vomiting, and diarrhea following Fluzone High-Dose® vaccine had pre-existing medical conditions or were using concomitant medications. The Post-Marketing Experience section of 2011-2012 Prescribing Information was updated to read, "The following events have been reported during the post-approval use of Fluzone High-Dose®. Gastrointestinal Disorders: Nausea, vomiting, diarrhea." The safety of Fluzone High-Dose® will continue to be monitored through sanofi pasteur's safety database, VAERS, and on-going clinical trials.

In summary, past season spontaneous and VAERS reports of nausea, vomiting, and diarrhea in 2010-2011 occurred at higher rates with Fluzone High-Dose® vaccine than Fluzone®. Most cases were non-serious and self-limited. When considered in the context of number of vaccine doses distributed, these events remain relatively rare. Of note, this phenomenon was not observed pre-licensure or in large HMO database. Data collected and analyzed to date continue to support a favorable benefit / risk profile for Fluzone High-Dose® vaccine.

There are other on-going or planned studies for Fluzone High-Dose® vaccine. FIM07, the original post-licensure efficacy trial, was somewhat of a bust because it began the same year as pandemic H1N1. Therefore, no efficacy information is available from this trial. The information on safety will be available, and a larger efficacy study will be conducted (FIM12). Additional information will continue to be gained from other on-going trials (FIM09, GRC48). FIM12 will begin in the fall of 2011. This will be a multi-year, multi-center study of Fluzone High-Dose® vaccine versus Fluzone® vaccine to begin Fall 2011. The results are expected in approximately 2014-2015. This will be a randomized, blinded trial with up to 26,000 subjects 65 years of age and older who will be recruited over two influenza seasons. Subjects will be randomized in a 1:1 ratio to high-dose or standard-dose vaccine. Passive and active surveillance will be conducted for influenza-like illness, and confirmation will be made by culture or polymerase chain reaction. Serious adverse events and deaths will be monitored during each surveillance period. The super superiority criterion will be the lower bound of the 95% confidence interval for relative vaccine efficacy for high-dose compared with standard-dose (>9.1%).

To summarize the first year experience, Fluzone High-Dose® vaccine licensed under accelerated approval based on super superiority of antibody responses and the potential to address an unmet medical need. Unfortunately, the uptake of Fluzone High-Dose® during the past season is best described as limited at approximately 10% of doses among persons ≥ 65 years of age. There is an obvious communication gap because what sanofi pasteur hears from many providers is the misperception that this vaccine is not recommended by ACIP. Post-marketing safety surveillance is consistent with pre-licensure studies, except that nausea, vomiting, and diarrhea were among the top 10 reported adverse events. Even so, nausea, vomiting, and diarrhea following Fluzone High-Dose® can be considered uncommon, and reported cases were typically not severe. Also, data from a large HMO showed no material difference in high dose and standard vaccine in healthcare visits for nausea, vomiting, and diarrhea.

Discussion Points

Regarding the limited uptake, Dr. Baker wondered whether there was any trend toward what type of people experienced gastrointestinal symptoms.

Dr. Johnson replied that upon further examining the reported cases, they found that about 50% had high risk conditions or were taking medications that might have helped to explain these gastrointestinal symptoms.

Dr. Meissner inquired as to whether there would be any change in the wording of the CDC statement in regard to the high dose vaccine for the upcoming year.

Dr. Bresee responded that no change was expected this year, or until efficacy or effectiveness data are received that might warrant a change.

Dr. Baker requested that Dr. Bresee respond to the comment that there is a misconception that ACIP does not think this is a good vaccine to use.

Dr. Bresee replied that he was surprised by this because it is not the recommendation. It is not recommended as a preferential vaccination, which perhaps has been misinterpreted as a “no” recommendation. However, it is in the same tables as all of the recommended vaccines.

Dr. Cieslak thought perhaps ACIP should recommended it as a preferential vaccine. A 25% better response to the H3N2 antigen seems like it might be significant unless they did not really believe that the 4-fold rise equals seroprotection.

Dr. Englund believes that they need to see efficacy data, which she thinks will show something. However, she also believes that ACIP should not preferentially indicate anything without some data. Serologic data are very helpful and promising, but she did not think it was enough to give the vaccine preference. It was already given equivalency. She has heard this misunderstanding herself, but perhaps it shows that people are not reading the recommendation.

Phil Hosbach (sanofi pasteur) noted that the VA was also confused and was seeking additional guidance. While they were not asking for a preference, it is clear when speaking with physicians that they believe ACIP does not recommend this vaccine. The only thing sanofi pasteur would ask is that when recommendations are published that it is clear that these are equivalent vaccines that are all recommended by ACIP.

Dr. Temte thought traditionally the challenge has been having sufficient vaccine to meet the needs of patients. In previous recommendations there have not been any distinctions between types even though there is some compelling data, especially in children, that live attenuated vaccine may work better than TIV. ACIP has been very careful not to designate any preferences until such time that both vaccine supply is fairly secure and there is good clinical outcome evidence that there is clear superiority, and that has to be shown over a number of seasons as opposed to just one.

For the record, Dr. Pickering noted that there were 9 ACIP members and 4 *ex officios* present at of the close of the meeting.

Day 2 Public Comments

No public comments were offered on the second day of the June 2011 meeting.

Certification

I hereby certify that to the best of my knowledge, the foregoing Minutes of the June 22-23, 2011 ACIP Meeting are accurate and complete.

9-28-2011

Date



Dr. Carol Baker, Chair
Advisory Committee on
Immunization Practices (ACIP)

Participant Roster

Last	First	Citizenship	Organization
Alexa	Pamela	United States	Pfizer
Allen	Curtis	United States	Pfizer
ARCY	Stephan Michael	United States	Advisory Committee on Immunization Practices
Armstrong	Jennifer	United States	Glaxosmithkline
Ashley	Don	United States	Pfizer Vaccines
Ault	Kevin	United States	Emory University School of Medicine
AVILES-MENDOZA	GUILLERMO J.	United States	National Vaccine Program Office (NVPO)
Bacott	Tameeca	United States	Westchester College
Baker	Carol J.	United States	Baylor College of Medicine
Bandell	Allyn	United States	Medimmune
Barden	Helen	United States	Meningitis Angels
Bardi	Janna	United States	WA Department of Health
Baxter	Bryan	United States	Novartis
Beaman	Ann	United States	Avalon Catering
Bennett	Echo	United States	National Meningitis Association
Berns	Abby	United States	National Association of County and City Health Officials (NACCHO)
Bibila	Theordora	United States	Merck & Co., Inc.
Biega	Lou	United States	Merck and Co. Inc.
Blalack	Gary	United States	GlaxoSmithKline
Boyce	Donna	United States	GlaxoSmithKline
Bozof	Lynn	United States	National Meningitis Association, Inc.
Bradley	Kimberly	United States	GlaxoSmithKline
Brady	Michael	United States	Nationwide Children's Hospital
Bresnitz	Eddy	United States	Merck & Co., Inc
Brewer	Katherine	United States	American Nurses Association
Brewre	Katherine	United States	American Nurses Association
Burnworth	Laura	United States	Children's Healthcare of Atlanta
Burstin	Stuart	United States	GlaxoSmithKline
Campos-Outcalt	Doug	United States	American Academy of Family Physicians
Carter	Laura	United States	Avalon Catering
Cary	Donna	United States	sanofi pasteur
Chaney	Mike	United States	GA Chapter, American Academy of Pediatrics
Chang	Jean	United States	Dynavax Technologies
Cheek	Jim	United States	Indian Health Service
Chesney	Elizabeth	United States	Johns Hopkins School of Public Health
Chilton	Lance	United States	University of New Mexico
Christophers	Gerard	United States	Somers Manor Nursing Home Inc.

Cieslak	Paul	United States	Oregon Public Health Division
Clark	Liana	United States	Merck & Company, Inc.
Claxton	Isabelle	United States	GSK Vaccines
Clover	Richard	United States	University of Louisville
Coelingh	Kathleen	United States	MedImmune
Collier	Antwon	United States	Albany Technical College
Conner	Penny	United States	Georgia Immunization Program
Conway	Catherine	United States	Avalon Catering
Cordell	Laura	United States	sanofi pasteur
Coyne-Beasley	Tamera	United States	Advisory Committee on Immunization Practices
Cullison	Mark	United States	Merck and Co., Inc.
Dalrymple	Donald "Dack"	United States	Dalrymple & Associates, LLC
Dana	Adrian	United States	Merck Sharp & Dohme Corp.
Dasbach	Erik	United States	Merck & Co., Inc.
Deal	Carolyn	United States	National Institute of Allergy and Infectious Diseases
Decker	Michael	United States	sanofi pasteur
Dinovitz	Richard	United States	Nuron Biotech
Donnelly	John	United States	Pfizer
Doskey	Richard	United States	America's Health Insurance Plans
Duchin	Jeffrey	United States	Public Health - Seattle & King County
Egge	Steven	United States	Merck and Co., Inc.
Ehresmann	Kristen	United States	Minnesota Department of Health
Elward	Alexis	United States	Healthcare Infection Control Practice Advisory Committee
Englund	Janet	United States	Seattle Children's Hospital
Erkman	Brett	United States	Great Point Partners
Etkind	Paul	United States	National Association of County and City Health Officials
Evans	Geoffrey	United States	Division of Vaccine Injury Compensation, HRSA, HHS
Fernandez	Carrie	United States	Pfizer
Florez	Jorge	United States	IMMUNOPROTECTION
Fortner	Angela	United States	Northeast Georgia Medical Center
Foster	Stephan	United States	American Pharmacist Association
Friedland	Leonard	United States	GSK
fryhofer	sandra	United States	american college of physicians
Gaffoglio	Diane	United States	Nancy Lee & Associates
Gall	Stanley	United States	The American College of Obstetricians & Gynecologists
Gantt	Lionel	United States	Iron Sharpens Iron
Gargano	Lisa	United States	Emory University
Garman	Patrick	United States	Military Vaccine (MILVAX) Agency
Gaskins	Diana	United States	retired

Geibe	Jesse	United States	DoD (LNO to CDC & ex-officio ACIP member)
Gilmore	Ruth	United States	GA EPIC program
Gonzales	Tara	United States	MedImmune
Gould	Philip	United States	Air Force Medical Support Agency
Grabenstein	John	United States	Merck & Co., Inc.
Greenaway	Richard	United States	Every Child By Two
Greenberg	David	United States	sanofi pasteur
Grogg	Stanley	United States	American Osteopathic Association
Groom	Amy	United States	CDC/Indian Health Service
Hahn	Christine	United States	CSTE
Halbert	Ron	United States	PriceSpective
Halsey	Neal	United States	Johns Hopkins Bloomberg School of Public Health
Haupt	Richard	United States	Merck Research Labs
Hazelwood	Kim	United States	Georgia Public Health
Henry-Wallace	Stephanie	United States	Cambridge Communications & Training Institute
Henzig	Brian	United States	Safeway Inc.
Herrera Taracena	Guillermo	United States	Glaxo Smith Kline
Hewlett	Dial	United States	Pfizer
Heyward	William	United States	Dynavax Technologies
Hoerger	Thomas	United States	RTI International
Hosbach	Philip	United States	sanofi pasteur
Howe	Barbara	United States	GlaxoSmithKline
Huang	Philip	United States	Merck & Co., Inc.
Humphrey-Franklin	Donelle	United States	Ga Division of Public Health
Hunter	Margie	United States	Dekalb Medical
Hutnick	Natalie	United States	University of Pennsylvania
Iarocci	Tom	United States	TIMD, LLC
Israel	Zimra	United States	Pfizer Inc.
Jacobs	Megan	United States	National Vaccine Program Office (HHS)
Janssen	Robert	United States	Dynavax Technologies
Janusz	Cara	United States	Pan American Health Organization
Johnson	David	United States	sanofi pasteur
Johnson	Erica	United States	APCO Worldwide
Judson	Frank	United States	University of Colorado School of Public Health
Kagan	Stephen	United States	Pfizer
Keitel	Wendy	United States	Baylor College of Medicine
Keyserling	Harry	United States	Society for Healthcare Epidemiology of America
Kimberlin	David	United States	AAP
Kinsinger	Linda	United States	Veterans Health Administration

Kitchen	Chester	United States	Merck & Co., Inc.
Knowlton	Rachel	United States	sanofi pasteur
Konz	John	United States	Merck
Krishnarajah	Girishanthy	United States	GlaxoSmithKline
LaBenita	Maribel	United States	Avalon Catering
Landry	Sarah	United States	NVPO
LaRussa	Philip	United States	Columbia University
Lawson	Herschel	United States	CDC, Retired
Leach	Patti	United States	Meade County Health Department
Lee	Ingi	United States	Merck & Co.
Leger	Marie-Michele	United States	American Academy of Physician Assistant
LEROY	JUDY	United States	CLEMSON UNIVERSITY
Lewin	Clement	United States	Novartis Vaccines and Diagnostics
Lewin	Susan	United States	None
Lewin	Sylvana	United States	None
Li	Xiaoming	United States	Merck Research Laboratories
Lievano	Fabio	United States	Merck Sharp & Dohme Corp.
Lindert	Kelly	United States	Novartis Vaccines and Diagnostics
Lyalin	David	United States	Northrop Grumman - CDC Contract
Malhame	Melissa	United States	Dynavax Technologies
Manzano	Yecenia	United States	Meningitis Angels
MARONEY	PATRICK	United States	sanofi pasteur
Martin	J. Tyler	United States	Dynavax Technologies
Martin	Maria	United States	sanofi pasteur
Mazur	Marie	United States	CSL Biotherapies
McGuffin	Colleen	United States	Merck
MEADE	BRUCE	United States	Meade Biologics LLC
Meissner	Cody	United States	Tufts Medical Center
Middleman	Amy	United States	Baylor College of Medicine
Milley	Frankie	United States	Meningitis Angels
Moburg	Christeen	United States	MedImmune
Montero	Jose	United States	New Hampshire Department of Health and Human Services
Moore	Kelly	United States	Tennessee Department of Health
Moore	Brandon	United States	I. D. R.
Mulach	Barbara	United States	NIAID/NIH
murphy	linda	United States	Centers for Medicare & Medicaid Services
Nesin	Mirjana	United States	NIH/NIAID/DMID
Neuman	William	United States	Pfizer Pharmaceuticals
NGUNDUE	JEROME	United States	WALDEN UNIVERSITY

Nicholson	Jennifer	United States	Emory University
Offit	Paul	United States	Children's Hospital of Philadelphia
Owen	Bill	United States	MedImmune
Paradiso	Peter	United States	Pfizer
Parrino	Janie	United States	Merck & Co., Inc.
Peter	Georges	United States	Warren Alpert Medial School of Brown University
Peterson	Diane	United States	Immunization Action Coalition
Plaskett	Theresa	United States	Elizabeth Seton Pediatric Center
Plotkin	Stanley	United States	Vaxconsult
Poland	Greg	United States	Mayo Clinic
Pontani	Dennis	United States	Pfizer Inc
Power	Elizabeth	United States	Novartis Vaccines and Diagnostics
Purdy	Jay	United States	Pfizer
Quinn	Carrie	United States	private practice pediatrician
Quinn	Jane	United States	GlaxoSmithKline
Read	Jennifer	United States	NVPO
Redwood	Lyn	United States	SafeMinds
Reeves-Hoche	Mary Kate	United States	sanofi pasteur
Rein	David	United States	RTI International
rennels	margaret	United States	GlaxoSmithKline
Reynolds	Megan	United States	Children's Healthcare of Atlanta
Reynolds	Joni	United States	Colorado Department of Public Health & Environment
Richardson López-Collada	Vesta	United States	National Center for Children and Adolscentes Healt (CeNSIA)
Richmond	Heather	United States	MedImmune
Ripley	Millicent	United States	Avalon Catering
robbins	patsy	United States	rite aid
Rosenbaum	Sara	United States	George Washington University
Saah	Alfred	United States	Merck & Co.
Sanyour	Mark	United States	Novartis Vaccines
Sato	Reiko	United States	Pfizer Inc.
Sattler	Carlos	United States	Merck & Co., Inc.
Sawyer	Mark	United States	UCSD School of Medicine
Schaffner	William	United States	Vanderbilt University School of Medicine
Schmader	Kenneth	United States	American Geriatrics Society
Schodel	Florian	United States	Philimmune LLC
Schuler	Christine	United States	University of North Carolina
Shaw	Brian	United States	Sabin Vaccine Institute
Sheek-Hussein	Mohamud	United States	Faculty Of Medicine
Sheffield	Tamara	United States	Intermountain Healthcare

Shelton	Jerry	United States	Fuld and Company
Sherner	James	United States	Pfizer
Shin	Tom	United States	Baxter Healthcare Corporation
SIEVERT	ALAN	United States	GA CHAPTER, AAP
Silber	Jeffrey	United States	Merck & Co., Inc.
Silverstein	Leonard	United States	GlaxoSmithKline Vaccines
Skjeveland	Eric	United States	Merck Vaccines
Smith	Susan	United States	Medscape
Snow	Vincenza	United States	Pfizer Vaccines
Splete	Heidi	United States	Pediatric News
Stephens	David	United States	Woodruff Health Sciences Center, Emory University
Stinchfield	Patricia	United States	NAPNAP
Strutton	David	United States	Pfizer Inc.
Stuerke	Stacy	United States	Merck Vaccine Division
Sullivan	Gina	United States	GlaxoSmithKline
Sun	Wellington	United States	Center for Biologics Evaluation and Research
Talkington	Kathy	United States	ASTHO
Taylor	Melinda	United States	Roanoke City and Alleghany Health Dept
Temte	Jonathan	United States	ACIP
Thomas	Lonnie	United States	Henry Schein, Inc
Thomas	Sabrina	United States	DeKalb County Board of Health
Thompson	Brad	United States	Pfizer
Titievsky	Lina	United States	Pfizer Inc
Tobar	Peter	United States	TOBAR LLC
Turner	James	United States	American College Health Association
Vaupel	Christine	United States	GlaxoSmithKline
Vaupel	Logan	United States	no organization -- citizen
Verdecia Alonso	Maykel	United States	Saint Francis Memorial Hospital
Vigliarolo	Peter	United States	Cooney Waters
Wain	Jennifer	United States	Northrop Grumman Corporation
Wallace	Fred	United States	Fuld & Co
Warner	Amy	United States	Take Care Health
Weston	Wayde	United States	GlaxoSmithKline
Wexler	Deborah	United States	Immunization Action Coalition
Whitley-Williams	Patricia	United States	University of Medicine & Dentistry of New Jersey-Robert Wood Johnson Medical School
Wu	Lauren	United States	National Vaccine Program Office, DHHS
Yamauchi	Terry	United States	Arkansas Children's Hospital
Yarn	Sandra	United States	GAAAP
Yeh	Michael	United States	Novartis Vaccines

Zahn	Matthew	United States	Louisville Metro Department of Public Health and Wellness
Zimmerman	Richard	United States	University of Pittsburgh
Zucker	Jane	United States	NYC Dept. of Health and Mental Hygiene

Non-US Citizens

Asahi	Kentaro	Japan	Pfizer Japan Inc.
Baehner	Frank	Germany	Novartis Vaccines & Diagnostics
Biehn	Brant	Canada	Dynavax
Dovali	Claudia	Mexico	Novartis Vaccines & Diagnostics
Durrheim	David	Australia	University of Newcastle
ElZein	Majed	Czech Republic	Department Of Treasury pan Majed El Zein
Florez	Jorge	Colombia	IMMUNOPROTECTION
Gomez	Cesar	Mexico	Ministry of Health
Hein	Pierre	United Kingdom	GlaxoSmithKline
Hollingsworth	Rosalind	United Kingdom	Pfizer
IWAMA	Masumi	Japan	sanofi pasteur KK
Kamiya	Hajime	Japan	National Institute of Infectious Diseases Infectious Disease Surveillance Center
Kanaras	John	Canada	Merck & Co., inc.
Kim	Jonghee	South Korea	Korea Centers for Disease Control
LesterSwindell	Mark	United Kingdom	Pfizer Inc
Mahmood	Asif	Canada	sanofi pasteur
Omanio	Roque Glenn	Philippines	Novartis Vaccines
Oselka	Gabriel	Brazil	National Technical Advisory Committee for Immunizations of Brazil
Park	Kwang Suk	South Korea	Korea Centers for disease control & prevention
Rey Benito	Gloria Janneth	Colombia	Instituto Nacional de Salud
Saddier	Patricia	France	Merck & Co., Inc.
seo	min jung	South Korea	korea centers for disease control & prevention
Tan	Litjen	Singapore	American Medical Association
Tsuzuki	Daisuke	Japan	sanofi pasteur Japan
UEMURA	NOBUO	Japan	PMDA
YORK	Laura Jean	France	PFIZER