

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

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



**Summary Report
October 25-26, 2011
Atlanta, Georgia**

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Final: October 20, 2011
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
October 25-26, 2011

<u>AGENDA ITEM</u>	<u>PURPOSE</u>	<u>PRESIDER/PRESENTER(s)</u>
<u>Tuesday, October 25, 2011</u>		
8:00 <u>Welcome & Introductions</u>		Dr. Jonathan Temte (ACIP Chair, acting) Dr. Larry Pickering (ACIP Executive Secretary; CDC)
8:30 <u>Human Papillomavirus Vaccines</u> · Introduction · Post licensure safety studies · Manufacturer safety studies · GRADE, considerations for male vaccination · Background Information: HPV Vaccines for males	Information & Discussion <u>Vote</u>	Dr. Joe Bocchini (ACIP, WG Chair) Ms. Julianne Gee (CDC/NCEZID) Dr. Christine Velicer, Merck Dr. Eileen Dunne (CDC/NCHHSTP) Dr. Lauri Markowitz (CDC/NCHHSTP)
10:30 <u>Break</u>		
11:00 · Proposed Catch-Up Recommendations for Males · VFC vote	<u>Vote</u> <u>VFC Vote</u>	Dr. Eileen Dunne (CDC/NCHHSTP) Dr. Jeanne Santoli (CDC/NCIRD)
11:30 <u>Child/Adolescent Immunization Schedule</u> · Introduction · 2012 immunization schedule 0-18 years of age	<u>Vote</u>	Dr. Cody Meissner (ACIP, WG Chair) Dr. Iyabode Beysolow (CDC/NCIRD)
12:00 <u>Adult Immunization Schedule</u> · Introduction · 2012 adult immunization schedule	<u>Vote</u>	Ms. Kris Ehresmann (ACIP, WG Chair) Dr. Carolyn B. Bridges (CDC/NCIRD)
12:30 <u>Lunch</u>		
1:45 <u>Hepatitis B Vaccine</u> · Introduction · HBV risk among adults with diabetes · Summary of Considerations · Assisted blood glucose monitoring · Implementation/vaccine coverage · GRADE (grading of evidence) · Proposed recommendations	Information & Discussion <u>Vote</u>	Dr. Mark Sawyer (ACIP, WG Chair) Dr. Sarah Shillie (CDC/NCHHSTP) Dr. Trudy Murphy (CDC/NCHHSTP) Dr. Pamela Allweiss (CDC/NCCDPHP) Dr. Kathy Byrd (CDC/NCHHSTP) Dr. Sarah Shillie (CDC/NCHHSTP) Dr. Trudy Murphy (CDC/NCHHSTP)
3:45 <u>Break</u>		
4:00 <u>Meningococcal Vaccines</u> · Introduction · Epidemiology of meningococcal disease in infants · Cost effectiveness considerations for meningococcal vaccines in infants · Considerations for use of meningococcal vaccines in infants	Information & Discussion	Dr. Amanda Cohn (CDC/NCIRD) Ms. Jessica MacNeil (CDC/NCIRD) Dr. Ismael Ortega-Sanchez (CDC/NCIRD) Dr. Amanda Cohn (CDC/NCIRD)
5:30 <u>Public Engagement</u> · Summary of public engagement for meningococcal vaccines in infants	Information	Dr. Glen Nowak (CDC/NCIRD)
5:45 <u>Public Comment</u>		
6:00 <u>Adjourn</u>		

Wednesday, October 26, 2011**8:00 Unfinished Business**

Dr. Jonathan Temte (ACIP Chair, acting)

8:15 Agency Updates

CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NVPO, NIH

Information

Ex officio members**8:30 13-valent Pneumococcal Conjugate Vaccine (PCV13)**

- Introduction
- Immunogenicity of PCV13 in adults: results of phase III studies
- Considerations for PCV13 use among adults with immunocompromising conditions: summary of immunogenicity and efficacy studies

Information &
DiscussionDr. Mike Marcy (ACIP, WG Chair)
Dr. Peter Paradiso (Pfizer)

Dr. Kathleen Dooling (CDC/NCIRD)

9:30 General Recommendations/Febrile Seizures

- Update on febrile seizures and vaccines

Information &
DiscussionDr. Jeff Duchin (ACIP, WG Chair)
Dr. Andrew Kroger (CDC/NCIRD)**9:40 Pertussis**

- Update: FDA expanded age indication for Tdap (Boostrix)
- Update: pertussis vaccines workgroup activities

Information

Dr. Mark Sawyer (ACIP, WG Chair)

Dr. Mark Sawyer (ACIP, WG Chair)

9:50 Immunization coverage of children/adolescents

Information

Dr. Lance Rodewald (CDC/NCIRD)

10:00 Vaccine Supply

Information

Dr. Jeanne Santoli (CDC/NCIRD)

10:10 Break**10:30 Measles**

- Introduction
- Epidemiology of measles in the United States
- Measles outbreak in Canada
- Measles prevention activities in Mexico
- Measles vaccination among children with HIV infection
- Summary of options

Information
&
Discussion

Dr. Jon Temte (ACIP, WG Chair)
 Dr. Huong McLean (CDC/NCIRD)
 Dr. Gaston de Serres (Institut national de santé publique du Québec)
 Dr. Vesta Richardson (ACIP, NICHP)
 Dr. George Siberry (NIH)
 Dr. Huong McLean (CDC/NCIRD)

12:15 Influenza

- Introduction
- Influenza activity update
- Vaccine efficacy
- Fluzone high-dose safety
- Influenza vaccine distribution and coverage

Information
&
Discussion

Dr. Wendy Keitel (ACIP, WG Chair)
 Dr. Lisa Grohskopf (CDC/NCIRD)
 Dr. Mark Thompson (CDC/NCIRD)
 Dr. Pedro Moro (CDC/NCIRD)
 Dr. James Singleton (CDC/NCIRD)

**1:00 Public
Comment****1:15 Adjourn**

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
AAPA	American Academy of Physician Assistants
ABCs	Active Bacterial Core Surveillance
ACCV	Advisory Commission on Childhood Vaccines
ACHA	American College Health Association
ACNM	American College of Nurses and Midwives
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
ACIP	Advisory Committee on Immunization Practices
ADA	American Diabetes Association
AEs	Adverse Events
AFIX	Assessment, Feedback, Incentives and Exchange
AFP	American Family Physician
AI/AN	American Indians/Alaska Natives
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
BARDA	Biomedical Advanced Research and Development Authority
BMI	Body Mass Index
BRFSS	Behavioral Risk Factor Surveillance System
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CIN	Cervical Intraepithelial Neoplasia
cLIA	Competitive Luminex immunoassay
CMS	Centers for Medicare and Medicaid Services
COI	Conflict of Interest
CSTE	Council of State and Territorial Epidemiologists
DHS	Department of Homeland Security
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DTaP	Diphtheria, Tetanus, and Pertussis
DVA	Department of Veterans Affairs
EIP	Emerging Infections Program
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
GMCs	Geometric Mean Concentrations
GMTs	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HAART	Highly Active Antiretroviral Therapy
HA1c	Hemoglobin A1c
HCP	Health Care Personnel
HEDIS	Healthcare Effectiveness Data and Information Set
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
HRSA	Health Resources and Services Administration
IDSA	Infectious Disease Society of America
IgG	Immunoglobulin G
IIS	Immunization Information Systems
ILI	Influenza-Like Illness
ILINet	Influenza-Like Illness Surveillance Network
IOM	Institute of Medicine
IPD	Invasive Pneumococcal Disease
ISD	Immunization Services Division
ISO	Immunization Safety Office (of CDC/NCIRD)

JAMA	<i>Journal of the American Medical Association</i>
MCO	Managed Care Organization
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Measles, Mumps, Rubella
MMRV	Measles, Mumps, Rubella, Varicella
MMWR	<i>Morbidity and Mortality Weekly Report</i>
MSM	Men Who Have Sex With Men
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization
NCATS	National Centers for Advancing Translational Sciences
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCHS	National Center for Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
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
NMA	National Meningitis Association
NNDSS	National Notifiable Diseases Surveillance System
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
OPA	Opsonophagocytic
PAHO	Pan American Health Organization
PATH	Program for Appropriate Technology in Health
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
<i>PIDJ</i>	<i>Pediatric Infectious Disease Journal</i>
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
SBIR	Small Business Innovative Research
SME	Subject Matter Expert
SNS	Strategic National Stockpile
SSAEs	Serious Systemic Adverse Events
Tdap	Tetanus and Reduced Diphtheria Toxoids
TIV	Trivalent Inactivated Influenza Vaccines
UK	United Kingdom
US	United States
USAMRIID	US Army Medical Research Institute of Infectious Diseases
VAERS	Vaccine Adverse Event Reporting System
VFC	Vaccines for Children
VICP	Vaccine Injury Compensation Program
VIS	Vaccine Information Statement
VSD	Vaccine Safety Datalink
VTE	Venous Thromboembolic Events
VTrckS	Vaccine Tracking System
WG	Working Group
WHO	World Health Organization

October 25, 2011**Welcome and Introductions**

Dr. Jonathan Temte
Acting Chair, ACIP

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

Dr. Temte called the meeting to order, welcoming those present. He reported that due to an illness in her family, Dr. Baker would not be attending the meeting and that he would serve as Chair on her behalf. He and Dr. Pickering said that everyone's hearts and prayers went out to Dr. Baker and her family.

Dr. Pickering welcomed everyone to the October 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.

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; Cindy Fowler; Suzette Law; and Tanya Lennon, Special Assistant. Those with any questions were instructed to see him or any of these individuals. 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.

Dr. Pickering emphasized that they had a full agenda for the next two days, with scheduled votes on four different topics. He noted that the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to developing evidence-based recommendations would be initiated in the HPV and the hepatitis B vaccine sessions. For additional information about the GRADE process, those in attendance were referred to the article appearing in *Vaccine* titled "Methods for developing evidence-based recommendations by the Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control and Prevention (CDC)" by Dr. Faruque Ahmed, Dr. Jonathan Temte, Dr. Douglas Campos-Outcalt, and Dr. Holger Schünemann. A copy of this article was made available on the table in the lobby, outside of the auditorium doors. In addition, the captioned DVD and the slide presentations from the GRADE workshop led by Dr. Holger Schünemann and presented at CDC on September 9, 2011 will be posted on the ACIP website as soon as they are made 508-compliant.

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 three months or 90 days following this meeting. Members of the press interested in conducting interviews with various ACIP members were instructed to contact Tom Skinner, who was in attendance, for assistance in arranging the interviews.

Dr. Pickering recognized the following *ex officio* members and liaison representatives:

Ex Officio Members

- ☐ Dr. Wellington Sun is the acting *ex officio* member for the Food and Drug Administration (FDA).
- ☐ Mary Beth Hance, Senior Policy Advisor, is the new *ex officio* member for the Centers for Medicare and Medicaid Services (CMS).

Liaison Representatives

- ☐ Dr. Jamie Loehr, from the Cayuga Family Medicine Group in Ithaca, New York, is the new American Academy of Family Physicians (AAFP) liaison.
- ☐ Mr. Christopher Barry will represent the American Academy of Physician Assistants (AAPA).
- ☐ Dr. Walt Orenstein, Associate Director, Emory Vaccine Center, will represent the National Vaccine Advisory Committee (NVAC). Dr. Orenstein will become the NVAC Chair and liaison representative to ACIP effective January 1, 2012.
- ☐ Dr. Kevin Ault, Emory University School of Medicine, will represent the American College of Obstetricians and Gynecologists (ACOG).
- ☐ Ms. Kathy Talkington will represent Association of State and Territorial Health Officials (ASTHO).

To avoid disruptions during the meeting, Dr. Pickering instructed those present 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.

Dr. Pickering explained that topics presented during the ACIP meeting include open discussion with time reserved for public comment. During this meeting, a time for public comment was scheduled following the afternoon sessions during both meeting days. 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, Dr. Pickering indicated that members of the ACIP agree to forego participation in certain activities related to vaccines during their tenure on the committee. For certain other interests that potentially enhance a member's expertise while serving on the committee, CDC has issued limited conflict of interest waivers. Members who conduct vaccine clinical trials or who serve on data safety monitoring boards (DSMBs) may present to the committee on matters related to those specific vaccines; however, they are prohibited from participating in 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>

Detailed instructions for submission of names of potential candidates to serve as ACIP members may be found on the ACIP web site as shown above. Applications for ACIP membership are due no later than November 18, 2011 for the term beginning July 2012.

The following information was shared pertaining to ACIP:

Next ACIP Meeting: Wednesday–Thursday, February 22-23, 2012

Registration Deadline: Non-U.S. Citizens *and* US Citizens **Monday, February 6, 2012**

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. A listing of recommendations that have been published since the ACIP meeting of June 2011 follows:

ACIP Recommendations Published since 07-01-11

Title	Publication Date	MWWR Reference
Licensure of a Meningococcal Conjugate Vaccine for Children Aged 2 Through 10 Years and Updated Booster Dose Guidance	08/05/11	Vol 60(30):1018-1019
Prevention and Control of Influenza with Vaccines	08/26/11	Vol 60(33):1128-1132
Use of Quadrivalent Meningococcal Conjugate Vaccine (MenACWY-D) Among Children Aged 9 Through 23 Months at Increased Risk for Invasive Meningococcal Disease	10/14/11	Vol 60(40):1391-1392
Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) in Pregnant Women and Persons Who Have or Anticipate Having Close Contact with an Infant Aged <12 Months	10/21/11	Vol 60(41):1424-1426
Addition of History of Intussusception as a Contraindication for Rotavirus Vaccination	10/21/11	Vol 60(41):1427
Immunization of Health-care Personnel: Recommendations of the Advisory Committee on Immunization Practices	11/11/11	Vol 60(RR-07):1-44 - pending

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

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These recommendations and schedules can be found on the ACIP web site.

Dr. Pickering confirmed that 14 ACIP members were present, which fulfilled the 13-member quorum required to conduct the meeting. Also present were all 30 liaison and 8 *ex officio* members. Due to the number of votes being taken throughout the day, he noted that adjournment may be somewhat later than usual.

Four members have been appointed by the Secretary, Department of Health and Human Services, to terms from July 1, 2011 through June 30, 2015. Dr. Temte introduced and welcomed the following new ACIP members:

- ☐ Dr. Nancy Bennett, Professor of Medicine and of Community and Preventive Medicine, University of Rochester School of Medicine and Dentistry.
- ☐ Dr. Joseph A. Bocchini, Professor and Chairman, Department of Pediatrics, Louisiana State University Health Sciences Center.
- ☐ Dr. Douglas Campos-Outcalt, Chair, Department of Family, Community, and Preventive Medicine, University of Arizona College of Medicine.
- ☐ Dr. Marietta Vázquez, Associate Professor of Pediatrics, Department of Pediatrics, Yale University School of Medicine.

The following conflicts of interest were declared:

- ☐ Dr. Tamera Coyne-Beasley: Research support is allocated to the University of North Carolina by Merck Pharmaceuticals
- ☐ Dr. Cody Meissner: Payments are made to Tufts University Medical Center by MedImmune and Pfizer
- ☐ The remainder of the ACIP members declared no conflicts

Human Papillomavirus Vaccines

Introduction

Joseph A. Bocchini, Jr., MD
Chair, ACIP HPV Vaccine Workgroup

Dr. Bocchini first reminded everyone of the recommendations ACIP has made for HPV vaccine. In 2006, the quadrivalent HPV vaccine was licensed for use in females. Subsequently, ACIP recommended routine vaccination of 11- or 12-year old females, and for those older than this age group, vaccination through 26 years of age. In 2009, the bivalent HPV vaccine was licensed for females. ACIP harmonized the recommendations for females for the two vaccines, with a recommendation of either vaccine for 11- or 12-year old females and 13 through 26 years old not yet immunized.

In October 2009, FDA licensed the quadrivalent HPV vaccine for males 9 through 26 years for prevention genital warts. ACIP stated that HPV vaccine may be given to males 9 through 26 years 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 Vaccines for Children (VFC) program. In December 2010, FDA advanced the licensure of this vaccine to include the indication for prevention of anal cancer in females and males. Since that time, the ACIP HPV Vaccine Working Group has been presenting data to ACIP in preparation for reconsideration of recommendations for HPV vaccine in males, including the following presentations:

October 2010

- Vaccine safety update
- Efficacy data in males
- Cost-effectiveness
- Provider survey
- Status of HPV vaccine program

February 2011

- Burden of HPV-associated cancer
- Anal cancer
- Cost-effectiveness

June 2011

- Persistence of antibody and duration of protection
- HPV-associated oropharyngeal cancer
- Cost effectiveness review and catch-up

Because of the adoption by ACIP in October 2010 of the GRADE system for evaluating recommendations, HPV Vaccine Working Group is one of first ACIP working groups to use this approach to clarify the evidence behind recommendations.

Post-Licensure Safety Studies

Julianne Gee, MPH
Immunization Safety Office
Centers for Disease Control and Prevention

Ms. Gee provided an overview of the safety of quadrivalent human papillomavirus vaccine (HPV4). She briefly updated the committee on the sources of HPV4 safety data; reviewed findings from pre-licensure trials, US surveillance efforts, and select manufacturer post-licensure commitments; and reviewed findings from 2011 Institute of Medicine's (IOM) report of adverse events and vaccines.

The sources of safety data for HPV4 include pre-licensure trials conducted by the manufacturer. The post-licensure safety data sources include US government-sponsored safety surveillance systems, which are comprised of the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD) Rapid Cycle Analysis (RCA). In addition, there are multiple manufacturer post-marketing commitments, which have been described in the Bonani et al paper published in *Vaccine* 2010 [Bonani P, et al. A summary of the post-licensure surveillance initiatives for GARDASIL/SILGARD. *Vaccine* 2010].

Among the multiple pre-licensure studies, the entire study population included 29,323 males and females. The most frequently reported serious systemic adverse events (SSAEs) in any study arm included headache, gastroenteritis, appendicitis, pelvic inflammatory disease, urinary tract infection, pneumonia, pulmonary embolism, bronchospasm, and asthma. Of the SSAEs, 0.04% were judged to be vaccine-related by the study investigator. Across the clinical studies, 40 deaths were reported. The events reported were consistent with events expected in healthy adolescents and adult populations. Based on the findings from these studies, FDA licensed HPV4 in June 2006 for females 9 through 26 years of age.

Briefly, for those not familiar with VAERS, Ms. Gee explained that this is a national passive surveillance system for vaccine adverse events that is jointly operated by CDC and FDA, and serves as an early warning system for vaccine safety surveillance. Because VAERS is a voluntary and passive surveillance system, it does face some limitations. Most importantly, VAERS is not designed to assess causality between an adverse event and a vaccine. It is subject to reporting biases; data are sometimes incomplete, missing critical pieces of information; and it does not provide denominator data.

In August 2009, VAERS published a 2-year summary surveillance report in the *Journal of the American Medical Association (JAMA)*. The authors concluded that the safety profile of HPV4 among females was consistent with pre-licensure data, with the exception of venous thromboembolism (VTE) and syncope. CDC has continued monitoring HPV4 reports among females and males. Based on the data through 9/15/11, there have been approximately 20,000

reports received in VAERS, of which 7% are considered serious. To date, no new adverse event concerns or new clinical patterns have been identified. The majority of the total reports received in VAERS through September 15th are female. The median age of all reports received was 17 years, with almost 44% of these reports among 13 through 18 year olds. There have been a total of 1,527 serious reports. Approximately 62% of the total reports were received by the manufacturer. Of all VAERS reports, 78.6% of subjects received HPV4 only. The median onset interval from vaccination to adverse event (AE) was 0 days. The most frequently reported terms for non-serious and serious reports following HPV4 in VAERS are shown in the following tables:

Non-serious (N=18,569)		Serious (N=1,527)	
MedDRA Preferred Terms*	%	MedDRA Preferred Terms*	%
Syncope	14.5	Headache	25.0
Dizziness	13.7	Nausea	18.6
Nausea	9.3	Fatigue	17.4
Headache	8.3	Dizziness	16.8
Injection site pain	7.0	Vomiting	14.7
Drug exposure during pregnancy	6.8	Pyrexia	13.7
Pyrexia	6.3	Computerized tomogram normal	13.0
Loss of consciousness	5.9	Syncope	12.6
Urticaria	4.9	Asthenia	11.7
Pain in extremity	4.9	Pain	11.6

Disproportional reporting of syncope was identified in the 2009 VAERS review of HPV4 published in *JAMA*. Since September 15, 2011, syncope continues to be one of the most common terms identified in both non-serious and serious reports. There have been 202 serious reports of syncope. Injuries that have resulted from syncopal events include fractures (nose, skull, maxillary), dental injuries, contusions, concussions, and intracranial hemorrhages (subdural hematoma, subarachnoid hemorrhage). There have been no reports of death received by VAERS from injury resulting from a vasovagal syncopal event.

In CDC's review of anaphylaxis reports to VAERS, 43 reports were found. All were female and 20 were considered serious. The median age was 17 years and the median onset from vaccination to event was 0 days. There were 12 reports in which CDC was able to confirm an anaphylaxis diagnosis by either physician diagnosis or Brighton criteria level 1-3. All were treated and recovered. There were no confirmed deaths due to anaphylaxis. Of the reports, 7 were reported as serious either due to "life threatening" being checked off or report by MFR. Of these, 3 had HPV alone and 1 did not have this information documented. All were treated and recovered. Of the remaining 32, 3 were hearsay reports, 2 had symptoms that ranged from 3 days to 20 days after the vaccination date, 3 had multitude of symptoms but doctors found difficult to come up with a diagnosis, and the remaining 24 did not have enough on the report to establish a diagnosis of anaphylaxis.

A total of 71 reports of death have been received by VAERS, of which 34 have been verified by autopsy, death certificate, or confirmation by a medical provider. Among the 37 unconfirmed reports of death, the majority have been considered hearsay—meaning that there is no specific knowledge about a patient or event; therefore, it is not possible to confirm the death. This included reports from people who read about a possible HPV death in a website, newspaper, or

magazine. “Other” are current death reports that are under investigation. Among the 34 verified death reports, 32 were female. The median age was 17 years and median days from vaccination to death was 15 days. Among these death reports, 15 received dose 1, 8 reports were following dose 2, and 11 were following dose 3. Of the deaths reported, 15 received HPV4 only and 13 received concomitant vaccinations. After clinical review, 7 were classified as neurological deaths, 7 as cardiac deaths (arrhythmia [3]; myocarditis [3]; congenital), 4 as pulmonary embolism, 5 as infectious (Group A Strep [2]; *N. meningitidis*, MRSA; HIV-CNS vasculitis), 4 as other non-infectious (suicide; type 1 DM DKA; drug overdose; dermatomyositis), and 7 were unexplained cause of death. For many of these reports, even upon autopsy, a specific cause of death could not be determined.

Given that ACIP would be voting on a routine HPV4 vaccine recommendation for males during this session, CDC wanted to provide the members with an in-depth review of male reports following HPV4 in VAERS. There have been a total of 569 reports; 504 male reports were received since the vaccine was licensed in October 2009. Of these, there were 33 serious reports, with 44% of reports from subjects who were given HPV4 alone (n=202). The median age was 14 years and the median onset interval was 0 days. The most frequently reported terms for non-serious and serious reports among males following HPV4 are shown in the following tables:

Non-serious (N=536)		Serious (N=33)	
MedDRA Preferred Terms*	%	MedDRA Preferred Terms*	%
Dizziness	18.8	Pyrexia	27.3
Syncope	15.3	White blood cell count increased	24.2
Injection site erythema	10.0	Nausea	24.2
Pallor	9.0	Pain in extremity	21.2
Nausea	8.4	Blood glucose increased	21.2
Pyrexia	7.7	Dyspnea	18.2
Headache	7.6	Cough	18.2
Wrong drug administered	7.4	Muscular weakness	18.2
Injection site swelling	7.2	Abdominal pain	18.2
Fall	6.3	Chest pain	18.2

Of the 33 serious male HPV4 reports, 3 have been death reports, 1 was incorrectly coded as a male, and 29 are serious. Serious non-fatal reported categories (n=29) included the following:

- ☐ Neurological: 9 (Guillain Barré syndrome [4]; seizures [2]; altered mental status; transverse myelitis; acute dystonic reaction)
- ☐ Immune/Allergic: 4 (Stevens-Johnson syndrome; allergic reaction [2], serum sickness)
- ☐ Cardiac: 2 (myocarditis; pericarditis)
- ☐ Gastrointestinal: 4 (acute pancreatitis [2]; appendicitis; colon cancer)
- ☐ Infectious: 2 (cellulitis; diarrhea)
- ☐ Other: 8 (syncope/presyncope [3]; pulmonary embolism; osteitis pubis; DM type 1; sickle cell disease; spontaneous pneumothorax)

Of the two deaths verified in VAERS for males, one was a 10-year old boy who died of myocarditis 9 days after vaccination. He received other vaccines on same day (meningococcal, hepatitis A, Tdap, HPV4 dose 1), and had no past medical history. The other verified death was a 15-year old who had an obstructive congenital subaortic membrane, who died 25 days following vaccination. He received only Dose 1 of HPV4 and had a past medical history of asthma and cardiac disorder.

Ms. Gee briefly described the VSD RCA analysis for HPV4 among females and findings. The VSD is a collaboration between CDC and 10 managed care organizations (MCOs), which was established in 1990 to address gaps in vaccine safety. Using automated data sources that already exist as part of the participating health plans infrastructure, the VSD collects medical and vaccination data on more than 9.8 million members annually (3% of the US population). RCA is an alternative to traditional post-licensure vaccine safety study methods, which generally take years to complete. RCA is not intended to be the final answer. It is a signal detection method for pre-specified adverse events. Potential signals need further study to determine whether signals are real or spurious. This monitoring system tests specific hypotheses with well-defined outcomes and relatively short-defined risk windows. The outcomes of interest are initially based on findings from pre-licensure trials and the literature. One of the strengths of VSD/RCA is that during the course of monitoring, CDC has the ability to add outcomes of concern to on-going RCAs that have been identified by VAERS or other sources. Each week, CDC evaluates the number of events in vaccine persons and compares it to the number of expected events, based on a comparison group that is historical or concurrent. Using sequential analyses methodologies, CDC adjusts statistically for multiple looks [Lieu TA, et al. Real-time vaccine safety surveillance for the early detection of adverse events. *Med Care*. 2007 Oct;45:S89-95].

Ms. Gee and her colleagues' paper was recently published online in *Vaccine*. The main finding from this analysis was that no significant risk was found for any of the pre-specified adverse events following HPV4 vaccination (e.g., GBS, seizures, syncope, appendicitis, stroke, VTE, and other allergic reactions). However, a possible non-statistically significant association was found between HPV4 and VTE. All confirmed cases in this analysis did have other risk factors for VTE. Further study of this issue is on-going. No increase was found in the rate of anaphylaxis following HPV4 as compared to previous VSD studies [Gee J, et al. Monitoring the Safety of Quadrivalent Human Papillomavirus Vaccine: Findings from the Vaccine Safety Datalink Vaccine. 2011 (in press)].

The next steps for VSD with regard to the safety of HPV4 include long-term surveillance of GBS and stroke since the RCA had limited power to assess associations between HPV4 and these very rare adverse events occurring in this particular age group. The investigators are currently conducting a self-controlled case series analysis assessing VTE and all vaccinations, with a focused analysis on HPV4 and VTE. Using this design, they can control for confounding such as birth control use, smoking, and other risk factors for VTE. The VSD has not yet initiated an RCA in males for HPV4, given that CDC is awaiting sufficient uptake to occur among this population.

There are multiple on-going studies, including a post-licensure surveillance program for the safety of GARDASIL™ in a managed care organization setting (Protocol 31); the Nordic long-term follow up study (Protocol 15); and a long-term immunogenicity, safety, and effectiveness study of GARDASIL™ among adolescents who received GARDASIL™ at 9 through 15 years of age (Protocol 18). Merck is conducting the long-term study in Nordic countries, which includes 5400 women who participated in one of their randomized control trials and were vaccinated at

varying time points. The planned duration of follow-up is approximately 14 years and multiple safety endpoints are being assessed. The conclusion for the interim analysis, as presented by Merck during the June 2011 ACIP meeting, was that vaccine is generally safe and well-tolerated for a mean of 6 years following vaccination [Saah A. HPV4 vaccine: Duration of Protection presentation to ACIP. June 2011]. The long-term study of GARDASIL™ in adolescents includes a population of 1661 adolescents vaccinated between the ages of 9 through 15 years. The duration of planned study follow-up is approximately 10 years. The findings from the first interim analysis show that safety is similar to that observed in pre-licensure studies, and that HPV4 is generally well-tolerated over the long-term [Saah A. HPV4 vaccine: Duration of Protection presentation to ACIP. June 2011].

The IOM recently published a report on adverse events following vaccination. Relevant findings for this presentation were that the IOM concluded that data convincingly supported a causal relationship between injection of a vaccine and syncope. For HPV4, the only outcome found to be causally related to the vaccine was anaphylaxis. The IOM concluded that the weight of published evidence favored an acceptance of a causal relationship between HPV vaccine and anaphylaxis [<http://www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx>].

Because of the recognized occurrence of post vaccination syncope, CDC wanted to highlight a few things for the committee. Multiple reviews have found that the majority of syncope occurs within 15 minutes following vaccination. The VSD conducted an analysis of syncope rates on day 0 following adolescent vaccination among 9 through 26 year olds and found that females have a higher rate than males. Specifically for HPV4, the package insert lists syncope as a warning, stating that syncope has been reported following vaccination with HPV4. ACIP recommends that providers should consider observing patients 15 minutes after vaccine administration.

In summary, monitoring and evaluation are on-going for HPV4 from multiple sources. VAERS continues reviewing reports following HPV4. No new adverse event concerns or clinical patterns have been identified. VSD rapid cycle analysis confirmed no significant risk for any of the pre-specified adverse events after vaccination for two age groups (9 through 17 years and 18 through 26 years). Further evaluation of VTE and HPV4 is on-going. Merck's long-term follow-up studies of adolescents have not identified any safety concerns.

Manufacturer Safety Study

Christine Velicer, PhD

On behalf of the GARDASIL Female Safety Study Team, Merck

Dr. Velicer explained that the post-licensure safety study of quadrivalent HPV vaccine was a large, retrospective cohort study with follow-up through electronic medical records (EMRs), supplemented with extensive medical record review. The study was conducted at two large MCOs, Kaiser Permanente Southern California and Kaiser Permanente Northern California in 189,629 females. The objective of the study was to evaluate the safety of GARDASIL™ administered to females as part of routine medical care. The study had several committees. The first was the Safety Review Committee (SRC), which was comprised of 5 members who were experts in various fields (e.g., vaccine safety, pediatric and adolescent medicine, teratology, pediatric rheumatology, and pharmacoepidemiology). The committee was independent and external to both the study team at Kaiser and Merck. The SRC followed pre-specified procedures to review study findings, request additional analyses or chart reviews, and

make conclusions regarding safety. There were four Clinical Case Review Committees (CRCs), each composed of 3 members who were clinician experts in their relevant fields. There was 1 pregnancy CRC and 3 autoimmune CRCs. They confirmed or refuted potential diagnoses identified from electronic medical records by reviewing medical records, and they were blinded to vaccination status.

Females were recruited from August 2006 through March 2008. Approximately 190,000 females received at least one dose of GARDASIL™. Of these, over 99% were within the indicated age range of 9 to 26 years of age at first dose. About half were 9 to 15 year olds, and about 18% were 11 to 12 year olds. The overall, or secondary safety population, was comprised of the 190,000 females who received at least one dose of GARDASIL™. This represented a total of 346,972 doses. The primary safety population of approximately 44,000 was the overall safety population who had received 3 doses per protocol. The autoimmune population was comprised of approximately 149,000 females, and was the overall safety population who had at least 12 months of membership in Kaiser Permanente prior to receiving the first dose. That was to help exclude preexisting conditions. The pregnancy population included about 2,700 females and was the overall safety population limited to those potentially vaccinated with GARDASIL™ at any time during pregnancy or up to 30 days prior to conception as identified in EMRs.

Regarding the pregnancy safety portion of the study, pregnancy outcomes were available in EMRs for 1,740 females (665 live births, 633 potential miscarriages, 442 potential elective abortions). In the EMRs, 170 potential congenital anomaly cases were identified. The medical records were reviewed for all 170 potential cases. Of these, 44 congenital anomalies diagnosed up to 6 months after birth were confirmed and spanned a wide range of diagnoses. Medical records of a random sample of 100 of the 633 potential miscarriages identified in the EMR were reviewed. Most of the unconfirmed cases were elective abortions, and 9 miscarriages were confirmed.

The SRC reviewed all of the pregnancy findings, including diagnosis, gestational age at vaccination and at miscarriage, maternal age, number of doses, concomitant vaccinations, and level of diagnostic certainty of congenital anomaly or miscarriage determined by the CRC. It was noted that rates of major congenital anomalies up to 6 months after birth (3.6%) were consistent with published background rates at birth for California and the US (3.0%). The SRC noted no apparent pattern or distribution of anomalies or miscarriages other than what would be expected in the general population, and determined that there was no association with vaccination.

An autoimmune safety analysis was done on 16 pre-specified conditions that were evaluated for new onset within 6 months after each vaccine dose. Medical records of all potential cases identified in EMRs were reviewed by the expert CRC to confirm diagnosis and estimate onset date with the exception of 5 conditions (Hashimoto's and Graves' diseases, SLE, RA, JRA) for which only a random sample of cases was reviewed due to logistical considerations. The number of confirmed diagnoses within 6 months after vaccination among 149,306 females were comprised of the following:

Neurologic/Ophthalmologic:

- ☐ Multiple sclerosis (4)
- ☐ Acute disseminated encephalomyelitis (3)
- ☐ Other demyelinating conditions of central nervous system (3)
- ☐ Optic neuritis (6), Uveitis (15)
- ☐ Vaccine-associated demyelination (0), Neuromyelitis optica (0), Guillain-Barré syndrome (0)

Endocrine:

- ☐ Type 1 diabetes (15)
- ☐ Hashimoto's disease (93 reviewed: 39 confirmed; 300 not sampled)
- ☐ Graves' disease (32 reviewed: 13 confirmed; 36 not sampled)

Rheumatologic/Autoimmune:

- ☐ Immune thrombocytopenia (9 confirmed)
- ☐ Autoimmune hemolytic anemia (0)
- ☐ Systemic lupus erythematosus (24 reviewed: 8 confirmed; 19 not sampled)
- ☐ Rheumatoid arthritis (16 reviewed: 3 confirmed; 10 not sampled)
- ☐ Juvenile rheumatoid arthritis (11 reviewed: 3 confirmed; 7 not sampled)

To provide further interpretation context for these numbers, the SRC requested a post-hoc autoimmune rate comparison in which rates in the vaccinated population were compared to rates in a background population. This analysis was undertaken by Kaiser Permanente Southern California using Kaiser Permanente Southern California confirmed vaccinated cases. Rates in the vaccinated cohort were compared to a background group at Kaiser Permanente Southern California of females within the same age range who were not vaccinated with GARDASIL™. As shown in the incidence rate ratio (RR) column in the following table, RR hovered around 1.00, with some slightly above and some slightly below 1.00. To provide further detail on any condition for which a RR was above 1.00, additional medical record reviews of all cases from both Kaiser Permanente Northern and Southern California were undertaken, and additional rate comparisons were conducted as sensitivity analyses to confirm that rates were not elevated above background:

Autoimmune Rate Comparison				
Condition	Vaccinated	Non-Vaccinated	Incidence Rate Ratio (RR)	95% CI (for RR)
	Incidence (per 100,000 py)			
Graves' Disease	18.23	25.84	0.72	0.50 – 1.01
Hashimoto's Disease	104.82	81.10	1.29	1.08 – 1.56
Type 1 Diabetes	10.25	18.00	0.57	0.47 – 0.73
ITP	6.84	5.88	1.16	0.85 – 1.83
JRA	3.42	7.66	0.48	0.26 – 0.91
MS	3.42	2.50	1.37	0.74 – 3.20
Optic Neuritis	5.70	3.92	1.45	1.00 – 2.91
Other Demyelinating Diseases of CNS	1.14	1.60	0.71	0.38 – 2.13
RA	4.56	6.95	0.71	0.39 – 1.45
SLE	11.39	10.34	1.07	0.69 – 1.60
Uveitis	7.98	11.94	0.67	0.49 – 1.02

The SRC found no apparent patterns or timing of diagnosis with respect to vaccination. In addition, temporal distribution graphs and extensive medical record reviews revealed that some cases with confirmed diagnoses after vaccination had symptom onset prior to vaccination. Rates were not found to be elevated above background rates. The SRC reviewed all of these results plus additional details not presented here, and found no association with vaccination. However, they noted that the vaccine visit often included a work-up for existing symptoms leading to new diagnosis of prevalent disease after vaccination.

In the general safety portion of the study, diagnosis codes from EMRs of all medical events resulting in emergency room (ER) visits or hospitalizations were evaluated. There were several comparison periods. The first comparison period was 14 days following each dose, and the second was 60 days following each dose. The day of vaccination was assessed for a subset of conditions (e.g., allergic events, syncope, epilepsy/convulsion). These risk periods were compared to control windows. There were 180-day self-comparison periods pre- and post-vaccination. Regarding general safety results, syncope diagnosis codes were more likely to occur on the day of vaccination than in a post-vaccination self-comparison period, with a relative risk (95% CI) of 6.00 (3.91-9.21). The SRC reviewed all of the findings and requested additional medical record reviews. They noted a temporal association and clinical plausibility. Syncope is known to be associated with vaccination in this age group. Therefore, the SRC determined that syncope was associated with vaccination. In addition, diagnosis codes for local skin infection (cellulitis/abscess) were assessed. These diagnosis codes were more likely within 14 days after vaccination than in the post-vaccination comparison period, with a relative risk (95% CI) of 1.64 (1.17-2.3). The SRC requested several medical record reviews, and determined that cellulitis/abscess was possibly associated with vaccination; however, they also noted the possibility that some cases were injection site reactions. All medical events resulting in ER or hospitalization in the immediate post-vaccination period were analyzed. The SRC requested medical record reviews for many events, but noted no association of any other diagnosis, including VTE and deaths, with GARDASIL™. They also noted no apparent patterns of elevation by population, care setting, dose number, or age. However, they did note a tendency of increased non-specific health care utilization following the vaccination visit.

In summary, this study of approximately 190,000 girls and young women receiving approximately 347,000 doses of GARDASIL™ reaffirms its favorable safety profile. No association was found between vaccination with GARDASIL™ and congenital anomalies, miscarriages, 16 pre-specified autoimmune conditions, VTE, death, any other general safety events (except syncope and possibly local skin infection). Syncope associated with GARDASIL™ is likely to be injection-related, and some of the local skin infection (cellulitis/abscess) possibly associated with GARDASIL™ could be the result of injection site reaction. All safety conclusions were made by an independent, external SRC of 5 experts.

Background Information: HPV Vaccine for Males

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The purpose of this presentation was to review information related to HPV vaccine for males presented to the committee at the last several meetings and to provide updates. Dr. Markowitz briefly reviewed a wide variety of topics, including HPV infection and associated disease, an overview of HPV vaccines, the status of the US vaccination program, information regarding

knowledge and acceptability, cost-effectiveness, an international update, and working group deliberations.

Dr. Markowitz explained that HPV is a common sexually acquired infection in both females and males. As in females, the first infection occurs soon after onset of sexual activity. Most infections clear, but persistent infection is the most important risk factor for cancer outcomes. There are some unknowns about natural history of HPV infection, particularly in males, and HPV persistence and clearance may differ in males and females.

Similar to females, males acquire HPV rapidly after onset of sexual activity. In a study of young men who have sex with women who were sampled at genital sites for HPV DNA, 24 months after enrollment, the cumulative incidence of genital HPV infection was over 60% [Partridge, JID 2007]. Onset of sexual activity starts at a similar age for both males and females in the US. National data show that by age 15, 23% of females and 21% of males have reported vaginal sex, increasing to 78% and 84% by age 20 years [National Survey of Family Growth (NSFG), 2006-2008].

The burden of HPV infection includes conditions due to both oncogenic types, primarily HPV 16 and 18, and non-oncogenic types, primarily HPV 6 and 11. Oncogenic types can cause cancer and pre-cancers lesions, including cervical cancers, anal cancers, vulvar/vaginal cancers, penile cancers, oropharyngeal cancers, and low/high grade intraepithelial neoplasias. Nononcogenic types can cause anogenital warts, recurrent respiratory papillomatosis (RRP), and low grade intraepithelial neoplasias.

Data from the US studies that have examined tissues from various cancers to determine whether HPV was present showed that while HPV infection is necessary for virtually all cervical cancers, a variable percentage of other anogenital cancers are associated with HPV, ranging from 35% for penile cancer to 93% for anal cancer. Oropharyngeal cancers, a subset of head and neck cancers, are the head and neck cancer considered associated with HPV. Cervical cancer is the cancer for which there is the strongest evidence that almost all cancers are due to HPV. For most other cancers, the best evidence available is detection of HPV in the cancers [Gillison et al. Cancer 2008].

The number of HPV-associated cancers annually in the US was estimated by combining data from cancer registries with data from special studies. The annual number of cases comes from the national cancer registries. Based on these data, there are about 15,000 HPV16/18 associated cancer in females and about 7,000 HPV 16/18 associated cancers in males. Among females, the most common cancer is cervical cancer and among males the majority of HPV associated cancers are cancers of the oropharynx [Watson M et al. Cancer 2008. Data source: National Program of Cancer Registries and SEER, covering 83% coverage of US population. ++ Gillison ML, et al. Cancer 2008].

To put HPV-associated cancers into perspective, Dr. Markowitz showed age adjusted rates for the top 15 cancers among US females in 2007. In 2007, cervical cancer, the most common HPV-associated cancer, was the 13th most common cancer among females in the US, followed by oral cavity and pharynx. It is important to remember that just a subset of oral cavity and pharynx cancers are considered HPV-associated. Vulvar and anal cancers ranked 21st and 23rd, respectively, and vaginal cancer was quite rare at a rank of 33rd. In the 1950s and 1960s, this would have been different, with cervical cancer being one of the most common cancers. However, screening and improved treatment of pre-cancerous lesions has changed the picture. In terms of age adjusted rates for the top 15 cancers among males, oral cavity and pharynx

cancers ranked 8th in the US during 2007. Again, remember that just a subset of these are considered HPV-associated. The next most common cancer with any association to HPV was anal cancer, which was the 26th most common cancer. Penis cancer was even more rare, with an estimated ranking of 31st.

With regard to trends in potentially HPV-associated cancers from 1973-2007 using SEER 9 data, covering about 9% of the population, the rates of cervical cancer have dramatically decreased from the 1970s. Vaginal and oropharyngeal cancers also declined during that time period in females, while anal cancer increased approximately 2% per year. In terms of trends in potentially HPV-associated cancers among males, oropharyngeal cancers, the most common HPV-associated cancer, increased about 1% per year, while penile cancer decreased. Anal cancer has increased about 3% per year.

As mentioned, the incidence of anal cancer is increasing in both males and females at approximately 2.7% per year. Incidence is higher in females (1.5/100,000) than males (1.0/100,000). Men who have sex with men (MSM) have a higher risk than heterosexual men, with estimates as high as 37/100,000. Currently, there is no recommendation to screen for anal cancer. The majority of anal cancer cases in males occur in MSM, but the exact percentage is not known because sexual orientation data are not collected in cancer registries. HIV-infected MSM have a higher risk of anal cancer than MSM without HIV infection. Studies have found no decrease in incidence in HIV-infected persons in the highly active antiretroviral therapy (HAART) era compared with pre-HAART era, which may be due to increased survival among HIV-infected individuals or increased chance of exposure to HPV over a lifetime.

Over the past decade, there has been accumulating molecular and epidemiologic evidence that 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 cancers. Risk factors for HPV-positive and negative oropharyngeal cancers differ. HPV-negative risk factors include tobacco and alcohol, while HPV-positive risk factors include measures of sexual behavior and tobacco.

Data presented to ACIP during the June 2011 meeting included an update on oropharyngeal cancers. Oropharyngeal cancers from three registries were analyzed and evaluated for HPV. While there was an overall increase in oropharyngeal cancer of 28% during the time period from 1988-2004, HPV-associated cancers increased over 200% and HPV-negative cancers decreased by 50% [Chaturvedi AK et al. J Clin Oncol 2011]. Trends of increasing oropharyngeal cancers have also been reported from several other Western countries, including the Netherlands, Sweden, the United Kingdom, and Australia.

In summary, cancers associated with HPV include cervical, vaginal, vulvar, anal, penile, and oropharyngeal cancers. There are approximately 25,000 HPV-associated cancers, including 22,000 HPV 16/18-associated cancers annually, with 7000 of these occurring in males and 15,000 occurring in females. Rates of cervical cancer are decreasing due to screening. There is a trend of increasing oropharyngeal cancers in men due to an increase in HPV-associated oropharyngeal cancers. There is a trend of increasing anal cancers in men and women. Anal cancer incidence is highest among MSM, particularly HIV-infected MSM.

Estimates of the total annual direct cost of HPV-associated disease in the US were recently updated. This includes all HPV-associated outcomes, not just those HPV vaccine type associated.

The following table shows the estimated annual number, and the estimated annual cost in millions of dollars and range. Costs shown here also include cost for cervical cancer screening and follow-up of abnormal Pap tests in the first two rows. As noted, the largest proportion of cost is for cervical cancer screening and follow-up of abnormal Pap tests, so even though cervical cancer rates are decreasing in the US, there is a large cost associated with detection and treatment of pre-cancerous disease. The estimated annual cost is \$8 billion dollars, with a range of \$4 to \$14 billion:

Cost component	Number of HPV-associated cases	Annual costs (millions, US dollars)	
		Baseline	Range
Cervical screening: routine	52 million	5,356	2,700 – 8,515
Cervical screening: follow-up	NA	1,224	617 – 1,946
Cervical cancer	11,370	441	345 – 604
Oropharyngeal cancer*	7,080	306	113 – 516
Anal cancer*	4,270	155	69 – 313
Vulvar cancer	1,560	37	18 – 63
Vaginal cancer	480	12	6 – 20
Penile cancer	360	7	3 – 18
Genital warts*	355,000	288	103 – 930
Juvenile-onset RRP*	820	123	6 – 604
Adult-onset RRP*	NA	48	2 – 236
Total burden		8,000	4,000 – 13,800

*Includes outcomes in males and females. Outcomes without asterisks are sex-specific. NA: not applicable. RRP: recurrent respiratory papillomatosis. Cost per case estimates and ranges obtained from Bruni et al (2006) and Graham et al (2006) for screening; Hu & Gittle (2006) for routine (baseline) and follow-up (range) (2006) and for (range) (2006) for cervical cancer; Hu & Gittle (2006) and Chaturvedi (2006) for genital warts and RRP. Incidence estimates obtained from Serlin (2010), Plummer (2007), Berman (2007), and Hodge (2002) for screening; Serlin (2010) for RRP. Outcomes (range) (2006) for genital warts, screening (2006) for RRP. Costs are reported in 2010 US dollars.

Dr. Markowitz then reviewed the vaccines and vaccine trial data, reminding everyone that there are two HPV vaccines. The quadrivalent HPV vaccine is directed against 4 HPV types, two of which are oncogenic (HPV 16 and 18) and two of which are non-oncogenic (HPV 6 and 11). The bivalent vaccine is directed against two types, 16 and 18. The quadrivalent vaccine was licensed in 2006 for females and in 2009 for males, and the bivalent vaccine was licensed for females in 2009. The adjuvants used in the vaccines are different, and both vaccines are given as 3 doses.

There were large clinical development programs for both vaccines (e.g., the Phase II and III efficacy trials that were conducted among persons through age 26). For the bivalent vaccine, there was one Phase II and a large Phase III efficacy study, the PATRICIA trial. For the quadrivalent vaccine, there were one Phase II efficacy study and 2 Phase III efficacy studies in females and one in males. There was also a Phase II study with a monovalent HPV 16 vaccine. The only HPV vaccine efficacy trial that was conducted among males was the quadrivalent vaccine trial 020.

Clinical programs for both vaccines included immunogenicity and safety studies in adolescents. Immunogenicity and safety studies for the bivalent vaccine included HPV-013 in females ages 9-14 years of age (n=1,035); HPV-012 in females 10-14 years of age (n=158); HPV-048 in females 9-19 years of age (n=158); and HPV-011 in males ages 10-18 years (n=181). Immunogenicity and safety studies for the quadrivalent vaccine included V501-16 in males and females ages 10-15 years (n=508 males and 506 females); and V501-18 in males and females ages 9-15 years (n=564 males and 614 females). (Note: “n” indicates the numbers receiving HPV vaccine in trials)

Both vaccines had high efficacy in the per protocol analysis (women who were sero- or PCR-negative to the respective HPV type) for prevention of the primary endpoint, which was vaccine type-related CIN grade 2 or worse [Paavonen et al. Lancet 2009; Kjaer et al. Cancer Prev Res 2009; Haupt R. personal communication]. For the quadrivalent vaccine, studies also have found high per protocol efficacy for prevention of vulvar and vaginal pre-cancers at 100% and genital warts in females at 99% [Kjaer et al. Cancer Prev Res 2009; Future I/II Study Group. Br Med J 2010].

In males, there are data for prevention of vaccine type related genital warts (89%) and anal pre-cancer lesions, anal intraepithelial neoplasia grade 2/3, (75%). The genital wart efficacy data come from a study that included in heterosexual males and MSM. A substudy in MSM provided data on efficacy against anal pre-cancer lesions [Food and Drug Administration. Highlights of prescribing information. Gardasil (human papillomavirus quadrivalent [types 6, 11, 16 and 18]). Available at <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111263.pdf>].

The remainder of this review focused on the quadrivalent vaccine, given that this was the topic of consideration during this session. The bivalent vaccine is not licensed for males, no efficacy studies are planned in males, and the manufacturer is not seeking FDA licensure for men. Similar to the studies in females, bridging studies with the quadrivalent vaccine were conducted in males. GMTs were higher in the 9-15 year old males compared with the males 16-26 years of age who were in the efficacy study. GMTs were more than 2-fold higher for each of the 4 types in the quadrivalent vaccine. Based on data from these studies, quadrivalent HPV vaccine has an indication for prevention of cervical cancer, vulvar cancer, vaginal cancer, anal cancer (males and females), genital warts (males and females), cervical adenocarcinoma in situ (AIS), cervical intraepithelial neoplasia (CIN) grades 1 – 3, anal intraepithelial neoplasia (AIN) grades 1-3, vulvar intraepithelial neoplasia (VIN) grades 2 and 3, and vaginal intraepithelial neoplasia (VaIN) grades 2 and 3. There are no data from the clinical trials on efficacy for prevention of oropharyngeal cancer, penile cancer, or prevention of RRP [<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM094042>].

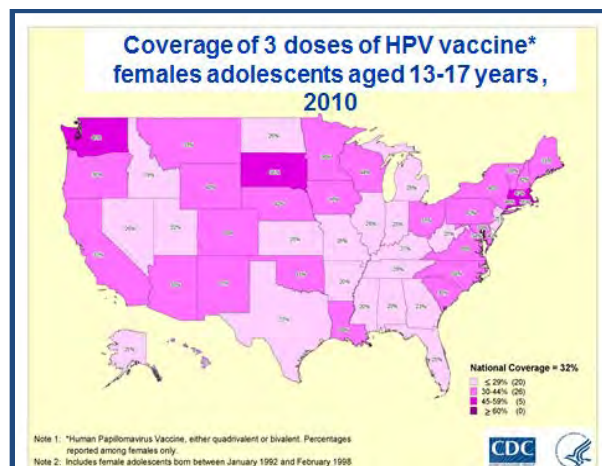
During the last ACIP meeting, the committee heard data on duration of protection for the quadrivalent vaccine. In brief there are data on 5 years of follow-up from Phase II study¹, 4 years of follow-up from Phase III studies² (~18,000 women), 8.5 years of follow-up from monovalent HPV 16 vaccine study³, and 3 years of follow-up from male study. Immune memory was demonstrated when an anamnestic response was elicited after a 4th dose administered 5 years after the initial 3 doses series⁴ [¹Villa et al. Br J CA 2006; ²Kjaer et al. Cancer Prev Res 2009; ³Rowhani-Rahbar et al. Vaccine 2009; ⁴Olsson et al. Vaccine 2007].

Longer-term data will be available from the Nordic Long-Term Follow-Up Study, which will follow women who were 16-26 years of age at the time of enrollment into one of the Phase III trials, and the effectiveness data from a long-term extension study of GARDASIL™ in adolescents ages 9-15 years. For the Nordic long-term follow-up of women in the Phase III efficacy study (protocol 15), no CIN2+ cases were detected during the first analysis 6 years post vaccination. Follow-up will continue for total of 14 years. In the effectiveness data from long-term extension of the immunogenicity study in 9-15 year-old boys and girls (protocol 18), no persistent infection, genital warts, or CIN were detected 6 years post vaccination. Follow-up will continue for total of 10 years. Long-term follow-up of men in Phase III efficacy (protocol 020) will continue for total of 10 years.

Duration of antibody response was also reviewed with ACIP in June 2011. Based on data from multiple studies and three groups of vaccinees (adolescent boys, adolescent girls, and women), almost all vaccinees remained seropositive to HPV 16 at different months post-vaccination for the competitive luminex assay (cLIA) and the IgG assay. The IgG assay is an assay which detects more than just the one neutralizing epitope detected by the cLIA. For HPV 18 antibody in adolescent boys, adolescent girls, and women, some participants lost detectable antibody by the cLIA at 24 months and later. Selected sera were retested by the IgG assay. Most of those tested had detectable antibody the IgG assay. For several populations enrolled in quadrivalent clinical trials (boys and girls 9-15 years, and men and women 16-26 years), HPV 16 GMTs followed similar kinetics for the different populations, falling to a plateau by 24 months and then remaining fairly stable [Courtesy, Al Saah]. It should be noted that in women who were in the efficacy study, there were no breakthrough infections due to HPV 18; no immune correlate of protection has been determined.

Dr. Markowitz then discussed the HPV vaccine program in the US. Coverage with HPV vaccine is increasing in females, but is still low. Based on National Immunization Survey-Teen (NIS) data pertaining to coverage in adolescents 13-17 years of age HPV vaccine coverage increased between 2007, the first year measured, to 2010. In 2010, 49% of females 13-17 years of age had received at least one dose of vaccine, while 32% had received all three doses. While in the first two years after introduction coverage with HPV vaccine was comparable to that of other vaccines at the same time period post-introduction, in 2009 and 2010, coverage increased more slowly for HPV vaccine. Between 2009 and 2010, HPV vaccine initiation increased only by 4.4%, less than half of the increase for Tdap and meningococcal conjugate vaccine. In 2010, 1.4% of males had initiated the HPV vaccination series. For all other vaccines, there was no difference in coverage for males and females.

Although national 3-dose coverage was 32% in 2010, there was a wide range of coverage with 3 doses of by state, ranging from 18% to 55% as reflected in the following map:



The states with the highest three-dose coverage included Washington State, Rhode Island, Massachusetts, and South Dakota.

Other findings of interest are that for at least one-dose coverage, there was no difference by poverty status, and coverage was higher for Hispanics and American Indians/Alaska Natives (AI/AN) than for Whites. However, for 3 doses of HPV vaccine, coverage was higher among those living at or above poverty than those below. No differences by race/ethnicity were observed.

Based on three years of data from the NIS, the percent of females who initiated vaccine increased from 37% to 49%, and the percent who reported being likely to initiate decreased from 28% to 17% so that the percent having initiated plus the percent reporting being likely to initiate remained fairly stable. Also remaining stable was the percent reporting not likely to receive vaccine in the next year at 26% to 28%. Data were also collected on the main reasons for not receiving vaccine for those who do not intend to vaccinate in next 12 months. The top reasons were lack of knowledge, vaccine not needed, daughter was not sexually active, no provider recommendation, and safety concerns [NIS-Teen 2008-2009].

Data on coverage in older age groups are available from other surveys. Data from the National Health Interview Survey (NHIS) for women 18-26 years of age reflected an increase between 2008 and 2010. In 2010, among 18-20 year olds, 35% had received at least one dose of HPV vaccine. Only 17.5% had received at least one dose among 21-26 year olds. These data suggest that initiation is limited in this age range, an estimated initiation about 3% to 5% per year [2008 data: Price et al. Cancer 2011; 2010 data courtesy Walter Williams and Peng-jun Lu].

In response to the low HPV coverage in adolescents, a variety of needed actions have been identified for both providers (e.g., making a strong recommendation and avoid delaying, creating of standing order programs to ensure systematic vaccine offering, administering all recommended vaccines during a visit, reporting to IIS) and parents (e.g., increase awareness and importance of early vaccination, completing the series, and safety). New Healthcare Effectiveness Data and Information Set (HEDIS) measure, which will really apply more to health plans than individual providers, will go into effect in 2012 that will measure the proportion of females aged 13 years who have received 3 doses of HPV vaccine by their 13th birthday. Actions have also been identified for immunization programs to increase initiation and completion of the vaccine series, including the following:

- ☐ Make adolescent vaccination a priority
- ☐ Add adolescent vaccines to VFC Assessment, Feedback, Incentives and Exchange (AFIX) visits
- ☐ Use Immunization Information Systems (IIS) data to target providers
- ☐ Use IIS to conduct reminder/recall (or encourage providers to do this)
- ☐ Work with schools to promote adolescent vaccination
- ☐ Establish relationships with and support school-based health centers
- ☐ Connect with Federally Qualified Health Center Network
- ☐ Partner with other stakeholders to make vaccines convenient and accessible at multiple venues (e.g., pharmacies)

A variety of recent activities have been undertaken by CDC, including *MMWR* publication of national and state vaccination coverage results and telebriefing, updating websites, disseminating information, and initiation of an call series for AIM members.

Studies have evaluated acceptability of HPV vaccine for providers, parents, and males. Acceptability of HPV vaccine for males has been found to be more varied than for females. General support of male vaccination was high, but intention rates were lower than for females. Impact of messaging was found in these studies, which were conducted at various times and some of which were conducted prior to availability of data on protection against anal precancers in males. Some of the studies assessed the impact of “self-protection” or “partner protection,” messages. The relevance of some of these studies to a situation in which there is a routine recommendation is somewhat questionable [Hood et al, International Papillomavirus Conference 2010].

Available data from providers, parents, and males suggested that acceptability of HPV vaccine is high. Data are available from a national survey of pediatricians and family practitioners conducted about a year ago, about 9 months after the vaccine was licensed for males and ACIP made a permissive recommendation. At that time, data were available on the prevention of anal precancers, but it was not yet added to the label. Concerning the statement, “Because HPV is commonly transmitted from males to females, the severity of HPV-associated diseases in females justifies the routine use of HPV vaccine in males,” 89% of pediatricians and family practitioners strongly or somewhat agreed. With regard to the statement, “HPV-associated diseases are severe enough in males to justify routine use of the HPV vaccine in males,” 73% of pediatricians and family practitioners strongly or somewhat agreed. Regarding the statement, “The parents of male patients will not think it is necessary to vaccinate their sons since they think that HPV infection is primarily of concern in females,” only 14% of pediatricians and family practitioners strongly agreed, but 54% somewhat agreed. In terms of the statement, “I think vaccination efforts should be targeted at females, not males, since HPV infection is primarily of concern in females,” only 19% of pediatricians and family practitioners strongly or somewhat agreed [2010 survey of pediatricians and family physicians. Survey conducted June to Sept 2010 Allison et al. Presented at Oct 2010 ACIP meeting; Survey conducted June to Sept 2010].

Dr. Markowitz next reviewed cost effectiveness data. The working group presented cost-effectiveness data to ACIP at each of the last three meetings. Dr. Markowitz reviewed the main points that were presented during those meetings. Key points that were summarized previously by Dr. Chesson are that routine vaccination of 12 year old girls is cost-effective. These have been consistent finding across models, provided that there is sufficient duration of protection. However, there is more uncertainty in the cost-effectiveness estimates for vaccination of adult women and vaccination of males. Cost-effectiveness depends upon a variety of inputs, including health outcomes and vaccine costs. In terms of health outcomes, the most favorable scenario is when all potential health outcomes are included. With regard to vaccine costs, with lower cost, male vaccination is more likely to be cost-effective over a wide range of scenarios (e.g., higher female coverage).

Routine male HPV vaccination at age 12 years could be cost-effective, particularly if coverage of females is low (<50%). This has ranged from \$24,000 to \$62,000 per QALY in published studies [\$24,000 per QALY is from Merck model (Elbasha & Dasbach, 2010) with effective coverage (all 3 doses) by age 18 of ~40% and ~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, such as in certain scenarios when key assumptions are varied (e.g., compared to a strategy of increased female coverage; if males vaccinated have mostly vaccinated partners).

In terms of the cost per QALY gained two scenarios were: a low coverage in which there is 30% coverage with 3 doses of HPV vaccine by age 12 and a higher coverage scenario in which there is 50% 3 coverage by age 12. For each coverage scenario, the cost-effectiveness was presented for vaccination of females from 12-26 years of age and the incremental cost per QALY for vaccination of males at age 12 years. When different outcomes are included in the model, ranging from only cervical cancer to all possible outcomes, the incremental cost per QALY if all of the indicated outcomes are included is \$68,000 for male vaccination in the low coverage scenario and in the higher coverage scenario is \$134,000 per QALY in the higher coverage scenario. If all outcomes are included, the cost per QALY of adding males to a female vaccination program vaccination is \$41,000 per QALY in the low coverage scenario and \$80,000 in the higher coverage scenario.

Questions were raised by ACIP about what specifically would be gained by male vaccination; that is, where are the QALYs coming from? In terms of specific QALYs due to disease prevented by male and female vaccination, for female vaccination, if all outcomes are included, cervical disease contributes the largest percentage of QALYs, followed by oropharyngeal cancers. The incremental benefit of adding males comes equally from prevention of cervical disease in females and from oropharyngeal cancers in males and females.

The cost-effectiveness of HPV vaccination, in general, decreases with increasing age at vaccination. This is because with increasing age, more people will have already been exposed to vaccine type HPV and therefore would have less benefit from vaccine. In the oldest age group, 22 through 26 years, the cost per QALY is \$75,000 for all outcomes and \$95,000 including indicated outcomes. The incremental cost per QALY when adding males to a female program, assuming coverage in females is 30% at age 12 and eventually (years after program starts) reaches 50% by age 26, for males, the cost per QALY is higher than for females, and in the oldest age group is about \$150,000 when considering all outcomes and over \$400,000 when considering only indicated outcomes [Chesson, June 2011 ACIP (from model published in Vaccine 2011)].

The estimated costs for the first year of a male vaccine program were also assessed. This is one example using a particular set of assumptions, including the probability of initiating the series, the probability of completing the series, and vaccine cost per dose. Different assumptions were made for the probability of initiating the series in different age groups. The estimated cost for the target age group of 11- to 12-year olds was \$136 million assuming about 11% probability of initiation. Adding vaccination through age 18 would cost an additional \$661 million. Also assumed was that uptake in those older than 18 was only 3.2% per year. In the oldest age group, those 22 to 26, this would add an additional \$103 million in the first year of the program.

A separate model has been developed to evaluate the cost-effectiveness of vaccinating MSM. This model showed that vaccination of MSM appears to be cost-effective through age 26, with a cost per QALY of <\$50,000 in most scenarios when including just two outcomes: genital warts and anal cancer only. Results were generally consistent, but did vary over a range of assumptions, including prior lifetime exposure to HPV and HIV infection, with vaccine being most cost-effective in scenarios where there is high HIV incidence, since HIV infected MSM have a higher risk of anal cancer [Kim JJ. *Lancet Infect Dis.* 2010;10:845-52. MSM: Men who have sex with men. QALY: quality-adjusted life year].

Regarding the status of vaccine introduction globally, more than 37 countries have now introduced vaccine into national programs. Most of these countries are in North America, Europe, and Australia. The cost of the vaccine is the major impediment to more widespread introduction, but infrastructure and delivery for an adolescent vaccine are also impediments. The price for HPV vaccine has come down in some areas. In the PAHO revolving fund, HPV vaccine is now \$14 per dose. All countries with national programs have introduced vaccine only for females. The target age group is in early adolescence. Catch-up recommendations are variable, with most of these through the late teens [WHO/IVB database, 193 WHO Member States. Data as of April 2011].

Australia is one country that has achieved high coverage of HPV vaccine in the target age groups through school-based vaccination and national funding of all vaccine in the recommended age groups. They also had a limited 2-year funded catch-up program that was funded for females up to age 26 years. Australia is the first country to demonstrate an impact on a population level of HPV vaccine. They introduced quadrivalent vaccine, and were able to observe an impact on genital warts outcomes, one of the first HPV-related outcomes expected to be observed since genital warts occur soon after infection. There has been a significant 73% decrease in genital warts since introduction of vaccine in resident women compared with a 25% decline among those who are non-residents and who had less access to vaccine. Also demonstrated was a decrease in genital warts diagnoses during the vaccine period in heterosexual males of 35%. No decrease was observed among MSM. These data are not only the first to show a population level impact of a vaccination program, but also suggest impact of herd immunity by vaccination of one gender on the other [Donovan B et al. ISSTD Quebec City, July 2011].

As a lead into the GRADE presentation, Dr. Markowitz discussed the ACIP HPV Working Group deliberations over the past year. The working group has considered HPV vaccine efficacy, safety, immunogenicity, burden of diseases/cancers in males, cost-effectiveness, acceptability and values, programmatic issues, and equity. While there is now consensus among working group members, Dr. Markowitz mentioned some of the issues that were considered over the past year in the group's discussions. With regard to data on efficacy and the burden of disease, some of the questions raised regarded how to consider outcomes for which there are no efficacy data, and how to consider AIN efficacy data from a trial conducted in MSM. Some working group members felt focus should be for females where burden of disease is greatest. In terms of cost-effectiveness, some working group members felt that there was uncertainty about cost-effectiveness at the current price. While most working group members did consider cost and cost-effectiveness, it was clear to members that there is no threshold or cutoff to use for cost-effectiveness. For those who were concerned about cost, it was unclear about how to impact a change in the vaccine cost. In terms of protection of MSM, some working group members felt that there should be recommendation for men with this sexual orientation. However; historically, risk-based strategies have not been successful vaccination programs.

Options considered by the working group members were to recommend routine vaccination of 11-12 year old males, or retain the current permissive recommendation for males 9-26 years of age. Working group members favored routine recommendation for a number of reasons; they considered quadrivalent HPV vaccine to be safe and effective in males; the burden of disease in males justified routine vaccination; there would likely be benefits against all HPV vaccine type associated disease; males as well as females should be protected against HPV for equity reasons; vaccination of adolescent males is cost-effective at current coverage levels in females; and historically, risk-based strategies have not been successful. In addition to protecting

heterosexual males and their female sex partners, for protection of MSM, routine vaccination would be the best way to reach men with this sexual orientation an age when they could most benefit. The discussion regarding routine recommendation focused on age 11 or 12 years because this is before onset of sexual activity, there is high immunogenicity at this age, and this is consistent with the female vaccination and the adolescent platform.

The ACIP HPV Working Group also engaged in deliberations regarding recommendations for 13-26 year-old males. The options considered were recommendation of vaccination through age 26 years with a statement about priority for males younger than 22 years; or a recommendation of vaccination through age 21 years with a statement that males 22-26 years may receive vaccine. Considerations discussed among working group members included impact and benefit of vaccination, cost-effectiveness, and programmatic issues, including harmonization with the female recommendation. Some working group members felt that direction should be provided so that resources could be used that would have the most public health benefit. There was no consensus among working group members on this issue.

GRADE and the Proposed Recommendation for Males

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Dr. Dunne addressed HPV vaccine policy consideration for males. She began the discussion of GRADE with the study question, "Should quadrivalent HPV vaccine be recommended for routine use in 11-12 year old boys?" In order to address this study question, the following additional important questions must be considered, including "Does HPV4 compared to no vaccine prevent condyloma, anal intraepithelial neoplasias (AIN 1/2/3), anal cancer, oropharyngeal cancer, and penile cancer? Does HPV4 in males prevent cervical cancer in females?" It is important to note that although the outcomes of oropharyngeal, penile cancers, and transmission to females are considered important, no clinical trial data on efficacy are available. Penile intraepithelial neoplasias (PIN) were evaluated in the clinical trial in men, but there were too few cases to evaluate efficacy.

There were three primary studies in males in support of licensure of quadrivalent HPV vaccine for males. First was a Phase III clinical trial, Protocol 20, which included about 4000 males aged 16-26 years. A sub-study evaluated outcomes in men who have sex with men. There were also two randomized controlled clinical trials in about 1400 boys aged 9-15 years. These trials primarily evaluated immune response and safety. Dr. Markowitz provided some of the background data on immunogenicity from these trials.

Protocol 20 was a randomized placebo controlled clinical trial that took place in 5 continents. Vaccine or placebo was administered at day 1 and months 2 and 6. The subjects included about 3500 heterosexual men and about 600 MSM. Exclusion criteria included a history of genital warts, genital lesions possibly HPV-related, and >5 or <1 lifetime sexual partner. All men were evaluated for genital warts or condyloma. MSM were also evaluated for AIN, including AIN 2/3, which is considered an anal pre-cancer lesion. The per protocol population from this study was evaluated, which included males who were naïve to the respective vaccine HPV type by DNA and serology at baseline. Efficacy in this naïve population of young men from the clinical trials would be what might be expected in boys aged 11 or 12 years.

In terms of the benefits of HPV vaccine for males, using the per protocol population from the clinical trial among all males, vaccine efficacy for HPV 6, 11, 16, or 18 related condyloma is 89.3%, the absolute risk difference per 1000 males is -18, and the number needed to vaccinate to prevent one case of condyloma would be 56. The follow-up period for this study was 2.3 years [Reference: Package Insert, page 504 Table 12: Analysis of Efficacy of GARDASIL in the PPE. Population of 16- through 26 year old Boys and Men for Vaccine.

Regarding the benefits of HPV vaccine for males using the per protocol population of MSM, the vaccine efficacy for HPV 6, 11, 16, or 18 related condyloma is 88.1%, for AIN 1/2/3 is 77.5%, and for AIN 2/3 is 74.9%. The absolute risk difference for AIN 2/3 is -48 per 1000 MSM, and the number needed to vaccinate to prevent 1 case of AIN 2/3 is 21. The follow-up period for this study was 2.6 years [Reference: Package Insert, page 504 Table 13: Analysis of Efficacy of GARDASIL for Anal Disease in the PPE Population of 16- through 26- year old boys and men in the MSM Sub-Study for Vaccine HPV types.

With respect to the benefits of HPV vaccine for a general population of males, a model by Dr. Chesson used a single birth cohort of males vaccinated at age 12 years, and assumed 90% efficacy against condyloma and 75% efficacy for prevention of anal cancer (similar to efficacies from the clinical trial). Based on this model, the number needed to vaccinate reflects the number of 12 year olds needed to vaccinate to prevent a single case of the outcome over the lifetime of the birth cohort. As a note, the model does not include herd immunity. If herd immunity was included, the number needed to vaccinate would be higher if female coverage is high. The absolute risk difference for condyloma is -57 and for anal cancer is -0.76. The number needed to vaccinate to prevent one case of anal cancer is 1581.

Dr. Dunne turned to a discussion of the working group's evaluation of type of evidence—a consideration for the evidence for both benefits and harms. The types of evidence are as follows:

Type of evidence	
Randomized controlled trials (RCTs), or overwhelming evidence from observational studies	1
RCTs with important limitations, or exceptionally strong evidence from observational studies	2
RCTs with notable limitations, or observational studies	3
RCTs with several major limitations, observational studies with important limitations, or clinical experience and observations	4

For the working group's considerations, the primary data were randomized controlled trials, with an evidence type of 1, and large observational studies, with an evidence type of 3.

The summary tables of evidence type for the benefits of quadrivalent HPV vaccine in males reviewed issues of risk of bias, inconsistency, indirectness, and other considerations—the considerations for downgrading the evidence type. The evidence table with the evidence type for all males included a randomized clinical trial with an evidence type 1. In terms of the evidence type for the studies in MSM, it is important to note that the outcomes of AIN 1/2/3 and

AIN 2/3 were evaluated in MSM, but the evidence type was not downgraded because the primary efficacy studies were performed in MSM. Because the evidence for prevention of anal cancer is indirect data (or data on prevention of AIN 2/3 an anal cancer precursor lesion) the evidence type for anal cancer was downgraded -1 for indirectness, leading to an overall evidence type of 2.

Regarding adverse effects of vaccination of males, the harms presented were those of primary interest for review, and included serious adverse events (SAEs), syncope, venous thromboembolism (VTE), and anaphylaxis. These events are characterized slightly differently by study. The methods for the evaluation of harm included a review of both pre-licensure data in males and females and post-licensure data in females. The pre-licensure data included RCTs with a comparison group. There were two RCTs of over 4700 males and 4 RCTs of over 19,000 females. For post-licensure data, 2 large observational studies in females were reviewed (the VSD study and a post-licensure study from the manufacturer. These studies included a large number of females, with over 190,000 in one study.

Based on data from the RCTs in males and females, there is no evidence of a difference between the vaccinated group and comparison group with regard to the outcomes of interest (e.g., SAEs, syncope, VTE, and anaphylaxis). There are several evaluations in which the risk ratio could not be estimated because there were no cases in either the vaccinated or control group, or both. Data from a post-licensure evaluation in the VSD RCA found that there was no difference in incidence of syncope, VTE, and anaphylaxis in the vaccinated group compared to the comparison group. As a reminder, for the outcome of syncope, the comparison group was a concurrent age-matched vaccinated group. For the outcome of VTE, the comparison group was a historic comparison.

Data from a post-licensure study from the manufacturer of almost 190,000 vaccinated females showed no difference in the allergic reactions or anaphylactic shock outcomes or VTE in the vaccinated group compared to the comparison group; however, there was a difference in syncope found for the vaccinated group compared to the comparison group, with a relative risk of 6 and a 95% confidence interval of 3.91 to 9.21. The outcome was the presence of a diagnostic code in an emergency room or hospital and the comparison group was a post-vaccination self-comparison period (e.g., control period in which vaccine was not administered). There were no record reviews to validate diagnoses.

Because syncope was the only harm that had a finding of a difference, the evidence type determined for this outcome was reviewed. The RCTs had direct evidence in males and an evidence type of 1; however, due to imprecision, these were downgraded to an evidence type of 2. The large observational studies were indirect as they were in females, and there was also possible confounding due to uncontrolled risk factors. For these reasons, the observational data was downgraded from an evidence type of 3 to 4. As noted earlier, differences were found between the two observational studies: the VSD, which found no difference with regard to syncope, and had a vaccinated comparison group; and the manufacturer-led study, which found an increase incidence in the vaccinated group, and had an unvaccinated comparison group. This evidence type was not downgraded further for inconsistency because the study designs and questions addressed as a result were different.

In summary of the overall HPV vaccine benefits and harms, there is decreased risk for the outcomes of condyloma and AIN and AIN 2/3 outcomes in vaccinated males. For harms in males and females, each outcome was listed and the RCTs were categorized separately from observational studies. For the summary evidence type of harm, the strongest study design was considered to be a randomized clinical trial, because there were no critical harms observed in large observational studies. Therefore, the overall evidence type for benefit and harm was determined to be a 2. As noted, 1 of 8 studies found an elevated risk of syncope. The study that found an elevated incidence of syncope in the vaccinated group compared to the comparison group had a self-comparison period in which vaccine was not administered, suggesting an increased risk of syncope related to injection.

In order to summarize the recommendation for HPV vaccine in males, Dr. Dunne reviewed the factors determining the recommendation category for GRADE. This included the balance between benefits and harms, evidence type, values and preferences, and economic analysis. Values represent the relative importance of a decision (outcomes related to benefits, harms, and costs) and play a role in every recommendation. The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely is a category B recommendation warranted.

Values and preferences were assessed through a survey administered to the ACIP HPV Working Group that used a 9-point scale to assess the importance of specific outcomes. The survey included prevention of genital warts, cancer in males, cervical cancer and other cancers in females, and adverse events. The survey responses were categorized as critical if they were 7-8-9 (the most important response category), moderate importance if they were ranked 4-5-6 (important) and less important if they were ranked 1-2-3, the lowest on the scale. The importance of the outcome was assessed as a median of workgroup members responses, and variability was assessed across the workgroup members by evaluating disparities in rankings across workgroup members. A study on willingness to pay was also reviewed.

The results of the survey found that all cancer outcomes were considered of critical importance. There was little variability in working group member responses, who were considered policy members or those who were also clinicians. Similar findings were found when members were asked to respond from the perspective of parents and patients. Genital warts were considered of lower value than the cancer outcomes, or of moderate importance, and there was substantial variability in working group member responses on the importance of this outcome. It is notable that clinicians placed higher value on genital warts than other working group members. A recent study found a similar relative importance, or value, of genital warts compared with cervical cancer. This study described willingness to pay by parents for prevention of cervical cancer compared with prevention of genital warts. Willingness to pay for prevention of cervical cancer was about 2 times higher than for genital warts protection [Brown et al, Vaccine 2010].

Another important consideration for formulating vaccine recommendations is cost-effectiveness. This has been presented at different times before the ACIP. A model by Dr. Chesson et al provides an overview of cost-effectiveness for vaccinating 12 year old boys, in a lower coverage scenario and a higher coverage scenario, with indicated and all outcomes for the cost-effectiveness of male vaccination. As a reminder, lower female vaccine coverage is 30% for 3-dose coverage at age 12 and 50% for 3-dose coverage by age 26, which is similar to the current coverage scenario in the US of approximately 32% for 3-dose vaccine coverage in 13-17 year olds. The higher coverage scenario is 50% for 3-dose coverage at age 12 and 70% for 3-dose coverage by age 26. In the lower coverage scenario the cost per QALY is about \$40,000 to

\$70,000 per QALY. As vaccine coverage in females increases, cost-effectiveness of male vaccination becomes less favorable.

Given this information, the benefits of vaccination for prevention of outcomes are greater than for potential harms, and the evidence type is 2 for benefit and 2 or 4 for harm, depending on the study design. There is high value placed on prevention of cancers in males, and HPV4 vaccine is most likely to be cost-effective if all HPV associated outcomes prevented, vaccine cost is lower than the current price, and female coverage is low (such as 30% for 3-dose coverage at age 12 years).

In summary, routine use of the quadrivalent HPV vaccine in 11 or 12 year old boys should be considered by ACIP. This would be considered a Category A recommendation in which benefits are greater than harm, there is high level of evidence, and there is high value placed on prevention of cancers in males.

As reviewed earlier by Dr. Markowitz, the options for policy considerations of quadrivalent HPV vaccine for males include retaining the existing guidance that HPV4 may be given to males 9 through 26 years to prevent acquisition of genital warts, or a routine recommendation for males aged 11 and 12 years. As a reminder, for a number of reasons presented earlier by Dr. Markowitz, most ACIP working group members favored the option of routine recommendation for boys aged 11-12 years. Draft language presented to the full ACIP membership for consideration was as follows:

ACIP recommends routine vaccination of males aged 11-12 years with 3-doses of HPV4. The vaccination series can be started beginning at age 9 years.

This language is the same as the female recommendation language, except that the female recommendation states "either vaccine."

Discussion Points

Dr. Temte inquired as to whether there were any projections over the next several years of the possibility of increasing vaccine uptake in the target audience of 11- through 12-year old girls.

Dr. Schuchat replied that CDC is trying to increase coverage and has initiated a series of steps with partners to try to shine a spotlight the challenges that have been observed with the trajectory that vaccine of girls has taken. She thinks that one key opportunity is the Healthcare Effectiveness Data and Information Set (HEDIS) measure that goes into effect in 2012, because managed care organizations (MCO) that use those measures will be feeding back to providers how they are doing in terms of 3-dose completion coverage by the 13th birthday, with an emphasis on completion and administering the vaccination at age 11 or 12. In addition, state-by-state patterns are quite different. A number of states have had important increases recently; however, whether they will reach a plateau remains unknown.

Focusing on the issue of all outcomes versus indicated outcomes only, Dr. Duchin thought the GRADE presentation was very important in helping them to understand the quality of the evidence on which to base a recommendation. Nevertheless, information was continually being presented on outcomes for which there is absolutely no information regarding efficacy (e.g., oropharyngeal cancers), but which seem to play a strong role in some of the policy discussions. He requested further clarification from the working group about why ACIP was continuing to be provided with information about outcomes for which there is no evidence of efficacy. He also

wondered whether duration of protection significantly impacts the cost-effectiveness conclusions.

Dr. Markowitz responded that the reason they continued to discuss all of the outcomes is because there was discussion early on regarding whether there would be data from efficacy trials for oropharyngeal outcomes. No efficacy studies are planned for these outcomes at this time; therefore, no efficacy data against oral pre-cancer lesions will be available. Part of the reason for that is that the natural history is not well-understood, and the pre-cancer state is not well-understood. During the last ACIP meeting, Dr. Aimée R. Kreimer of the National Institutes of Health (NIH) reported that NIH has a trial underway in Costa Rica with the bivalent vaccine. NIH is conducting a post-hoc analysis. They have added a one-time oral HPV infection endpoint in that trial, and will eventually have efficacy data from that trial against prevention against HPV infection. However, CDC does not anticipate there being any data available on oropharyngeal cancer outcomes. That said, the feeling of the working group members was that there is a fair amount of data currently regarding efficacy against persistent infection and a variety of other pre-cancers at a variety of other sites. Thus, many working group members felt that there was a high likelihood that there would be efficacy against all HPV-related endpoints.

Dr. Duchin thought it was somewhat inappropriate to show ACIP members cost-effectiveness data that use outcomes for which there are no data at all. He thought they should understand that the cost-effectiveness they were talking about was only the indications for which there are outcomes. At \$120,000 or \$130,000 per Quality-Adjusted Life Year (QALY) it was misleading to suggest that perhaps if everything works out right and they are lucky, the cost will be much lower.

Dr. Markowitz replied that this was why they were very careful to present it both ways (e.g., indicated only and all outcomes) in all of the analyses.

Dr. Meissner also had concerns about how the working group dealt with this issue. While it was certainly biologically plausible because the vaccine is so effective at preventing malignancies and infections in other mucous membranes, it remained unclear to him how much emphasis the committee should place on this issue in terms of prevention of penile cancers and, in the absence of any data, how much that should factor into the members' thinking in terms of cost-effectiveness. That sort of data is not usually included in a cost-effectiveness analysis. It is usually hard data.

Dr. Temte emphasized that the cost-effectiveness study was intended to provide estimates with hard data as well estimates using broad sensitivity analysis, and he thought this was very helpful because they could see what there is and what is possible.

Regarding safety, Dr. Campos-Outcalt inquired as to whether the number of deaths in females was what would be expected by chance. In addition, of the autoimmune diseases, Hashimoto's was the one that was statistically significant. Regarding the Institute of Medicine (IOM) report, it was unclear to Dr. Campos-Outcalt why anaphylaxis was considered to be probably related when none of the safety studies show that.

Dr. Dunne responded that the IOM report considered different data than CDC did for the GRADE evaluation of harm. The IOM considered data from Australia and other reports, and reviewed slightly different considerations (pre- and post-licensure data) for anaphylaxis than CDC did.

Regarding the expected number of deaths, Ms. Gee indicated that based on the National Center for Health Statistics' (NCHS) background rates of death, the range was less than what was expected. In the pre-licensure trials there were 40 deaths, and what has been observed is similar to background rates.

Regarding Hashimoto's Disease and the incident rate ratio that was above 1, Dr. Velicer indicated that several follow-up activities were undertaken to investigate that further. First, temporal distribution graphs were evaluated and it was found that there were prevalent cases around the time of vaccination in the vaccinated cohort. In addition, an evaluation was undertaken to combine Graves' and Hashimoto's due to their potential similarities in pathogenesis. However, no increased risk was observed. Several sensitivity analyses also did not point to a potential concern with regard to Hashimoto's. Additional in-depth medical reviews confirmed that there were, in fact, some prevalent symptoms at the time of vaccination.

Dr. Sawyer expressed the opposite point of view on the theme that Drs. Duchin and Meissner addressed (e.g., how the lack of direct evidence should be considered in the cost-effectiveness studies for oropharyngeal and anal cancer). Dr. Meissner made the point that it is biologically plausible, and as far as Dr. Sawyer knew, it was biologically probable that this vaccine would prevent those cancers. If there is some scientific reason to raise some doubt about that, he would like to hear it. Otherwise, he would be inclined to assess the cost-effectiveness data with the non-indicated conditions in mind because it may be a long time before there are any direct data. The reason to assemble a committee such as ACIP is to make some judgments based on less than adequate data.

Regarding the percent QALY benefit attributable to HPV diseases prevented, Dr. Duchin pointed out that about a third is oropharyngeal. When the cost-effectiveness estimates are obtained, he wondered whether the oropharyngeal benefit would be removed from the QALY estimate. It was not clear to him how to interpret the model when a third of the model of cost-effectiveness is based on the unproven benefit of oropharyngeal cancer prevention.

Dr. Markowitz responded that there is a graph like this for the only indicated outcomes as well, and she asked whether that was what Dr. Duchin was interested in seeing.

Dr. Duchin clarified that he wondered whether that was incorporated into the models. He assumed that the cost-effectiveness models were based on QALYs gained. He asked whether the model she showed at the end of the presentation, Cost Per QALY Gained at Age of Vaccination, included oropharyngeal or they were removed.

Dr. Markowitz answered that in that graph, there are two sets of bars for females and two sets of bars for males. One includes all outcomes and the other includes only indicated outcomes. When the only indicated outcomes are included oropharyngeal cancer, penile cancer and RRP QALYS are removed.

Dr. Duchin requested further information regarding duration of protection, pointing out that Chesson model estimates duration of protection to be lifelong. He wondered whether there were other scenarios that would significantly impact the conclusions.

Dr. Markowitz responded that other models have assessed duration of protection. If duration of protection is at least 20 years, it does not have a major impact on cost-effectiveness.

Dr. Chesson added that for female only vaccination, it could be said for sure that if vaccine duration is shorter, the cost-effectiveness becomes less favorable. When adding male vaccination to female vaccination, it is possible with shorter duration male vaccination might become even more cost-effective because there are more gaps to fill in female vaccination. The models have shown that when the duration of protection is changed, there is not as great an impact on male vaccination cost-effectiveness as there is on female vaccination cost-effectiveness.

To put this into perspective, Dr. Marcy noted that in 1952 when there was a polio outbreak, there were 57,000 cases and 3,000 deaths. That was enough to mobilize an entire country and a research project to create vaccines. That was 40% of the number of deaths related to HPV of 7,000 in males. He is constantly being told that there is no money to pay for this. However, there is money there are just other priorities. If those in the room who care for children, adolescents, and young adults did not help set those priorities, he did not know who would. He said that the cost of immunizing 11- to 12-year olds, \$138 million for the first year (based on 11% initiation), buys 12 hours in Afghanistan. He thought it was ACIP's job to reset priorities.

Dr. Markowitz pointed out that there were 7,000 associated cancer cases in males not deaths.

Regarding safety, it remained unclear to Dr. Campos-Outcalt why CDC did not consider the same data considered by the IOM.

Dr. Markowitz replied that one reason is because CDC used GRADE. The way GRADE is set up, it is necessary to use either a randomized controlled trial (RCT) or an observational study to assess this. The IOM included case series reports which were not included in GRADE.

Dr. Dunne added that for CDC's harm considerations, pre-licensure studies with comparison groups for both males and females were included.

Ms. Gee indicated that the sources of data for the IOM report were passive reports from Australia and VAERS reports. The reviews were through December 2010 and at that time, the only published reports were from passive surveillance.

Dr. Schuchat noted that this marked the first vote for which the GRADE system would be used. However, a considerable amount of other information is presented to the ACIP membership. ACIP is supposed to incorporate everything into their decisions, so the IOM results were not being thrown out. This information was presented and CDC hoped that the membership would incorporate all of the information deliberated about in terms of making their decisions. While this represented an opportunity to understand how to use GRADE information, it did not mean that other information should be excluded from consideration. CDC has been trying to engage in better messaging regarding anaphylaxis in general for immunizations to ensure that people are prepared to deal with this when administering vaccines.

Dr. Temte pointed out that mention had been made of venous thromboembolic events (VTE), and he was curious about the reported mechanism of this. He thought in a lot of cases, there was a concurrent other cause for VTE (e.g., contraceptives).

Ms. Gee responded that for the Rapid Cycle Analysis (RCA) in VSD, 8 cases of VTE were found in the automated electronic data on which the analyses are conducted. Chart reviews confirmed that 5 of those cases were true VTE and all of them had another risk factor. CDC is now conducting a self-controlled case series analysis so that they can control for those confounding factors.

It appeared to Dr. Keitel that for the VSD RCA, HPV vaccinated individuals were compared to people who were receiving other vaccines.

Ms. Gee responded that because the ICD-9 code is very non-specific for anaphylaxis, there were a lot of false positives. Chart reviews were conducted for every anaphylaxis code found in the analyses to determine whether they were true anaphylaxis cases. In that analysis, one confirmed case was found for an incidence rate of 1.7 cases per million doses. That was compared to a background rate that has been published in the VSD in which they had done the same analysis. VSD identified anaphylaxis cases following childhood and adolescent vaccines and generated a rate of 1.5 cases per million doses. What was found following HPV vaccine was very similar to the background rate within the population.

Dr. Keitel pointed out that this does not mean that the vaccine is not associated with anaphylaxis. It just means that the rate is similar to other vaccines. She noted that in the first presentation, they heard about 12 cases of anaphylaxis. She wondered whether any of those individuals had received concomitant vaccinations or other substances that might have been associated with anaphylaxis. In terms of using evidence and relying on an RCT, the denominator is thousands. It was not clear to her how to weigh the evidence because it was not a relevant comparison because they would not observe more than one case with a sample size like that.

Dr. Dunne responded that the evidence from the RCTs was downgraded due to the sample size (imprecision), from an evidence type of 1 to 2.

Ms. Gee indicated that regarding the VAERS reports, three subjects had HPV alone and one did not have that information documented, and the remainder had concomitant vaccinations.

Dr. Duchin noted that the first year cost of implementation is estimated to be \$980 million, which is a staggering amount of money. The cost is about \$14 per dose in Pan American Health Organization (PAHO) countries, but is almost 10 times that in the US. He wondered whether there was a reason why the US could not approach that level of efficiency in vaccine price. Given that there has been some recent data about good immunological response and duration with two doses of vaccine, Dr. Duchin also wondered whether ACIP would have the opportunity to revisit this recommendation and not be locked into a very expensive three-dose series should it be determined that a two-dose series is sufficient.

Dr. Schuchat replied that in general, while the prices that the US government pays in the public sector are less expensive than the private sector prices, they are substantially higher than both industrialized and developing countries. There are probably a number of reasons the manufacturers could subscribe about that. Regarding the two-dose series, she reminded everyone that in the US only 32% of girls 13 through 17 years of age have actually received three doses, 40% have received two doses, and 49% have received one dose. The various post-licensure evaluations that are on-going, at least in the short-term, have a variety of schedules. The interesting data from Costa Rica that examined partial results was actually of the bivalent vaccine; therefore, it is unclear whether this will translate to the quadrivalent

vaccine. It is quite exciting to see efficacy for partial schedules, particularly because the US has so many partially vaccinated people currently.

Regarding price in the US, Carlos Sattler (Merck) indicated that Merck priced GARDASIL® so that it would be cost-effective at the current price for vaccination of both males and females. Merck truly believes that the price accurately reflects the value of the broad indications of this vaccine. Referring to GARDASIL® pricing outside of the US, in June Merck announced a \$5 per dose access price for GAVI-eligible countries—the poorest countries in the world.

Dr. Markowitz acknowledged that there is interest in the two-dose data. There are not only data from Costa Rica regarding the bivalent vaccine that were recently published, but also there are data from other countries. At least two countries have adopted what is being referred to as an “extended dosing schedule.” Mexico and two provinces in Canada (Quebec and British Columbia) are administering 2 doses of vaccine 6 months apart at 9 years of age, with a third dose administered 5 years later. Along with this, Canada has conducted an immunogenicity study and will be looking at efficacy against infection. The immunogenicity data have been presented, and based on those data, British Columbia adopted the extended dosing schedule. They found that the GMTs after 2 doses in 9-year olds were comparable to the GMTs in women in the 16 to 26 years of age who received 3 doses. In a sense, this extended schedule is an early 2-dose schedule with a third dose later. This cohort will be followed to determine whether the third dose is actually needed.

Regarding what appears to be a very dramatic increase in estimated vaccine costs in the first year between the 11- and 12-year old group and the second cohort of 12- to 18-year olds, Dr. Coyne-Beasley reported that the 11- to 12-year olds is a 1-year cohort, while the 13 to 18 year olds are a 5-year range of individuals. What appears to be a significant increase in cost is really for a span of 5 years of individuals as opposed to 1 year cohort of individuals from 11 to 12.

Ms. Rosenbaum thought there was an aspect to the cost discussion that was worth reflecting upon. A lot of the boys or young men who would be vaccinated today pre-health reform essentially would move from an early age into a cohort of disproportionately uninsured people. In a couple of years, hopefully this will not occur. Instead, they will maintain continuous health insurance. Regardless of the cost exposure is at this point, she was worried about not moving forward because of the far greater cost exposure at a point at which the proportion of young- and middle-age men with insurance would rise, and the long-term consequences of not having adequately immunized them will also rise.

Dr. Bennett was not so troubled by the broader perspective on indications, but she was somewhat concerned about the difference in the cost-effectiveness depending upon the baseline female vaccination rate. If it was assumed that the HEDIS parameters would be a factor, and that the vaccination rate would rapidly increase, she wondered whether consideration was given to whether a very high price would be paid to vaccinate males. The analysis presented showed that with a higher vaccination rate among females, vaccinating males would be very expensive. She wondered if any projections had been made regarding how rapidly the rates of vaccination in females might increase post-HEDIS.

Dr. Markowitz replied that it is correct that with higher coverage in females, the incremental costs per QALY for including male vaccination will increase as female coverage increases. CDC can produce estimates based on higher coverage in females as well.

Dr. Schuchat added that it is impossible to determine how rapidly the rates of vaccination in females might increase post-HEDIS. One thing that is extremely disappointing is that the female rate is getting worse. The 2010 data had an even slower increase than the 2009 data, so the rate is really plateauing. There are also probably differences in who is and is not being vaccinated. While the first dose coverage does not have the poverty disparity, the 3-dose coverage does. They are probably succeeding in reaching those who currently have the best care, and are not doing so well with everyone else.

Based on watching HEDIS guidelines over the years, Dr. Temte doubted that the HEDIS guideline for HPV vaccine would be set at 100% of coverage. Having a HEDIS guideline is not going to change the dynamics of adolescents presenting in practices, which is the largest barrier. There is also the issue of parental refusal and many other barriers. Therefore, he did not anticipate a rapid rise in coverage moving forward.

Dr. Keitel noted that the data presented indicated that the older one is the less effective the vaccine will be for several reasons (e.g., more likely to have acquired genotypes in the vaccine; less likely to have a good vaccine response). Data in the older cohort, 18 to 26 or 21 to 26 years of age, indicate that effectiveness is considerably low as well. Information was also presented to indicate that vaccination is incredibly less cost-effective when vaccinating the older group in the 9- to 26-year old age range. She wondered what consideration was given in the working group to modifying an age for males that would make the cost-effectiveness more attractive.

Dr. Dunne responded that CDC would be addressing considerations for 13- to 26-year old males during the second half of the HPV session.

Regarding the likelihood of uptake, Ms. Ehresmann noted that the information that addressed intent among parents to vaccinate, there was a consistent resistance of nearly 30%. Based on the experience at the state level and what has been observed nationally on this vaccine, that resistance rate may stay consistent for quite a while and may also affect female uptake.

In view of recent political discussions, Dr. Schaffner (NFID) wondered whether there were any indications in the safety data regarding central nervous dysfunction, personality disorder, or what might be loosely described as mental retardation associated with the administration of this vaccine. He thought ACIP should have an explicit discussion or at least mention of this.

Dr. Dunne responded that there is no evidence.

Dr. Grogg (AOA) indicated that AOA is in favor of the recommendation. At the end of the discussion, he wondered whether someone from Merck or GlaxoSmithKline (GSK) could address the issue that was on the news the previous evening regarding HPV infection, not vaccine, that showed that women with HPV disease had two times the rate of heart disease. The study was sponsored by the American Heart Association, so he thought it was non-biased. It would be interesting to see some follow-up information about this issue.

Dr. Salisbury (DOH, UK) thought that in the first presentation, Slide 7 with the summary of VAERS reports broken down by age, was an unhelpful analysis. He suggested that it is not necessary to know the proportion by age, but instead is important to know the proportion by dose by age. He also noted that in a number of European countries, parts of Canada, and parts of Australia high coverage has been achieved with 3-dose coverage of more than 80% in 12- to 13-year old girls, for instance. In those circumstances, it is not cost-effective to vaccinate males

of the same age. It would be unhelpful if a recommendation from a program that has not achieved that success was seen as a recommendation that others would need to consider. Where high coverage has already been achieved, it is not likely to influence policies if low coverage countries adopt vaccination of males. Language on Page 4 of the draft, lines 104 through 116, makes this point. As a corollary, he wondered what the US policy might be if high coverage of females is reached. Would the US stop vaccinating males?

Dr. Temte responded that ACIP is forced into making recommendations for the US population. After hearing Dr. Salisbury's presentation in February 2011, everyone was jealous of what a sophisticated country can do with appropriate vaccine policy. In terms of the GRADE recommendation and the format, he thought there would be ample room in the remarks section of a recommendation to highlight issues such as those raised by Dr. Salisbury. ACIP is in a difficult position because of the difficulty in the US of getting above a first dose coverage of greater than 50% and a third dose coverage of more than about 30%.

Ms. Ehresmann noted that one issue which had not been addressed in terms of vaccination of males was the importance of providing vaccine for men who have sex with men (MSM). While she is not a member of the working group, her understanding was that part of the discussion was that while vaccination is not specifically targeted to that group, it would be very cost beneficial. However, it is not practical to engage in targeting, which is another consideration when assessing overall vaccination of all young men because it is not necessarily effective or perhaps even appropriate to be making such determinations at the 11- to 12-year old age.

Dr. Middleman (SAHM) stated that SAHM strongly supports the recommendation to immunize males for many of the reasons discussed. Although it is hoped that female immunization rates will rise in the US, in the face of the struggles there are in this age group in this country in terms of access and a lack of school requirements, SAHM strongly supports a universal recommendation for both males and females.

Dr. Brady (AAP) indicated that the AAP Committee on Infectious Disease reviewed the information and was very supportive of the current recommendation. There was discussion regarding the possibility that if there is equity and both males and females are included, this may make it easier to provide vaccine to both groups. However, given the cost-effectiveness information, this may be a self-defeating situation. Nevertheless, there may be some advantage to increasing female coverage if vaccine was gender-neutral. He also thought the issue of potentially changing cost needed to be addressed in order to significantly increase the number of eligible individuals. The argument that the cost is good for value is not adequate when it is going to cost this much.

Dr. Sawyer pointed out that at least as far as ACIP members had been instructed, "cost-effectiveness" is a relative term, not an absolute one. The cost-effectiveness numbers projected to date, even for a high coverage in females, are on the order of the cost-effectiveness for the second dose of meningococcal vaccine, which was voted on during the last ACIP meeting, and on the order of rotavirus vaccine. Thus, ACIP has gone into this territory previously.

Vote: Routine Vaccination of Males Aged 11-12 Years with 3-doses of HPV4

Dr. Sawyer made a motion to approve the draft language as presented, with the assumption that the issues of interval between the three doses would be covered in the background material and would be identical to the female vaccination. Ms. Ehresmann seconded the motion. The motion carried with 13 affirmative votes, 0 negative votes, and 1 abstention. The motion passed by a majority vote. The disposition of the vote was as follows:

13 Favored: Bennett, Bocchini, Campos-Outcalt, Duchin, Ehresmann, Jenkins, Keitel, Marcy, Meissner, Rosenbaum, Sawyer, Temte, Vazquez
0 Opposed: N/A
1 Abstained: Coyne-Beasley

Proposed Catch-Up Recommendation for Males

Eileen F. Dunne MD, MPH

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

Dr. Dunne reported that there had been considerable discussions over the last 6 months regarding options for vaccinating males 13-26 years. She outlined these considerations, including vaccine efficacy, cost-effectiveness, and programmatic issues including issues of implementation and harmonization. She also outlined that she would present a summary of work group member opinions and draft language for consideration.

The intent to treat analysis of the efficacy trials in males may provide the best information on efficacy of vaccine for boys and young men aged 13 through 26 years. As a reminder, the intent to treat analysis included all males enrolled in the trials ages 16-26 years, regardless of baseline HPV DNA or serology. The same exclusion criteria apply to this population and analysis including genital warts, genital lesions possibly HPV-related, and >5 or <1 lifetime sex partner. In terms of the efficacy in the intent to treat analysis for the outcomes of HPV 6, 11, 16, 18 related condyloma, AIN 1/2/3 and AIN2/3, the efficacy for prevention of condyloma was 68.1%, AIN was 50.3%, and AIN2/3 was 54.2 %. As a reminder, the outcomes of AIN were evaluated in the clinical trial of MSM.

Regarding cost-effectiveness of male vaccination through age 26 years and the incremental cost per QALY gained by adding male vaccination to female only vaccination, the cost per QALY increases with increasing age at vaccination, and ranges from \$150,000 to \$450,000 US dollars per QALY in the oldest age group of males, the 22-26 year olds. When including all outcomes and when including indicated outcomes only for females, in the oldest age group, the 22-26 year olds, the cost per QALY is \$75,000 for all outcomes and \$95,000 for indicated outcomes. So to summarize for both females and males, the cost per QALY increases with age at vaccination; however, it is important to note that the scale differs as far as the magnitude of this cost per QALY. In females the cost per QALY in the oldest age group is considerably less than for males, assuming coverage in females is 30% at age 12 and eventually (years after program starts) reaches 50% by age 26 [Chesson, June 2011 ACIP (from model published in Vaccine 2011)].

Pertaining to age at vaccination and the potential benefits of reduction of oropharyngeal, anal, and penile cancer, the number of lifetime cancer cases averted by vaccination of 1 million males at various ages is demonstrated. The benefits of reduction of these cancers are greatest when vaccination is administered at a younger age.

A consideration for vaccination recommendations of 13-26 year old males is vaccine uptake. The best measure of this may be vaccine implementation in females. As shown earlier, most implementation in females occurs in those less than 18 years of age. Two studies may provide more information on those over the age of 18 years: The National Health and Nutrition Survey (NHANES, 2007-2008), which found a first dose vaccine coverage of 19.7% in 11-18 years old females, and 10.5 % in 19-26 year olds females. However, vaccine coverage in this age group may not be indicative of vaccine initiation. Using another survey, the National Health Interview Survey (NHIS), the estimate for vaccine initiation in 22-26 year old females is approximately 3% per year. As noted by Dr. Markowitz, although vaccine implementation is less in this older age group, the cost for the first year is still considerable. This cost would decrease as vaccination of the younger age groups increased with time.

Another important point discussed with the working group has been the interest in prioritizing the younger age groups for HPV vaccine. The focus on the younger age group (those less than 22 years) is because the cost per QALY increases with increasing age, especially after age 21 years, and there is great interest in the best use of public health resources, and clear communication about this priority. This younger age group would include boys and young men through college age, and many young adults who may be making decisions on their own. Some working group members wonder if the focus on this younger age group may facilitate vaccination at a younger age when there is likely to be the greatest benefits from vaccination.

As far as ACIP HPV Working Group members' opinions, two primary options have been discussed by the working group as highlighted earlier: vaccination through age 26 years and vaccination through age 21 years, with a permissive recommendation for those 22-26 years. The working group is divided between these options. The working group favors an approach that may support vaccination through age 26 years, but emphasizes the younger age group (those less than 22 years) for vaccination. This is an opportunity to provide the greatest public health benefit and use resources most effectively.

In terms of the pros and cons of vaccination through the different ages, as stated earlier, harmonization with the female recommendations would be an advantage for vaccination through 26 for males, and this option also would likely provide more access to vaccine for all males through age 26 years, including MSM seeking care. The con of vaccinating through age 26 years is that cost-effectiveness models show higher cost and decreased benefit in the older age group. For vaccination through age 21, a pro is a focus on the younger age group where there is greatest benefit and vaccine is most cost-effective. This is still inclusive of young adult men, including college students. A con is this vaccine option would not be harmonized with female recommendations. In addition, with a permissive recommendation for those 22-26 years, which would be part of this recommendation, insurance coverage for those who want vaccine in this age group is uncertain.

The draft language presented for vaccination of males 13-26 years of age was as follows:

Option 1: Vaccination is recommended for males aged 13 through 26 years who have not been vaccinated previously or who have not completed the 3-dose series. Priority should be given to males aged <22 years as vaccination of young men and boys would provide the greatest benefit.

OR

Option 2: Vaccination is recommended for males aged 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series. Males aged 22 through 26 years may be vaccinated. Priority should be given to males aged <22 years as vaccination of young men and boys would provide the greatest benefit.

For Option 1, which states vaccine through age 26 years, and a priority statement to young men and boys, the options for the female recommendations include making no changes, or changing to harmonize, which would mean a minor modification. For Option 2, through age 21 years, the options for the female statement include no change, or changing with a modification to harmonize with a statement “through age 21 years” and “may be vaccinated in the 22-26 year old age group.”

The current female recommendation and draft recommendations were presented for vaccination of females 13-26 years with harmonized options, which read as follows, with the proposed changes in bold:

Current: Vaccination is recommended for females aged 13 through 26 years who have not been vaccinated previously or who have not completed the 3-dose series.

Harmonized with Option 1: Vaccination is recommended for females aged 13 through 26 years who have not been vaccinated previously or who have not completed the 3-dose series. **Priority should be given to females aged <22 years as vaccination of young women and girls would provide the greatest benefit.**

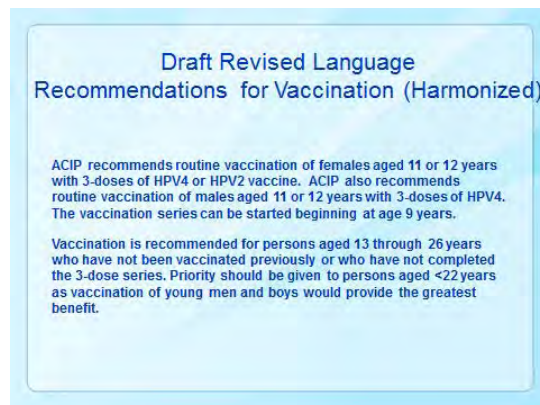
Harmonized with Option 2: Vaccination is recommended for females aged 13 through **21 years** who have not been vaccinated previously or who have not completed the 3-dose series. **Females aged 22 through 26 years may be vaccinated. Priority should be given to females aged <22 years as vaccination of young women and girls would provide the greatest benefit.**

Discussion Points

Dr. Temte pointed out that the GRADE information was presented for the first component of the vote, but the safety and efficacy data and recommendations are the same. What changes here are the values in the cost-effectiveness. He surmised that the values were still the same, with a high value placed on prevention of cancer in males.

Dr. Keitel noted that if they harmonized, there would not be a female and male recommendation. It would be all children.

Dr. Dunne indicated that she had drafted some ideas of harmonizing language as one of the options, which read as follows:



Dr. Sawyer indicated that he would be interested in more discussion / comment from CDC representatives regarding the importance of harmonization, because the older male population really focuses on the MSM population. Thus, he did not see the value in harmonizing a single message for all males and all females. For young boys, the message is for everyone. But older boys have identified as MSM and there should be a separate message for that.

Dr. Campos-Outcalt requested clarification regarding whether the B recommendation would be covered under the ACA.

Ms. Rosenbaum responded that a recommended vaccine is covered. This has been an on-going discussion in terms of whether vaccines that are recommended on a permissive basis are covered. She has been asking this for a year.

Dr. Campos-Outcalt thought that MSM deserved a separate recommendation over age 21, although it was not clear to him whether they were planning to consider this. In addition, he thought harmonization would be difficult because for females there are two vaccines, both of which are licensed and approved; whereas, for males, there is only one. For that reason, it may be difficult to harmonize the recommendation.

Regarding harmonization, Ms. Ehresmann pointed out that some of the rationale for encouraging vaccination or prioritizing vaccination for the under 21 group has to do with cost-effectiveness and immunogenicity. She wondered if that was also true for females. It appears that the cost-effectiveness data for ages 12 through 26 may not be the same rationale for females. In addition, there was clearly a better response in GMTs in the younger age groups.

Dr. Dunne responded that there are differences in the cost per QALY between females and males for the older age groups, with cost per QALY greater for males than females in the oldest age group. The better response in GMTs in the youngest age groups is seen for females as well males.

While it was unclear to Dr. Marcy what the effect of the ACA would be, unless they use the word “recommended,” third party payers will not cover this. This is an expensive vaccine, and they will do everything they can not to cover it. He has already heard from several people who said they know employers who will simply eliminate coverage for this. He said he could guarantee this would happen if they simply make a permissive recommendation.

Dr. Vazquez said that as clinician, she thought harmonization would be very important. She worried that changing the wording for females would lead to lack of coverage and reimbursement for this vaccine.

Ms. Rosenbaum reiterated that the fact that they had not been advised by council regarding whether a recommendation that essentially says that ACIP is recommending based on the clinical judgment of the provider is tantamount to not making a recommendation. The ACA is ambiguous on this point. There is no reason why ACIP cannot continue to recommend with a caveat of clinical discretion as opposed to routine. As far as she could determine, this would be a perfectly valid position to take. However, they were facing the concern that somehow, the ACA does not honor clinical discretion. They must get a read on that, and the question is: Is it clinical discretion? If so, does the clinical discretion lie with the treating clinician or is it at the discretion of the medical director of an insurer? There are two very different questions.

In terms of the two vaccines, it seemed to Dr. Meissner that based on the vote just taken in regard to vaccinating males, the bivalent vaccine would be used even less infrequently than it is currently. This would certainly dramatically increase the sales of the quadrivalent or tetravalent vaccines. Thinking optimistically, he wondered whether this would be enough of an increase in sales such that the price of the tetravalent vaccine might decrease, and conversely if there was more of a monopoly and less competition between the two vaccines, whether there was any assurance that the price of the tetravalent vaccine would not increase.

Regarding the group of people from 22 to 26 years of age, as an internist / pediatrician / adolescent medicine specialist, Dr. Coyne-Beasley thought that there would be a large proportion of individuals who would not identify as MSM. In fact, the messaging may not be specific to that group of men, so they should allow themselves to have a much broader message for males between the ages of 22 to 25 years of age.

Regarding permissive recommendations for males, Dr. Bocchini pointed out that this has been in place for two years. Based on the data from the teen survey, only 1.5% of males 13 to 17 years of age are getting vaccine. There has not been a high uptake, which suggests that a permissive recommendation is not an effective approach for that age group.

Ms. Rosenbaum inquired as to what the policy was under VFC in terms of ACIP making permissive recommendations.

Dr. Temte replied that permissive recommendations are not fully covered.

Ms. Rosenbaum pointed out that it has been presumed for years, at least in terms of public insurance sphere, that ACIP can make permissive or routine recommendations and either way it will be covered. Frankly, what is needed is alignment of that policy with the policy that will occur in exchange and private sector plans.

Dr. Duchin's take on this was that the epidemiology and the conditions they were trying to prevent and their costs were sufficiently distinct in the male and female populations such that they should not feel compelled to harmonize the male and female recommendations at this point. ACIP can revisit this in the future if necessary.

Dr. Campos-Outcalt clarified that the vote just taken for 11 to 12 years of age was for the quadrivalent vaccine only.

Dr. Dunne responded affirmatively, and indicated that even though the statement for the 13 and older age group does not say quadrivalent vaccine, it would follow the first statement.

Dr. Turner (ACHA) commended the CDC staff members who have been working with the ACHA's work group. His concern from the college health standpoint was that the cost-effectiveness models did not include all possible outcomes. For example, the costs associated with evaluating the "worried well" are not included, such as those who want a specialist to biopsy an uncertain lesion. His doctors in the student health center send 10 to 12 young men per year to a dermatologist to have biopsies. Also not included are any consideration of the very serious psycho and social consequences associated with HPV. College health sees the acute consequences of HPV, which rarely include cancer but always include anxiety, depression related to suspicion about the nature or origin of the lesion, partner's fidelity, or a devastating feeling of having damaged goods and never being able to enter into a permanent long-term relationship. There are untold numbers who enter counseling and terminate relationships, some ending in separation or divorce. Therefore, Dr. Turner believed that the cost-effectiveness models included a large degree of uncertainty and he did not agree with using these models as a major reason for creating a permissive recommendation for males, because insurance companies likely will not cover the vaccine for young men over 21 years of age. As Ms. Rosenbaum pointed out, it remains unclear whether a permissive recommendation will require insurance coverage under the Affordable Care Act. He thought by making a firm recommendation, ACIP would remove any ambiguity about covering this vaccine. It has been suggested that resources really need to be focused on younger men, which is admirable, but this statement assumes that resources are devoted to older men. Dr. Turner was unaware of vaccine resources being devoted to males between the ages of 22 and 26, with the exception of the Department of Defense (DoD), which provides HPV vaccine to males over the age of 21. These Americans pay for their own healthcare. If they are lucky enough to have health insurance that covers the vaccine, they will receive it. Because of the high cost, if a male has no insurance coverage, he likely will not receive the vaccine. This will only result in increasing health disparities among the under-served and the under-represented. As a side note, Dr. Turner indicated that he has a small college health surveillance network of 15 schools of a half a million students that has been collecting electronic medical record data since January 1, 2011. Out of 4,000 HPV vaccines, 70% have been administered to males and females over the age of 21. Thus, the majority of college students receiving this vaccine are actually over the age of 21. If ACIP made a recommendation only up to the age of 21, it would potentially eliminate two-thirds to three-quarters of the recipients from coverage.

Dr. Fryhofer (ACP) indicated that as a practicing general internist, she sees adolescents, young adults, and older adults in her practice. She is also the mother of male twins who are 21 years of age, both of whom received the HPV vaccine when they were 16 years of age. She urged the ACIP to make this vaccine available to both males and females, so that males and females would have equal access. She implored ACIP not to underestimate the overall health implications of genital warts. The treatments are expensive and the emotional consequences are devastating. Harmonization would be great, and would make it so much simpler. Having

different age groups and recommendations will be very confusing for clinicians. There is also the parental factor. This vaccine is not mandated in order to enter school. Texas tried this and there were repercussions, which brings forth the importance of misinformation and misinformed parents. Youth who are informed should be permitted to have the ability to access this vaccine at a later age. The bottom line is that not all youth begin having sex when they are 13. She assured everyone that hers did not.

Ms. Moore (AIM) indicated that in preparation for this meeting, the AIM conducted a Rapid Survey Monkey questionnaire of program managers to get a sense of their thoughts on harmonization of this schedule specifically. While AIM knows that there are a number of other considerations, 31 different programs responded overwhelmingly that having a non-harmonized schedule for males and females would pose challenges for programs in implementing this, largely due to confusion in how to provide guidance to parents, confusion of what parents of young men and women would think, confusion among providers, and confusion about insurance coverage for males and females. Concern was also expressed that backing off of a female recommendation in order to harmonize with males might raise questions about the value of the vaccine in females and might make it even more difficult to implement this. In addition, most state programs are not paying for this vaccine in the adult population. The focus is on teens for both genders. The priority is on education and clarity of education. Thus, AIM overwhelmingly supports a harmonized schedule.

Dr. Grogg (AOA) stated that AOA favored Option 1.

Dr. Loehr (AAFP) said that speaking on behalf of practicing family physicians, it was pretty clear that insurance companies are not covering a permissive recommendation. In addition, if harmonization was considered only for those under the age of 21, they would be losing the yellow box for women (slide 36), which was equally cost-effective as the red box for males. Therefore, he had a difficult time justifying harmonization for 21 year olds, as well as harmonization up to 26-year olds based on the cost-effective data for 22 to 26 year olds.

Regarding the options shown on Slide 46, it was unclear to Dr. Jenkins why there was an emphasis on the prioritization of young men and boys less than 22, because the prioritization was really for both genders less than 22. She was happy to hear about the implementation issues, which are very real. It was useful to hear that even though the departments of health have been challenged in terms of reaching the 22 to 26 year old population, the value of the educational message is still there. In terms of the fine line of age 21, in reality, these individuals receive their healthcare in different venues. Therefore, a couple of sets of physicians are involved in terms of whether this is really going to occur. The data are not as compelling in terms of being able to reach the older age group; however, she resonated with the message about education.

Dr. Loehr (AAFP) emphasized that they could not harmonize because there are two different vaccines. As a practicing physician, he also did not think it would be that hard to have two different schedules because of two different circumstances. They have this for other vaccines already, so it was not clear to him that harmonization was such an important goal in this situation.

Dr. Campos-Outcalt favored a 21-year old cutoff due to immunogenicity and the cost above that age group. Time after time there are complaints about the cost, but they do not do anything about it. The only thing ACIP can do about it is not approve a vaccine based on cost-effective analysis. It seemed to him that this was a clear cut place to use it. They could always put a vaccine back on the schedule or change it later, but once it was on there, all incentive would be taken away to lower costs and it would be very difficult to get it off of the schedule.

Dr. Jenkins pointed out that if they approved Option 2, the last sentence should be changed to indicate that priority should be given to persons less than 22, not just to young men.

Dr. Dunne clarified that this option is specifically for males. Although she showed the potential harmonization language, this particular option related strictly to males.

Dr. Bennett noted that Option 2, by its very nature, meant that harmonization would not be possible unless they back off on the recommendations for women. She did not think this was what they wanted to do. That is, by definition, if someone was voting for Option 2, they were voting against harmonization.

Dr. Jenkins inquired as to whether, for the female's current recommendation, there was a statement about priority for younger women.

Dr. Dunne replied that there was not a current prioritization statement in the female statement. The current language is that "Vaccination is recommended for females aged 13 through 26 years who have not been vaccinated previously or who have not completed the 3-dose series."

Dr. Jenkins thought that they needed to make a decision one way or the other about prioritization language.

Dr. Coyne-Beasley thought that with Option 2, there needed to be discussion about the fact that this may lead to insurance companies not paying for the vaccine, and there being differential access between populations, even with the Affordable Care Act.

Dr. Bocchini agreed that with Option 2, they would be increasing the likelihood that an individual may not be able to obtain the vaccine because it may not be covered.

Dr. Sawyer thought that would be the intent, that ACIP was saying they would not harmonize these schedules because the cost-effectiveness data is not harmonizable and, therefore, a separate recommendation would be made.

Ms. Rosenbaum requested clarity regarding whether, if some ACIP members voted "no" for Option 2, there would be a separate vote for Option 1.

Dr. Temte responded that there would be if there was a motion for Option 1. Hearing no other discussion, he called for a vote.

Vote: Catch-Up Recommendation for Males

Dr. Duchin made a motion to approve Option 2, "Vaccination is recommended for males aged 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series. Males aged 22 through 26 years may be vaccinated. ~~Priority should be given to males aged <22 years as vaccination of young men and boys would provide the greatest benefit.~~" Dr. Campos-Outcalt seconded the motion. The motion carried with 8 affirmative votes, 5 negative votes, and 1 abstention. The disposition of the vote was as follows:

8 Favored: Campos-Outcalt, Duchin, Jenkins, Keitel, Meissner, Sawyer, Temte, Vazquez
5 Opposed: Bennett, Bocchini, Ehresmann, Marcy, Rosenbaum,
1 Abstained: Coyne-Beasley

Clarification of the language for Option 2 occurred (after the motion), because the priority was already implicit with the language. The language voted on was Option 2 without the last statement, "Priority should be given . . ." and was revised to read "Vaccination is recommended for males ages 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series. Males ages 22 through 26 years may be vaccinated."

Special Populations

Eileen F. Dunne MD, MPH

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

As presented earlier by Dr. Markowitz, Dr. Dunne reminded everyone that the burden of HPV-associated disease and cancer is highest in MSM, and is especially high in HIV-infected persons. The conditions include genital warts, anal intraepithelial neoplasia, and anal cancers. There are no routine screening recommendations for anal cancers. As a consideration of this vaccine for immunocompromised populations, this is a non-live vaccine. Quadrivalent HPV vaccine is cost-effective for males through age 26 years at less than \$50,000 US dollars per QALY. In this same model, the vaccine was found to be even more cost-effective for HIV-infected MSM. Two completed studies in HIV-infected adolescents and men have found the vaccine to be safe and immunogenic, and on-going studies will further evaluate vaccine in immunocompromised populations [MJ Levin et al, JAIDS 2010, Wilkins et al, JID 2010, Kim J et al, Lancet ID 2010].

The working group proposed revising the language under special population recommendations to be consistent with current recommendations in males and offer guidance for these populations. The proposed draft language for a special population recommendation read as follows, with draft language in bold and the previous language under the immunocompromised section not bold:

Because men who have sex with men (MSM) may especially benefit from prevention of HPV types 6, 11, 16, and 18, and disease and cancers associated with these types including condyloma and anal cancer, MSM through age 26 years should be vaccinated.

The quadrivalent vaccine is not a live vaccine and can be administered to males who are immunocompromised as a result of disease or medications. **Quadrivalent vaccine is recommended routinely for 11 or 12 year old HIV-infected boys; vaccination is also recommended for males aged 13 through 26 years who have not been vaccinated previously or who have not completed the 3-dose series.** As in all males, the vaccine would be most effective when given before exposure to HPV through sexual contact. The immune response and vaccine efficacy might be less than that in immunocompetent persons.

Discussion Points

Dr. Keitel requested clarification that this language was specifically for the MSM, and if so, that should be indicated in the second paragraph.

Dr. Dunne responded that the second paragraph pertained to immunocompromised and the first paragraph pertained to MSM. The language was specific for HIV-infected boys within the new information; however, there was broad language for those who are immunocompromised.

Ms. Rosenbaum pointed out that this underscored the dilemma currently faced in terms of what “should” meant in this contest. Were they saying that immunization for people ages 22 through 26 was permissive, but where there existed an underlying condition, vaccination should be administered routinely? If they wanted to avoid the permissive problem, they would have to be much clearer in the recommendation that while a subset of people fall into the permissive category, a special population is not treated as permissive. Immunization for special populations is treated as routine. That way, pending clarification at some point from General Counsel regarding the impact of the ACA on permissive recommendations, ACIP would at least inoculate itself against being misunderstood.

Dr. Dunne inquired as to whether some clarification in the language that would include something similar to the language below regarding those who have not been vaccinated previously or who have not completed the 3-dose series added to that statement would address Ms. Rosenbaum’s concerns.

Ms. Rosenbaum replied that the second paragraph states that “Quadrivalent vaccine is recommended routinely for 11 or 12 year old HIV-infected boys; vaccination is also recommended for males aged 13 through 26 years who have not been vaccinated previously or who have not completed the 3-dose series.” She thought the same kind of language was needed in the first paragraph to indicate that vaccination “should be routine.”

Dr. Bennett agreed that ACIP should focus on this population, and that it was of great concern. However, she pointed out that the reason they called this population MSM was because these are men who often do not care to disclose. If the recommendation is only permissive or does not make clear that the vaccine is recommended, there is a potential that these men will not disclose to their insurance companies. An identical situation was observed with Hepatitis B vaccine.

Dr. Campos-Outcalt favored making a population-specific recommendation for those ages 22 through 26; however, he did not believe they should mention anything about HIV-infected boys below that age group because there is already a general recommendation for all boys below that age group. There is already enough parent resistance, so he was extremely concerned about sending a message that boys ages 11 to 12 and through age 21 who are HIV-infected or who are potentially MSM would increase resistance. Self-identification occurs in different places. For example, men who will not identify to their primary care providers will often identify in STD clinics. He did not believe they should confuse the message at all for those under the age of 21.

Dr. Dunne clarified that the language should be changed to read that males ages 22 through 26 should be vaccinated for both the MSM and HIV considerations.

Given that ACIP voted for Option 2, Dr. Coyne-Beasley wondered what would happen to those individuals ages 22 through 26 who may fall into those categories. Will the insurance companies pay for them? Will the ACA pay for them since the broader recommendation actually includes more permissive language? Do they have to declare that they are MSM or HIV-infected for their vaccine to be paid for?

Ms. Rosenbaum emphasized that this was the reason she voted against Option 2 to begin with. Not knowing how the permissive issue would be resolved by HHS, she thought they would stand a slightly better chance of making clear that for a sub-group of 22 to 26 year olds, ACIP emphatically recommends a routine immunization, which may not be technically needed if the permissive ruling is correct. Then, obviously, it will be clinical judgment if a patient who has these risk factors receives a vaccine. Given everybody's sentiment that they are potentially facing a complete wipeout of any recommendations that are permissive, she thought to be prudent, they should send a strong message about the recommended status for people with certain risk factors who fall into the "permissive" group.

Dr. Sawyer agreed that they should emphatically recommend the vaccine. He believed the A type recommendation, the word "should" was intended to convey that. He thought ACIP's language should be consistent. He still had difficulty with the second part of the bolded sentence in the second paragraph after the semi-colon, and he could not figure out whether that was going to be removed, given that they had eliminated the younger population. If it was going to remain, he thought they needed to restate that they were talking about immunocompromised patients. Otherwise, someone might construe that to mean all 22 to 26 year olds.

Dr. Markowitz pointed out that this part of statement was used to communicate that it "can be given." It is not a live vaccine. That was why the full age range was included. In general, this statement pertains to immunocompromised individuals. However, it sounded as though ACIP wanted to change the focus to 22 to 26 year olds. Given the previous vote, the Work Group would have to figure out how to modify the wording.

Ms. Ehresmann noted that the second bolded statement specifically indicated 11 or 12 year old HIV-infected boys. She wondered whether the statement after the semi-colon said “HIV-infected males” that would deal with any confusion and achieve the goal without changing the statement dramatically.

Dr. Sawyer strongly agreed with Dr. Campos-Outcalt that they should not single out younger HIV-infected boys. It seemed to him that they could make a general statement, if not here in another part of the document, that indicates that this vaccine is safe regardless of age given to an immunocompromised patient. This section is about who should receive the vaccine, and is where they are going to call out the 22 to 26 year olds.

Ms. Ehresmann said she had to correct herself and that it should be immunocompromised males ages 13 to 26 years of age versus just HIV-infected individuals.

Dr. Keitel thought this should be rewritten in one paragraph because it only relates to 22-year old to 26-year old males who are either MSM, HIV-infected, or immunocompromised.

Dr. Bennett thought they were struggling with exactly how this would be written and had not yet had a motion about recommending vaccinations for immunocompromised individuals and MSM. She wondered whether she could make that motion.

Dr. Temte responded that she could make that motion; however, he suggested that perhaps the working group should revise the statement and bring it back to the full ACIP membership following the lunch break when it could be presented clearly in front of them. Because this added to the previous recommendation, he thought it was correct to entertain a motion, second, and vote on this. Therefore, he moved for modification prior to the vote.

Dr. Markowitz requested clarity on the first vote and proposed that they would revise the language and present it to the ACIP membership following the lunch break.

Following the Lunch Break

Dr. Dunne began by highlighting the language for the approved option, which read “Vaccination is recommended for males ages 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series. Males ages 22 through 26 years may be vaccinated.” She then turned to the special populations draft with the requested revisions, which read as follows:

The quadrivalent vaccine is not a live vaccine and can be administered to persons who are immunocompromised as a result of infection (including HIV), disease or medications. Quadrivalent HPV vaccination is recommended for males at age 11 or 12 years and through age 21 years. Vaccination is also recommended for immunocompromised males aged 22 through 26 years who have not been vaccinated previously or who have not completed the 3-dose series. As in all males, the vaccine is most effective when given before exposure to HPV through sexual contact. The immune response and vaccine efficacy might be less than that in immunocompetent persons.

Men who have sex with men will benefit from prevention of HPV types 6, 11, 16, and 18, and conditions associated with these types, including condyloma and anal cancer. Quadrivalent HPV vaccination is recommended for males at age 11 or 12 years and through age 21 years. Vaccination is also recommended for MSM aged 22 through 26 years who have not been vaccinated previously or who have not completed the 3-dose series. As in all males, the vaccine would be most effective when given before exposure to HPV through sexual contact.

Based on her understanding of what they were saying previously, Ms. Rosenbaum thought that given the earlier discussion regarding “permissive,” if they wanted to be sure that they were clear regarding how routine they believe vaccinations should be for 22 to 26 years olds who are immunocompromised, they should carry over and parallel the word “routinely” from the first sentence to the second. She would state that, “Vaccine is also recommended routinely for immunocompromised adults” so that the two are the same style of draft.

Dr. Meissner inquired as to why the language read “would be most effective,” instead of “is most effective.”

Dr. Dunne responded that this could be changed to be less tentative.

Dr. Brady (AAP) wondered whether they meant all immunocompromised individuals, or just those who are HIV-infected.

Dr. Dunne responded that the focus she primarily took with the first draft was for those who are HIV-infected; however, there are potential benefits in other immunocompromised populations in general.

Dr. Markowitz requested clarification regarding whether ACIP agreed with adding the word “routinely” as suggested, given that often the word “routinely” is used to signify the routine age of 11 or 12 years.

Dr. Dunne also added that “routinely” was not used in the recommendation for males 13 through 21 years. This language focused on those who had not been vaccinated previously or who had not completed the 3-dose series.

Dr. Pickering pointed out that there are a number of primary and secondary immunocompromising conditions, many of which are seen in pediatrics. He wondered whether they really meant all immunocompromised, secondary malignancies and radiation, or just HIV.

Dr. Dunne responded that they had not clarified the specific populations that they term “immunocompromised.” There are data regarding HPV-related cancers and disease in immunocompromised populations, but there are no data on vaccine efficacy that she knows of.

Dr. Marcy thought it pertained to the specificity / sensitivity issue. He said he would rather draw a broad blanket than have a practitioner not be clear about what constitutes an individual being immunocompromised. Harm can be done by the vaccine being withheld from someone who the practitioner is not sure needs it.

Vote: Special Populations

Dr. Sawyer made a motion to adopt the revised language, with the minor modifications suggested. Ms. Ehresmann seconded the motion. The motion carried with 12 affirmative votes, 0 negative votes, and 1 abstention. The disposition of the vote was as follows:

12 Favored: Bennett, Campos-Outcalt, Duchin, Ehresmann, Jenkins, Keitel, Marcy, Meissner, Sawyer, Rosenbaum, Temte, Vazquez

0 Opposed: N/A

1 Abstained: Coyne-Beasley

VFC Vote

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

Dr. Santoli indicated that in each of the VFC resolutions, proposed changes from the current resolution are highlighted in yellow. The purpose of this resolution is to allow routine use and catch up of the quadrivalent HPV vaccine for VFC-eligible males, 9 through 18 years old, and to streamline the resolution through the use of links to published documents. Eligible groups for the bivalent vaccine include females ages 9 through 18 years. Eligible groups for the quadrivalent vaccine include females and males ages 9 through 18 years.

The recommended schedule and intervals proposed were as follows:

A 3-dose series for HPV vaccine is recommended for females and males at age 11 or 12 years old with the following schedule: the bivalent HPV (for use in females) and the quadrivalent HPV (for use in females and males) vaccines are each administered in a 3-dose schedule. The second dose should be administered 1 to 2 months after the first dose and the third dose should be administered 6 months after the first dose.

The HPV vaccines series should be completed with the same HPV vaccine product whenever possible.

Catch-up vaccination

- Vaccination is recommended for females and males 13 through 18 years of age who have not been previously vaccinated or who have not completed the full series.

Other vaccination

- Eligible females and males as young as 9 years old may be vaccinated.

Interrupted vaccination schedule

- If the vaccine schedule is interrupted for either the quadrivalent or bivalent HPV vaccine, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose should be administered as soon as possible, and the second and third doses should be separated by an interval of at least 12 weeks with a minimum interval of 24 weeks between the first and third doses. If only the third dose is delayed, it should be administered as soon as possible.

Dosage Intervals

The minimum interval between the first and second doses of vaccine is 4 weeks and the minimum recommended interval between the second and third dose of vaccine is 12 weeks. The minimum interval between the first and third dose is 24 weeks. Inadequate doses of HPV vaccine or vaccine doses received after a shorter-than-recommended dosing interval should be readministered.

Recommended dosage for the bivalent and quadrivalent HPV vaccine can be found in the package inserts available at:

<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833>

Contraindications/Precautions:

Quadrivalent HPV vaccine:

Refer to ACIP recommendation at:

<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5602a1.htm>

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5920a5.htm?s_cid=mm5920a5_e

Bivalent HPV vaccine:

Refer to ACIP recommendation at:

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5920a4.htm?s_cid=mm5920a4_e

Statement regarding update based on published documents:

[If an ACIP recommendation regarding human papillomavirus vaccination is published within 12 months following this resolution, the relevant language above (except in the eligible groups sections) will be replaced with the language in the recommendation and incorporated by reference to the publication URL.]

Discussion Points

Dr. Hahn (CSTE) expressed concern that the way the first recommendation was written to state that “the bivalent HPV (for use in females) and the quadrivalent HPV (for use in females and males) vaccines are each administered in a 3-dose schedule,” could be interpreted to be a preference for bivalent vaccine in females. She thought the sentence should be rewritten to be clearer that for females, either vaccine could be used.

Dr. Pickering inquired as to whether Dr. Hahn would be more comfortable with the phrase “licensed for use in females.”

Dr. Hahn responded that it should state that for females, either the bivalent or quadrivalent could be used.

Dr. Marcy suggested that the problem could be resolved by putting quadrivalent first (e.g., rearrange the way the sentence is ordered).

Dr. Sawyer noted that since the VFC only applied up to the age of 18, they did not have to address the issue of the permissive recommendation.

Vote: VFC Resolution

Dr. Sawyer made a motion to approve the VFC resolution with the minor modification suggested. Dr. Keitel seconded the motion. The motion carried with 13 affirmative votes, 0 negative votes, and 1 abstention. The disposition of the vote was as follows:

13 Favored: Bennett, Bocchini, Campos-Outcalt, Duchin, Ehresmann, Jenkins, Keitel, Marcy, Meissner, Sawyer, Rosenbaum, Temte, Vazquez
0 Opposed: N/A
1 Abstained: Coyne-Beasley

The following letter was submitted regarding HPV vaccine was submitted for the record:



October 25, 2011

Advisory Committee on Immunization Practices
Centers for Disease Control and Prevention
1600 Clifton Road, N.E., Mailstop A27
Atlanta, GA 30333

Dear Members of the Committee:

We write as a growing coalition of health care advocacy organizations committed to reducing rates of human papillomavirus (HPV)-related cancers, and the virus that causes these cancers, HPV. HPV-related cancers and diseases affect men, women and their families. We urge the Advisory Committee on Immunization Practices (ACIP) to vote to change the status of male HPV vaccination from permissive to routine. The ACIP has already issued routine recommendations for females and permissive recommendations for males to obtain the vaccine for the prevention of HPV-related diseases. The effect of expanding the vaccination recommendation to include boys will result in a decrease in HPV-related malignancies for future generations of men and women.

- **HPV causes cancer in both males and females.** Every year, approximately 30,000 men and women in the United States are diagnosed with a cancer caused by HPV. HPV causes multiple cancers, which include cervical, anal, vulvar, vaginal, penile and head and neck cancers.
- **The vaccine is our best chance at preventing HPV-associated malignancies.** Screening protocols for HPV-associated cancer sites other than the cervix are not widespread, while systemic therapies for those with advanced HPV-associated disease are limited. The most effective way to reduce the risk of future generations developing cancer and HPV-related disease is by vaccinating both males and females.
- **The vaccine protects against the HPV types that cause the majority of HPV-associated illnesses.** The vaccine prevents infection from HPV types 16 and 18, the two strains responsible for most HPV-related cancers in the United States. Protecting against high-risk HPV types will dramatically decrease the amount of people living with HPV-associated cancers. The quadrivalent vaccine also protects against genital warts, which carries a heavy social stigma.
- **The federal government has recognized the benefits of the vaccine.** The Food and Drug Administration has certified that the quadrivalent HPV vaccine protects against the development of cervical, vaginal and vulvar cancers in women, as well as anal cancer and genital warts in both genders. The ACIP has issued routine recommendations for women and

permissive recommendations for men to obtain the vaccine for the prevention of these diseases.

- **HPV-related cancer and precancer is difficult to have and to treat.** Therapeutic treatments that target HPV-related lesions and cancer are often toxic and uncomfortable. Systemic disease is difficult to cure and the therapeutic pipeline remains underdeveloped. The stigma associated with such cancers also presents social challenges for patients living with the disease.
- **By promoting a female-only campaign which focuses on girls and women to routinely vaccinate against HPV, we are sending the incorrect message that HPV is a single-sex issue.** As men and women both harbor HPV infections and act as transmitters, we must acknowledge the reality of this virus by educating the public so that men are also aware of HPV-related malignancies that can affect them and their partners. The focus on women also results in the exclusion of entire populations who would otherwise benefit from herd immunity, including men who have sex with men (MSM).
- **The MSM community is especially at risk for anal cancer as they are not protected by the benefit of herd immunity from female HPV vaccination.** However, we warn against considering a recommendation for males based on their sexual behavior. A recommendation to routinely vaccinate only MSM would require self-reporting, a particularly sensitive issue among adolescent boys who may fear stigma from disclosing same-sex behavior and may result in missed opportunities to vaccinate those at increased risk of anal cancer. Moreover, young men may not identify as MSM until sexual activity has commenced.
- **Vaccination rates for females in the United States are very low, and rates for males are significantly lower.** By routinely vaccinating men we can actively protect a larger portion of the population as vaccination rates in the U.S. are low, especially when compared to the United Kingdom and Australia. In a recent study of girls aged 13 to 17 in the U.S., the Centers for Disease Control and Prevention found that 32% completed the HPV vaccination three-dose series in 2010. Adolescent female vaccination rates in Australia, in contrast, were higher than 70% for all three doses in 2009, the most recent year for which data could be obtained. Australian citizens will thus see a lower HPV-associated cancer burden in the coming decades. The United States can follow this model and decrease future cancer burdens by routinely vaccinating males and increasing female vaccination and catch-up vaccination campaigns.

The HPV cancer burden is significant. There are tens of thousands of men and women in the United States who are currently living with an HPV-related cancer. The quality of life effects and deaths caused by this disease are preventable for future generations of people by increasing vaccination rates.

Cervix: It is estimated that there will be 12,710 patients with 4,290 mortalities in 2011. Almost all cases of cervical cancer are caused by HPV.

Anus: It is predicted that there will be 5,820 males and females diagnosed with anal cancer this year. About 770 patients will die from anal cancer in the same time. There has been an increasing trend in diagnosis of around 2% a year since the 1970's, a trend that continues today. About 95% of anal cancer is caused by HPV.

Vulva: 4,340 cases of vulvar cancer are diagnosed in the United States and 940 mortalities are expected from it this year. Approximately half of vulvar cancers are caused by HPV.

Vagina: 2,570 women receive a vaginal cancer diagnosis in the United States every year, and 780 women lose their lives to this cancer. About 65% of vaginal cancers are caused by HPV.

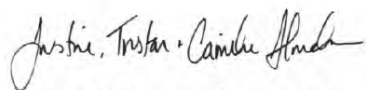
Penis: 1,360 men are diagnosed with penile cancer and approximately 320 deaths are expected this year. Approximately 35% of penile cancers are caused by HPV.

Head and Neck: It is estimated that 5,700 men and 1,700 women receive a diagnosis of HPV-associated head and neck cancers each year, and that number is growing. According a recent study published in the Journal of Clinical Oncology, there could be more HPV-related oropharyngeal cancers in the United States than cervical cancers by the year 2020. The study also found that the incidence rate of HPV-positive oropharyngeal cancers increased by 225% from 1988 to 2004. Males are more likely than females to be diagnosed with HPV-related oropharyngeal cancers. Around 60% of oropharyngeal cancers are HPV-related.

HPV types 6 and 11 also causes genital warts and recurrent respiratory papillomatosis, a rare and serious throat condition that is passed from mother to child during childbirth. Genital warts are generally medically harmless, but have social and emotional impacts on the people who have them. Treatment of warts is associated with substantial cost and morbidity.

We urge you, as members of the body charged to evaluate immunization programs, to consider the impact you will have on future generations of Americans. A vaccine exists that can decrease stigmatized and painful diseases from development in thousands of people. Please use your capacity as advisors to the federal government to advance a routine recommendation for males. We thank you for your consideration of this testimony and your commitment to examining the data regarding U.S. men and women affected by HPV.

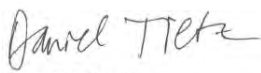
Sincerely,



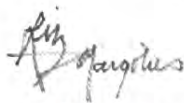
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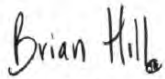
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National LGBT Cancer Network



Alan Kaye
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Dana Van Gorder
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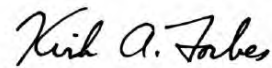
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2012 Immunization Schedules for Children 0 Through 18 Years of Age

Introduction

Cody Meissner, Chair Harmonized Schedule Working Group

Dr. Meissner presented an overview of the activities of the Harmonized Schedule Working Group during the past year. The three childhood and adolescent immunization schedules are revised annually to reflect recommendations that have been approved by the ACIP during the past 12 months. The updated 2012 schedules will be published in February 2012 in the *MMWR*, *Pediatrics*, and *American Family Physician*. In order to meet the deadline for February publication, it is important for the schedules to be approved during this meeting; therefore, a vote was taken after the proposed changes were presented and discussed. The responsibility of the working group was to accurately describe existing ACIP recommendations for the three schedules. No changes were proposed to the basic layout of the 2012 Immunization Schedules for Children 0-18 Years. There are three schedules, including 0 through 6 years; 7 through 18 years; and a "Catch-Up" for 4 months through 6 years and 7 through 18 years of age.

The version of the schedules presented for approval during this session was developed using a process in which input was first obtained from working group members during monthly telephone calls. ACIP recommendations published since January 2011 were added at this stage. The working group's revised document was then circulated among CDC subject matter experts (SMEs). Comments provided by subject matter experts were then discussed during a working group call. A document consolidating both working group and subject matter expert revisions was submitted for internal CDC clearance in October 2011. The proposed changes to the footnote reflect the increase in complexity of the vaccine schedule and the limited amount of space for footnotes. An effort has been made to maintain or increase the font size of the footnotes wherever possible. To accommodate the limited space for footnotes and to improve footnote readability, several changes were made. First, redundancy was eliminated between the footnotes and the figures. Information displayed in the figure is not shown in the footnotes. Second, references were provided to direct the reader to the respective *MMWR* document for detailed information that cannot be accommodated in the footnotes. Third, readers will now be encouraged to utilize all three schedules together. In previous years, each of the three schedules was intended to stand alone. By making reference to information in another schedule, it is possible to conserve space.

2012 Immunization Schedule 0-18 Years of Age

Iyabode (Yabo) Beysolow, CDC Lead Harmonized Schedule Working Group

Dr. Beysolow discussed the specific changes for each schedule. The recommended schedule for persons aged 0 through 6 years of age is shown as follows:

Recommended Immunization Schedule for Persons Aged 0 Through 6 Years—United States • 2012
For those who fall behind or start late, see the catch-up schedule

Vaccine ▼	Age ►	Birth	1 month	2 months	4 months	6 months	9 months	12 months	15 months	18 months	19-23 months	2-3 years	4-6 years
Hepatitis B ¹		HepB	HepB					HepB					
Rotavirus ²				RV	RV	RV ²							
Diphtheria, Tetanus, Pertussis ³				DTaP	DTaP	DTaP		see footnote ³	DTaP				DTaP
Haemophilus influenzae type b ⁴				Hib	Hib	Hib ⁴		Hib					
Pneumococcal ⁵				PCV	PCV	PCV		PCV					PPSV
Inactivated Poliovirus ⁶				IPV	IPV			IPV					IPV
Influenza ⁷								Influenza (Yearly)					
Measles, Mumps, Rubella ⁸								MMR	see footnote ⁸				MMR
Varicella ⁹								Varicella	see footnote ⁹				Varicella
Hepatitis A ¹⁰								HepA					HepA
Meningococcal ¹¹								MCV4 — see footnote ¹¹					

This schedule includes recommendations in effect as of February 11, 2011. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Providers should consult the relevant Advisory Committee on Immunization Practices statement for detailed recommendations: <http://www.cdc.gov/vaccines/imz/updates.html>. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS) at <http://www.vaers.hhs.gov> or by telephone, 800-822-7967.

1. Hepatitis B vaccine (HepB). (Minimum age: birth)
At birth:
• Administer monovalent HepB to all newborns before hospital discharge.
• For infants born to hepatitis B surface antigen (HBsAg)-positive mothers, administer HepB and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg 1 to 2 months after receiving the last dose of the series.
• If mother's HBsAg status is unknown, within 12 hours of birth administer HepB for infants weighing ≥ 2000 grams and Hep B plus HBIG for infants weighing < 2000 grams. Determine mother's HBsAg status as soon as possible and, if HBsAg-positive, administer HBIG for infants weighing ≥ 2000 grams (no later than age 1 week).
Doses following the birth dose:
• Administer HepB to all infants at 1, 2, and 6 months of age.
• For infants born to HBsAg-positive mothers, administer HepB at 1, 2, and 6 months of age.
• For infants born to HBsAg-negative mothers, administer HepB at 1, 2, and 6 months of age.

6. Inactivated poliovirus vaccine (IPV). (Minimum age: 6 weeks)
• If 4 or more doses are administered prior to age 4 years an additional dose should be administered at age 4 through 6 years.
• The final dose in the series should be administered on or after the fourth birthday and at least 6 months following the previous dose.

7. Influenza vaccine. (Minimum age: 6 months for trivalent inactivated influenza vaccine [TIV]; 2 years for live, attenuated influenza vaccine [LAIV])
• For most healthy children aged 2 years and older, either LAIV or TIV may be used. However LAIV should NOT be given to some children, including children with asthma; or children 2 through 4 years who had wheezing in the past 12 months; or children who have any underlying medical conditions that predispose them to influenza complications. For all other contraindications to use of LAIV please see MMWR 2010.59(No. RR-8).

The MCV4 purple bar was expanded to reflect licensure of Menactra® (MCV4-D) to age 9 months. For Hepatitis A, the wording “2 doses” was removed from the yellow bar, and the word “series” was removed from purple bar. The wording “2 doses” that was in this bar previously has been a source of confusion for providers and managed care companies. Because of the span of the bar and the wording, it was interpreted to mean that the 2 doses had to be completed by 2 years of age. This was never the intent of this recommendation; therefore, the wording has been removed and the footnotes updated to reflect this. In the interest of time, Dr. Beysolow discussed only significant changes made to the footnotes. She also noted that the proposed footnotes had been reviewed and approved for presentation by the respective subject matter experts.

For the Hepatitis B vaccine footnote, two of the older footnotes were consolidated. These addressed management of infants born to HBsAg positive mothers and when to order serology after vaccine series completion. New footnotes were added that take infant birth weight into consideration when determining management of infants born to mothers with unknown HBsAg status. Information regarding minimum intervals between doses, as well as management of infants who did not receive a birth dose, was also added.

Pneumococcal vaccine footnotes were also condensed. Some references to PCV7 were removed, given that this vaccine is no longer being used. Because there will still be a cohort of children recommended to receive a supplemental dose of PCV13 for a year or two longer, this language was retained. There is reference to the ACIP recommendations for further details.

Significant changes were proposed for the influenza footnotes. Contraindications to the use of LAIV were expanded to indicate that LAIV may not be used in children with asthma or children 2 through 4 years of age with a diagnosis of wheezing in the past 12 months, and reference was made to the respective ACIP recommendation as an attempt to make room on the schedules. New footnotes were proposed to address dosing in children 6 months through 8 years old not only for this season, but also for the 2012-13 season. For the 2012-13 season, providers are basically being referred to next year's ACIP influenza recommendations, given that the 2012 schedule will span both influenza seasons.

A new MMR bullet was proposed to remind providers that infants 6 through 11 months of age who are traveling internationally may be vaccinated with MMR, but that they will need a repeat dose at 12 months of age and a third dose at 4 through 6 years of age.

As mentioned earlier, in order to clarify the interval between dose 1 and dose 2 of HepA vaccines, this footnote was revised to read, "Administer 2 doses 6 to 18 months apart."

Proposed changes to the meningococcal conjugate vaccine footnotes include removal of the footnotes from the 2011 schedule, with the addition of new footnotes and a reference made to the ACIP recommendations for further guidance. The heading was updated to include the licensed minimum ages for Menactra® and Menveo®. The first of the 2 footnotes addresses the new recommendation for use of MCV4 in high risk infants. For children older than 2 years of age, recommendations were included along with a reference to use of MCV4-D in children with asplenia to match the information published in the October 2011 MMWR document, and to state that if MCV4-D Menactra® is being used, it should be administered at a minimum age of 2 years and at least 4 weeks after completion of all PCV doses. This discussion was held during the June 2011 ACIP meeting.

The recommended schedule for persons aged 7 through 18 years of age is shown as follows:

Recommended Immunization Schedule for Persons Aged 7 Through 18 Years—United States • 2012
For those who fall behind or start late, see the schedule below and the catch-up schedule

Vaccine ▼	Age ▶	7-18 years	11-12 years	13-18 years	
Tetanus, Diphtheria, Pertussis ¹		1 Dose (if indicated)	1 Dose	1 Dose (if indicated)	
Human Papillomavirus ²		See footnote ³	3 Doses (females)	Complete 3-Dose Series	Range of recommended ages for all children
Meningococcal ⁴		See footnote ³	Dose 1	Booster at 16 years old	
Influenza ⁵		1 Dose (yearly)			
Pneumococcal ⁶		See footnote ³			Range of recommended ages for catch-up immunization
Hepatitis A ⁷		Complete 2-Dose Series			
Hepatitis B ⁸		Complete 3-Dose Series			
Inactivated Poliovirus ⁹		Complete 3-Dose Series			Range of recommended ages for certain high-risk groups
Measles, Mumps, Rubella ¹⁰		Complete 2-Dose Series			
Varicella ¹¹		Complete 2-Dose Series			

This schedule includes recommendations in effect as of February 11, 2011. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Providers should consult the recent Advisory Committee on Immunization Practices statement for detailed recommendations: <http://www.cdc.gov/acip/www/immunization/immunization.htm>. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS) at <http://www.vaers.hhs.gov> or by telephone, 800-622-7397.

1. Tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap). (Minimum age: 10 years for Boostrix and 11 years for Adacel)
 - Persons aged 11 through 18 years who have not received Tdap should receive a dose followed by Td booster doses every 10 years thereafter.
 - Tdap should be substituted for a single dose of Td in the catch-up series for children aged 7 through 10 years. Refer to the catch-up schedule if additional doses of tetanus and diphtheria toxoid-containing vaccine are needed.
 - Tdap can be administered regardless of the interval since the last
2. For children aged 6 months through 8 years:
 1. for the 2011-12 season, give 2 doses (separated by at least 4 weeks) to (a) those who are receiving influenza vaccine for the first time or (b) to those who did not receive at least 1 dose of the 2010-11 vaccine.
 2. for the 2012-13 season, follow dosing guidelines in the 2012 ACIP influenza vaccine recommendations.
3. Pneumococcal vaccines.
 - A single dose of PCV may be administered to children aged 6 through 18 years who have functional or anatomic asplenia, HIV infection or

This schedule was updated to include the number of doses for each vaccine as in the adult schedule. Information regarding the recommended age for the booster dose of MCV4 was added (16 years old).

Language for the HPV footnote, as discussed with the subject matter expert, was proposed as follows, with the bolded text being the new language proposed:

- 2. Human papillomavirus vaccine (HPV). (Minimum age: 9 years)
 - Quadrivalent HPV vaccine (HPV4 Gardasil) or bivalent HPV vaccine (HPV2 Cervarix) is recommended for the prevention of cervical precancers and cancers in females.
 - **HPV4 Gardasil is recommended for prevention of cervical precancers and cancers in females; anal cancer and genital warts in both females and males.**
 - **Routine vaccination for females and males is recommended as a 3-dose series starting at 11 to 12 years of age. The series can be started beginning at 9 years of age.**
 - Administer the second dose 1 to 2 months after the first dose and the third dose 6 months after the first dose (at least 24 weeks after the first dose).

The working group did engage in deliberations regarding vaccine indications. While this is not done for other vaccines, the HPV SME agreed that language could be crafted later to make this simpler. The concern expressed by the working group was that the quadrivalent and the bivalent vaccine have separate indications, so it may be necessary to keep the first bullet but the next two could be combined.

Regarding the proposed changes to the MCV4 footnotes, as in the 0-6 year schedule, the heading was updated to reflect licensed ages for both vaccines. The first 2 bullets remained the same in terms of the routine recommended ages. The bullet that deals with those persons who receive their first dose at 13 through 15 years of age was updated to include the minimum interval between the 2 doses; that is, the minimum interval of 8 weeks between the recommended initial adolescent dose and the booster dose. Reference to the ACIP recommendations were included in these footnotes for all the other details that pertain to MCV4 in adolescents.

Proposed changes were made to the influenza footnotes for the 7 through 18 year schedule as follows:

4. Influenza vaccine (seasonal).

- For **most** healthy nonpregnant persons aged 7 through 18 years (i.e., those who do not have underlying medical conditions that predispose them to influenza complications), either LAIV or TIV may be used, **except LAIV should NOT be used for some persons, including those with asthma or any other underlying medical conditions that predisposes them to influenza complications.** For all other contraindications to use of LAIV please see MMWR 2010;59(No. RR-8).
- Administer 2 doses (separated by at least 4 weeks) to children aged 6 months through 8 years who are receiving seasonal influenza vaccine for the first time or who were vaccinated for the first time during the previous influenza season but only received 1 dose.
- Children 6 months through 8 years of age who received no doses of monovalent 2009 H1N1 vaccine should receive 2 doses of 2010-2011 seasonal influenza vaccine. See MMWR 2010;59(No. RR-8):33-34.
- Administer 1 dose to persons 9 years and older.
- For children aged 6 months through 8 years:
 - 1.) for the 2011-12 season, give 2 doses (separated by at least 4 weeks) to (a) those who are receiving influenza vaccine for the first time or (b) to those who did not receive at least 1 dose of the 2010-11 vaccine.
 - 2.) for the 2012-13 season, follow dosing guidelines in the 2012 ACIP Influenza vaccine recommendations.

A new bullet was proposed for IPV to clarify that IPV is not routinely recommended for US residents 18 years or older. This is depicted on the grid by the bar ending before the 18 year mark; however, concern was expressed by some providers that further clarity was needed.

Proposed changes to the 2012 “catch-up” schedule include addition of MCV4 to the grid. MCV4 was not included in the past, but now with newer recommendations that involve catch-up, this had to be done. Because of the need to conserve space on all 3 schedules and remove redundant footnotes, in several instances providers are referred to another schedule. For example, because no new information is being presented with the MCV4 footnotes in the catch-up schedule, it is proposed that providers be referred to the 0 through 6 year and 7 through 18 year schedules respectively. The statement “Always use this Table in combination with the Childhood and Adolescent Immunization Schedules (Figures 1 and 2) and their respective footnotes,” is included to remind providers that all 3 schedules should be used together and not as standalones.

The Hep B footnote was removed and wording relevant to the catch-up schedule, specifically the minimum age for the 3rd dose of Hep B in infancy, was included in the grid. Other bullets were removed, for example, the bullet referencing the 2 dose series licensed for adolescents because it is already included the 7 through 18 year old schedule.

Changes made to the Hib footnote included removal of the reference to number of Hib vaccine doses in unvaccinated high risk persons over the age of 5 years. There is some discrepancy between the schedule and the AAP Red Book on the number of doses recommended. This is being investigated by the SME.

For the IPV footnote the first bullet was removed. This bullet addressed the minimum age for the final dose and the words were inserted into the grid instead. Again, as was done with the 7 through 18 year schedule, a bullet was added to state that IPV is not routinely recommended for persons 18 years of age and older. For the MCV4 footnote, as mentioned earlier, rather than repeat all of the information relevant to catch-up in this schedule, as there is no new information, providers are referred to the respective age schedules. The HepA footnote was also entirely removed, given that the wording is already discussed in the 0 through 6 years and 7 through 18 years schedules and the grid graphically shows 6 months as the minimal interval between doses.

Proposed language for the HPV catch-up schedule footnote, based on the October 2011 vote, was proposed as follows:

2012 Schedule – Catch-up Schedule HPV Footnote (footnote 10)

- 10. Human papillomavirus vaccine (HPV).
 - Administer the series to females **and males** at age 13 through 18 years if not previously vaccinated or who have not completed the vaccine series.
 - Quadrivalent HPV vaccine (HPV4) may be administered in a 3-dose series to males aged 9 through 18 years to reduce their likelihood of genital warts.
 - Use recommended routine dosing intervals for series catch-up, see Figure 2 (Recommended Immunization Schedule for Persons 7 through 18 years of Age).
 - (i.e., the second and third doses should be administered at 1 to 2 and 6 months after the first dose). The minimum interval between the first and second doses is 4 weeks. The minimum interval between the second and third doses is 12 weeks, and the third dose should be administered at least 24 weeks after the first dose.

The next steps are to make revisions as necessary; submit the schedules to *MMWR* for editing during the first week in December 2011; and submit the edited copy to AAP and AAFP by January 1, 2012. Publication in *MMWR* is expected on February 10, 2012 and publication in *Pediatrics* and *American Family Physician* is anticipated in February 2012.

Discussion Points

Dr. Temte pointed out that everything presented had already been approved as ACIP recommendations.

Referring to the 0 to 6 years of age schedule for Hepatitis A and the removal of the wording “2 dose,” Dr. Sawyer wondered what the intent was in terms of duration and why the bar turned purple after that since it implied that only a subset would potentially need the vaccine later. He wondered whether the bar should be entirely yellow. With all other schedules (e.g., adult and adolescent), wherever there is more than one dose, the number of doses is written. If it was not confusing there he wondered why it was confusing for Hepatitis A.

Dr. Beysolow responded that the actual ACIP recommendation for Hepatitis A states that the first dose should be given routinely between ages 12 and 23 months. With the span of the bar as it was and the wording “2 doses” it was being interpreted that both doses had to be completed by 23 months of age. Providers were being penalized by not completing the 2 doses as interpreted by HEDIS Removal of that wording and reference to the footnote that states “administer the second dose 6 to 18 months later” would allow providers to vaccinate with the second dose after the age of 2.

To be consistent with the color coding, it was unclear to Dr. Sawyer why the bar would not be yellow at 2 to 3 years of age, or even 4 to 6 years of age, if there is no upper limit at which the second dose needs to be completed.

Dr. Beysolow responded that, while she understood Dr. Sawyer’s point, she would have to consult the subject matter experts with regard to this question. Currently, Hepatitis A vaccine is not a routine recommendation for those 2 years of age and older as stated in the recommendations.

Dr. Sawyer thought people may be confused and interpret this as one dose, given that for every other vaccine when it is just listed that way, it means a single dose.

Bryna Warshawsky (NACI) wondered about the influenza recommendation for the 2 doses. It seemed to her that if it was an “or” statement such as “never vaccinated before or one dose last year,” the first statement would not be needed because the second statement trumps the first.

Dr. Beysolow replied that this could be reviewed and revised.

Dr. Pickering thought there was no call back on Hepatitis A for children if they received the vaccine at the recommended times it should have been given. He requested further clarification regarding whether this was a routine recommendation or not.

Trudy Murphy responded that she was not aware of a call back indication one way or another, but clearly two doses should be completed on the recommended schedule 6 to 18 months after the first dose. She wondered whether ACIP would consider removing the purple bar completely. There is a permissive indication for giving Hepatitis A vaccine for anyone who

wishes to be protected against Hepatitis A at any age. The purple bar would indicate those who are at increased risk because of communities and outbreak settings, so she agreed that the purple bar was somewhat confusing.

Dr. Sawyer noted that consideration would need to be given to removing the purple bar from the adult schedule as well, which is also meant to cover those who wish to be protected and perhaps includes high risk groups. Some pediatric high risk groups would be specifically indicated. The purple bar may be needed, but he was worried about the implication for routine use possibly being interpreted as just one dose.

Dr. Marcy indicated that the common situation in practice is children who have had one dose of influenza vaccine two years in a row and presenting for a third dose. He wondered whether anything should be stated specifically about this.

Dr. Beysolow responded that as stated in the current ACIP recommendations, only the previous year's vaccine history is being assessed.

Referring to the first bullet in the footnote changes for the IPV schedule for those 7 to 18 years of age stating that the final dose in the series should be administered at least 6 months following the previous dose, Wayne Westin (GSK) pointed out that the schedule for those 0 to 6 years of age and the catch-up schedules include the statement, "The final dose should be administered on or after the fourth birthday." He wondered whether this should be made consistent throughout the schedules.

Dr. Beysolow responded that the reason for removal of this wording in the 7 to 18 years schedule was that this schedule applied to children over the age of 4 years, so this statement was not necessary here.

Dr. Keitel suggested that they needed to see what was written for HPV before making a final vote.

Dr. Beysolow responded that this could be presented after lunch along with the revised working group statement regarding HPV vaccine.

Vote: Child/Adolescent Immunization Schedule

Dr. Meissner made a motion to accept the changes as itemized, including the suggestions made regarding Part A of the influenza vaccine and the purple bar for hepatitis A vaccine. Dr. Sawyer seconded the motion. **The motion passed by a majority vote.** The disposition of the vote was as follows:

14 Favored:	Bennett, Bocchini, Campos-Outcalt, Coyne-Beasley, Duchin, Ehresmann, Jenkins, Keitel, Marcy, Meissner, Rosenbaum, Sawyer, Temte, Vazquez
0 Opposed:	N/A
0 Abstained:	N/A

2012 Adult Immunization Schedule

Introduction

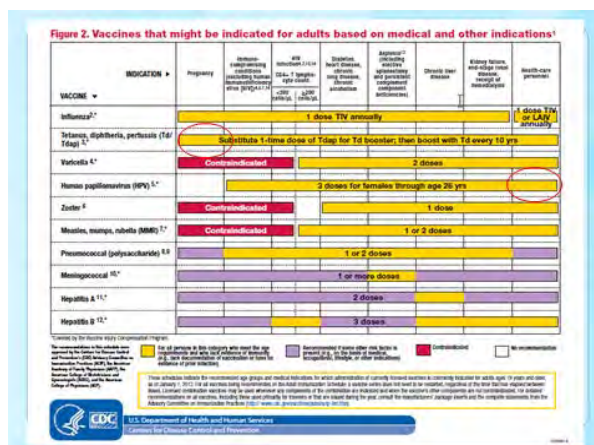
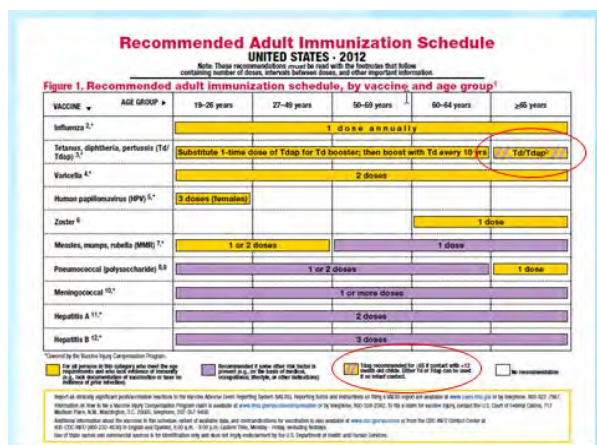
Kristen R. Ehresmann, ACIP Lead Adult Immunization Working Group

Ms. Ehresmann reported that the Adult Immunization Working Group had a similar mode of operation as for the Childhood/Adolescent Schedules in that they are not creating any new policy. They are simply trying to clarify the schedule each year based on changes that have been made, as well as the ever present issue of space and making sure that the font size is completely unreadable.

2012 Adult Immunization Schedule

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

Dr. Bridges shared the draft recommended 2012 Adult Immunization Schedule, which includes 2 figures, and which she emphasized were a reflection of existing policy and which are shown as follows:



The 2012 schedule incorporates changes to the Tdap recommendations that were voted on during previous ACIP meetings, including recommendations for vaccination of pregnant women with Tdap and vaccination of adults 65 years of age and older. Clarifications were also made that healthcare personnel (HCP) are recommended to receive HPV vaccine if they are in the recommended age group, although HPV vaccination is not recommended based on occupation. The prior schedule was left blank on that front. In terms of the changes to the graph for the Tdap vaccination for those aged 65 and older, this is now a yellow and purple hash bar. This indicates that Td/Tdap is recommended for people 65 years of age and older who are in contact with children less than 12 months of age. For others aged 65 and older, Tdap is an option. For Figure 2, which is the medical or other indications schedule, a change was made to the Td/Tdap line. Pregnancy has a solid yellow bar going across. Previous to this year, only Td was indicated for pregnancy. The other change is for HPV vaccine, the yellow bar now goes all the

way across in Figure 2 and includes healthcare personnel. Previously, there was no bar in that section.

The footnotes are now bulleted so that they are now more consistent in formatting with the pediatric schedule. Redundancy was reduced, an attempt was made to harmonize the formatting between the different vaccines, and minor clarifications of wording were added. A footnote was added to refer readers to the full ACIP recommendations and to additional information regarding vaccines for travelers. Previously, reference to the full ACIP recommendations was made in several different footnotes. For the influenza vaccine footnotes, the use of an activated vaccine versus live vaccine for healthcare providers was clarified to be consistent with the ACIP recommendations. Information was also added about other inactivated vaccine formulations, and an age indication was included for these formulations.

Again, the HPV footnotes clarifies that healthcare providers ages 18 to 26 years may receive the HPV vaccine if they are in the age indication, and redundancy was eliminated by reducing one sentence stating that, "Vaccination is less beneficial for females who have already been infected with one or more of the HPV vaccine types" because the footnote already acknowledged that vaccination prior to exposure to HPV was best and would provide the best benefit.

The herpes zoster footnote offers clarification similar to the HPV footnote in that healthcare providers may receive the herpes zoster vaccine if they are in an indicated age group, and this footnote acknowledges that herpes zoster vaccine is approved by the FDA for people aged 50 and older, but that ACIP recommends this vaccine beginning at 60 years of age.

The MMR footnote was simplified somewhat in that it now focuses on routine use of MMR vaccine. Information about use of the vaccine in outbreak settings was removed. Otherwise, there were no additional changes for MMR.

The pneumococcal polysaccharide vaccine footnote includes additional information regarding more high risk indications. No high risk conditions were removed from this footnote. In addition, a word was added to make sure that the footnote is clear that routine use of PPSV is not recommended for American Indians/Alaska Natives or other persons younger than age 65 years unless they have underlying medical conditions that are PPSV indications. Additional language was added to clarify the recommendation about the second dose of pneumococcal polysaccharide vaccine for persons 65 years of age and older.

The meningococcal footnote clarifies the use of MPSV4 versus MCV4 for age and risk group indications, and clarifies the use of MCV4 among college students living in dormitories. This language was approved last year, but did not make it into the adult schedule. The footnote was reorganized to improve consistency in formatting between vaccines. The working group had requested clarity regarding whether the recommendation stating that a single dose of meningococcal vaccine should be administered to college students living in dormitories should be expanded to include the wider range of types of living facilities in which college students may reside. An initial suggestion was that persons up to age 21 in college and living in Freshman dormitories should be vaccinated if they have not received a dose on or after their 16th birthday. The most recent suggestion made was that first year college students through the age of 21 living in residence halls should be vaccinated if they have not received a dose on or after their 16th birthday.

Again, the Td/Tdap footnote was updated to indicate that Tdap vaccination is now recommended for pregnant women >20 weeks gestation consistent with the updated ACIP statement. The footnote indicates that Tdap can be administered regardless of interval since the most recent tetanus or diphtheria-containing vaccine, and that pregnant women not vaccinated during pregnancy should receive Tdap immediately postpartum. The footnote was also updated to reflect that adults 65 years of age and older may receive Tdap vaccine if they are in close contact with children less than 12 months of age.

A pull-out contraindication table was added in order to provide more ready access to this information for adult vaccine providers, which could be provided in the pull-out section of the *MMWR* for the adult schedule. The contents of this contraindication table were derived from the contraindications table in the "Pink Book" [12th Edition of Epidemiology and Prevention of Vaccine- Preventable Diseases, 2011, table A-23]. Dr. Bridges showed the pull-out tables.

The next steps are to revise the schedule based on comments received during this ACIP meeting; seek CDC clearance, including re-review by vaccine-specific SMEs; submit the schedule to *MMWR* in early December 2011; submit the schedule for approval and/or publication with AAFP, ACP, and ACOG; and publish the schedule in the *MMWR*, which is anticipated in early February 2012.

Discussion Points

Dr. Keitel suggested that cigarette smoking be added to the list of risk conditions for polysaccharide vaccine.

Dr. Bridges replied that this appears in the full footnote and that she only showed changes for items that were altered.

Dr. Keitel pointed out that the HPV vote taken earlier in the day would be hard on the schedule because the age cutoffs are different. There may have to be two separate lines for males and females to make the cutoffs clear.

Dr. Bridges responded that depending upon the results of the clearance process, it is possible that they will not be able to incorporate the HPV vote into this schedule. However, they will do their best to try to include it.

Dr. Campos-Outcalt said he has never understood why varicella goes all the way through ages greater than 65 when those born before 1980 are considered to be immune. The only group this applies to is healthcare workers, which could be reflected in the table below that.

Dr. Bridges indicated that the working group engaged in a number of discussions about this specific issue. One of the concerns that was raised by the varicella and herpes zoster SMEs was that people not living in temperate climates may be less likely to be immune. Given the potential exceptions that may occur, the SMEs did not want to make an age change and list exceptions.

Dr. Schmader (AGS) reported that he has worked on zoster vaccines with AGS, and that it is very difficult to define the age group. There are people in the US in that range who are not immune.

Dr. Fryhofer (ACP) said she noticed that HPV2 and HPV4 was used in the adult schedule, while the brand names are used in the child/adolescent schedules. Given that this is supposed to be viewed as a continuous document, this should be harmonized to read HPV2 and HPV4. She was surprised that brand names were used on this sort of document, and felt that using HPV2 and HPV4 would make the difference more recognizable than using the brand names. She also mentioned that adult immunization has taken a step up in the ACP, in that they are now a Technical Advisory Committee. They recently developed a new adult immunization guide, a copy of which she offered to share with the ACIP members.

Dr. Meissner agreed that it is important to standardize the use of HPV2 and HPV4 between the two schedules, pointing out that the trade names were used because many practitioners did not recognize the distinction between the two.

Dr. Turner (ACHA) felt that the second suggestion regarding the college recommendation for meningococcal vaccine made more sense, given that Freshman dormitories may not exist on some campuses.

Dr. Marcy wondered whether the term “residence halls” was specific enough to guide people, and whether fraternity and sorority houses would be included in the category of “residence halls.”

Dr. Turner (ACHA) replied that “residence halls” is the new term being used in the higher education industry, and it is probably more politically correct. “Dormitory” is an old term that is outmoded. “Residence halls” are not merely a place to sleep. They are also a place to teach and have programs and activities. Fraternity and sorority houses would not technically be included as “residence halls,” given that they fall under a different purview. Students live in so many types of high density residences, it is difficult to sort them all out. In terms of meningococcal, the only data regarding increased risk is for Freshman dormitories. There are not data for Freshman living in sororities, fraternities, or apartments.

Vote: 2012 Adult Immunization Schedule

Ms. Ehresmann made a motion to accept the changes as presented, using the second note for meningococcal vaccine. Dr. Coyne-Beasley seconded the motion. **The motion passed by a majority vote.** The disposition of the vote was as follows:

14 in Favor:	Bennett, Bocchini, Campos-Outcalt, Coyne-Beasley, Duchin, Ehresmann, Jenkins, Keitel, Marcy, Meissner, Rosenbaum, Sawyer, Temte, Vazquez
0 Opposed:	N/A
0 Abstained:	N/A

Dr. Pickering emphasized that both schedules would be published in February 2012. This will likely be the process in the future as well for two reasons. First, this allows the changes that are made during the ACIP meeting to be incorporated such as adding HPV into the adult schedule. Second, this offers more time to work with partner organizations. It is very complex to get this into all of the professional journals in a short period of time. Online publication is likely in January 2012. The working groups will do a remarkable job in the time between this meeting and publication, working with the organizations, to get these schedules published in all of the journals simultaneously.

Hepatitis B Vaccine

Introduction

Mark Sawyer, MD, Chairman Hepatitis B Vaccine Working Group

Dr. Sawyer indicated that during this session, the Hepatitis B Vaccine Working Group would bring forth its deliberations and summarize nearly two years of work on the issue of hepatitis B vaccination for persons with diabetes, followed by the presentation of a recommendation for a vote. The term of reference for the working group was to review data from hepatitis B outbreaks among adults with diabetes in institutional care to determine whether vaccination is appropriate. This was prompted by a number of outbreaks of hepatitis B in institutional settings. After reviewing the data, the working group realized that the issue is somewhat broader than the adult population living in institutional settings. They learned by reviewing a broad range of topics that there is an increased risk of hepatitis B in the general adult population with diabetes, and that the increased risk appears to be associated with the use of assisted blood glucose monitoring that occurs in a wide variety of settings.

The working group reviewed the literature on infection control practices in diabetes care and monitoring, which are intended to prevent transmission of infections when assisted blood glucose monitoring is achieved. The working group concluded that infection control measures alone are unlikely to be sufficient to prevent subsequent outbreaks. A number of initiatives have been introduced from 1990 to the present to address infection control issues. However, there continue to be outbreaks of disease. The working group has assessed the safety and effectiveness of hepatitis B vaccination, including studies in the general population and more recently, among residents in long-term care facilities. The working group concluded that hepatitis B vaccine is safe in these populations, but there is an issue with declining seroprotection with age.

During this session, presentations were delivered to summarize the evidence that led to the working group's proposed recommendations. Topics presented upon during this session included risk estimates for hepatitis B infection among adults with diabetes, including updated cost estimates; a summary of evidence leading to the proposed recommendations; the spectrum of settings for assisted blood glucose monitoring; considerations for implementation of a vaccination program; and the GRADE analysis.

HBV Risk Among Adults with Diabetes

Sarah Schillie, MD, MPH, MBA National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention Centers for Disease Control and Prevention

In a previous ACIP meeting, National Health and Nutrition Examination Survey (NHANES) data were shared, indicating a 60% increase in seroprevalence of *past* hepatitis B infection among persons with diabetes. The risk of *acute* hepatitis B was assessed from Emerging Infections Program (EIP) surveillance data. Data from 4 sites suggested an increased risk of acute hepatitis B among adults with diabetes. Data were sought from 4 additional EIP sites, or 8 total, to perform additional analyses and to assess for diabetes risk independent from other hepatitis

B risks. Acute hepatitis B cases from 2009-2010 were reported from EIP sites, and the comparison group consisted of Behavioral Risk Factor Surveillance System (BRFSS) survey respondents. A multivariate analysis was performed and controlled for age, gender, race/ethnicity, and "Other hepatitis B risk factors." A confirmed case was determined by the Council of State and Territorial Epidemiologists (CSTE) definition of acute hepatitis B. Cases less than 23 years of age were excluded because of high vaccination coverage.

The comparison group consisted of 2009 and 2010 BRFSS survey respondents. BRFSS is a large health survey conducted annually. Responses are weighted so that the results are representative of the non-institutionalized US population, and questions vary by year. The comparison group was restricted to respondents in EIP surveillance states and counties aged 23 years and older. BRFSS respondents were assumed to not have acute hepatitis B because of the low incidence of acute hepatitis B. Diabetes status was determined for cases by self-report of a physician diagnosis or medical record review. Diabetes status was determined for comparison group records by self-report of a physician diagnosis. Gestational diabetes and pre-diabetes were considered to not have diabetes. Because diabetes could have been diagnosed in conjunction with recent medical attention for acute hepatitis B, cases diagnosed with diabetes within 6 months of their hepatitis B diagnosis were considered to not have diabetes.

The definition for "other HBV risk factors" differed slightly between cases and comparison group records. For cases, "other HBV risk factors" were defined by at least one of the following in the 6 weeks to 6 months prior to symptom onset: injection drug use, male sex with a male, or multiple sex partners. For comparison group records, the BRFSS HIV risk question was used as a surrogate for hepatitis B risk, and risk was defined as at least one of the following in the past year: intravenous drug use, treated for a sexually transmitted disease, given or received money or drugs in exchange for sex, and anal sex without a condom. "Other HBV risk factors" was not assessed for BRFSS respondents 65 years and older.

A univariate analysis was performed to calculate unadjusted odds ratios. Effect modification was evaluated on unweighted data for interaction of age, gender, race/ethnicity, and other HBV risk factors and diabetes. A multivariate analysis was performed to calculate the adjusted odds ratio and 95% confidence intervals for diabetes and hepatitis B, and an analysis was performed to control for intraclass correlation by EIP site. A sensitivity analysis was performed, which produced 2 odds ratios: one assuming all records with unknown diabetes status had diabetes, and the other assuming all records with unknown diabetes status did not have diabetes. Finally, a regression diagnostic analysis was performed.

There were 865 cases and over 90,000 records in the comparison group. Cases were younger, more often male (64.9%), less often non-Hispanic white (53.1%), and had more hepatitis B risk factors. Diabetes was present among 11.9% of the cases and 9.1% of comparison group records. Diabetes information was unknown for 7.3% of cases and 0.1% of those in the comparison group. Among cases with diabetes, 19.5% had "other HBV risk factors." Among cases without diabetes, 34.6% had "other HBV risk factors." This difference was statistically significant. Among comparison group records, presence of "other HBV risk factors" was nearly identical for persons with and without diabetes.

Cases with diabetes had fewer hepatitis B risk factors than cases without diabetes. Injection drug use was present among 1.5% of cases with diabetes versus 10.8% of cases without diabetes. This difference was statistically significant. Male sex with a male and multiple sex partners were present more often among cases without diabetes than with diabetes, although these differences were not statistically significant. Unadjusted odds ratios for acute hepatitis B were calculated for several characteristics (e.g., age, gender, race/ethnicity other than non-Hispanic white, "other HBV risk factors," and diabetes). The unadjusted odds ratio for diabetes was 1.3.

In terms of the results of tests for effect modification, the interaction term for "other HBV risk factors" and diabetes was significant. Therefore, separate analyses were performed for those with and without "other HBV risk factors." Persons with diabetes without "other HBV risk factors" had 1.89 times the odds of acute hepatitis B than those without diabetes, controlling for age, gender, and race/ethnicity. Among persons with diabetes with "other HBV risk factors," the odds ratio was 1.1. These data suggest that diabetes is a marker of hepatitis B risk among persons without other HBV risk factors, and subsequent analyses were performed for records without "other HBV risk factors." No observations were deleted based on the DF beta results from the regression diagnostic analysis.

Adjusted odds were calculated for 2 age groups. Among persons aged 23-59 years without "other HBV risk factors," those with diabetes had 2.09 times the odds of acute hepatitis B when controlling for potential confounders, with a 95% confidence interval of 1.48 – 2.95. For persons 60 years and older without "other HBV risk factors," the adjusted odds ratio was 1.45, with a 95% confidence interval of 0.79 – 2.68, which is not statistically significant.

An analysis to control for possible intraclass correlation by EIP site was performed. The confidence intervals remained essentially unchanged when controlling for intraclass correlation by EIP site, suggesting that correlation within EIP sites did not affect results. If there is clustering, confidence intervals on the original analysis will be falsely narrow, and confidence intervals on the adjusted analysis will be wider.

A sensitivity analysis was performed. When the records with unknown diabetes status were coded as having diabetes, the adjusted odds ratio was 2.82. Conversely, when the records with unknown diabetes status were coded as not having diabetes, the adjusted odds ratio was 1.77. Cases with diabetes were more likely to be hospitalized or die from acute hepatitis B, although the results were not statistically significant. Of cases with diabetes, 52.5% were hospitalized versus 45.4% without diabetes, and 4.6% of cases with diabetes versus 2.0% without diabetes died.

A cost-effectiveness analysis using the updated odds ratio was performed. For adults with diabetes aged 20 through 59 years, the cost per QALY saved was approximately \$75,000. For those 60 years and older, the cost per QALY saved remained unchanged at approximately \$2.8 million, and for those 20 years and older, the cost per QALY saved was approximately \$197,000.

There are several limitations to this analysis. Case and comparison group data were from different sources, and comparison group records included non-susceptible persons and only non-institutionalized persons. The definition of "other HBV risk factors" differed slightly for cases and comparison group records, and "other HBV risk factors" were not assessed for BRFSS respondents aged 65 years and older. Other limitations include missing diabetes status

for 7.3% of cases and 0.1% of comparison group records. An estimated 10% of cases are reported. Undiagnosed and unreported cases represent another limitation.

In summary, acute hepatitis B is independently associated with diabetes after controlling for risk factors. Persons aged 23 through 59 years with diabetes without “other HBV risk factors” have twice the odds of acute hepatitis B than persons without diabetes.

Summary of Considerations

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Dr. Murphy summarized the issues that framed the deliberations of the working group and led to the proposed recommendations. This included gaining an understanding of how persons with diabetes are exposed to hepatitis B virus; reviewing the evidence for an elevated risk of hepatitis B infection among adults with diabetes and how infection control practices might modify that risk; and assessing vaccine efficacy, age at diabetes diagnosis, and vaccine cost-effectiveness.

With regard to how persons with diabetes are exposed to hepatitis B virus, blood glucose monitoring is an essential component of diabetes care and management. In the US, surveys have shown that among persons with diagnosed diabetes, including types 1 and 2, about 86% measure their blood glucose at least once monthly. This includes persons treated with insulin, oral medications, and nutritional therapy. The frequency of monitoring is determined in consultation with a physician. The monitoring procedure begins with a new test strip inserted into a glucose meter. A fingerstick device containing a sharp lancet is used to draw a drop of blood, the blood is applied to the test strip and drawn into the meter, and within a few seconds, a reading is provided. The blood glucose level reported guides therapy.

Person-to-person transmission of hepatitis B in diabetics occurs through exposure to blood from an infected person. First, a person infected with hepatitis B receives blood glucose monitoring. Their blood contaminates the equipment, supplies, gloves, or hands of the person assisting with the monitoring procedure. The exposure of the next person who is tested is indirect through contact with contaminated equipment, supplies, hands, or possibly when insulin is administered. A new generation of devices, including multi-dose insulin pens and multi-lancet fingerstick devices made for single person use has increased opportunities for contamination of equipment through misuse.

Person-to-person transmission of hepatitis B is facilitated by special characteristics of hepatitis B virus that make it easier to transmit than other bloodborne pathogens. First, high titers of hepatitis B virus can be present in tiny or invisible amounts of blood, and in dried blood on surfaces and on equipment such as gloves or devices. Second, the virus is stable on surfaces, remaining viable and infectious for at least 7 days. Together, these characteristics explain an important role in transmission of hepatitis B via contaminated lancets, surfaces, or medication vials that are used inappropriately for more than one person.

Misuse of diabetes equipment and lapses in infection control are usually not identified unless there is an outbreak of bloodborne infection, or unless it involves potential exposure of a large number of people to bloodborne pathogens. The following list of patient notifications for misuse of diabetes equipment was taken from media reports. Note that all episodes occurred in 2008 or more recently. Examples are from hospitals, community centers, a health fair, and an HMO that involved a certified diabetes educator:

Mis-use of Diabetes Equipment: Recent Patient Notifications			
Recommendation for bloodborne pathogen testing (HBV, HCV and HIV) to groups of individuals potentially exposed to another person's blood ¹			
Year, setting	Equipment misused	Length of misuse	Persons at risk
2008, Hospital	Insulin pen	7 months	908
2009, Hospital	Insulin pen	7 months	2114
2009, Community Health Center	Multi-lancet finger stick device	6 months	283
2010, Health fair	Multi-lancet finger stick device	1 day	64
2011, HMO, certified diabetes educator	Multi-lancet finger stick device, insulin pen	5+ years	2345
Total at risk			5714
1: Guh et al. Patient Notifications for Bloodborne Pathogen Testing Due to Unsafe Injection Practices in U.S. Healthcare Settings, 1999-2009. [Abstract 633]. Presented at International conference on healthcare associated infections 2010, Atlanta, GA, 2011, media release			

The equipment misuse included insulin pens, multi-lancet fingerstick devices, or both for multiple persons though these devices were designed for single person use. Misuse continued for months or years without being recognized or corrected, with the potential for bloodborne pathogen exposures of almost 6000 people.

Since most people with diabetes monitor their own blood glucose, they do not think they could be exposed to blood from another person. However, *assisted* blood glucose monitoring takes place in a wide variety of settings. Exposure to hepatitis B contaminated blood comes primarily from persons with chronic hepatitis B infection. The reservoir of chronic hepatitis B infection has been estimated to be between 550,000 to 940,000 US residents according to NHANES data from 1999 through 2006. Given the large reservoir of hepatitis B, exposure to blood remains a potential source of hepatitis B virus infection for adults with diabetes.

Regarding the morbidity and mortality of hepatitis B in adults, approximately 30% of cases are symptomatic and are debilitated for an average 1 to 4 months. Of the cases reported to CDC, approximately 40% are hospitalized and 1% to 2% of cases develop fulminant liver failure. In 2009, the case fatality rate was 1.3% overall, but varied with age. Fatality rates were 2% to 4% in adults 50 years and older, and 6% to 18% in older adults in outbreak settings such as long-term care facilities. The risk of developing chronic hepatitis B infection is similar for symptomatic and asymptomatic infection. Of healthy young adults, 5% to 10% develop chronic hepatitis B after acute infection. Of older adults with a median age in the mid-70s, limited data suggest chronic hepatitis B infection rates of 45% to 59%. Each person with diabetes who develops chronic hepatitis B increases the reservoir for transmission in the diabetes community [Polish LB N Engl J Med 1992;326:721-5; Kondo K Hepatology 1993;18:768-774].

Given the potential for transmission of hepatitis B virus, the working group examined the evidence for an elevated risk of hepatitis B virus infection among adults with diabetes. There is

a history dating to the 1920s in other countries of hepatitis transmission with diabetes-associated blood glucose monitoring. In the US, outbreaks of hepatitis B among residents in long-term care facilities (nursing homes, assisted living facilities) were reported to CDC beginning in 1996. Some of the outbreaks included multiple facilities. Cases were focused among persons with diabetes who were exposed to an infected person's blood during assisted glucose monitoring. Outbreaks continued despite infection control guidance published in the *MMWR* in 1997, and 2005.

Given that outbreaks were occurring in institutional settings, the working group asked whether transmission was also occurring among people not in institutional settings. The National Health and Nutrition Examination Survey includes only non-institutionalized adults and is a nationally representative sample of the US population. Data from 1999 to 2010 comparing adults with diabetes to adults without diabetes showed that adults with diabetes 18 years and older had a 60% increase in antibody to hepatitis B core antigen (anti-HBc), a measure of past or present hepatitis B infection. This was true over a wide range of age groups and demographic characteristics. For example, after excluding from the results persons with injecting drug use, adults with diabetes overall had an 80% increase in the presence of antibody to hepatitis B core antigen. Addendum: Without adjusting for demographic characteristics, or risk behaviors among adults with diabetes ages 18-59 years and ≥ 60 years, there was a 70% ($P < 0.001$) and 30% ($P = 0.03$) increase, respectively, in the seroprevalence of antibody to hepatitis B core antigen.

As Dr. Schillie reported, the working group then evaluated the characteristics of 865 acute hepatitis B cases among adults with diabetes reported from 2009 through 2010 from 8 EIP sites. The objective was to assess the risk of acute hepatitis B among adults with diabetes who did not have other well-established risk behaviors for hepatitis B infection. Acute hepatitis B was independently associated with diabetes of more than 6 months duration. That is, diabetes diagnosis had been made before exposure to hepatitis B virus. In those persons less than 60 years of age without other risk behaviors, the odds of hepatitis B were 2 times higher than for adults without diabetes. For adults with diabetes 60 years of age and older, the odds of hepatitis B were 1.5 times higher than in persons without diabetes.

Thus, the increased risk of hepatitis B infections for adults with diabetes was documented in two different types of data sources (e.g., seroprevalence and acute disease cases). Among the acute cases, it was established that 24 of the 28 outbreaks occurred in healthcare settings. Diabetes is a marker for increased risk of hepatitis B infection, not really a risk factor. The increased risk is associated with exposure to hepatitis B virus in blood or body fluids in the course of diabetes care and management. There is no evidence to suggest that immunologic changes in diabetes increase the susceptibility to hepatitis B virus infection. However, adults with diabetes may experience greater morbidity and mortality from hepatitis B infection, and underlying liver disease.

Infection control practice guidelines for blood glucose monitoring have been in place and have been updated since 1990. During the last two and a half years, CDC, FDA, and CMS intensified efforts in infection control practice. There were initiatives to alert patients and care providers to the potential for transmission of bloodborne pathogens and how to prevent transmission during glucose monitoring. Device manufacturers were encouraged to make improvements to monitoring equipment. Patient guidance has been made easily available, and additional training is being provided for diabetes educators. These efforts are on-going, and improvements have likely already taken place in infection control practice and will continue, especially in highly regulated settings such as nursing homes. However, the working group, especially infection control practitioners who were members of the working group, felt that lapses in infection control

would continue given the diversity of settings where assisted blood glucose monitoring takes place.

With this information on the increase in the risk of hepatitis B among adults with diabetes, the working group considered the potential benefits that might be achieved by vaccination, how age of diabetes diagnosis might affect the proportion of persons with diabetes who would be protected by vaccination, and the cost-effectiveness of vaccination related to age. These considerations led to the formulation of the proposed recommendations.

There is a well-defined serologic correlate of protection for hepatitis B vaccination. Antibody to hepatitis B surface antigen (anti-HBs) of ≥ 10 mIU/mL correlates with more than 22 years of protection from symptomatic hepatitis B chronic infection after completion of a hepatitis B vaccine series (usually ≥ 3 doses) [McMahon et al. J Infect Dis 2008]. Increasing age and co-morbidities, including diabetes, result in declining proportions of adults who achieve protection after a standard series of vaccination. Data from trials involving persons with diabetes and persons for whom diabetes status was unknown show that seroprotection remains high in the majority of adults up to 60 years of age. In some studies, starting at around age 40, seroprotection achieved is somewhat lower for persons with diabetes than for persons without diabetes in trials not exclusively addressing persons with diabetes. Preliminary results were assessed from several vaccine trials among residents of long-term care where hepatitis B outbreaks occurred. These persons had major co-morbidities leading to their residence in the long-term care facilities.

From these results, and a review of the individual vaccine trials, the working group drew several conclusions. Seroprotection proportions remain high, or at least relatively high, in the majority of adults to about age 60 and then gradually declined. Because younger age and fewer co-morbidities result in better responses, vaccination soon after diabetes diagnosis will maximize achievable protective responses to hepatitis B vaccination. Fewer adults older than 60 years of age and adults with co-morbidities may be partially or fully protected. No special safety concerns were identified with regard to vaccinating aging adults.

Because of the decline in vaccine response among older adults, the age of diabetes diagnosis is important. Regarding the age distribution of diabetes diagnosis in 2008, the median age of diagnosis was 52.9 years. By age 50 years, less than 40% of diabetes diagnoses have been made. By age 60 years, two-thirds of diagnoses had been made [Source: CDC. Diabetes Data and Trends: National Diabetes Surveillance System www.cdc.gov/diabetes/statistics. Data from the National Health Interview Survey]. Recall that relatively good responses were achieved to age 60 years. The working group then evaluated the age-related response to vaccination and the age at diabetes diagnosis as they relate to the cost-effectiveness of vaccination by decade of life.

Regarding the impact of age on cost-effectiveness by decade of life, vaccination was most cost-effective to age 50 because of the larger number of life years left to benefit from vaccination. There is a somewhat higher risk of hepatitis B among adults with diabetes younger than 60 years of age compared with older age groups, and the response to vaccination is better among adults to age 50 than among older adults. Vaccination was not shown to be cost-effective after 60 years of age [Data provided by RTI International, September 2011].

The working group discussed in detail the increase in cost of vaccinating adults 50 to 60 years of age, and adults 60 years of age and older. Emphasizing the information on vaccine response, age of diabetes diagnosis, and cost-effectiveness, the working group concluded that

one of the proposed recommendations should have two age categories with different strengths of recommendation, which would maximize the proportion of adults protected and be most cost-effective. To vaccinate those 20 to 59 years of age, the cost per QALY saved would be \$75,000. To vaccinate those 60 years of age and older, the cost per QALY saved would be \$2.7 million. Vaccinating all adults with diabetes who are 20 years of age and older, the cost per QALY saved would be approximately \$197,000. These considerations led to the following two proposed recommendations:

- ☐ Option 1:
 - Hepatitis B vaccination *should* be administered to unvaccinated adults with diabetes who are <60 years
 - Hepatitis B vaccination *may* be administered to unvaccinated adults with diabetes who are ≥60 years
- ☐ Option 2:
 - Hepatitis B vaccination should be administered to unvaccinated adults with diabetes

Assisted Blood Glucose Monitoring

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Dr. Allweiss discussed the myriad of places in which assisted blood glucose monitoring can be done, such as places where people live, work, play, and pray (e.g., schools, worksites, community centers, et cetera). Many locations have screening, therapeutic programs, et cetera where one meter is used for more than one person. Self-monitoring of blood glucose is a very effective tool. In the old days, there was double voided urine testing. There are many medications that might interfere with the measurements. Also, this was only an indirect way of giving a person the blood glucose value. When blood glucose meters came out, it really changed the way people could treat those with diabetes. The blood glucose meter is a wonderful tool for therapeutic adjustment of medications, especially insulin, for people with either type 1 or type 2 diabetes. Monitoring may be done several times a day, and is a part of the overall treatment plan that a person with diabetes will go over with his or her healthcare provider.

Assisted glucose monitoring with one meter for multiple people may be used for different reasons, and there has been increasing use of one meter for multiple people. One reason would be for therapeutic purposes for pattern recognition, especially for people who are using insulin so that they can see when their blood sugar is high or low and their medication can be adjusted to reach their blood glucose goal. One meter is used for multiple people for educational and screening purposes as well. Values by a finger stick or alternative site, such as the forearm, must be followed up by venipuncture for a glucose or A1c value to truly be diagnostic of diabetes or pre-diabetes. The point is that these educational and screening methods are being used, and follow-up is required and it is important to know that using one meter for multiple people is possible in multiple settings.

Although it might be presumed that an individual meter would be used by an individual, sometimes a family may have more than one member with diabetes or other family members at risk of developing diabetes. It is not uncommon for a person to share a meter with another

family member or friend. Therefore, this is another setting in which there is a possibility of transmitting bloodborne pathogens. Living facilities (e.g., group homes, shelters, nursing homes, prisons, dorms, camps, et cetera) are other venues in which one meter may be used for more than one person. Medical venues are by far the most common places where one meter might be used for more than one person (e.g., hospitals, public or private clinics, physicians' offices, pharmacies, et cetera). Worksites represent another venue in which one meter may be used for multiple people. The worksite is a wonderful place for education, especially regarding chronic conditions. The evidence is increasing to show that keeping people healthy, especially those with chronic conditions, can positively impact productivity. In worksites, one monitor may be helpful for therapeutic decision-making. Many worksites have occupational medicine clinics with occupational medicine physicians and nurses. If a person with diabetes presents to the clinic with symptoms of hypoglycemia, their blood glucose will be checked. An increasing number of worksites are striving to keep their workers healthy through on-site disease management, education, and screening. Sometimes worksites contract an outside vendor to conduct screening, and the vendor will have its own meter. One meter may be used for multiple people in the school setting as well. Although many children with diabetes will have their own meter, sometimes school clinic nurses will have a meter that may be used for multiple individuals. Many disease management vendors will contract with venues other than worksites as well. For example, diabetes education and screening programs are also conducted in malls, convention centers, faith-based locations, and community centers. Emergency Medical Responders (EMR) may also do a blood test to evaluate a patient using a blood glucose meter that is used for multiple people.

The experience of personnel performing assisted blood glucose monitoring varies. Monitoring is done by nurses, pharmacists, physicians' assistants, lay workers, community health workers, health coaches, contract labor, full-time employees, or volunteers. It is vital to inform everyone who may conduct blood glucose monitoring about the importance of infection control. There are other possible sources of bloodborne pathogens than blood glucose meters. There is a variety of point-of-service testing done with other monitors, such as those for CLIA-waived tests (A1c, cholesterol, INR). Thus, other types of offices must be considered, such as cardiology offices, where people might have a finger stick done for testing. It is also important to consider insulin pens and vials. Among adults with diagnosed type 1 or type 2 diabetes, 12% take insulin only and 14% take both insulin and oral medication. Education is key, given that there are a number of preconceived notions that must be overcome. For example, many people think that it is just the lancets that can be the problem. However, the transmission of hepatitis B during the glucose monitoring process has many factors. Consideration must be given to how to reach all of the people using monitors for multiple use testing. Having to clean the device between each use adds one more thing to the already long list of "things to do," especially when screening hundreds of people.

In terms of whether the meter can actually be a source of transmission, a survey of 12 hospitals of 609 blood glucose meters found that 30.2% of meters had blood contamination. It is a difficult concept to think that a tiny drop of blood might be on a meter, but there are many reasons that this does occur. Maybe someone did not wash his/her hands, or did not change gloves. There is an outbreak example in which fingerstick devices were not shared in a nursing home in North Carolina. Even with that variable eliminated, hepatitis B was being spread during the glucose monitoring procedure [Louis et al. *Point of Care* 2005;4:158-163; *MMWR* – March 11, 2005/54(09):220-223]. Practices associated with hepatitis B transmission during assisted monitoring of blood glucose include use of fingerstick devices on multiple persons, failure to clean and disinfect blood glucose testing meters between each use, and failure to change or use gloves or perform hand hygiene between procedures [CDC. *MMWR* 2005;54:220-23].

www.cdc.gov/injectionsafety/providers/blood-glucose-monitoring_faqs.html].

An emerging problem is the use of a new generation of devices. Sharing of multi-lancet fingerstick devices was reported as cause of a hepatitis B infection outbreak in a nursing home¹, and sharing of multi-dose insulin pens has also been reported^{2,3} [1: Gotz et al. Eurosurveillance 2008;13:1-4; 2: www.newsinferno.com/archives/3066 ; 3. www.lcsun-news.com/ci_11670031]. Facilities should select and use single-use, auto-disabling lancing devices for each patient [http://www.cdc.gov/injectionsafety/blood-glucose-monitoring.html].

There are a number of resources for clinics, disease management vendors, et cetera. The following is an Infection Prevention Checklist for Outpatient Settings that reflects the minimum expectations and should be disseminated widely:

4. Point-of-Care Testing (e.g., blood glucose meters, INR monitor)	Practice Performed	If answer is No, document plan for remediation
a. New single-use, auto-disabling lancing device is used for each patient (Note: Lancet holder devices are not suitable for multi-patient use.)	Yes No	
b. If used for more than one patient, the point-of-care testing meter is cleaned and disinfected after every use according to manufacturer's instructions (Note: If the manufacturer does not provide instructions for cleaning and disinfection, then the testing meter should not be used for >1 patient.)	Yes No	
For additional guidance on infection prevention during point-of-care testing consult the following resource(s): • Infection Prevention during Blood Glucose Monitoring and Insulin Administration • Frequently Asked Questions (FAQs) regarding Assisted Blood Glucose Monitoring and Insulin Administration		

<http://www.cdc.gov/HAI/settings/outpatient/outpatient-settings.html>

In summary, education is key. It is critical to increase awareness of the history of outbreaks related to assisted monitoring of blood glucose, as well as other types of fingerstick monitoring. Dissemination of information about infection prevention from CDC, CMS, and FDA to people involved in the care of people with diabetes in multiple venues is extremely important. It is also important to work with industry to “build a better bread box,” and assess other interventions to prevent the most common blood borne pathogens. CDC infection prevention resources can be found at the following:

- ☐ Infection Prevention during Blood Glucose Monitoring and Insulin Administration
<http://www.cdc.gov/injectionsafety/blood-glucose-monitoring.html>
- ☐ FAQs regarding Assisted Monitoring of Blood Glucose (AMBG) and Insulin Administration
http://www.cdc.gov/injectionsafety/providers/blood-glucose-monitoring_faqs.html

Implementation/Vaccine Coverage

Kathy Byrd, MD, MPH
Prevention Branch, Division of Viral Hepatitis
Centers for Disease Control and Prevention

Dr. Byrd presented information on the implementation of hepatitis B vaccination among persons with diabetes by presenting data on current hepatitis B coverage among persons with diabetes to give an idea of the proportion of persons with diabetes who are vaccinated against hepatitis B; vaccination uptake of currently recommended vaccines for persons with diabetes; opportunities for vaccination; possible methods of dissemination of recommendations; and methods to measure progress toward a recommendation for hepatitis B vaccination for persons with diabetes.

Persons with diabetes may be vaccinated against hepatitis B for a variety of reasons, including chronic renal or liver disease. With regard to the proportion of adults 20 years of age and older who reported receiving 3 or more doses of hepatitis B vaccine, overall, 17% of persons with diabetes received 3 or more doses of hepatitis B vaccine compared with 26% of persons without diabetes. However, there is no difference in vaccination coverage between persons with and without diabetes in any age group, with the exception of persons between the 20 and 29 year age group among whom persons with diabetes have higher coverage. This difference may in part be due to the small number of persons with diabetes within this age group. Coverage was generally higher among the younger age groups at between 23% to 29%, and persons with diabetes 20 to 44 years of age and decreased to 7% in persons 70 years of age and older [National Health Interview Survey, 2009].

In order to understand vaccination coverage in adults with diabetes for other vaccinations, Dr. Byrd presented data for influenza and pneumococcal vaccination coverage, both of which are recommended for persons with diabetes. Assessing vaccination coverage for these vaccines may offer an idea of what vaccination coverage for hepatitis B might be expected if it were to become a recommendation. Influenza vaccination is recommended annually for all adults with diabetes, and pneumococcal vaccination is recommended as a one-time vaccine for all adults with diabetes. A one-time revaccination is recommended for individuals over 64 years of age who were previously vaccinated when they were under 65 years of age if the vaccine was administered more than 5 years prior.

Regarding vaccination coverage for intramuscular influenza vaccine in persons 20 years of age and older by diabetes status and age group in 2009, overall, influenza vaccination coverage was significantly higher in persons with diabetes at 57% compared to 33% in persons without diabetes. Influenza vaccination coverage among persons with diabetes ranged from 34% to 74% and increased with age. Persons with diabetes have significantly higher vaccination coverage in all age groups, with the exception of persons 55 to 59 years of age. It should be noted that the 2010 general recommendation to vaccinate all adults against influenza did not come into effect until after these survey data were collected. In terms of the proportion of adults who received pneumococcal vaccination by diabetes status and age group in 2009, overall, pneumococcal vaccination coverage was significantly higher in persons with diabetes at 46% compared to 19% in persons without diabetes. Pneumococcal vaccination coverage among persons with diabetes ranged from 22% to 68%, with generally increasing coverage with increasing age. Persons with diabetes have significantly higher rates of vaccination coverage in all age groups, with the exception of persons 70 years of age and older who fall under the

general recommendation for pneumococcal vaccination [National Health Interview Survey, 2009].

While vaccination coverage for both influenza and pneumococcal is below the Healthy People 2010 goals for vaccination among persons with diabetes, these data demonstrate that there is an existing platform for vaccination in persons with diabetes that leads to increased vaccine uptake. This existing platform can be used to vaccinate persons with diabetes against hepatitis B.

Persons with diabetes have frequent contact with the healthcare system. The 2009 NHIS was used to determine the number of healthcare provider visits among persons with diabetes in the previous year. The majority of persons with diabetes saw a physician 2 or more times per year, with little difference between persons with diabetes younger and older than 60 years of age. Between 16% and 19%, of persons with diabetes age ≤ 59 years and ≥ 60 years respectively, saw a provider two to three times per year, 40% to 42% had 4 to 9 visits, and approximately 30% had 10 or more provider visits per year. Therefore, there are multiple opportunities to vaccinate adults with diabetes. In addition, since there is no apparent effect on the immunogenicity of the 3-dose hepatitis B vaccination series when the spacing of the vaccination series is longer than the recommended intervals, the hepatitis B vaccine schedule is somewhat flexible and can be accommodated by intermittent healthcare visits.

Providers often use a diabetes care checklist to keep track of recommended care. While checklists vary between healthcare settings, there are quarterly tests that are recommended for persons with diabetes, including HbA1c and blood pressure. Annual visits and tests listed on most diabetes checklists include cholesterol, microalbumin, and immunizations. Since persons with diabetes are recommended for quarterly tests and yearly immunizations, a diabetes care checklist may be a useful reminder for hepatitis B vaccination.

Persons with diabetes are most often seen for medical care by their primary care physicians; therefore, the greatest access to vaccine is within primary care offices. Freed et al. conducted a study of 1990 office-based primary care practices to determine the proportion of adult primary care physicians who stock various vaccines for adults and to explore reasons for not stocking vaccine. "Primary care" was defined as either a family practice or internal medicine practice. Of the 1990 practices surveyed, 96% stated that they stock vaccines for adults. Of the practices that carry vaccines, while a high of 97% stock influenza vaccine, only 54% stock varicella or meningococcal vaccines for adults. Essentially in the middle of all vaccines stocked, 76% of practices stocked hepatitis B vaccine for adults. The proportion of those who carry adult hepatitis vaccine differed by practice type, with 82% of family practices carrying the vaccine compared to 67% of internal medicine practices. The difference in stocking practices by practice type may reflect greater experience of family practices in providing vaccinations for their patient population. The reasons practices stated for not carrying adult vaccines included cost of maintaining inventory (46%), vaccines available elsewhere (35%), inadequate reimbursement (34%), inconsistent insurance coverage (30%), few patients for whom indicated (23%), and adult patients don't want vaccines (2%) [G. Freed et al. Vaccine 29 (2011): 1850-1854].

While most primary care offices carry hepatitis B vaccine for adults, inventory costs and the logistics of forecasting need, there is a potential need for complementary vaccination venues. One such alternative venue is pharmacies. Pharmacists are currently authorized by 51 states and territories to administer immunizations. Pharmacists have access to sophisticated tracking and recall systems for follow-up dosing. Over 80,000 pharmacists have been trained to administer vaccinations and pharmacists have shown their capacity to vaccinate. For example, over 5 million influenza vaccinations were administered by pharmacists during the 2009-10 influenza season.

Another opportunity to increase vaccinations among persons with diabetes might be with diabetes educators, who might be able to educate persons with diabetes about hepatitis B vaccination. Diabetes educators educate persons with diabetes about self-care behaviors, such as healthy eating, glucose monitoring, and active lifestyles. Diabetes educators also use quality assurance checklists that follow the American Diabetes Association guidelines. Quality assurance checklists may prompt diabetes educators to review recommended preventive services for persons with diabetes (e.g., annual eye exams, foot exams, and immunizations). Diabetes education has historically been provided by nurses and dietitians; however, the role of diabetes educators has expanded to providers in other disciplines. This is especially true of pharmacists who have demonstrated successful implementation of diabetes education programs in the retail pharmacy setting. In addition to providing education, nurses and some pharmacist are able to administer vaccinations.

In long-term care facilities, there is an existing immunization platform based on CMS quality indicators for influenza and pneumococcal. In October 2005, CMS required that as a condition of participation in Medicare or Medicaid programs, all certified nursing homes offer their residents influenza and pneumococcal vaccines and report patients' immunization histories. Methods to vaccinate within nursing homes include making vaccination a standard part of the admission process. This may be accomplished by using pre-printed admission orders in which the admitting physician can order vaccinations by checking off the appropriate boxes on the admission form. Standing orders for vaccination and written institutionalized policies and plans are also used to implement vaccination within nursing homes.

Uptake of any new recommendations is often dependent on the dissemination of recommendations to the targeted group of individuals who would be involved in implementation. The American Diabetes Association publishes an updated version of its clinical guidelines each year. Representatives of the ADA have stated that if a hepatitis B vaccination for persons with diabetes becomes a recommendation, they may include the recommendation in the ADA clinical guidelines. Inclusion of the hepatitis B vaccination on diabetes educators' quality assurance checklists may also increase uptake. A recommendation could also be added to the ACIP Adult Immunization Annual Chart.

There are a couple of ways to monitor progress for a potential recommendation. First, NHIS collects data on hepatitis B vaccination and diabetes status on a yearly basis. The NHIS can be used to monitor vaccination coverage among persons with diabetes. Second, the Division of Viral Hepatitis (DVH) of CDC will be initiating several new surveillance sites that will collect information on hepatitis B infection and diabetes status. The surveillance data can be used to monitor incident hepatitis B infection among persons with diabetes.

In conclusion, there are existing platforms for vaccinating persons with diabetes that can be built upon to implement hepatitis B vaccination among persons with diabetes. Persons with diabetes often have frequent healthcare contact, which provides multiple opportunities for hepatitis B vaccination. In addition, there are potential alternatives for vaccine delivery outside of the primary care office.

GRADE (Grading of the Evidence)

Sarah Schillie, MD, MPH, MBA

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Dr. Schillie reviewed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process for hepatitis B vaccination among adults with diabetes. There are four components to determining a recommendation category: evidence type, balance between benefits and harms, values, and economic analysis. Recall that results from the economic analysis were presented in detail at the June 2011 ACIP meeting.

The question under consideration is “Should hepatitis B vaccine be recommended for routine use among adults with diabetes?” Prevention of hepatitis B virus infection will prevent disease outcomes associated with hepatitis B virus, as well as associated hospitalizations.

Regarding the evidence type, two search strategies were used to systematically identify and review relevant studies. One strategy identified randomized controlled trials (RCT) that included a placebo group and assessed the efficacy of hepatitis B vaccine among adults. The outcome consisted of rates of hepatitis B infection events. Because no placebo-controlled RCTs were found that focused on adults with diabetes, we conducted a search to identify observational studies among persons with diabetes. The outcome consisted of serologic correlates of protection, and it is worth noting that experience using serologic correlates for predicting hepatitis B vaccine protection is extensive. Only published studies were included in the search. The databases and search terms are depicted as follows:

1. MEDLINE (PubMed) search
 - Limited to RCTs
 - Combinations of the following search terms: hepatitis b vaccin*, hbv vaccin*, hepatitis b immuni*, hbv immuni*, immunogeni*, immune response, antibody, placebo
2. MEDLINE (PubMed), EMBASE (Ovid), Cochrane Library, and Web of Knowledge search, search terms:

(hepatitis b vaccin* OR hbv vaccin* OR hepatitis b immuni* OR hbv immuni*)
AND
(immunogeni* OR immune response OR antibody)
AND
(diabetes)

Regarding the search for RCTs, 6 studies were identified of hepatitis B vaccine efficacy among adults that met the search criteria. Of these, 3 were among healthcare personnel and 3 were among men who have sex with men (MSM). None of these studies reported results for persons with diabetes. With regard to the search for seroprotection studies among persons with diabetes, 183 articles were reviewed and 5 studies were identified that met the search criteria.

Among excluded articles were those that examined response to vaccinating adults with diabetes who had major co-morbidities such as renal failure. The 6 RCTs were conducted in the early 1980s and included on average approximately 1000 subjects each. The RCTs included subjects with a mean age generally in the low 30s who received plasma vaccine. Most studies used a 20 microgram vaccine dose administered intramuscularly on a 0-, 1-, 6-month schedule. As noted, the RCTs in the GRADE analysis used plasma vaccine. However, studies have documented the similarity between plasma and recombinant vaccine in terms of safety and immunogenicity, although these studies were not focused on persons with diabetes [E Dandolos et al. *J Medical Virol* 1985;17:57-62; S Hadler, H Margolis. *Curr Clin Top Infect Dis* 1992;12:282-308; W Jilg et al. *Lancet* 1984;2:1174-5; C Lee et al. *BMJ* 2006;332:328-36].

The 5 observational studies included a fewer number of subjects, although the subjects had diabetes. The studies by Douvin and LiVolti were actually RCTs, but without a placebo group, and therefore are considered observational for the purposes of GRADE. The observational studies included children, adolescents, and adults who received recombinant vaccine. Most studies used a 20 microgram vaccine dose administered intramuscularly on a 0-, 1-, 6-month schedule. Note that 30 of Douvin's 71 subjects received a booster dose at month 4. The vaccine efficacy from the RCTs ranged from 71% to 82% when all hepatitis B infection events were considered. Vaccine efficacy is even greater when only clinical outcomes are considered. No serious vaccine related adverse events were reported in any study.

The Forest Plot for the RCTs showed that the aggregate risk ratio for all hepatitis B infection events was 0.37, favoring vaccination. The I squared statistic of 19% indicates there was little heterogeneity or inconsistency between studies. A Forest Plot was not depicted for the observational studies because of the differences in comparison groups.

The number needed to vaccinate was calculated from a modeling analysis based on Emerging Infections Program (EIP) data. To prevent one hepatitis B infection, 124 persons with diabetes aged 20 – 59 years need to be vaccinated. For persons aged 60 years and older and 20 years and older, the numbers needed to vaccinate are 1071 and 261, respectively¹. The numbers needed to vaccinate were based on a model using EIP data demonstrating persons age 23-59 years and 60 years and older with diabetes without other hepatitis B risk factors have 2.1 times and 1.5 times, respectively, the odds of acute hepatitis B than those without diabetes². The modeling analysis indicated that a 10% vaccine uptake among persons with diabetes aged 20-59 years would prevent over 4000 infections, 256 chronic cases of hepatitis B infection, 33 cases of hepatocellular carcinoma, 13 transplants, and 130 deaths for persons aged 20-59 years. These figures are less for vaccination of persons aged 60 years and older. For persons 20 years and older, nearly 5000 infections would be prevented¹ [¹T Hoerger et al. *Research Triangle Institute, Int.* 2011; ² M Reilly et al. *IDSA* 2011].

Regarding the observational studies, the proportion seroprotected ranged from 75% to 95% among persons with diabetes, compared to 97% to 100% among persons without diabetes. The confidence intervals were overlapping. No serious adverse events occurred among the 3 studies that reported on adverse events. As previously noted, studies indicate hepatitis B surface antibody levels greater than or equal to 10 mIU/mL correspond to protection when a vaccine series has been administered, although these studies were not focused on adults with diabetes [S Hadler, H Margolis. *Curr Clin Top Infect Dis* 1992;12:282-308; A Jack et al. *J Infect Dis* 1999;179:489-92].

According to GRADE, the body of evidence from RCTs starts with an evidence type of 1 and the body of evidence from observational studies starts with an evidence type of 3. Evidence type is then moved down or moved up based on certain criteria. Observational studies that were moved down cannot be moved up. The final evidence type ranges from 1 to 4, with 1 being the strongest type. The criteria for moving down and moving up are applicable to the body of evidence, and not to individual studies. RCTs are evaluated separately from observational studies. Because GRADE emphasizes transparency and the need to be explicit regarding evidence type, details for individual studies are presented, although the final evidence type is assigned based on the body of evidence. Regarding the RCTs, indirectness was present in all studies because the subject population was not focused on adults with diabetes. Additionally, 2 studies utilized on a non-standard vaccine dose, route, or schedule, and were therefore classified as having serious indirectness. The body of evidence from RCTs was moved down 1 level for indirectness. For observational studies, the body of evidence was moved down for imprecision because the total number of events was fewer than 300.

Regarding evidence of benefits, the evidence type was 2 for the RCTs and 4 for observational studies, for an overall evidence type of 2. Note that the overall evidence type is not the mathematical average. For example, in instances where a multitude of high quality studies exist, the overall evidence would be type 1 regardless of how many lower quality studies exist. There were no serious vaccine-related adverse events in any of the evaluated studies, although 4 of the 6 RCTs reported more non-serious adverse events among the vaccinated group. Of the observational studies, 3 reported on adverse events, and no adverse events occurred in 2 studies, while 1 study documented mild fever and fatigue, local tenderness and/or erythema. Note that the number of subjects may not have been large enough to capture rare adverse events. The Institute of Medicine (IOM) notes that evidence supports a causal relationship between hepatitis B vaccine and anaphylaxis in yeast-sensitive individuals, which is listed in the package insert as a contraindication for vaccination. Anaphylaxis following hepatitis B vaccine occurs in about 1.1 out of every million doses administered [K Bohlke et al. *Pediatrics* 2003;112:815-20. L DiMiceli et al. *Vaccine* 2006;24(6):703-7. IOM 2011. *Adverse Effects of Vaccines: Evidence and Causality*. Washington, DC: The National Academies Press].

No serious vaccine-related adverse events were reported in any of the studies, although the study sizes may have been too small to detect rare adverse events. The recent Institute of Medicine Report noted anaphylaxis in yeast-sensitive individuals [IOM 2011. *Adverse Effects of Vaccines: Evidence and Causality*. Washington, DC: The National Academies Press]. Recommendations that may be helpful but do not need grading are typically those in which it is sufficiently obvious that desirable effects outweigh undesirable effects and that no direct evidence is available because no one would be foolish enough to conduct a study addressing the implicit clinical question. Regarding the balance between benefits and harms, after approximately 30 years of vaccine experience, serious hepatitis B vaccine related adverse events remain extremely rare.

Values were assessed through a survey of work group members for which there was an 80% response. Outcomes of hepatitis B infection from clinician and policy maker perspectives were ranked in terms of "importance" on a 9-point scale (in groups of 3 as not-important, somewhat important, or very important). Variability of responses was then determined according to established criteria. Items consistently ranked very important were assigned a high value, and items consistently ranked not important were assigned a low value. Other items were assigned a moderate value. This process was completed separately for clinician and policy maker perspectives. When values differed for clinician and policy maker perspectives, the higher value was assigned. The "disease state" (e.g., acute hepatitis, fulminant hepatitis, chronic hepatitis,

cirrhosis, hepatocellular carcinoma, liver transplantation, death) values were higher for those less than 60 years of age than those 60 years and older. The non-disease state values (e.g., vaccine cost effectiveness, personnel time to obtain consent for vaccination, and pain from vaccination) are somewhat lower than the disease-state values.

In terms of the cost per quality-adjusted life year (QALYs) saved, the final odds ratios from the EIP data were used to update the cost-per QALY saved. The cost per QALY saved was approximately \$75,000 for persons 20-59 years of age and \$197,000 for persons older than 20 years of age. For the age group 60 years and older, the cost per QALY saved remained high at approximately \$2.8 million. Program costs are approximately \$110 million for the 20-59 year age group, \$161 million for the ≥ 60 year age group, and \$270 million for the ≥ 20 year age group [T Hoerger et al. Research Triangle Institute, Int. 2011].

This following depicts the proposed wording for the 2 options for a recommendation:

Option 1 (Majority Work Group):

- Hepatitis B vaccination should be administered to unvaccinated adults with diabetes who are < 60 years of age (GRADE Category A, Evidence type 2)
- Hepatitis B vaccination may be administered to unvaccinated adults with diabetes who are ≥ 60 years of age (GRADE Category B, Evidence type 2)

Option 2 (Minority Work Group):

- Hepatitis B vaccination should be administered to unvaccinated adults with diabetes (GRADE Category A, Evidence type 2)

Recall that category A or B refers to the strength of the recommendation, and evidence type refers to the strength of the evidence. For Option 1, the recommendation would be category A for persons less than 60 years and category B for persons 60 years and older. For Option 2, which does not have an age break-down, the recommendation would be category A. The evidence is type 2 for both options. Note that this is different from the evidence type in the background materials, as further review indicated the evidence is more appropriately type 2.

The following graphics summarize how a category A and B recommendation were reached for Options 1 and 2:

GRADE component	Category A more likely if:	Option 1
Evidence type	Higher evidence type	Age < 60 years: Type 2 Age ≥ 60 years: Type 2
Balance between benefits/ harms	Benefits outweigh harms	Serious adverse events extremely rare (1.1 cases anaphylaxis per million doses)
Values of Work Group members	Higher values	Preventable outcomes: Age < 60 years: High value Age ≥ 60 years: Moderate or high value
Economic analysis	Higher cost-effectiveness	Cost per QALY saved: Age < 60 years: \$75,094 Age ≥ 60 years: \$2,760,753

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GRADE component	Category A more likely if:	Option 2
Evidence type	Higher evidence type	Type 2
Balance between benefits/ harms	Benefits outweigh harms	Serious adverse events extremely rare (1.1 cases anaphylaxis per million doses)
Values of Work Group members	Higher values	Preventable outcomes: High value
Economic analysis	Higher cost-effectiveness	Cost per QALY saved: \$196,557

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A GRADE category A recommendation, as opposed to a category B recommendation, is more likely with higher evidence type, a larger difference between benefits and harms, higher values, and greater cost-effectiveness. For Option 2, evidence is type 2, serious adverse events are extremely rare, preventable outcomes have a high value, and cost per QALY saved is approximately \$197,000.

Proposed Recommendations

Trudy V. Murphy, MD
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Dr. Murphy pointed out that Option 1 has the 2 components that differ in strength of the recommendation for ages <60 and 60 years and older. For adults <60 years of age, the wording is:

- Hepatitis B vaccination *should* be administered to unvaccinated adults with diabetes who are <60 years.
- This is a GRADE category A recommendation.

For a adults 60 years and older, the wording is:

- Hepatitis B vaccination *may* be administered to unvaccinated among adults with diabetes who are ≥60 years.
- This is a GRADE category B recommendation, providing for individual clinical decision making

Dr. Murphy emphasized that the 50% higher odds of hepatitis B for the older age group was not statistically significant, although most of the outbreaks occurred in this age group. There were overlapping confidence intervals.

Noting that italics were added to illustrate wording that is in both Option 1 and Option 2, Dr. Murphy indicated that the accompanying “Remarks” for Option 1:

- *Continued efforts are needed to increase adherence to recommended infection control practice. Shared use of blood contaminated equipment increases the risk of exposure to bloodborne pathogens including hepatitis B virus, which is highly infectious.*
- 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 vaccination series should be completed as soon as feasible after diabetes is diagnosed.*
- In 2008, the median age of diabetes diagnosis was 52.9 years; two thirds of diabetes diagnoses were made before age 60 years.

- *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 who received a complete series of hepatitis B vaccine at any time in the past*
- Decisions to vaccinate adults with diabetes who are 60 years and older should incorporate consideration of the particular adult's likelihood of acquiring hepatitis B virus infection; the likelihood of experiencing chronic sequelae or other complications if infected; and the declining immunologic responses to vaccines that are associated with frailty.
- *Flexible schedules for hepatitis B vaccination (i.e., those with no maximum intervals between doses), along with reminder check-lists for providers, will allow for administration of hepatitis B vaccine during health-care visits scheduled for other purposes. These types of considerations are expected to minimize patient and provider burden, facilitating implementation of these recommendations in clinical and public health settings.*

The wording of the second proposed recommendation, Option 2, has one component:

- Hepatitis B vaccination *should* be administered to unvaccinated adults with diabetes.
- This is a GRADE category A recommendation.

Recall that the italics were added to illustrate wording that is in both Option 1 and Option 2. The following are the accompanying "Remarks" for Option 2:

- *Continued efforts are needed to increase adherence to recommended infection control practice. Shared use of blood contaminated equipment increases the risk of exposure to blood borne pathogens including hepatitis B virus, which is highly infectious.*
- 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.*
- Providers are encouraged to use clinical judgment to determine the suitability of hepatitis B vaccination for frail elderly adults with diabetes.
- *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*

- *Flexible schedules for hepatitis B vaccination (i.e., those with no maximum intervals between doses), along with reminder check-lists for providers, will allow for administration of hepatitis B vaccine during health-care visits scheduled for other purposes. These types of considerations are expected to minimize patient and provider burden, facilitating implementation of these recommendations in clinical and public health settings.*
- For adults in whom a reduced response to the initial series might be expected (e.g., adults 60 years and older, or who are obese), revaccination would be medically appropriate.
- If revaccination is planned when a protective level (antibody to hepatitis B surface antigen [anti-HBs]) of ≥ 10 mIU/mL is not achieved, testing for anti-HBs is recommended 1-2 months after completion of the initial hepatitis B series.
- In the footnote, ... additional guidance can be found in Appendix A of the current ACIP adult hepatitis B vaccination statement.

Regarding the working group rationale for each of the options, Dr. Murphy indicated that Option 1 was preferred by the majority of the working group members. Option 1 encourages infection control practice, recommends vaccination for ages < 60 years, addresses the ages with the best response to vaccination and the highest observed rate of hepatitis B infection, and has the potential to protect two-thirds of adults with new diagnosis of diabetes. For adults with diabetes ages 60 years and older, Option 1 presents no barrier to vaccination, but encourages individual clinical decision for vaccination. It does not mention revaccination, which is not cost-effective. Overall, Option 1 is more cost-effective at approximately \$75,000 per QALY saved.

Option 2 was the preferred recommendation by a minority of the working group members. Option 2 encourages infection control practice and targets most adults with diabetes. It is simple and consistent with other hepatitis B vaccine recommendations, which do not make age distinctions or require consideration of other criteria for vaccinating persons at risk of hepatitis B infection. Option 2 encourages individual clinical decision making for determining the appropriateness of vaccination for frail elderly adults. It suggests that post-vaccination serology would be appropriate only if revaccination of non-responders is planned; post-vaccination serology with revaccination of non-responders is not cost-effective. Option 2 is considerably less cost-effective at approximately \$197,000 per quality adjusted life year saved.

Discussion Points

Dr. Keitel requested an explanation regarding why the assumption of a 10% uptake of vaccine was made.

Dr. Murphy replied that this was an arbitrary decision. The uptake in the first two to three years of two other vaccines, Tdap and zoster, was used as a model to estimate hepatitis B vaccine uptake for at least the first year. Actually, 10% is quite high compared with the uptake of those two vaccines.

Regarding the NHANES data, Dr. Duchin was curious as to whether there was a hypothesis regarding why the incidence of hepatitis B was increasing among diabetics who did not have other risk factors, and whether all of it was attributed to blood glucose monitoring.

Dr. Murphy indicated that none of the data from NHANES or EIP sites collected that information. Obviously, that would be beneficial to know. She said she thought there were plans to add this information to the next surveillance cycle.

Ms. Rosenbaum indicated that she reviewed the Affordable Care Act and the Interim Final Regulations that implement the preventive benefits section of the act. The Interim Final Regulations, which now are in effect, make pretty clear that only ACIP's routine recommendations will be considered binding. With that in mind, she thought consideration should be given to the working of the proposed language depending upon ACIP's final decision. She found the ambiguity in the language to be difficult to understand. It appeared that in the case of unvaccinated adults with diabetes under the age of 60, ACIP would be recommending routine immunization for hepatitis B. In the case of adults with diabetes aged 60 years and over, there were suggesting that clinicians might want to vaccinate. If what was meant by the first bullet was "routine," then it should say "routine," because it is only when a recommendation states "routine" as opposed to "should" that ACIP's recommendations will translate to the CDC the type of recommendation on routine practice that CDC can then consider for final adoption.

Dr. Coyne-Beasley asked whether that meant the second option would be permissive and would not be covered.

Ms. Rosenbaum responded that not only would it not be covered, but under the express terms of the Interim Final Rule, HHS would not consider that ACIP had made the kind of recommendation that translates into the preventive benefit coverage level. There may be many times when ACIP does not, in fact, want to make that kind of recommendation. Her cautionary note was that if what they were saying was that routine practice ought to encompass certain kinds of things, they need to be very clear that this was what they were saying.

It appeared to Dr. Temte that there needed to be a discussion at some point in terms of the use of language in general in recommendations. He thought the Evidence-Based Working Group assessed this carefully and recommended words like "should" for routine or universal and words like "may" for Category B recommendations. It becomes very linguistic and lawyerly.

Ms. Rosenbaum quipped that it was no more technobabble than the GRADE analysis. It is just a different kind of technobabble, but is essential technobabble if they want to ensure that people are covered.

Dr. Temte thought they would all agree upon that aspect. The goal is to try to provide the best preventive services to as many people as possible.

Dr. Sawyer clarified that if they were going to change the language, he wanted to make sure that people understood the two options. Option 1 is that ACIP would recommend routinely immunizing adults under the age of 60, while Option 2 would be that ACIP would recommend routinely immunizing all adults with diabetes.

Dr. Campos-Outcalt thought it was more complicated. The age group of 60 to 65 would be uncovered, at age 65 Medicare kicks in, and the coverage for vaccines under Medicare is even more complicated because some people are covered under Part B, some are covered under Part D, and some are covered under both depending upon the indication for the vaccine. In order to avoid the issue, they could go to age 65 with recommended and over 65 for optional. That does not get into Affordable Care Act coverage.

Ms. Rosenbaum clarified that it was the under 65 years of age population about whom she was the most concerned about who would be affected by how recommendations were termed with regard to new coverage, and that it was not accurate that this did not get into Affordable Care Act coverage. The Secretary now has discretion under the Affordable Care Act to restructure preventive coverage, so if ACIP thought routine immunization beyond age 65 would be an appropriate recommendation to make, they could make that recommendation, which would then carry over into Medicare policy considerations. However, this clearly seemed to be a 65 years of age and under recommendation.

Dr. Vazquez inquired as to whether the proportion of non-responders was known and, if so, whether those data were specific for diabetics. She also wondered if it was known that revaccination solved the problem of non-responders and, if so, whether revaccination was included in the cost-effectiveness analysis.

Dr. Murphy indicated that many of the trials included subsets people with diabetes. For instance, there were 80 people with diabetes in a trial that involved 800 people. It is known in people without diabetes, primarily healthcare workers, that each additional dose increases the proportion of recipients who are protected. The recommendation for healthcare workers who do not respond to the first three doses is to give them one to three more doses, and there is no age distinction for adult healthcare workers who are being vaccinated over 60 years of age.

Dr. Schuchat recognized that the committee wanted to think carefully about insurance coverage and vaccine responsiveness, and emphasized that there is not a significantly higher risk of hepatitis B among diabetics who are over 60 years of age compared to other people over the age of 60 according to the data that have been reviewed. The significantly elevated risk is in the 60 years and under age group at about 2-fold.

Dr. Bennett requested that Dr. Schuchat comment on why this is thought to be the case. She could not imagine why this would be the case, except for a methodologic issue.

Dr. Schuchat replied that earlier data were reviewed in previous ACIP meetings that suggested a different level of risk in different sites, and some years with no elevated risk. It is unknown whether that is due to a methodologic issue, completeness of ascertainment of risk factors, or is not diabetes but something else for which diabetes is a marker.

Dr. Murphy added that the outbreaks in long-term care are pretty convincing that there is an increased risk, but in the EIP sites, the proportion of cases over 60 years of age was relatively small. There is speculation regarding whether there is a detection problem for older adults.

Dr. Marcy asked what percentage of people 60 years of age and older already have antibodies.

Dr. Murphy responded that because the numbers are so small in the NHANES data, she could not say, but overall in the age curve it is about 2% to 2.5% higher for anti-core antibodies across most age groups. Among persons with diabetes who are over the age of 65, the numbers start going down because there is an increase in mortality. Of those who survived longer, based on other data the percentage may differ. The people who survive to older age groups e.g., into their 90's have response proportions in the 35% range.

Dr. Bennett thought it was remarkable in the NHIS data that there was a significantly higher rate of vaccination in those without diabetes, and she was curious as to what might be the reason. While she did not recall how long hepatitis B had been a routine childhood vaccine, but the rates of vaccination remain very low. There is an epidemic of diabetes in this country and these younger age groups are going to age into the epidemic, and she was curious as they looked forward as to what that would mean.

Dr. Byrd responded that once they did an age stratification, there was not actually a huge difference between people with and without diabetes. The difference was observed between the 30 to 39 year old age group. That is likely because there was such a small number of persons with diabetes in that age group at less than 100 compared to about 3000 persons without diabetes. Therefore, there is little difference between persons with and without diabetes for hepatitis B vaccination coverage. The routine recommendation for hepatitis B was from 1991 and these data were from 2009, so these individuals would not fall under routine vaccination recommendations for children.

This discussion made Dr. Duchin wonder about obesity and the relative lack of responsiveness in obese persons to hepatitis B vaccination. He inquired as to whether the proportion of obese persons with diabetes was assessed in terms of being less likely to respond to the vaccine as they got older, which would provide a rationale for vaccinating at a younger age.

Dr. Murphy responded that they do not have obesity or body mass index (BMI) data from the EIP sites; however, they do have some data from the NHANES data which showed that the risk was increased for both low and high BMI for past hepatitis B infection. Regarding response to vaccine, there is a great deal of literature suggesting that if an appropriate sized needle is not used, there will be a lower response. There may be a somewhat lower response anyway, but certainly needle length is the most important factor. Many of the early trials did not specify needle length.

Dr. Elward (HICPAC) indicated that as a member of the working group, she favored Option 2, which was the minority opinion and wanted to make some comments about that as the most effective way to protect the population that brought this issue to light—the people who are in nursing homes. It is biologically plausible that people over age 60 with diabetes would have risk. They have a lot of contact with the healthcare system and clearly have a higher case fatality rate in these outbreak settings of 6% to 18% above baseline of 2% to 4%. Option 2 is simpler, there is less ambiguity for providers, and there is less ambiguity in terms of reimbursement. She thought it was also important to remember that if everyone over age 60 with diabetes was vaccinated, the proportion over age 60 would decrease over time. It is also to remember that cost-effectiveness is only one part of the consideration in terms of a decision to routinely recommend vaccination.

Dr. Fryhofer (ACP), a practicing general internist, indicated that she was speaking on behalf of the entire ACP Adult Immunization Technical Advisory Committee. She reminded everyone that the American College of Physicians is the nation's largest medical specialty society, representing over 132,000 doctors of internal medicine and medical students throughout the country who provide the majority of primary care for adults, including elderly patients. ACP strongly urged that ACIP should recommend routine hepatitis B vaccination for Americans of all ages who suffer from diabetes. Diabetes is the 7th leading cause of death in this country. It is now known that the risk of contracting hepatitis B is 1.5 to 2 times higher for diabetics, not to mention double the risk of death for diabetes who contract hepatitis B. Nearly one-third of patients over age 65 have diabetes. The average life expectancy for Americans is more than 78

years old. With the current trend of obesity, the number of diabetics is expected to rise even more. The rationale for hepatitis B vaccination for diabetics began with recognition of outbreaks of hepatitis B in settings of older patients. While vaccine efficacy decreases somewhat with age, not offering vaccine leads to 100% susceptibility, which is zero efficacy. On behalf of ACP, she requested that ACIP please ensure that all diabetics, including older diabetic patients, have the opportunity to stave off this illness and not to deny them access to this vaccine.

Ms. Rosenbaum noted that since January 2011, Medicare has covered hepatitis B vaccines at no cost share for individuals of medium to high risk. That group includes people with end stage renal disease, people with hemophilia, clients and staff at institutions for developmentally disabled people, people who live in the same household as a hepatitis B carrier, homosexual men, illicit drug users, healthcare professionals who have frequent contact with blood or other body fluids. What they were really talking about in the case of people 65 and older was a routine recommendation, and whether this group should be added as a group of people for whom there is a medium to high risk. If ACIP thought that there was a medium to high risk, the Secretary could adopt that recommendation if she so chooses as one of the medium to high risk groups.

Dr. Loehr (AAFP) pointed out that every decade there is a 4-fold increase in cost per QALYs, and he wondered whether any consideration was given to stopping at age 50 instead of 60 since the cost per QALYs jump dramatically at age 50.

Dr. Murphy responded that these data were very influential in leading the working group to come up with the two age categories.

Dr. Sawyer added that the working group did consider stopping at age 50, but the concern in doing so was that a large percentage of the diagnosed diabetics would be missed. This drops to 40% or less if the cutoff is made at age 50. Regarding Dr. Fryhofer's comment, there is a list considerations that would be included in a statement should ACIP adopt Option 1 to give clinicians some guidance about making a decision to vaccinate in adults over 60 years of age. This includes the likelihood of acquiring hepatitis B, which would translate into the kind of setting they are in, and whether they are receiving frequent assisted blood glucose monitoring. The working group was not proposing an all-or-none phenomenon, the insurance coverage aside. In terms of clinical decision-making, they were saying that the physician would use judgment about the risk of someone over age 60.

Dr. Temte indicated that Catherine Counard from the Skokie Health Department, and liaison for NACCHO to the Hepatitis B Working Group, had signed up for public comment.

Catherine Counard (NACCHO): Good afternoon. My name is Dr. Catherine Counard. I am a family physician and the Director of the Skokie Health Department in Illinois. I think I am representing all local health departments as I am speaking here. I have served for three years as the NACCHO liaison for the Hepatitis B Vaccine Working Group. I have no conflicts of interest. Four years ago, I worked on two outbreaks of hepatitis B virus in assisted living facilities among older adults with diabetes. The results of those investigations revealing that nursing staff spread the disease during routine finger stick blood glucose monitoring were published. I can assure you that these were not rogue facilities. It is very, very, very easy despite sound infection prevention policies for one healthcare professional having a distracted moment to spread hepatitis B during routine procedures such as assisted blood glucose monitoring. Because it is possible for adults with diabetes to become infected during routine encounters with the healthcare system or other locations, I urge ACIP to recommend protecting

all persons with diabetes against hepatitis B regardless of age. This is especially important for the residents of long-term care facilities where the potential risk of exposure through the use of shared equipment may be greater than for persons living in the community. It would seem inconsistent to me to exclude the very population that experienced outbreaks triggering this term of reference. I realize that vaccine efficacy declines with advancing age, but surely some immunity, echoing earlier comments, particularly in congregate living settings would seem better than none. I do want to thank you for considering this issue. It is really heartening for me to have this kind of a response by the federal government, ACIP, and CDC to a concern that originated at the local level. Thank you.

Dr. Temte requested that Dr. Murphy restate the findings for the risk over the age of 60.

Dr. Murphy responded that the confidence interval for ≥ 60 years was 0.79 to 2.68. In other words, it overlapped zero and, therefore, for the acute hepatitis B infection analysis, it would not be considered statistically significant. The adjusted odds ratio was approximately 1.5.

Dr. Temte indicated that the other point was that they were basically considering two separate recommendations. One would be an age- and risk-based recommendation, the risk being diabetes to the age of 60 for Option 1. For age of 60 and older, there would be a permissive recommendation that would take into account things like placement in an assisted living center. He did not perceive this as denying a recommendation for people at increased risk. Based on the data presented, simply being over the age of 60 did not connote an increased risk; whereas, some of the factors mentioned do result in increased risk.

Ms. Rosenbaum offered a friendly amendment. Given the fact that they were “comparing apples and oranges” in that ACIP talks one way and other programs talk other ways, consideration might be given to the way Medicare frames the issues. Perhaps ACIP could make a recommendation that, in the case of Medicare beneficiaries who may be 60, the Secretary consider recognizing certain factors as creating medium to high risk. What that would do, given the language of Medicare, is make it possible for a clinician to administer the vaccine to individuals falling into the medium to high risk category. The challenge was that ACIP was making scientific recommendations, but those recommendations were supposed to have meaning in other contexts. With the Medicare context, they could consider a bridging recommendation that would translate what ACIP was saying into the language of that program so that HHS could consider taking action.

Dr. Brady (AAP) noted that earlier in the morning they were discussion the cost per QALY for the HPV vaccine. Regarding hepatitis B, it was pretty clear from the evidence that certain infection control issues seemed to be responsible for the increased risk in diabetics—not just being diabetic. To age 50, it appeared that everyone should be vaccinated. However, at age 50 the cost per QALY dramatically increases and perhaps that is the age at which individuals at higher risk should be identified in order to be more prudent with funding. Clearly, someone who never shares devices is not going to be at the same risk as someone in an assisted living facility.

Dr. Keyserling (SHEA) pointed out that if it was established that admission to an assisted living or nursing care facility would trigger the need for being immunized, the first immunization is not going to provide protection. Therefore, it would be difficult to anticipate 6 months prior to the need for someone to be institutionalized that that would be the time to start the immunization series.

Dr. Sawyer indicated that the working group discussed all of these options, and one issue they struggled with was declining immunity after about age 60. However, that is the age at which people start to become institutionalized. The logic of the working group was that it made the most sense to maximize immunization in the younger age group, which is how they selected 60 as a compromise of cost-effectiveness, percentage of diabetics diagnosed already by that age, and efficacy of vaccine.

Dr. Marcy asked whether he understood that what Ms. Rosenbaum was saying was that if ACIP made the introductory sentence to either Option 1 or 2 that the ACIP considers diabetes a high risk condition, that would fulfill the requirements to which she was referring.

Ms. Rosenbaum replied that as she understood the Medicare coverage rules, the vaccine is covered for beneficiaries who have medium to high risk. In terms of the issue of age cutoff, the group that probably most benefit from this recommendation among Medicare beneficiaries are Medicare beneficiaries with disabilities who are under 60 years of age and living in assisted living and other facilities, such as group homes. Already the Secretary has opened the door on this issue by recognizing institutional status for people with disabilities. Given the fact that Medicare beneficiaries are over and under 65 years of age, and because the standards for Medicare already recognize health burdens as creating medium to high risks, ACIP should be responsive in its recommendations to the extent that there is evidence that supports this. This means that the medium to high risk group would be expanded under ACIP's recommendation to include individuals with diabetes, and they could consider whether to go on to state something about living situations. She thought it would be appropriate to specify this in the recommendation.

Dr. Temte called on CMS to respond.

Dr. Hance (CMS) responded that she had nothing to add, and that Ms. Rosenbaum was correct that those with pre-existing conditions are eligible to receive the vaccine under the Medicare program.

Dr. Pickering pointed out that ACIP had never before tried to craft recommendations such that they fit Medicare. He asked Dr. Schuchat whether that was reasonable to do, given that ACIP basically makes recommendations based on science and cost-effectiveness and have never really wandered into this area.

Dr. Schuchat replied that it is important to remember the charter for ACIP and the formal review of evidence. During this meeting they began reviewing evidence based on the GRADE system. There are multiple ways that Medicare covers vaccines, some that predated the Affordable Care Act. There are vaccination recommendations in Medicare Part D, not in Medicare Part B. For example, zoster vaccine for everyone 60 years of age and older has a different situation. Therefore, she did not think it was advisable or within the ACIP charter for the deliberations to focus on what Medicare will do. There are the formal issues of burden of disease, effectiveness, immune response, safety, cost-effectiveness, programmatic issues, feasibility, and values and preferences that ACIP members as individuals have. Unless guided otherwise, that is the focus ACIP should take.

In terms of the discussion of diabetes being the risk factor, Dr. Brewer (ANA) recalled that Dr. Murphy had reported in her first presentation that diabetes is a "marker" for increased risk of hepatitis B infection, not a "risk factor." She wondered if that would pose a contradiction if the committee moved forward with indicating that diabetes being a risk factor in the ACIP statement.

Dr. Murphy responded that she did not know whether it would be helpful to keep that information in the statement. The risk is thought of as being more analogous to the healthcare worker in terms of the occupational, medical, or dental exposure.

Ms. Rosenbaum said that, in fact, ACIP makes recommendations about insurance coverage all of the time in terms of the VFC votes. By law, ACIP's recommendations now become binding on insurance. She has raised questions herself about whether the ACIP charter needs to be fundamentally reexamined. Given the altered nature of the role of this committee in light of health reform, it would not be unusual for ACIP to speak about insurance coverage because they do this all of the time with the VFC. The Medicare situation is a somewhat unusual one because Medicare itself has endeavored to identify medium to high risk situations on its own. Therefore, she did not think this was an unwise extension of ACIP's authority to add its scientific voice if they thought that it would be good policy to give clinician's the discretion to immunize in the case of older people who have diabetes and maybe be in institutions or have other risk factors. Medicare rules invite ACIP to explain to CMS how this committee thinks its science knowledge should translate into Medicare coverage policy.

Dr. Pickering indicated that ACIP was mandated in its charter for the VFC resolution votes, but not for Medicare.

Ms. Rosenbaum emphasized that whatever the charter says must be reconsidered in light of the Affordable Care Act. The charter does not supersede the Affordable Care Act. Whether the charter needs to be updated is an important question. This is an example in which CMS has essentially laid out a policy, and she thought it was certainly within ACIP's charter to explain how the science might relate to Medicare policy.

Dr. Keitel reminded everyone that there is no observed significant increase risk of hepatitis B in diabetics who are over the age of 60 years.

Dr. Murphy clarified that this was according to the EIP surveillance site data. However, 24 out of 28 outbreaks were in older adults.

Dr. Keitel stressed that this is the dataset with which they are dealing. In addition, the estimated QALY cost is \$2.5 million. ACIP just voted not to recommend routine vaccination of males with HPV vaccine when the estimated QALYs were \$400,000 for known outcomes and considerably lower for outcomes that they expect as clinicians and scientists to occur (e.g., prevention of oropharyngeal and other cancers). She hopes they would reach some consistency in how the committee is making decisions from vaccine to vaccine as well. They made a decision about HPV not being worth the price, but now they were looking at \$2.5 million without solid evidence. She suggested including language to identify the risk factors for those over the age of 60 who were infected, because they are a small subset.

Dr. Campos-Outcalt noted that they kept returning to the institutional outbreaks and using those as evidence for an overlay of diabetics. Essentially what they were talking about was a case series—a series of cases in institutional outbreaks. He wondered whether an analysis was done of these to determine whether it was the diabetes, the age, or the institution that raised the risk for those individuals. The study showing that risk of hepatitis B in people with diabetes is not elevated with age made him wonder whether the infection risk was due to being in the institution rather than the age being above 60.

Dr. Murphy responded that she did not think it was the age. In the outbreaks, the investigation showed that it was the association of diabetes and assisted glucose monitoring and the various procedures associated with that. In the NHANES data, there was also an increase in the older age groups, but it was not statistically significant because the numbers were too small.

[Correction (10/31/2011): The increase in *unadjusted* seroprevalence of anti-HBc (past or present hepatitis B infection) for adults with diabetes ≥ 60 years was 30% ($P=0.032$).

Dr. Sawyer attempted to summarize the discussion, which played out the discussion that the working group had had for two years. It is clear that the initial problem was with outbreaks in skilled nursing. It seemed to the working group that, given the vaccine responsiveness with age, the cost-effectiveness data, and the EIP data on clearly documented risks that the best compromise was to try to get diabetics immunized when they are younger before they enter assisted living facilities when they will still respond to the vaccine at a reasonable cost-benefit analysis, and to leave discretion for physicians with their older patients to take into account all of the other potential issues, such as living in a skilled assisted living facility (not the potential that someone will live in one, but that they actually are living in one), or that someone is getting their blood glucose checked every week at church, et cetera and to use that as a factor to make an individual decision in the older age group. This is the rationale for the majority opinion of the working group. To be fair, there was a significant minority who felt that all diabetics should be immunized. It is certainly true that the cost-benefit analysis has been the major issue weighing on those falling within the majority opinion.

Ms. Ehresmann motioned to accept Option 1 and Dr. Campos-Outcalt seconded the motion, following which the discussion continued.

Ms. Rosenbaum recommended amending the language of Option 1 to state “should be routinely administered to unvaccinated adults with diabetes who are under the age of 60.” The second bullet should be amended to read, “should, at the discretion of the treating clinician, be administered to adults with diabetes who are 60 years of age and older.”

Dr. Bennett said she was struggling about the older age group who would also be exposed to these devices and, therefore, potentially infected. Their protection would not be covered with this recommendation. She wondered if it would be possible to add a statement about heightened risk from exposure to devices to the second part of Option 1.

Dr. Duchin thought that would be reasonable, but it seemed to be devices in specific settings versus devices per se. Regarding the tweaking of the language to respond to Ms. Rosenbaum’s interpretation of what will lead to coverage, he wondered whether this was a “slippery slope” because legislation may change, the Secretary’s opinion may change, and what the Secretary considers to be acceptable language may change. Therefore, he wondered whether ACIP should try to be consistent in helping people with their interpretation of ACIP’s recommendations rather than trying to change recommendations to meet whatever language is being used at the time by the administration of the moment.

Ms. Rosenbaum clarified that she was trying to point out that when ACIP uses the word “should,” it means routine use. Because the regulations that are now binding law use the word “routine,” if what ACIP means is routine, they should use the word that is used in the regulation. Someday the regulation may change and ACIP will have to change along with it, but the concept of routine use is as conservative a concept as they could use because it leaves out the permissive. Assuming that routine preventive services continue to be covered, she thought ACIP would want to make sure that its evidence-based recommendations use the terminology

that is in formal use as much as possible. Otherwise, they risk not recommending coverage when actually it is what they mean.

Dr. Campos-Outcalt wondered whether the GRADE methodology that states that an A recommendation is for routine use, and the fact that ACIP has said this is an A recommendation, would take care of that without having to include the word “routine” in the language.

Ms. Rosenbaum replied that it would not from a legal standpoint.

Regarding Dr. Bennett’s comment, Dr. Sawyer clarified that the intent of the actual statement would be to outline the exposure risk factors to settings and / or equipment that puts people at risk, and that would then be one of the factors that a physician considers in the over 60 years of age group to make a decision to immunize.

Dr. Bennett pointed out that there is no recommendation attached to that. It is a consideration and it is permissive, so it does not ensure that those vaccines will be covered.

Dr. Temte wondered for the sake of time whether consideration would be given to wordsmithing and bringing this recommendation back in the morning. This would require the willingness of Ms. Ehresmann to withdraw the motion.

Ms. Ehresmann requested clarification about what the wordsmithing would include.

Dr. Temte thought what was needed was consideration of comments made by Ms. Rosenbaum in terms of whether a Category A recommendation stating that the vaccine should be given would need additional language regarding routine use, and the addition of text in the remarks section that would address some of the high risk considerations that clinicians would use to recommend this vaccine for individuals over the age of 60, such as use of monitoring devices, those within assisted living situations, and so on.

Dr. Campos-Outcalt thought they should take a vote first and then wordsmith. If this did not pass, the wordsmithing would not matter. They had not actually determined whether more people favored Option 1 than Option 2.

Dr. Temte reminded everyone that there was an active motion still on the floor.

Ms. Ehresmann agreed that they should vote and go from there.

Dr. Loehr inquired as to whether Category A and B were identified someplace.

Dr. Temte responded that it was identified that the first part of Option 1 was a Category A, Evidence Level 2 and the second part was a Category B, Evidence Level 2.

Dr. Pickering pointed out that unless Ms. Ehresmann and Dr. Campos-Outcalt agreed to any changes, the vote would be on the recommendations as shown on the screen.

Vote: Hepatitis B Vaccine in Adults with Diabetes

Ms. Ehresmann made a motion to accept Option 1, with the recommended wordsmithing to be completed following the vote. Dr. Campos-Outcalt seconded the motion. **The motion passed by a majority vote.** The disposition of the vote was as follows:

12 in Favor:	Bennett, Bocchini, Campos-Outcalt, Duchin, Ehresmann, Keitel, Marcy, Meissner, Rosenbaum, Sawyer, Temte, Vazquez
2 Opposed:	Coyne-Beasley, Jenkins
0 Abstained:	N/A

Dr. Meissner inquired as to whether there was or was not an option for changing the wording, and how much flexibility there would be to change the wording.

Dr. Pickering responded that there is flexibility. If someone brought a motion back to the committee the next day and it was seconded, it could be voted on.

Ms. Ehresmann thought that the additional language would address the issue of GRADE, routine, et cetera and would merely be to clean up the language to ensure that it was congruous with the meaning of the GRADE. She requested clarification with regard to whether there would need to be a new vote.

Dr. Pickering suggested that Ms. Ehresmann, Dr. Campos-Outcalt, Ms. Rosenbaum, Dr. Sawyer meet with Dr. Murphy to determine whether the motion as made would be adequate. Minor word changes could be made, but changes that would significantly impact the recommendation would have to be presented to the full committee.

Dr. Keitel suggested striving toward standardization of language when recommending a vaccine by saying “routine immunization with X, Y, or Z is recommended for . . .”

Dr. Temte noted that the Evidence-Based Working Group did find evidence of multiple renditions of the same thing and use of language all over the place. There is a hope to strive for much more narrow use of language so that it is clear to the recipient of the recommendation.

Dr. Paradiso (Pfizer) noted that as far as he could tell, people in the field know that when ACIP states that vaccine “should” be given, then they should be given. It is considered to be routine. Those who reimburse do so if ACIP says a vaccine “should” be given. He did not believe there was much confusion in the field.

Dr. Sawyer thought that in the final iteration of this recommendation, they would still be able to convey all of these thoughts without changing the actual language. Unless there was a strong opinion otherwise, he thought the vote was pretty strong in favor of Option 1. He said he would like to see the language that surrounds the Option 1 recommendation, as well as the background material that would convey the concerns of the group.

Dr. Jenkins noted that the strategy they were considering at one point regarded making a recommendation to the Secretary around modification of language that already existed in Medicare. She wondered whether that was an acceptable option.

Dr. Pickering thought this was something they should discuss with the CDC policy experts, and moved forward through that mechanism rather than making decisions about this or discussing it further within ACIP. He said they would acquire more information, and would come back to the ACIP membership with more data.

Dr. Schuchat reminded everyone that ACIP deliberates, votes, and makes recommendations to CDC. CDC issues recommendations. There is a period of wording and drafting that the agency engages in, which they always have the option to do, to issue final recommendations through the *MMWR*. There is separately a considerable amount of discussion about the interpretation of the Affordable Care Act. She thought the process was fairly clear with regard to what ACIP wanted as a Category A routine recommendation and a Category B recommendation related to specific circumstances. She felt that this was plenty for CDC to work from.

Meningococcal Vaccines

Introduction

Amanda Cohn, MD
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National Center for Immunization and Respiratory Diseases
Advisory Committee on Immunization Practices

In an effort to consolidate presentations, Dr. Cohn presented the introduction to the meningococcal vaccines session on behalf of Dr. Cody Meissner, the Meningococcal Working Group Chair. She acknowledged the incredible commitment of the working group members, many of whom have participated in this group for well over 5 years and continue to impress her with their thoughtful approach to complex questions.

The working group has been considering infant meningococcal vaccines for over three years, since before these vaccines were under FDA review. On monthly conference calls and in person meetings around ACIP meetings, the working group has reviewed published and unpublished data on the epidemiology and burden of disease; presentations from the pharmaceutical companies on the immunogenicity and safety of these vaccines; duration of protection; programmatic considerations; public and provider perspectives, including meningococcal public engagement; and cost-effectiveness analyses. The working group focused on a primary question: Should meningococcal vaccines be routinely recommended for the 4 million infants born each year? During this session, vaccination strategies were not compared. When necessary to differentiate, “infant vaccination” was used to describe the 4 dose series starting at 2 months, and “toddler vaccination” was used to describe the 2 dose series starting at 9 months.

Dr. Cohn noted that there were a couple of important things to consider while listening to the rest of this session. Meningococcal disease trends cannot be predicted. In prior meetings, information about the epidemiology was presented based on an average incidence over a large time period, to account for the peaks and troughs. During this meeting, a “high” incidence period was added to better understand the burden of disease at the time these vaccines began development, and to compare to the burden of disease in the more recent “low years.” In addition, circulating antibody levels are predictive of protection against meningococcal disease. Pre-licensure effectiveness studies are not feasible, and the adolescent post-licensure effectiveness results correlate well with the proportion of persons with circulating antibody at

different times since vaccination. For meningococcal vaccines licensed and under consideration in children age <2 years, there is no comparison group for the immunogenicity portion of the clinical trials because at that time there were no licensed products for this age group.

This session focused on whether there should be a routine infant recommendation, and no vote was taken. In the interest of time, Novartis and GSK, who were originally scheduled to present during this session, allowed Dr. Cohn to present the highlights of their immunogenicity and safety data. She thanked both companies for being so flexible, and reminded the ACIP members that the company data were presented more completely in their background documents. Also reviewed during this session were the epidemiology of meningococcal disease in infants, a cost-effectiveness analysis, and a summary of working group considerations. In February 2012, a vote is anticipated on routine infant vaccination. GRADE evidence tables, language options, guidance for use, and discussion of high-risk recommendations will be presented at that time.

There are three vaccines licensed or under development for infants and toddlers. MenACWY conjugated to diphtheria toxoid, or Menactra®, is licensed in 2-55 years as a single dose, and was licensed as a 2-dose series for ages 9-23 months in April 2011. MenACWY conjugated to CRM 197, or Menveo®, is licensed in 2-55 year olds as a single dose. A 4-dose infant series at 2, 4, 6, and 12-16 months) is under FDA review. HibMenCY conjugated to tetanus toxoid, or MenHibrix®, is combined with Hib as a 4-dose series given at 2, 4, 6, and 12-15 months, and is also under FDA review.

Data were presented on MenACWY-D at the June 2011 ACIP meeting. Immune response was demonstrated after the second dose, and was modestly immunogenic for serogroups A and C after dose 1. Most subjects did not have protective antibody levels 3 years after the second dose, but there was a strong response to a booster dose given 3 years after the 2 dose primary series.

Novartis submitted a supplemental license application for MenACWY-CRM use in infants against serogroups A, C, W, and Y as a 4-dose series. The goal of this vaccine is to provide early and broad serogroup protection that fits with the current vaccination schedule. The application also included supportive data for an alternative schedule: a 2-dose series given at 7-9 months and 12 months of age. No safety signals were identified during phase III clinical trials. Of the subjects, 96% to 97% of subjects achieved hSBA titers equal to or greater than 1 to 8 against serogroups C and Y after dose 3, and 98% to 100% after dose 4. There was similar immunogenicity of all concomitant vaccine antigens when administered with MenACWY-CRM. It met all non-inferiority criteria for co-administration with PCV7 after dose 4, and all except serotype 6B after dose 3. In a phase 2 study conducted in the UK and Canada, immunogenicity was evaluated 1 month after dose 2 was administered at 4 months of age. Of the subjects, 83% to 90% and 69% to 86% had hSBA titer equal to or greater than 1 to 8 for serogroups C and Y, respectively. Additional data are anticipated. The 3- and 5-year antibody persistence data after a 4-dose series are being evaluated, and the 3-year time point should be available in early 2012.

HibMenCY-TT is a combination vaccine consisting of meningococcal serogroups C and Y, and Hib components. GSK has submitted an application for licensure of this vaccine as a 4-dose series. The vaccine was developed according to the Hib immunization schedule without additional shots. The safety profile is comparable with US licensed Hib vaccines. After 3 doses, at least 96% of subjects achieved hSBA titers equal to or greater than 1 to 8 against

serogroups C and Y. This rises to 99% after the 4-dose series, with a 12-fold titer increase. The immunogenicity of the Hib component is non-inferior US licensed Hib vaccines post-dose 3 and post-dose 4. No immune interference was observed with routine pediatric vaccines, including Prevnar®. One month after dose 2, 94% and 83% of subjects achieved hSBA titers of equal to or greater than 1 to 8, respectively. Three years after dose 4, 81% and 67% of subjects had hSBA titers equal to or greater than 1 to 8 for MenC and MenY, respectively.

In summary, MenACWY and HibMenCY-TT are safe and highly immunogenic in subjects after completing the 4-dose series. For both vaccines, a high proportion are protected after dose 2, and more than 95% of subjects are protected after dose 3, although there is evidence of waning protection in the 6 months between doses 3 and 4. There was no significant interference when co-administered with PCV7. Antibody persistence at 3 years after HibMenCY-TT is reassuring, but there is evidence of waning immunity. The 3-year persistence data for MenACWY-CRM are expected in the next several months.

Epidemiology of Meningococcal Disease in Infants

Jessica MacNeil, MPH

Advisory Committee on Immunization Practices

Ms. MacNeil presented an overview of the epidemiology and burden of meningococcal disease in infants and young children, focusing on the current epidemiology and overall trends in incidence among all age groups, cases of meningococcal disease, and the morbidity and mortality observed in infants and young children.

Historically, meningococcal disease has been cyclical, with peaks in disease incidence every 8-10 years. Rates of disease have cycled around 1 case/100,000 population, but have been declining for the last 10-15 years, and we have remained at a nadir of disease incidence for the last 5-6 years. The reasons for this sustained low in disease incidence are unknown, but there is no indication, even looking at preliminary 2010 and 2011 data, that rates are increasing [1970-1996 NNDSS data, 1997-2009 ABCs data estimated to U.S. population].

There are two sources of surveillance data that provide information on meningococcal disease incidence. The first is the Active Bacterial Core surveillance system (ABCs). ABCs is an active laboratory and population-based surveillance system that collects data on culture confirmed cases of meningococcal disease in 10 states. Cases in the ABCs sites can be projected to the US population to estimate incidence. The second is the National Notifiable Diseases Surveillance System (NNDSS) is a passive surveillance system that all states and territories report data to for all nationally notifiable diseases. NNDSS captures information on all cases, including cases confirmed by PCR and those with clinically compatible illness; however, serogroup information is limited.

ABCs typically underestimates cases compared to NNDSS, mainly because it does not capture non-culture confirmed cases. In recent years, there has been a 15% to 20% difference between cases from ABCs and NNDSS, which means that when using ABCs to estimate the US meningococcal disease burden, cases are potentially being underestimated by 15% to 20%. To account for this potential underestimate, a correction factor of 18% were applied to all data presented [NNDSS includes all case statuses (confirmed, probable, suspect, unknown)].

Showing a base case of average annual incidence from 1993 through 2009 compared to the incidence from 1997 through 1999 (the highest incidence years during this timeframe) and the incidence for 2007 through 2009 (the lowest incidence years), Ms. MacNeil indicated that most of the analyses presented would use the 1993 through 2009 time frame and the high and low incidence years would be used to provide perspective of the impact of incidence on key data [Average annual incidence of serogroup C, Y, and W135 meningococcal disease; 1993-2009 ABCs data estimated to U.S. population with 18% correction for under reporting; 1993-2005 for adolescents 11-22 years].

Rates of disease have declined for all serogroups, including serogroup B, which is not included in currently licensed meningococcal vaccines [ABCs cases from 1993-2009 estimated to the U.S. population with 18% correction for under reporting]. In 2008 and 2009, the first evidence of an impact of the adolescent vaccination program on disease incidence in the US was observed. Regarding the incidence of serogroup C, Y, and W135 meningococcal disease among less than 1 year olds, 11-19 year olds, and persons over 20 years of age, in 2008 and 2009 incidence among 11-19 year olds decreased by approximately 50%. The same declines were not observed in the other age groups. In 2008 and 2009, coverage with meningococcal conjugate vaccine in 13-17 year olds was 40% to 50%. While the adolescent vaccination program is impacting rates of disease in the adolescent age group, it is not believed that vaccine coverage is high enough or the data support any evidence of herd immunity impacting rates of disease in other age groups [Incidence of serogroup C, Y, W135 meningococcal disease; ABCs cases from 2004-2009 and estimated to the U.S. population; does not include 18% correction for under reporting]. Looking more broadly at meningococcal disease incidence across the entire timeframe, incidence has declined in all age groups, not just among adolescents [ABCs cases from 1993-2009 estimated to the U.S. population with 18% correction for under reporting].

To summarize the current trends in meningococcal disease, rates of meningococcal disease are at historic lows, and declines have been observed in all serogroups and among all age groups.

In terms of incidence of meningococcal disease by 5-year age intervals, there are three peaks in disease incidence: one in infants, a second in adolescents, and a third in older adults. The incidence in children less than 5 years of age is higher than rates of disease seen in later peaks during adolescence, and in older adults [ABCs cases from 1993-2009 and projected to the U.S. population with 18% correction for under reporting]. With respect to incidence by age and serogroup, in children less than 5 years of age, a large proportion of disease is caused by serogroup B compared to serogroups C, Y, and W135 combined. The proportion of disease that caused by serogroups C, Y, and W135 increases with increasing age. Although W135 is included here, very little disease is caused by serogroup W135, especially in the younger age groups [ABCs cases from 1993-2009 and projected to the U.S. population with 18% correction for under reporting].

If the incidence of disease in children less than 5 years of age is broken down further, the greatest incidence in this youngest age group is among children less than 1 year of age. Of the disease in this group, 50% to 60% is caused by serogroup B. This remains true throughout the first 5 years of life. Regarding the estimated annual number of cases caused by each of the three major serogroups for children less than 5 years of age, 50% of disease in this age group occurs in children 0-8 months. In 0-8 month olds serogroup Y is more common than serogroup C; whereas, serogroup C is more prevalent in children over 1 year of age. With regard to estimated annual cases and incidence from serogroups C and Y meningococcal disease in children less than 5 years during the three incidence time frames, an average number of 222

cases are estimated to occur each year on average in terms of the base case scenario. This compares to 475 cases during the high incidence years and 77 cases during the current low incidence years [Average annual cases and incidence of serogroup C and Y meningococcal disease; 1993-2005 for adolescents 11-17 years; 1993-2009 ABCs data estimated to U.S. population with 18% correction for under reporting].

To summarize, the largest burden of disease in infants and young children is in infants less than 6 months of age and a high proportion of infant cases are caused by serogroup B. In low incidence years, the absolute number of serogroup C and Y cases in infants and young children is low.

Measuring the severity of disease and long-term outcomes is challenging. Data were combined that are available from the surveillance systems, along with data that have been collected from reports published in the literature to estimate the severity of meningococcal disease in infants and young children. Based on this, Dr. MacNeil presented data on hospitalization, mortality, and long-term sequelae.

Overall, 86% of meningococcal cases in children less than 5 years were hospitalized. The median length of hospitalization was 7 days, and the length of hospitalization did not vary by month of age for children less than 1 year, or by serogroup or syndrome. The overall case-fatality ratio in children less than 5 years is 6%; however, the case-fatality ratio for serogroup C is higher [Limited to hospitalized patients; 1993-2009 ABCs data].

Data from a multicenter study of pediatric meningococcal disease in the US during 2001-2005 shows the frequency of sequelae that were recognized at hospitalization in 146 surviving children. Two children had amputations, one lost all 4 limbs, and one had toe losses. Skin necrosis occurred in 14 children with invasive infections. Of these children, 9 were 4 years of age or less. Unilateral and bilateral hearing loss occurred in 14 patients with meningitis. All were 10 years of age or less, and 8 were 2 years of age or less [Kaplan et al., *Pediatrics* 2006, 118(4):e979-84].

Long-term neurological sequelae are difficult to measure and many of these conditions are subtle, including deficits such as impaired school performance, behavioral problems, and migraines. Published data limited to all-cause bacterial meningitis and estimates of neurologic deficits in long-term survivors range from 20% to 50%. However, many of the minor neurologic deficits do resolve over time [Bedford et al., *BMJ* 2001, 323: 533-7; Chandran et al., *PIDJ* 2011, 30:3-6].

With regard to annual cases, deaths, and serious sequelae due to serogroups C and Y during the three incidence time frames in children less than 5 years of age, looking at the base case scenario, there were on average 11-22 deaths and 22-33 survivors with serious sequelae each year¹. This compares to 24-48 deaths² and 48-71 survivors with serious sequelae³ during the high incidence years and 4-8 deaths and 8-12 survivors with serious sequelae during the current low incidence years [¹1993-2005 for adolescents 11-17 years; ²5-10% case-fatality ratio; ³10-15% of survivors with serious sequelae 1993-2009 ABCs data estimated to U.S. population with 18% correction for under reporting].

To summarize the morbidity and mortality from meningococcal disease, although morbidity and mortality from meningococcal is high and each of these individual cases is terrible, 75% to 80% of children less than 5 years of age with meningococcal disease survive and recover from their illness. Fortunately, major complications are less frequent in infants than adolescents and the case-fatality ratio is lower compared to older age groups.

The amount of meningococcal disease that could potentially be prevented with infant vaccination is low at this time. The reasons for this are multifactorial, and include that there is currently a stable low in disease incidence in the US. A low proportion of infant disease is caused by serogroups C and Y, and a large proportion of disease occurs in the first 6-8 months of life. Additionally, morbidity and mortality in infants is lower than in other age groups. The epidemiology of meningococcal disease is highly dynamic and will need to be monitored frequently for changes in disease patterns in infants and young children.

Cost-Effectiveness Considerations for Meningococcal Vaccines in Infants

Ismael Ortega-Sanchez, PhD

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Dr. Ortega-Sanchez discussed the cost-effectiveness of meningococcal vaccination in the US for infants and toddlers, presenting an update to the analysis presented to ACIP in early 2010 and in 2005. This presentation followed the ACIP guidance for health economics studies. For this presentation, the effectiveness and cost-effectiveness of a meningococcal vaccination program in infants and toddlers in the US was assessed under the changing epidemiology. This comparison was done under marked reductions in the incidence of meningococcal disease, and uncertainty of duration of efficacy. In this analysis, the societal perspective was used.

For this purpose, the investigators referred to the previously constructed model to compare the three strategies, one without vaccination and two with vaccination. To calculate the number of cases, number of deaths, and number of survivors with sequelae, the model includes disease infection and the specific outcomes. It also includes adverse events after vaccination. To deal with key uncertainties, the decision tree model is also designed with Monte Carlo simulation. Simulations include the most likely or base case estimates for health benefits and costs, and also the ranges around these estimates. For this, the investigators used a hypothetical birth cohort with a population of 4 million. This cohort was followed over a 10-year period. The benefits of vaccination were calculated over an age-specific life expectancy, and a 3% discount rate was used to calculate costs and benefits.

Once the core model was set, it was filled with inputs based on the best data and assumptions. This included data on the epidemiology of the disease, vaccine characteristics, HCRU and cost data, indirect cost data, quality of life data, and other parameters. Epidemiological data included age-, year-, and C+Y+W135 serogroup-specific incidence rates; age- and serogroup-specific case fatality ratios; and the proportion of survivors with sequelae by condition.

Marked changes were observed in disease incidence for vaccine serogroups for all age groups as reported by ABCs data. In particular, the high (1997-1999) and low incidence rates (2007-2009) were compared in children less than one year of age, and a large reduction of one-fifth what it used to be during disease peak from 1997-1998 was found. To keep the data consistent with the model, a wider time range of incidence data was used from ABCs from 1993 to 2009 in most age groups, except for adolescents 11-22 years for which the data are only from 1993 to

2005 to avoid any potential interference from the vaccination program in the analysis. Likewise, adjustment was made to a range of case fatality ratios to equal survivability in age-specific mortality. Note that the high variability in the 2007-2009 case fatality ratios across all age groups may be due to the small number of deaths in those years.

In terms of vaccination strategy and effectiveness, a 2-dose strategies was used for toddlers at 9 to 15 months of age and a 4-dose strategy was used for infants at 2, 4, and 6 months of age with a booster dose at 15 months. Since vaccination begins partway through Year 1, month- and age-specific incidence data were used. For the toddler 2-dose strategy, it was assumed that the first dose effectiveness was 45% and second dose effectiveness was 98%. For the infant the first dose effectiveness was zero, the second dose was 84%, the third dose was 95%, and the fourth dose was 93%. Waning vaccine efficacy was also assessed for each strategy, which is the core of the assumptions.

The incidence data on duration of persistence and immunogenicity from HibMenCY (Menactra®) were included in the model. Vaccine efficacy continued to decline over the 10-year period after vaccination. The number of potential preventable cases and the reduction in efficacy for the 4-dose infant vaccine were also assessed to help to understand what could be prevented with vaccine. Likewise, based on the data from Menactra®, the model assumes a much faster decline in vaccine efficacy duration for the 2-dose toddler strategy. For both situations, confidence intervals are given for some variability. The rates of vaccine coverage for infants and toddlers were based on the national data collected on vaccines currently and routinely administered to infants and toddlers, specifically on 2010 Immunization Coverage in the US from CDC that uses dose-specific coverage.

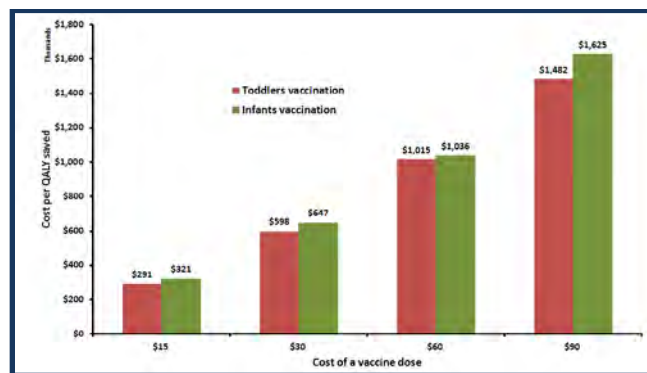
Since each strategy uses a different vaccine, calculations for vaccine costs were differentiated in some form. For infants, only the cost of the MenCY component was used out of the Hib-MenCY. The cost of the MenCY component used per dose ranged from \$15 to \$90 plus the cost of moderate and severe adverse events, and the cost of vaccine administration at approximately \$15 per dose. For toddlers, the cost per dose for MCV4 was used at a range of \$15 to \$90, plus the cost of moderate and severe adverse events and the cost of vaccine administration at approximately \$15 per dose. Adverse event rates were taken from the UK experience with MCC [Trotter et al., *BMJ* 2002; Ortega-Sanchez et al., *CID* 2008].

Other benchmark elements included the proportion of survivor cases with sequelae by type of condition; meningococcal disease incidence under vaccination; direct and indirect costs of meningococcal disease (e.g., acute phase costs and long-term costs; productivity loss to deaths and sequelae); health related quality-of-life scores for estimating QALYs lost to sequelae; and cost-effectiveness ratios [Shepard et al., *Pediatrics* 2005; Ortega-Sanchez, et al., *CID* 2008].

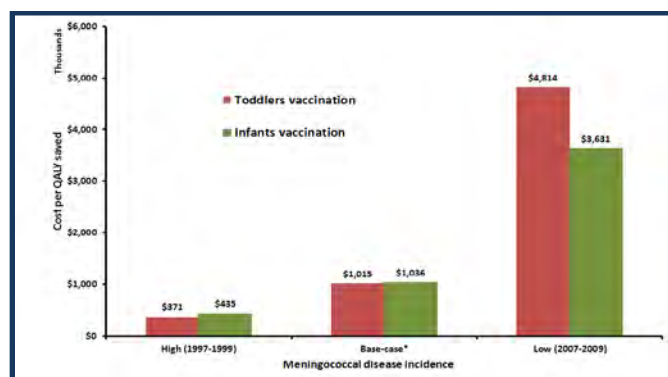
The results of the Monte Carlos simulation are reported mostly for the mean values and the 5th and 95% percentiles. First, the baseline was estimated for serogroups C, Y, and W135. Following the cohort over a 10-year period, there were expected to be 377 cases, 29 deaths, 897 life years lost, 2247 QALYs lost, and a total cost of illness of \$168 million. The average cost per meningococcal case in the US is approximately \$446,000, including premature mortality costs. With vaccination, based on the mean number of cases prevented by each strategy, the infant 4-year dose strategy would have a bigger impact on the reduction of meningococcal disease cases than the toddler 2-dose strategy (n=135 versus 73, respectively); for deaths (n=10 versus 6); life years (n=314 versus 175); and QALYs (n=851 versus 439). While the infant strategy seems more effective than the toddler strategy, the number of doses

required by the infant strategy is twice that of the toddler strategy and so would be the vaccination program costs.

The base-case cost per QALY saved by vaccine cost, excluding indirect costs from deaths, is shown in the following table:



The cost per QALY saved, excluding indirect costs from deaths, for the three meningococcal incidence rates, assuming \$60 per vaccine dose, are compared in the following table:



In terms of the impact of vaccine price on the current adolescent vaccination program, hypothetically, the adolescent vaccine price would decrease if the infant vaccine price is lower. The analyses of cost-effectiveness was recalibrated at different price points and with incidence data from 1993 to 2005, including the 18% correction for under-reported cases. Also included was the specific waning immunity after Dose 1 and Dose 2. The purpose was to assess the potential benefits of a routine infant recommendation on adolescent cost-effectiveness. The cost per QALY saved, excluding the indirect cost of deaths, in Adolescents with a two-dose vaccination program with the first dose at 11 years of age and the second dose at 16 years of age, at the current price of \$90 would be \$157,000; at a cost of \$60 would be \$103,000; at a cost of \$30 would be \$72,000; and at a cost of \$15 would be \$43. As with similar analyses, this one has some strengths and limitations, which Dr. Ortega-Sanchez said he would save for the discussion.

In conclusion, cost estimates are much higher than in prior analyses because of declining incidence and shorter duration of protection. Infant vaccination prevents twice as many cases as toddler vaccination, but at twice the cost. Cost per QALY saved is similar for both strategies.

Considerations for Use of Meningococcal Vaccines in Infants

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Dr. Cohn discussed the considerations for use of meningococcal conjugate vaccines in infants. For the past several years, the working group has been grappling with the question: Should meningococcal vaccines be routinely recommended for the 4 million infants born each year? The working group answered this question by breaking it down into three separate questions. The critical question is the first: Is the public health impact based on the amount of potentially preventable disease sufficient to recommend routine infant vaccination? The next two questions were meant to determine whether people moved in a different direction by either by the programmatic aspects of vaccination (e.g., ease or challenge of implementation) or the cost or cost-effectiveness of vaccination.

While ACIP members heard much of the data regarding the potentially preventable disease and the cost-effectiveness, working group members reviewed the data through their values systems. Therefore, Dr. Cohn addressed the values that emerged from working group discussions. The meningococcal working group is made up of pediatricians, infectious disease specialists, family medicine doctors, nurses, and public health professionals. They are also parents, friends, and neighbors. Over the years, many of them have taken care of children who suffered the devastating consequences of meningococcal disease. It goes without saying that the major driving value of the working group is to prevent children from dying or suffering long-term consequences of infectious diseases such as this, and they highly value vaccines as an effective prevention tool. At the same time, there is also a strong value of public health stewardship, and a recognition that the working group is supposed to evaluate the impact of interventions at the population level rather than the individual level. Balancing these two values were apparent in all of the working group discussions.

To evaluate the first question, the working group considered data on vaccine efficacy and duration of protection, and the current burden of preventable disease. The three meningococcal conjugate vaccines in current use are safe and immunogenic. As seen in the first presentation and during the June 2011 ACIP meeting, antibody responses after completion of the series are well-above the titers considered protective. There are data showing that some infants will be protected after the 4 month dose for the infant series and 9 month dose for the toddler series. There were no concerns for increased adverse events with these vaccines.

If infants could be vaccinated against meningococcal disease and they would be protected until adulthood, even at such low disease incidence the impact of vaccination would be greater. However, it is now understood that long-term protection after 2 or 4 doses of vaccine is unlikely. There is evidence of declining antibodies 3 years after vaccination, and these antibodies are critical for protection. There is evidence of more antibody decay after the 2-dose series compared to the 4-dose series combined with Hib. Both the US adolescent vaccine effectiveness estimates and the infant vaccine effectiveness estimates from the UK have offered

an understanding of waning immunity, and a booster dose at age 4-6 years would likely be needed to protect children until the 11-12 year old meningococcal vaccination.

Meningococcal disease incidence has declined 85% in young children since 1997-1999, in the absence of infant vaccination, which is really good news. There is no indication that rates of disease are going to increase in the near future. The current adolescent vaccination program may contribute to disease incidence remaining low. Unlike Hib and strep pneumo where carriage rates were high in young children, meningococcal carriage rates are higher in adolescents and young adults. Adolescents are considered a reservoir of transmission for *N. meningitidis*. Increased vaccination coverage rates in adolescents and the increased immunity from the booster dose may interrupt transmission to infants and young children. However, vaccinating infants will unlikely protect unvaccinated age groups [Caugant et al, 1994].

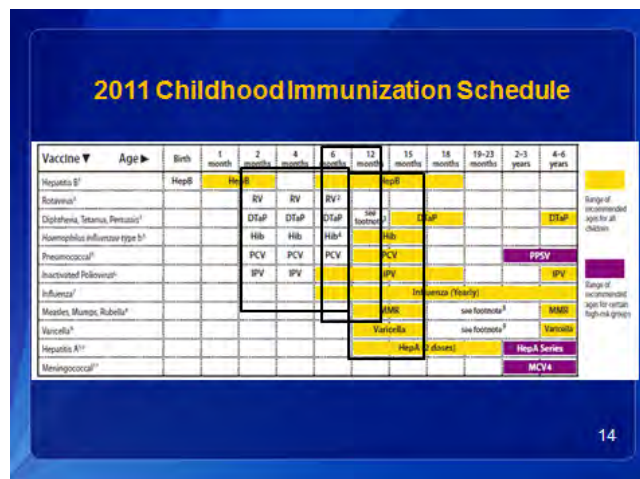
Data from Dr. Ortega-Sanchez's cost-effectiveness model incorporates the current epidemiology and our current understanding of waning immunity. During 1997-1999, infant vaccination would have prevented about 300 cases and 20-30 deaths; during 2007-2009, infant vaccination would prevent about 44 cases and 2-4 deaths. This means the number needed to vaccinate to prevent a case is over 75,000 and the number needed to vaccinate to prevent a death is over 600,000. While understanding that meningococcal disease is dynamic and rates may increase in the future, the ACIP working group believes decisions about vaccination need to be made based on current disease burden [Data from Ortega-Sanchez CE model, presented at ACIP, October 2011]. In the setting of historic low disease burden, it becomes even more important that vaccination prevent a high proportion of cases. Of the estimated 205 cases in children less than 5 years annually during 2007-2009, only 44, or about 20-25%, are prevented by the 4 dose infant schedule, and even fewer with the 2 dose schedule.

The working group believes that at this time, in 2011, the public health impact is not strong enough to recommend adding meningococcal vaccines to the routine infant schedule. They came to this conclusion because long-term protection is unlikely, disease incidence is at a stable low, vaccinating infants is unlikely to protect unvaccinated age groups, and the proportion of disease that is preventable in infants is low.

After the working group came to its conclusion about the first question, they asked if the programmatic aspects of meningococcal vaccination impacted their initial conclusion based on public health impact alone. The working group focused on multiple aspects of programmatic issues, but the two most important are the differences between the three products and the timing of disease in relation to when doses are given.

Each of these three vaccines would pose different challenges to providers and to health departments purchasing vaccines. HibMenCY protects against 2 serogroups of meningococcal disease without adding shots, but providers would not be able to use other combination vaccines that include Hib. MenACWY-D would be a two-dose series starting at 9 months, but there is no current 9 month vaccination visit. This vaccine would require half the number of doses, but does not protect the younger infants at risk. MenACWY-Crm is a stand-alone vaccine, but is an additional 4 shots in the first 12-15 months of life. These differences would pose challenges with vaccine interchangeability, and catch-up schedules.

This 2011 Childhood Immunization Schedule offers a visual of how the vaccine products would fit into the childhood schedule:



The first 3 doses of the infant series would be given at 2, 4, and 6 months along with rotavirus vaccine, DTaP, Hib, PCV, and IPV. The first dose of the toddler series would be given at 9 months. At this time catch-up doses are frequently given at 9 months, but there are no vaccines specifically recommended at 9 months. During 12-15 months, the fourth dose of the infant series and the second dose of the toddler series would be administered.

In terms of incidence by month of life and the timing of when the 4-dose schedule occurs, if meningococcal vaccines are routinely recommended, the impact of the program will be exquisitely sensitive to timing of vaccination. Many infants do not get vaccines during the month they are currently recommended, so achieving maximum impact of the vaccine program might be challenging. The same is true with the timing of the 2-dose series starting at 9 months [ABCs, 1998-2007 average annual estimated rates to the U.S. population].

The working group agreed that implementation would not be easy enough to overcome the limited public health impact of vaccination. Challenges include that three different product types would be confusing, and there is a need to attain high coverage early. However, the opposite is also true. These challenges would be overcome if there was a sufficient public health impact.

The last question the working group addressed is whether the cost, either total costs or cost-effectiveness, would impact their conclusion about the public health impact. There are a couple of important points. One year ago, ACIP recommended the booster dose for adolescents despite the high cost-effectiveness estimates. The rationale of this booster dose was to ensure teenagers were protected as long as initially anticipated. However, the working group felt that it was important to not use the adolescent program as a measure for a cost-effectiveness that would compel them to recommend infant vaccination. In fact, there was no threshold identified by working group members, and primarily the cost-effectiveness analysis was used to provide perspective on the impact of vaccination. But two issues on which Dr. Cohn went into more detail included vaccine price and the potential impact of price reductions on adolescent vaccination.

The price of infant meningococcal vaccines is unknown. Because of the limited disease burden and despite the incredibly high cost per case, there would be a high cost per QALY saved regardless of the price. The cost-effectiveness analysis was shared with each of the companies prior to this meeting. Some companies have indicated that in the setting of a routine recommendation, the price of the 4-dose vaccines series would likely be lower than the adolescent price. This is because of increased demand and competition between the three companies. They explained that if there were a routine recommendation and the price was reduced for the infant vaccines, because two of these products are the same as the adolescent product, the adolescent price would be lower as well. Based on their feedback, the potential benefits of a lower price to the adolescent vaccination program was evaluated, as shown in the previous presentation.

Dr. Cohn summarized an analysis done by Novartis which models the infant meningococcal program from infancy through adolescence with the assumption of a 4-dose infant series and no booster dose at 4-6 years. This model has not been evaluated by the ACIP economic group and uses incidence data that is slightly higher than in Dr. Ortega-Sanchez's model, but was presented to illustrate the principle that by lowering the price, not only would the cost-effectiveness of the adolescent program be improved, but also the cost per QALY saved would be lowered for the whole program. For example, if the price of all meningococcal vaccines was \$45, the cost per QALY of a 6-dose series starting at 2 months through adolescence would be approximately \$210,000 to \$230,000. The working group also thought it was important to assess the implication on the whole program cost [Estimates courtesy of Novartis Vaccines, based on Ortega-Sanchez model, using 1993-2007 data with assumed 10-20% disease underestimating].

Based on the program costs in Dr. Ortega Sanchez's model and the total costs of the different strategies, at \$90 a dose, the adolescent program costs approximately \$483 million dollars annually. If the price were \$30 a dose, the toddler and adolescent series combined would be equivalent to the current program costs. If the price were \$15, the infant and adolescent series combined would have a cost equivalent to the current program. The working group believes the vaccine price may be between \$30 to \$60 a dose, which would result in total program costs will be between \$750 million and \$1.5 billion dollars annually. So even though the cost-effectiveness is improved by looking at the infant and adolescent program together, the overall program costs are high [Total program costs for the adolescent + 4 dose infant based on assumptions in Cost-effectiveness analysis, Ortega-Sanchez, October 2010 ACIP]

While the cost-effectiveness analysis was informative and the working group does understand that having a routine infant recommendation might drive down the price of the adolescent dose, the pricing or cost-effectiveness did not shift the opinion of the working group based on the burden of disease alone. In the setting of current disease burden, even a very low price would have a high cost per QALY saved. There are several additional considerations that the working group considered. There was discussion about the impact meningococcal vaccine would have on the infant schedule in terms of increasing vaccine hesitancy or spacing of vaccines. There was agreement on the working group that if a routine infant program was implemented, it would be hard to leave a gap in coverage from waning immunity to the timing of the 11 year old dose, so a booster dose would likely be needed. The working group is also acutely aware of the potential implications for vaccine development, including progress with a serogroup B vaccine. While important, there are either limited data to support these considerations, or they are based on conjecture, and therefore did not impact the working group opinion.

The working group impression was that data do not support routine infant meningococcal vaccination at this time, based on the low number of preventable cases. The working group was in agreement. It is difficult to accept that there will be cases that are preventable. Nevertheless, the risk for serogroup C and Y disease is low in the absence of vaccination. No routine recommendation would not mean the vaccine is recommended against. If the ACIP agreed with the working group's assessment during this session, the working group would continue to address language for permissive use, recommendations for infants at increased risk for meningococcal disease, recommendations for vaccinating infants in outbreak settings, and the issue of having equitable access to vaccine for parents who choose to vaccinate their infants prior to the February 2012 ACIP meeting. The working group is committed to evaluating the epidemiology of disease and how changes might impact vaccination decisions frequently.

Discussion Points

Dr. Bocchini said it would be great for the price of the vaccine to decrease, and inquired as to whether the model addressed the issue of administration cost.

Dr. Cohn responded that the model included a \$15 per dose administration fee.

Dr. Jenkins noted that while the model was addressed from the point of view of how the infant immunization would impact adolescent cost, because she works with adolescents she viewed it from the perspective of these adolescents and young adults being parents. She wondered what the impact might be of adolescents and young adults being vaccinated on infants being protected and how that may be a factor.

Dr. Cohn replied that the working group discussed this quite a bit. Theoretically, there should be impact on other age groups by vaccinating adolescents who are soon to become parents. The booster dose should help that; however, at this time it is very difficult to measure herd immunity on the infant age group. They would have to take a "wait and see" approach.

Dr. Keitel wondered why, since the incidence of disease in the 5 to 10 year old age group is so low, there was a concern about the need to boost.

Dr. Cohn indicated that this was also a discussion the working group had several times. The issue of the working group is that if vaccination begins in infants, protection is being provided, but is not being provided again until 11 years of age. This leaves a gap that is difficult to explain, so even though the incidence is so low, it is very similar to why the working group did not recommend moving a dose from 11 years old to 15 years, but recommended a booster dose. Since 11 year olds were already being protected, the working group did not feel that they could leave a gap in coverage if the commitment was made to protect infants.

Dr. Campos-Outcalt pointed out that there were many unknowns, because the infant doses may actually change the need for a booster dose for adolescents and young adults. This is not really known, nor is it known whether there will be some protection even if antibody levels might decline. He wondered whether anything was known about carriage rates.

Dr. Cohn replied that it is known that the vaccination programs in the UK and several other European countries that use MenC conjugate vaccine did impact carriage. There are also data from MenA in Africa that those conjugate vaccine impact carriage. However, in the US no impact has been observed of conjugate vaccine on carriage, primarily because US carriage rates are so low to begin with.

Dr. Duchin agreed with the conclusions of the working groups, with the exception of the gap proposal just discussed.

Dr. Marcy said the message is clear that maternal immunization is needed.

Dr. Temte commented that when the target is so small in terms of the current number of cases and deaths, it becomes very apparent that the risk / emergence of an adverse event, which will be nearly impossible to detect in the pre-licensure and pre-recommendation period, could quickly overwhelm the benefit of such a program.

Dr. Plotkin (Vaccine Consultant) noted that three companies spent millions of dollars developing vaccines for this target. This is not to cry for the vaccine companies, but they developed these vaccines with the idea that a peak of infection in infancy could be suppressed by the use of these vaccines. The working group reached the conclusion, in view of the declining incidence of serogroups C and Y that this may not be something the committee wants to undertake as a public health measure. He suggested that consideration be given to whether use of a pentavalent vaccine, including serogroup B, would be worthwhile as a public health measure. There are companies trying to develop a serogroup B vaccine, and the committee can either promote or inhibit that depending upon what predictions are made with respect to cost-effectiveness, public health desirability, et cetera. He said he knew the ACIP was not strong on making predictions or giving judgments in advance, but at least they could do some factual analyses as Dr. Ortega-Sanchez did for serogroups C and Y, and give some idea to the companies as to whether it is worthwhile to develop a serogroup B or pentavalent vaccine.

Dr. Cohn responded that this was a good suggestion, and that the working group is already deliberating what the impact of a serogroup B vaccine or a serogroup B that protects against other serogroups would be.

Dr. Salisbury (DOH, UK) found some of the options the working group considered somewhat bewildering when compared with the UK's experience, because in 12 years on, the UK still has no serogroup C meningococcal disease. That is in the face of program in which there was a very extensive catch-up initially up to 20 years, but then have maintained the program with just an infant program with 2 doses in infancy, and then a combined HibMenC boost after the first birthday. The UK still has no resurgence of disease in any age group; however, they are very carefully assessing the possibility of moving one of the infant doses so that there would be one infant dose, one toddler dose, and one adolescent dose. All of that is in the complete absence of disease. Nevertheless, this may very well be something that the UK perceives as a reasonable strategy to prevent adolescent disease resurgence and maintain the record they have, which is pretty much a flat line along the X axis. Again, it was puzzling to him to be hearing about strategies involving 6 and 7 doses when the practical experience, when the UK has achieved high coverage at 94% by the first birthday with 2 doses, and 93% for the booster. He understood fully the evidence of waning immunity, but the practical experience shows that there simply has not been resurgence of disease.

Dr. Warshawsky (NACI) reported that the Canadian experience was similar to the UK. A lot of Canadian provinces give only one toddler dose at 12 months of age of MenC and one adolescent dose of either MenC or MenCV4. The rates of disease have been very low because of high coverage, but with a small number of doses because of herd immunity.

Regarding the UK and Canadian response, Dr. Brady (AAP) pointed out that the US has had a pretty dramatic reduction in meningococcal disease without using a B vaccine of any type. The question regarding whether the strategies that were used are completely, partially, or not responsible for this remains to be determined. The US has not yet figured out why there has been a dramatic reduction in meningococcal disease that is independent of the vaccine.

Dr. Campos-Outcalt thought this raised the interesting question regarding who, once the adolescent and young adult schedule was started, it could ever be changed to another schedule that might protect younger age groups as well as older age groups. It was unclear to him how to proceed at this point, given the limitations of it all.

Dr. Meissner summarized what Dr. Chesson said in a conversation earlier in the morning that with the rates of disease so low, if an infant vaccination program was initiated for a million children, it might increase the total number of deaths among people who are in automobile accidents going to their pediatrician to obtain the vaccine.

Following up on Dr. Plotkin's comments, Dr. Narasimham (Novartis) requested that the working group continue to provide the vaccine manufacturers guidance on how to further develop meningococcal vaccines in this setting. Novartis has a serogroup B vaccine that has been filed for licensure in Europe, Australia, Canada, and Brazil and is progressing a pentavalent vaccine for both adolescents and infants globally. In the context of this conversation, and the level of investment required to build the factories and conduct the clinical trials to bring one of these vaccines forward, this entire discussion certainly gives Novartis pause on whether it should continue developing an ABCWY pentavalent vaccine for infants, or could even fund such an effort given the failed effort to achieve a routine recommendation for a quadrivalent vaccine.

Dr. Marcy asked Dr. Salisbury whether there had been any change in the age distribution of meningococcal disease in the UK, specifically in infants in the first 4 to 6 months of life.

Dr. Salisbury (DOH, UK) replied that there is no group C disease in which to find a change. They have a flat line that is approximately zero. They have observed some reduction in group B disease compared with the situation in the late 1990s and early 2000s without a vaccine, but it is a reduction of about a third to a half and he did not believe that they could trust that group C disease would be absent without the vaccine. He disagreed quite firmly with the hypothesis about the adverse reaction potential, given that in the years that the UK has been using group C conjugate vaccines they have had an outstanding safety record. He was not aware of any vaccine-specific serious adverse events that could compromise the immunization program.

Dr. Temte clarified that he was saying safety would have to be monitored very carefully. In terms of analogy, use of MMRV in a birth cohort would result in roughly 2000 to 3000 febrile seizures per year. That is very different than in the case of meningococcal disease, but he was just doing the comparison.

Public Engagement

**Glen Nowak, PhD, Senior Advisor
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention**

Dr. Nowak reported that the public engagement project was an effort to actively involve representatives of stakeholder groups and members of the public in dialogue and deliberation regarding meningococcal vaccines and infants and toddlers. He noted that it was a pilot project that sought to surface the beliefs, perspectives, and values that exist regarding the issues at hand, including use of licensed vaccines to protect children from rare but severe illness; as well as insights and information that those making or implementing decisions would benefit from knowing. The pilot project also sought to determine what could be learned about the process of engagement itself. CDC had used public engagement a few years ago to get input regarding the prioritizing of initial supplies of pandemic influenza vaccines, but had never embarked upon such a project with a newly licensed vaccine.

When it comes to vaccines and immunization recommendations, people can have different values on many things, including the following:

- ☐ Disease threat or risk
- ☐ Government spending, deficits, funding (e.g., priorities)
- ☐ Cost, financial, economic considerations
- ☐ Access and availability of preventive measures
- ☐ Equity / equality
- ☐ The likelihood or possibility of being personally affected by a disease or condition
- ☐ Protecting others, helping to protect others
- ☐ Role and importance of personal autonomy
- ☐ Investments required to obtain protection

Stakeholder and public engagement can help inform decision makers in many ways. It can provide a sense of range of views that exist. It can also provide a sense of the values that people place priority on in terms of the issue. It can offer insights into the landscape of a new policy or recommendation will be facing, including the bounds or boundaries of permissiveness; and the beliefs, perceptions, et cetera that may be encountered by a new policy or recommendation. GRADE has a place for values, and the investigators assessed whether this could be of value in terms of identifying and surfacing values. Ultimately, policies and recommendations do go into the work and acceptance and implementation can be facilitated or hindered in many ways. Some of the information uncovered can foster acceptance and implementation.

Public engagement is a potential supplement to current inputs, including experts (e.g., CDC, ACIP and *ex officio* members), published and unpublished research data, clinical trial results, information provided in the manufacturer's labeling or package inserts, recommendations of other professional liaison organizations, surveys and/or focus group findings, formal economic evaluations (cost effectiveness, cost benefit, cost-utility), and public comments solicited at each ACIP meeting.

Two national stakeholder meetings were convened, one at the beginning of this project on May 25, 2011 in Washington, D.C. to outline a draft project plan and acquire input and suggestions on process, questions to ask or consider asking, general approach, et cetera. The second meeting was at the end of the project on October 5, 2011 in Atlanta to present findings from the four community meetings and to get input and suggestions regarding those findings.

Stakeholder participants included the following:

- ☐ AMA, AAP, AAFP, APHA, ASTHO, NACCHO, NFID, CIGNA, NAPNP
- ☐ BIO, representatives from vaccine manufacturers
- ☐ Every Child by Two, Immunization Action Coalition
- ☐ Partnership for Prevention, Women in Government, Heritage Foundation
- ☐ National Vaccine Information Center, National Meningitis Association, Meningitis Angels
- ☐ University of Pennsylvania Center for Vaccine Ethics and Policy

The investigators learned early on when trying to expand the list of stakeholders to reach out to non-traditional partners (e.g., legislative groups, groups involved in healthcare but not immunization, business groups) that while these groups found the project interesting, it was not on their list of priorities. They wished CDC luck, but did not see this as an issue in which they wanted to be engaged. People often suggest that a list of partners / perspectives be expanded, but this can be easier said than done.

Four community meetings were conducted in sites where health departments were interested in the topic and were willing to help organize the meetings, because CDC knew that this would be difficult and challenging. The goal was to have approximately 100 participants per meeting. One of the financial constraints was that there was a stipend of \$75 for each participant and a \$75 childcare stipend was also offered to make it more possible for parents to participate. Participants were recruited through coalitions, community organizations, local parent groups, advocacy groups, the media, and posting of flyers. There was a structured agenda for each 5 to 6 hour meetings that ran from 9:00 am to 3:00 pm. Presentations were delivered that provided everyone with information that enabled them to engage on the issue. Drs. Cohn, Clark, and Messonnier participated and each went to at least one of the meetings to provide background information on meningococcal disease, meningococcal vaccines, and the options that ACIP has and what those options mean. There were large and small group discussions and polling questions were designed to be challenging, provocative, and to guide and foster discussion. They were not designed to be scientifically generalizable, because the people who attended these meetings were not a random sample. They were people who were interested enough in the topic to attend. The four sites selected and their characteristics are show in the following table:

Location	% Female	% White % Hispanic	%18-50 Yrs. old	% Parent (% under 18)	% Healthcare
Concord June 15 47 participants	62%	71% (4%)	41%	45% (32%)	59%
Seattle July 12 94 participants	73%	74% (5%)	49%	47% (28%)	46%
Chicago July 21 101 participants	85%	41% (42%)	74%	59% (35%)	32%
Denver July 25 35 participants	83%	83% (2%)	62%	45% (30%)	63%

Note: based on participants who provided information

Dr. Nowak emphasized that the participants were comprised of very interested people, some of whom were interested because they were very skeptical of vaccines and others of whom were interested because they favored meningococcal vaccines and broader use. Through this process, CDC discovered that people with both perspectives could be in the same room and engage in productive dialogues and meetings.

With regard to the findings, there is relatively little knowledge about meningococcal disease among the public and parents. They had heard of meningitis, but no meningococcal disease. Many healthcare professionals noted they did not have extensive experience with meningococcal disease. There was much surprise about the relative lack of risk factors, the swiftness with which disease can progress, and how much remains unknown about disease initiation and transmission. Regarding meningococcal vaccines for infants, participants had little knowledge or awareness of meningococcal vaccines, particularly with respect to vaccines for infants. Many understood after the presentations that neither the recently licensed vaccine nor those pending licensure provided protection against serogroup B. The lack of protection against serogroup B was seen by many as a significant shortcoming (e.g., they wanted an infant vaccine to provide protection against serogroup B as well). Many did not understand why the vaccine did not include that protection or why there was not a vaccine that protected against serogroup B.

There was much interest in the safety of meningococcal vaccines for infants, including the following questions: 1) What are the most common/likely vaccine reactions and how often do they occur?, 2) What are, or could be, the serious vaccine reactions and how often might those occur (and is it possible those could occur more often than deaths prevented by these vaccines)?, and 3) What are the long-term effects of vaccination? Many participants assumed that CDC had access to complete or much data regarding the outcomes of all or most childhood vaccinations.

There was a spectrum of beliefs regarding meningococcal vaccine financial considerations. Some believed that cost/resources matter. They thought that morally, costs should not matter but in reality, they do. They also thought that all costs count given the national financial crisis. Some believed the costs were too high. They thought that because there is such a low level of disease and so few deaths, the cost-benefit did not seem worth it for a recommendation. They wondered why a lot of money would be spent for such small results. Some believed costs should not inhibit access/availability. They thought that because vaccine could save lives, it should be available no matter what the cost and that every child should be able to get any vaccine their parents' want.

At the end of the meeting day, participants were asked to consider which of the following options best aligned with their values:

- ☐ Add meningococcal vaccination to the childhood schedule as a routine recommendation for all children
- ☐ Have a permissive recommendation; that is, leave it up to doctors and parents
- ☐ Have a permissive recommendation, but add this to the Vaccines for Children Program

Regarding the option to add meningococcal vaccine to the childhood schedule as a routine recommendation, overall about two thirds indicated that this option was most in line with their values. There was much recognition that adding the vaccine to the schedule would provide clear direction; foster the greatest vaccine education, awareness, access, and likely use; and bring the need for education and resources. That said, many also noted that they had concerns. These concerns regarded the fact that most parents do not know about this disease; whether the number of cases or number of cases prevented justified a routine recommendation; the schedule having more shots; and no serogroup B protection. It is important to note that wanting an option for access to meningococcal vaccines for infants is not the same as wanting or believing there should be a recommendation that all children be vaccinated. Some only chose this option because they thought it was the only way to ensure awareness, availability, and widespread access to the vaccine. Many did not believe that the potential public health impact warranted universal recommendation, and that significant impact could be achieved without large investment in educational efforts/campaigns.

About one third of the participants favored the permissive option. Some favored it because they saw this most in line with personal choice. There was much recognition that this approach would limit awareness, access, and availability of these vaccines; it would foster confusion (e.g., mixed messages) and inconsistencies; and it could foster inequities in use and access to these vaccines. Some favored adding the vaccine to the VFC program as a way to foster availability and access, but others did not favor this because it could foster access inequities.

A number of participants were not satisfied with either option and desired a different option. Many expressed dissatisfaction with the available options (e.g., universal or permissive). They did not believe disease incidence and/or protection provided by vaccines warranted a universal recommendation. However, they did not believe that a permissive recommendation would result in physician or parent awareness of vaccines, availability of vaccines, or consistency regarding use of meningococcal vaccines for infants. Many participants believed there should be another option or an effort to find another option (e.g., one that fostered awareness, access, and availability without it being added to the routine schedule).

The most frequently voiced values included safety first and foremost. They wanted vaccines to have few side effects and no serious risks. They strongly believed that parents should be aware of infant meningococcal vaccines or any FDA licensed vaccines. They believed that if a vaccine is FDA licensed, parents should be able to easily access the vaccine, ideally through their regular provider, and that permissive recommendations should not inhibit vaccine availability. They valued affordability in the sense that parents should have coverage through their insurance or VFC, and that cost should not be a barrier to individuals when it comes to vaccines. A strong, frequently voiced value regard choice or the freedom and ability to choose/options. That played out in many ways with some parents preferring to be provided with the facts in order to make their own decision or be involved in the decision-making process; some wanting the vaccine to be recommended, but not required; and some wanting the vaccine to be recommended, but not aggressively. The "recommend but don't require" value reflected sentiment among many parents that when a vaccine is added to the childhood schedule, they perceive that to be a mandate in the sense that their doctor is now going to advocate that their child receive all of the routinely recommended vaccines. They were not thinking in terms of daycare or school entry laws. Instead, they were looking at it as doctors mandating that their child receive the vaccine.

Other values-related considerations included equity in education, awareness, access, availability, and choice; and concern about mandates. Many people felt that routine recommendations usually led to state mandates and/or were mandates because doctors "pushed" vaccines that were on the schedule. Less frequently voiced in the meetings was the desire for and importance of community protection, and the need to provide incentives for continued vaccine research/development. In other CDC research conducted with parents and moms, they have often heard the value of a strong desire for a doctor's recommendation.

Provider values voiced in meetings included clarity, simplicity, and clear direction. They want and easy to follow and implement vaccination schedule. The schedule is already very crowded. Also noted was that permissive recommendations do not help providers. They also value equity in that all children should be treated alike unless there is reason not to, and that permissive recommendations foster inequities. Access to assistance and resources is very important to providers (e.g., materials that address safety-related questions and concerns; materials that make a strong and compelling case for vaccination). They also want to avoid unintended consequences. Concern was expressed that new recommendations lack or divert resources, that additions to the vaccination schedule foster vaccine delays or deferrals, and that there is lack of protection up until adolescent recommendation.

In terms of whether the cost of a vaccine should matter in terms of recommending its use for all, participants generally expected that cost and cost-effectiveness would be a part of the ACIP/CDC decision process. In the three meetings in which the question was included in the polling, about half indicated cost or potential cost should be taken into account, though it should not be one of top two or three factors. About 4 in 10 indicated "not at all" with respect to vaccine cost, while about 2 in 10 said it should matter "very much."

Many noted that a vaccine that prevents a rare but serious disease is more important when prevention is achieved at a relatively low cost. Many participants supported or advocated for cost-benefit and long-term analyses (e.g., compare the cost of a vaccine to cost of treating a disease). Those who said cost does matter thought that vaccines must be balanced against other health concerns and monetary demands within the government; and that if a vaccine is less expensive, more people will get it. Those who said that cost does not matter thought that if a vaccine helps save any children, cost should not be a factor; and that cost should not matter because the cost of vaccination would most likely be less than the cost of the disease.

There are some limitations and challenges to the approach used for this project. Public meetings do not provide representative samples. Rather, they involve self-selected participants who are interested in the topic or issue. Values and views are primarily from people at the ends of continuum (e.g., "for" or "against"). Not all the participants were parents, or parents of infants and young children. People primarily looked at the issues from personal or individual level versus a broad public or public health perspective. If the goal is projection to a broad or more specific population, a different approach would be needed. Regardless of participants, values are often relative or depend upon specifics and can change quickly with new information, including pictures of serious disease or personal stories. Values are often not known or strongly held until an issue becomes personally tangible. Individual values can, and may, differ from societal or public health values or needs. Lay person experiences and knowledge base often different from that of experts. Individuals are often more focused on short-term outcomes.

In terms of the meeting evaluation findings, many participants indicated that they were glad community input was being taken; that the meeting included informative, helpful, uncomfortable, worthwhile discussion; and that it was helpful/valuable to hear diverse views. Many participants suggested expanding the effort using social media, more promotion, more communities, and additional venues; and that a survey would be more helpful/useful. Some participants desired a broader meeting topic about vaccines in general; and indicated that the dialogue was good but recommendations should be based on science and data, not on input like this.

Discussion Points

Ms. Rosenbaum thought it was wonderful that CDC engaged in this effort, which she found to be very illuminating. Of most concern to her was the resistance of healthcare professionals to the permissive standard. To her, the essence of practicing in the healthcare field is judgment. There are going to be many times that ACIP will not make a routine recommendation, but will say that there are a number of judgment factors that come into play when thinking about certain immunizations and contexts. She wondered whether there were any recommendations for follow-up about ways to engage with healthcare professionals about the fact that a major part of immunization practice is that ACIP is often recommending that practitioners use their judgment. It is difficult to think about ACIP's work without this aspect.

Dr. Duchin said that speaking for the Seattle meeting, he would not necessarily generalize from the audience responses since this is not a representative sample. There was not a real cross-section of healthcare professionals. Almost all of the healthcare professionals there were public health nurses.

Ms. Rosenbaum suggested thinking about doing something more representative to be sure that as ACIP moves increasingly into permissive decisions that they are doing so in a way that creates decision aids for physicians under the Affordable Care Act, given that there is major emphasis on decisions aids in the act. There are a number of ways ACIP should zero in on this if it is an issue on which they should focus.

Day 1: Public Comment

Samantha Bennett
National Meningitis Association

Hello, my name is Samantha Bennett and I am with the National Meningitis Association (NMA). NMA receives funding from educational incentives from various sources, including vaccine manufacturers. My presence today is solely funded by NMA. I am here for two reasons. First, I'm here as a survivor of meningococcal disease. I had it when I was 9 months old. My story is similar to others you have heard. Within hours, my body was ravaged, leading to amputations and scarring over much of my skin. Today, I am an artist. My earliest memories of drawing are from the many hospital rooms I stayed in throughout my childhood, and during reconstructive surgeries. I've had more than 25 surgeries throughout my life, and the physical and economic impacts have been enormous. The emotional impact, which is less visible, is also profound, not just for me, but for my family, especially my mother.

That's the second reason I'm here. I'm here as a mother with two young boys. I wanted to protect them from this disease, but during a recent check-up for my 3-year old son, I was told that my insurance company would not cover the vaccine, and this wasn't an expense that we could afford. After all my family has been through, it scares me to death that I had to walk away without vaccinating my child. If this vaccine isn't recommended for infants, none of the parents will be given a choice to make informed decisions—a choice—and those who are informed may not be able to afford to protect their children. No family should have to forego a vaccine because of cost, and my family is not alone. Many others have been terribly affected by this disease, and I am also here for them. I am here for Lisa and her daughter Sara, for Mollie and her son Kenyon who was just one year old when he passed away, for Echo and her son Gavin, for Christie and her daughter Jayelee, for Anna Grace Davis and her son Terrance, and for all the others who cannot be here today. The National Meningitis Association supports recommendations of meningococcal vaccines for infants, and I really hope that you consider my story and everybody else's stories as you move forward. Thank you.

Frankie Milley
Meningitis Angels

My name is Frankie Milley. My personal interest is the fact that I buried my only child after I watched him die a horrific death. I literally watched him bleed to death on an emergency room table in less than 14 hours after he became ill. My personal conflict is the fact that it was preventable and I didn't know it, and today my conflict is that many infants, children, teens, and young adults are still dying and still being left debilitated in this country, and it's preventable. That's a conflict in my mind. I am the Founder and National Executive Director of Meningitis Angels. Meningitis Angels does receive unrestricted grants from pharmaceutical companies. It enables us to do the education and provide a lot of the materials that we provide free to many of the health departments and schools around this country, and educate the public. For many years I have been doing this. Since Ryan's death I have fought this fight, and I have the honor and the privilege to stand with many of you right here to do that, and I have seen you make some amazing decisions to protect infants and children and all Americans. Last summer, not this last summer but summer before last, we saw meningococcal come out of its comfort zone of college teens. We saw it attack an elementary school in a little town in the middle of nowhere in Oklahoma, attacking six children with two of them dying in less than 48 hours. Another you saw on the screen earlier, Jeremiah Mitchell, who has become one of the angels that we now support and help take care of. He lost his face, his arms, his legs. He gets made fun of. His mother has to take him for many, many surgeries to reconstruct his face. He has to have someone feed him, to change his pants, to assist him to the bathroom. He is now 8 years old. We saw a man's hockey team with an outbreak in Colorado. The average age was about 25 to 35, with several deaths. It's coming out of its comfort zone.

This summer I had the honor and the privilege, and I want to thank the CDC, for allowing me to be a national stakeholder with the infant meningococcal disease process. It was an honor, and it was an experience, and I learned a lot. I met a lot of parents. I went to every meeting over the summer, and I met many, many parents who were on both sides of the spectrum. It gave us an opportunity for the first time to sit down with those parents face-to-face and have an open discussion about their fears of vaccine and for them to learn how devastating this disease can be. Many of those same parents, each time, went back, picked up their clickers, and voted to recommend this vaccine. That was amazing to me.

Today, we've talked about HPV. We've talked about Hepatitis B for diabetics. You've made recommendations today to protect boys and men, and even the oldest of Americans in this country. I am asking you to do the same thing—over the next year, we're going to be looking at more data, more information—there are important decisions to be made, and I don't envy you guys. Your job is very hard and I respect the dedication that everyone one of you on this committee gives to the American family to protect them from deadly disease. I look forward to working beside you, and supporting you, and I look forward to seeing a recommendation that would prevent this deadly, debilitating disease. No child should have to go through life without their face, or their arms, or their legs, or have organ transplants. No parent should have to have a child who has seizures so bad that they are afraid to go and wake them up in the morning because they are afraid they are going to be gone, even 8 or 9 years after the disease. No parent, no child, should have to suffer that. So, I encourage you to do the same thing you've always done in this committee—what is best for the children and the prevention of deadly disease. Thank you.

October 26, 2011

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Schuchat reported that since the June 2011 ACIP meeting, CDC has made awards for funding through the Prevention in Public Health Funds that provided resources to help modernize state and local immunization programs. With these funds, investments have been made to help states develop billing capacity so that funds can be recovered when they provide vaccine to insured individuals; to help states upgrade the information systems or registries and the electronic health record interface with interoperability to ensure continued progress on the Vaccine Tracking System (VTrckS) ordering system that states have; and to strengthen the evidence base and support the policies that ACIP issues in order to assess the impact of recent recommendations, duration of protection, effectiveness, and actual use. The other issue the agency has been working on since the summer is measles, though the US is fortunately not experiencing a situation as difficult as Canada.

Centers for Medicare and Medicaid Services (CMS)

Regarding the VFC program, though the process has taken longer than expected, Dr. Hance indicated that CMS hopes to update the administration fee schedule in the near future. CMS is also working on a larger regulation related to the VFC. The Medicare Food Campaign is underway. CMS is making a conscious effort this year to reach hard-to-reach Medicare beneficiaries, and is working with many partners to reach that vulnerable population. In addition, the agency has reached out to over 4000 partners to encourage them to use the new CMS website, which features a guide that helps providers learn how to file for payment for the administration of an influenza vaccine.

Department of Defense (DoD)

Dr. Geibe reported that on October 24, 2011, the DoD restarted adenovirus vaccination for military recruits due to FDA approval of the vaccine for acute febrile respiratory disease caused by adenovirus types 4 and 7. The new adenovirus vaccine was developed by Barr Pharmaceuticals, recently acquired by Teva Pharmaceutical Industries Ltd. Teva Pharmaceuticals shipped 39,600 doses on October 18, 2011 to 9 basic training sites for the Army, Navy, Air Force, Marines, and Coast Guard.

Department of Veterans Affairs (DVA)

Dr. Kinsinger reported that DVA is well underway with its annual influenza campaign. Dr. Nichol, who formerly served as the DVA liaison to ACIP, planned to conduct a national call to VA staff throughout the country about influenza. Each year, DVA closely monitors the rates of vaccination for influenza and pneumococcal vaccine. Although they continue to be well above the national average, DVA has noticed a slight, gradual decline in its rates. Of persons 65 years of age and older, 84% were immunized in 2007, but that has now drifted down to 79%. There has been a similar decline in those under 65 years of age, of whom 71% were immunized two years ago and 65% were immunized in 2010. DVA is not clear why this has occurred, or whether others are observing the same trend. The DVA Office of Public Health convened a meeting in September 2011 to assess the issue of mandatory employee vaccination for influenza. They heard many pros and cons, and are in the process of developing a report and recommendations about this soon. DVA is also working with NVAC on this issue. In 2010, DVA used approximately 40,000 doses of the high dose influenza vaccine for those ages 65 and older. That was out of several million doses ordered and disseminated. Use of the high dose vaccine was an interesting experience in terms of providers deciding who to should receive the high dose product. DVA and DoD are working closely together on the joint electronic medical record (EMR). Over the years, each agency has developed world class medical records, but they were developed independently. There is considerable pressure from Congress for a joint record to be developed. The first module currently being developed is the immunization module.

Food and Drug Administration (FDA)

Dr. Sun highlighted some of the FDA-approved indications since the last ACIP meeting, including the following: concomitant use of MMR®, Varivax®, and Havrix® was approved; the age indication for Cervarix® was extended down to 9 year olds; the 5th dose using Daptacel® in children previously vaccinated with 4 doses of Pentacel® was approved; the age indication for Afluria® influenza vaccine was revised from ≥ 6 months to ≥ 5 years; and the use of Boostrix® for those over age 65 was approved. The FDA will convene a vaccine advisory committee meeting on November 16-17, 2011 to deliberate on the topics of evaluation of GBS with influenza vaccines this season, and to make recommendations on the safety and immunogenicity of the use of Prevnar 13® in adults.

Health Resources and Services Administration (HRSA)

Dr. Evans indicated that since the last ACIP meeting, the IOM released its report titled, "Adverse Effects of Vaccines: Evidence and Causality." This was a HRSA-CDC sponsored project. The IOM committee reviewed more than 1000 medical and scientific research articles regarding 8 vaccines or 12 vaccines in various combinations and 76 different adverse events, for a total of 158 adverse event combinations. This was a significant amount of work over this nearly 3-year project. Twice before the program has utilized major literature reviews by the IOM, which were published in 1991 and 1994, to make changes to the Vaccine Injury Table and its definitional counterpart known as the Aids to Interpretation. This was done through public notice and comment. The IOM's analyses and conclusions will be used by HRSA to update the Vaccine Injury table and provide the scientific basis for future reviews and adjudication of Vaccine Injury Compensation Program (VICP) claims. This is a process by statute, so the comment period alone is 6 months. A public hearing occurs during that time, and the first public step will be to present the proposed changes to the Advisory Commission on Childhood Vaccines (ACCV), which is anticipated later in 2012.

Indian Health Services (IHS)

Dr. Cheek indicated that IHS is gearing up for the upcoming influenza season. The IHS's electronic automated influenza-like illness surveillance system is up and running, the results of which are posted every Thursday on the internet. At this point, approximately 150,000 doses of influenza vaccination have been distributed. The IHS is continuing its collaboration with the FDA to monitor for potential adverse events for influenza vaccine, and is expanding this to PCV as well.

National Vaccine Program Office (NVPO)

Dr. Gellin reported that NVPO is currently in the process of developing an implementation plan for the National Vaccine Plan (NVP), which will be how NVPO measures progress over time. That is due to be released later in 2011. In the development of the plan, a number of stakeholder engagements have been convened throughout the country. Thanks to IHS, Amy Groome, and others, NVPO would be in Lawrence, Kansas the week after the ACIP meeting for the Tribal Summit to obtain input there regarding the issues for vaccines and immunizations. NVPO is also organizing a meeting about maternal immunizations, given that there are a number of issues that they would like to address improve use of vaccines that are currently available and those that in the pipeline. NVPO's current focus is on influenza. Since the declaration that the pandemic was over, NVPO has had a task force that has been led by the Assistant Secretary for Health on seasonal influenza, to improve seasonal influenza vaccine uptake and annual practice for pandemic preparedness. That continues on a weekly basis, with a number of featured areas. Among these has been consideration of how to reduce disparities, and there is good news about that this year, particularly with children and influenza vaccine. To bridge onto influenza in another way, they recognize that influenza is a good model for improving adult immunization. The plan is to work with the Influenza Summit as a bridge to have an Adult Immunization Summit as well. This event is planned for Spring 2012. Dr. Gellen acknowledged that the work Dr. Birkhead did as the Chair of the National Vaccine Advisory Committee (NVAC), and said he looked forward to working with Dr. Orenstein who would begin his term as the new Chair starting with the February 2012 meeting.

National Institutes of Health (NIH)

Dr. Gorman indicated that under Dr. Collins there continues to be an emphasis on translational research. This has been demonstrated by his continued support of the National Centers for Advancing Translational Sciences (NCATS). For the National Institute of Allergy and Infectious Diseases (NIAID), the development of the HIV Leadership Groups and Networks and the Antibacterial Resistance Leadership Group is on-going, and the RFP development is still on the timeline suggested at the public meetings. Dr. Frederick J. Cassels is the newly-appointed Chief of the DMID Enteric and Hepatic Diseases Branch (EHDB). On-going work at DMID that might be of interest to ACIP is evaluation of HPV vaccination in terms of immune responses in adolescent girls when vaccine is given off schedule. It has been remarkably harder to recruit subjects than anticipated, given that the people they have approached have received the vaccine on schedule. For influenza, there was an article in *Pediatrics* from colleagues in Canada who evaluated influenza vaccine in the 6 month to 36 month age range using 15 micrograms for each of the three antigens compared to 7.5 micrograms. They demonstrated comparable safety and better immune response. There is a similar on-going study in the BTUs in the US. DMID is working closely with NIH's companion agencies, FDA and Biomedical Advanced Research and Development Authority (BARDA), to expand the database of safety and immunogenicity of adjuvants given with known antigens. Especially being studied are MF59 and ASO3, which are in the Strategic National Stockpile (SNS). In terms of on-going trials, NIH recently completed enrollment for a tetravalent inactivated candidate for dengue, and completed a dose ranging trial for a Norwalk Virus challenge pool.

A number of publications for NIH-funded clinical work have recently appeared in prestigious journals, including *Oral Acyclovir Suppression and Neurodevelopment after Neonatal Herpes* by Kimberlin et al; *Cytomegalovirus Glycoprotein-B Vaccine with MF59 Adjuvant in Transplant Recipients: A Phase 2 Randomised Placebo-Controlled Trial* by Griffiths et al was published in *The Lancet*, which showed good immunogenicity and there is just enough hint that this is going to be effective in terms of preventing CMV infections in transplant patients; and *Immunogenicity of an Inactivated Monovalent 2009 H1N1 Influenza Vaccine* was published by Jackson et al in *The Journal of Infectious Disease*. To follow up on Dr. Gellin's theme, DMID is also working in special populations that require additional protections in clinical research. Dr. Nesin, who served as the NIH liaison during the June 2011 ACIP meeting, is leading a working group to facilitate future clinical trials in pregnant women. This is an on-going process with 2 of 3 face-to-face meetings having been completed. The output of this work should be a rudimentary toxicity tables Incident Estimates for Commonly Occurring Pregnancy Outcomes: Reactogenicity Tables for Vaccine Studies. There will be general guidance on considerations for study designs' inclusion and exclusion criteria.

13-Valent Pneumococcal Conjugate Vaccine (PCV13)

Introduction

S. Michael Marcy, MD
Pneumococcal Vaccines Working Group Chair
Advisory Committee on Immunization Practices

Dr. Marcy reminded everyone that the proposed indication for 13-valent pneumococcal conjugate vaccine (PCV13) for adults is prevention of pneumococcal disease (including pneumonia and invasive disease) caused by *S. pneumoniae* 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) in adults ≥50 years. The licensure will be based only on immunogenicity data, comparing the immune response of PCV13 to PPSV23 and is anticipated in early 2012.

The task for the Pneumococcal Vaccines Working Group was to review data on the immunogenicity, efficacy, and cost-effectiveness of pneumococcal conjugate vaccines in adults; determine whether data available to date on PCV13 immunogenicity and cost-effectiveness are sufficient to determine value of immunizing adults with PCV13; and develop a revised statement on pneumococcal immunization if it is determined that one including PCV13 recommendations for adults is necessary.

Thus far, evidence has been reviewed and presented to ACIP includes immunogenicity results from Phase III studies provided by Pfizer, immunogenicity data for PCV from published literature, and the cost-effectiveness and public health impact of different adult pneumococcal vaccination strategies. Evidence will not be available prior to anticipated licensure include efficacy against pneumonia (the trial ongoing in Netherlands and the results anticipated in early 2013), and the indirect or herd effects of PCV13 as it becomes more widely used in children in the US.

Based on their deliberations, the working group recognizes that PCV13 provides immune responses as good or greater than PPV23 in both PPV23 naïve and previously immunized adults; that PCV13 revaccination does not lead to hypo-responsiveness, and there are no data on the duration of protection generated by that vaccine. The clinical relevance of these immunogenicity data are unclear without established correlates of protection. The PCV13 strategies appear cost-effective; however, are based on assumptions on the burden of vaccine-preventable disease after potential herd immunity impact and efficacy against non-bacteremic pneumonia.

The working group plans to continue discussions regarding whether PCV13 should be recommended for adults 50 years of age and older as additional data on herd effects and efficacy against pneumonia become available; and to evaluate the potential utility of PCV13 for adults with immunocompromising conditions. To that end, the working group presented information regarding Phase III studies with extended follow-up on immunogenicity and safety of PCV13 in adults; and considerations for PCV13 use among adults with immunocompromising conditions during this session.

Immunogenicity of PCV13 in Adults: Results of Phase III Studies

Dr. Peter R. Paradiso Pfizer Vaccines

Dr. Paradiso reiterated that the proposed indication for PCV13 for adults in the US. This vaccine was licensed for children in February 2010, and Pfizer has since developed and completed a Phase III program for this vaccine in adults over 50 years of age. Pfizer applied for a supplement to the license for children, since it is the same vaccine, in December 2010. In September 2011, the company received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) in Europe to add this indication to the label. Pfizer has an FDA advisory committee on November 16, 2011 and the target date with the FDA is January 1, 2012. This is a timely discussion, because Pfizer hopes that the supplement will be completed by the time of the next ACIP meeting in February 2012.

In the US, pneumococcal vaccination is currently recommended for all persons ≥ 65 years of age. One dose is recommended for the majority of those persons. Approximately 60% to 70% of adults over the age of 65 have received the 23-valent pneumococcal polysaccharide vaccine. At-risk persons 50-64 years of age are also recommended to receive this vaccine. This currently includes approximately 40% to 50% of this population. The number increased to this range in the last couple of years when asthmatics and smokers were added to the recommendation. Again, one dose is recommended for the majority of the at risk population. Overall, compliance is poor in the at-risk group, and a significant burden of disease remains, as reflected in the following table:

	Age Group	
	50 – 64 yrs	≥ 65 yrs
Estimated number of cases		
IPD	11,297	18,155
NPP requiring inpatient care	33,749	164,852
NPP requiring outpatient care only	104,494	199,526
Number of Deaths		
IPD	1,762	4,415
NPP requiring inpatient care	2,086	17,081

[Weycker D, Strutton D, Edelsberg J, Sato R, Jackson L. Clinical and economic burden of pneumococcal disease in older US adults. *Vaccine*. 2010;28:4955-4960].

It is estimated that between 20,000 to 25,000 adults over the age of 50 die from pneumococcal disease each year. This is a very significant burden in the face of the immunization program. What is interesting is that from 1998 to 2006, there have been increases in the 16 serotypes only in 23vPS ranging from 18% to 50% by age group, even though 60% or more of the population of adults over age 65 have been immunized. It is believed that the rate of 60% to 65% has been consistent over this time period. The increases have been observed predominantly in serotypes 19A, 7F, and 3 but the burden of disease is across all serotypes. There is clearly a need for a new strategy, and that is really the reason that Pfizer assessed the conjugate vaccine in adults. The company has had considerable experience with the conjugate vaccines in children and adolescents with meningococcal, Hib, and pneumococcal vaccines. The goal was to use this conjugate vaccine to determine whether the types of responses observed in children could be achieved in adults.

The advantage of conjugate vaccines is that they act through a T-cell dependent pathway. Conjugation of bacterial polysaccharide provide foreign peptide antigens that recruit antigen-specific CD4⁺ T_H cells, and induces immune memory. Unlike polysaccharides, conjugated vaccines elicit an immune response that permits re-vaccination and is generally boostable. Pneumococcal conjugate vaccines are highly efficacious against invasive disease and pneumonia in children [Siegrist CA, Vaccine immunology: General aspects of vaccination. Pg 17-36. www.who.int/immunization/documents/Elsevier_Vaccine_immunology.pdf. Accessed January 13, 2011].

In terms of why it is believed that a pneumococcal conjugate vaccine could be a good idea and could work in adults, the French 2000 23vPS HIV study tested the efficacy of 23vPS in preventing the first episode of invasive pneumococcal disease (IPD) in an HIV-infected adult population in Uganda¹. There are no details on viral loads or antiretroviral therapy, but the CD4 counts for the two groups are reported. In the vaccine group 43% with CD4<200 were reported and in the placebo group 45%. The study found 23vPS to be ineffective in preventing a first episode of IPD in this population. The French 2010 Malawi HIV study was a double-blind, randomized, controlled study of subjects who had had one previous episode of IPD². This study tested the ability of PCV7 to prevent a second episode of any pneumococcal disease (IPD and pneumonia) caused by the serotypes in the vaccine and type 6A. This study found vaccine efficacy for preventing a recurrence of IPD 74% (30%, 90%), and a 25% (-19%, 53%) reduction in all-cause pneumonia, although the lower confidence interval was below zero so they did not achieve significance but the trend was clearly in the right direction. The study groups were well-matched for severity of HIV disease as evidenced by CD4 counts (median: 212 for PCV7 and 214 for placebo), viral load, and number of patients receiving antiretroviral therapy. Vaccine efficacy was expressed as 1 minus the hazard ratio in keeping with Halloran et al³. Corresponding confidence limits for vaccine efficacy falling beyond ± 1 were constrained to that point. These data are interesting because this population is probably the most difficult to protect, but more importantly, this looks very much like the data in children. The two studies clearly distinguish the polysaccharide and conjugate responses [¹French N, Nakiyingi J, Carpenter LM, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet*. 2000;355:2106-2111; ²French N, Gordon SB, Mwalukomo T, et al. A trial of 7-valent pneumococcal conjugate vaccine in HIV-infected adults. *N Engl J Med*. 2010;362:812-822; ³Halloran ME, Struchiner CJ, Longini IM. Study designs for evaluating different efficacy and effectiveness aspects of vaccines. *Am J Epidemiol*. 1997;146:789-793].

From efficacy and immunogenicity perspective, the population recommended to receive the vaccine is adults over 65 years of age. Approximately 60% of that population has received the polysaccharide vaccine, and there is currently no recommendation for another dose. Approximately 25 million adults who have received polysaccharide vaccine are no longer recommended to receive any protection against pneumococcal disease and clearly would be candidates for the conjugate vaccine. Previous immunization with polysaccharide tends to blunt the response to subsequent immunizations. The other group would be naïve adults, who have a current recommendation to receive the polysaccharide vaccine for whom the conjugate vaccine would be an option once this vaccine is recommended. For those at risk who are 50 to 60 years of age, the scenario is pretty much the same except the majority have not been immunized. When these individuals reach 65 years of age, they are recommended to receive another dose of polysaccharide vaccine.

The studies conducted were in healthy adults or immunocompetent adults with chronic, stable medical conditions over 50 years of age. The total of 5667 subjects were distributed across age ranges, with 2616 (46.2%) 50–64, 646 (11.4%) 65–69, 1139 (20.1%) 70–74, 760 (13.4%) 75–79, and 506 (8.9%) ≥80. Immunocompromised patients were excluded. People with underlying chronic conditions were not excluded. Those include people with chronic pulmonary disease, diabetes, cardiovascular disease, renal disease, and chronic liver disease. In the over 65 year olds in the study, 37% to 56% had an underlying condition that made them at increased risk and recommended to receive pneumococcal vaccine. In those 50 to 64 years of age, this was 17% to 26%. The percentage of the subjects who engaged in any smoking was approximately 46%, and about 11% were currently smoking during the time of the study. The program's make-up can be said to grossly approximate to what a generalist physician might see in his or her practice in these age groups, and is a fairly representative population.

Dr. Paradiso shared pivotal non-inferiority comparisons from two studies, Study 3005 of 23vPS pre-immunized adults and Study 004 of pneumococcal vaccine naïve adults. Study 3005 was comprised of adults over 70 years of age who previously received polysaccharide vaccine, but not within the last 5 years. Study 004 was comprised of naïve adults 50 to 64 years of age. Study 004 is important because the investigators were able to administer another dose to this group 4 years later following the first dose to assess the kinetics of the response to the two vaccines.

In Study 3005, subjects were randomized to receive either the conjugate vaccine or the polysaccharide vaccine. The primary endpoint of this pivotal trial for licensure was to demonstrate non-inferiority of the response to the polysaccharide. A year later, many of those individuals were given a second dose of conjugate vaccine, in some cases the first dose. In terms of the ratio of the response to the conjugate over the response to the polysaccharide, if the ratio was 1 these were equivalent. If greater than 1, the conjugate was better and if less than 1, the polysaccharide was better. If the confidence intervals did not surpass 1, it was statistically significantly higher for the conjugate vaccine. The study met non-inferior criteria, which was the licensing criteria, for all of the serotypes. For 11 of the 13 serotypes, there was a statistically higher response after the conjugate vaccine. Serotype 6A is in the conjugate vaccine but is not in the polysaccharide vaccine, so in all cases there was a better response from 6A in the conjugate for that reason.

In terms of the immune response to the conjugate vaccine to a 2 microgram dose of polysaccharide in the conjugate per serotype compared to a 25 microgram dose of the polysaccharide in the polysaccharide vaccine, to induce a response such as this with two different vaccines with a tenth of the antigen is a clear indication of the fact that they are going down a different pathway when inducing an immune response. This refers back to the pathway of receiving T-cell help from the conjugate vaccine to make a better response and that primes the recipient for a subsequent response. This is important, and is also important to the regulators to show non-inferiority and better quality of response. In this study, the investigators were able to assess subjects by age. Comparing the response to conjugate and polysaccharide, regardless of the age group, the response to the conjugate was higher than the response to the polysaccharide for the majority of serotypes. A second dose of the conjugate vaccine was administered to these two populations. Following the receipt of the first dose of conjugate vaccine antibodies wane, and when a dose of conjugate is given a year later a response that is comparable or in some serotypes greater than the response of the first dose; whereas, subjects who had a previous dose of polysaccharide and is then given a dose of conjugate a year later, the antibody response is clearly blunted. The blunting of the response of the polysaccharide observed in the literature and with other polysaccharides to a subsequent dose of polysaccharide is also observed with a subsequent dose of the conjugate vaccine.

The conclusions from Study 3005 are that PCV13 induces a response in previously immunized ≥ 70 year olds that is non-inferior to 23vPS for all serotypes; statistically significantly greater response is observed for 11/13; statistically significantly higher responses to PCV13 were seen throughout the age range over 70 years; a second dose of PCV13 one year later induces a response comparable to the initial dose of PCV13; and immunization with 23vPS significantly blunts a subsequent response to PCV13.

In Study 004, adults 60 to 64 years of age were randomized to receive either the conjugate or the polysaccharide vaccine similar to Study 3005, and a non-randomized group of naïve 50 to 59 year olds received only PCV13 by direction of the regulatory authority, and a booster dose 4 years later. It is generally not recommended to administer PPSV23 to these younger adults unless they have a comorbidity that puts them at risk. The 1-month time point indicates when blood was drawn to assess immunogenicity. In this case, there was not a polysaccharide group, but the response in the 50 to 59 year olds was compared to the response to the conjugate in the 60 to 64 year olds. This was also suggested by the regulators, given that polysaccharide is not recommended in the majority of the 50 to 59 year old age group. Importantly, if the 50 to 59 year olds are given a booster 4 years later with either conjugate or polysaccharide, the response to the two vaccines can be observed in sequence.

The primary end point in the naïve subjects looks quite similar to those previously immunized. For 9 of 13 serotypes there was a statistically significantly higher response to the conjugate vaccine than to the polysaccharide vaccine. Interestingly, when the 50 to 59 year olds are compared to the 60 to 64 year olds, the 50 to 59 year olds make an even better response than the 60 to 64 year olds. There is about a 10-year average in the difference in the average age of those groups at about 52 to 53 in the 50-59 year old group and about 63 in the 60 to 64 year old group. Pfizer is also assessing lower age groups, with the best response observed in those in their 20s.

In Study 004, subsets of people with underlying conditions were also evaluated (e.g., cardiovascular disease, chronic pulmonary disease, and diabetes). While the numbers are small, Pfizer has more data across studies. This is just to show that these subjects are not immunocompromised, and they also respond well to the vaccine in comparison to the overall group. Subjects 60 to 64 years of age received a second dose of the conjugate vaccine after 3.5 to 4 years. The response was actually better to the second dose than it was to the first dose for 7 of 13 of the serotypes. This is clearly evidence that a memory has been induced that can result in a higher response. It is important to note that when a similar study was conducted with 1-year interval, results were achieved that were near those achieved with the first dose, but a considerably better response was reached at the 3.5- to 4-year interval. Therefore, this interval is probably important for a second dose.

In terms of the response of the conjugate followed by the polysaccharide vaccine compared to the response to just the polysaccharide vaccine without a first dose of conjugate, the response to the polysaccharide dose after the conjugate was better than the response to the initial polysaccharide dose. Clearly, giving a conjugate first followed 4 years later by the polysaccharide induces a response that shows that the immune system was primed with the conjugate and the response is boosted by polysaccharide 4 years later. This is an important finding in terms of giving the conjugate vaccine first in order to maximize the response.

Comparing two doses of the conjugate to two doses of the polysaccharide vaccine, for all serotypes there was a better response to two doses of conjugate. In the group who received only polysaccharide, comparing those who received only polysaccharide to people after their first dose of polysaccharide, for 8 of the 12 serotypes there was a statistically significantly lower response to the second dose of polysaccharide and the point estimates are lower for the vast majority of those.

In terms of the kinetics of the response, as an example, for serotype 1 three groups received conjugate vaccine and one group received polysaccharide. Antibody wanes over a year, and then at 3 to 4 years a dose of the conjugate or polysaccharide is given, and a response is induced that is as good or better than the initial response for the 13 types. In contrast, there is a blunted response if the polysaccharide is given followed by polysaccharide at a later time period. Looking across the average of all of the serotypes, the pattern is the same. For 7 of the serotypes, particularly 4 and 9V, the pattern is generally of priming and boosting. The important point is that at the time period 4 years later when polysaccharide vaccine is given, the ability to subsequently respond is clearly different. A study published in 2003 by Torling is probably the most comprehensive study of multiple dosing with polysaccharide in adults in which a dose of polysaccharide was given. It waned for 4 to 7 years, and a second dose of polysaccharide looked very similar to the pattern observed by Pfizer in its trials.

The conclusions from Study 004 in naïve adults are that PCV13 induces a response that differs from 23vPS both in quantity and in quality; PCV13 primes the immune system for a subsequent response to vaccination and likely infection; 23vPS induces a response that blunts future responses to either PS or conjugate even after 3-4 years; and PCV13 provides an opportunity to sustain immunity through either natural exposure or vaccine-induced booster responses. Regarding considerations for use of PCV13 in adults, in previously immunized adults ≥ 65 years of age, PCV13 induces a statistically significantly higher response that does not blunt future responsiveness. This cohort represents a large, currently unprotected population where the majority of morbidity and mortality from pneumococcal disease occurs. In naïve adults ≥ 50 year olds, PCV13 induces a statistically significantly higher response that primes for future

immunization. If the use of pneumococcal vaccine is considered appropriate, Prevnar 13® should be given first.

There was mention of the efficacy trial Pfizer is conducting in the Netherlands, which is a placebo controlled efficacy trial in adults over 65 years of age. Although it was indicated that data would be available in 2012, it is more likely to be available in the first half of 2013. The trial is completely enrolled and follow-up is currently being done in collecting cases, but it is a case-driven endpoint, so they have to reach a certain number of cases before moving on to data.

Discussion Points

Dr. Keitel inquired as to whether a forest plot was done for the groups who received two doses of conjugate versus conjugate followed by polysaccharide, and about the other serotypes that are not in the conjugate vaccine.

Dr. Paradiso responded that he did not have a forest plot for the groups who received two doses of conjugate versus conjugate followed by polysaccharide. For a number of serotypes, the response to the polysaccharide is higher than the response to the conjugate when a second dose is given 4 to 5 years later. There was quite a robust response to the polysaccharide, which he thought reflected the fact that the system is primed when 25 micrograms of antigen are given later. While he did not expect this, it was quite a nice result because it offers an option to prime with conjugate followed by polysaccharide. The 23-valent vaccine contains 11 serotypes that are not in the conjugate vaccine, but Pfizer has not assessed the immune response to those. The population of adults over the age of 65 in the US who are covered by the 13-valent serotypes contribute to about 75% of disease caused by the 23-valent serotypes. With the conjugate vaccine, there is less coverage to a certain extent, but there are priming and boosting responses as shown.

Dr. Vazquez asked whether the mechanism by which the polysaccharide vaccine induces blunting was known.

Dr. Paradiso responded that he did not know the mechanism, but there has been speculation in the literature that because of the dose level, the polysaccharide binds to the memory cells that are available and somehow causes them to no longer be available at the time of a subsequent dose of vaccine. This is sometimes referred to as hyporesponsiveness or suppression, and is fairly common for polysaccharides in general. This has been documented even more for the meningococcal polysaccharide vaccine.

Regarding the average fall off of antibody response, Dr. Bennett noted that at one year the antibody response is pretty much the same. She wondered what the expectation was for the future in terms of what the antibody levels will be, pointing out that this pertains to the correlate of protection problem.

Dr. Paradiso replied that this is important because the efficacy observed with conjugate vaccines is a combination of the response produced in the antibody and the memory induced so that someone who is exposed can respond. Pfizer does not have this efficacy data in adults with the exception of what they saw in HIV. However, it is known in children that the best example of long-term protection is a study conducted in Gambia in which 2 doses were administered to infants and they were not given a booster dose in the second year. The subjects made a nice peak of antibodies that waned quite dramatically, but they were protected against invasive disease and pneumonia out to 6 years of age. Clearly, protection is a

combination of the antibody made and the ability to respond to a challenge. This kind of kinetics with this conjugate is observed in children for pretty much all of the conjugates.

Dr. Whitley-Williams (NMA) asked about the make-up of the study population, particularly with regard to the high risk population, given that invasive pneumococcal disease is an issue also in under-represented populations such as American Indians/Alaska Natives (AI/AN).

Dr. Paradiso indicated that he did not have demographic, though he had the demographic of underlying conditions that place people at increased risk for pneumococcal disease. The population overall was representative of the US population from an ethnic perspective, but in non-native populations. That is, no native populations were included in these studies.

Dr. Marcy inquired as to whether any assessments had been done of co-administration with Menactra® and PVC13 studies in adults to determine whether there is blunting, and if not whether he thought such studies should be done. In children, Menactra® blunts some of the PCV7 responses and he wondered whether this was occurring in adults as well. Asplenic, for instance, receive both vaccines.

Dr. Paradiso responded that they had not conducted such studies.

Dr. Decker (sanofi pasteur) indicated that while he is a target of the ACIP recommendations for pneumococcal vaccine, he steadfastly refused pneumococcal vaccination until PCV13 was licensed, at which point they ordered a batch and those in his age group in the office received the PCV13. He stressed that this was a testimony to how seriously he takes the data. This has been observed consistently and uniformly for a decade. Dan Granoff and Andy Pollard wrote an interesting article in the *Pediatric Infectious Disease Journal (PIDJ)* in 2007 describing this phenomenon and making a strong call, with which Dr. Decker wholeheartedly agrees, that pneumococcal vaccine should never be used in anyone if a conjugate is available. Though speculative, the process appears to be that when one receives a polysaccharide vaccine they convert the appropriate clone of B-cells into plasma cells where they live gloriously for a few years and then are gone forever. When next exposed to antigen, the individual has very few remaining cells that can be stimulated. He has always been concerned that the more religiously 65 year olds are given pneumococcal polysaccharide vaccine, the more trouble is ensured with their response at 70 to 75 to pneumococcus. Therefore, he urged the working group to consider this, which he believes is far more important than whether the initial dose of PCV versus PPV achieves higher antibody levels. To protect someone for more than 3 to 5 years, conjugate should be administered first.

Regarding dose 2 of PCV13, Dr. Tan (AMA) wondered whether any kinetics in terms of how quickly the antibody response comes back up, especially with the more elderly population. The duration of when the antibody response rises is going to be important in terms of how quickly a person will respond to a wild challenge.

Dr. Paradiso responded that the data shown was one month after the second dose. Pfizer has not studied anything at a shorter interval, but it would be an interesting study. They have a study in which they are following subjects annually and plan to give them a second dose at 5 years with more kinetics. He said he would take back the suggestion to assess the week or two after at the antibody response.

Consideration for PCV13 Use Among Adults with Immunocompromising Conditions: Summary of Immunogenicity and Efficacy Studies**Kathleen Dooling, MD, MPH
Pneumococcal Working Group**

Dr. Dooling indicated that the policy question under consideration during this session was, “Assuming PCV13 is licensed for use in adults over 50, should ACIP recommend PCV13 for immunocompromised or other very high risk adults?”

The Pneumococcal Working Group has considered this question by reviewing a number of issues / information, including existing ACIP recommendations for immunocompromised children and adults; the burden of disease among different risk groups; the distribution of pneumococcal serotypes causing invasive pneumococcal disease (IPD) among immunocompromised adults; and reviewed published studies of the vaccine characteristics of efficacy, effectiveness, and immunogenicity.

Recalling that PCV13 is currently licensed for children 6 weeks through 71 months of age, in 2010 ACIP made an off label recommendation for PCV13 in high risk children. One dose of PCV13 is recommended for children 6-18 years old with anatomic or functional asplenia, cochlear implants, CSF leaks, and those who have immunocompromising conditions such as HIV. These children should receive 23-valent polysaccharide pneumococcal vaccine; that is, PPV23 after PCV13 with a minimal interval of 8 weeks. Children who have already received PPV23 should still receive PCV13. The rationale for the off label PCV13 recommendation in children and adolescents was that a small proportion of the population is at very high risk of disease. There was a desire to provide this group with additional protection beyond that afforded by PPV23. Does the risk in immunocompromised adults warrant similar consideration?

The current ACIP adult pneumococcal vaccination recommendations consist of 23-valent pneumococcal polysaccharide vaccine for all individuals over 64 years and those 19 through 64 years of age with high risk conditions. In those recommendations, PPV23 indications are categorized as either immunocompetent, but with underlying medical conditions such as chronic heart or lung disease or alcoholism; functional or anatomic asplenia; or immunocompromised individuals suffering from conditions such as HIV or cancer.

The off label recommendation for children and adolescents includes CSF leaks, sickle cell, congenital or acquired asplenia, HIV, hematological cancer, solid cancer, transplants, and cochlear implants. Given this array of high risk conditions, among adults, which groups are at the highest risk of invasive pneumococcal disease? In terms of the incidence of IPD among all adults, with and without underlying conditions by age, the incidence rates increase with increasing age. Adults older than 85 years have an incidence of 68 cases per 100,000 [CDC, ABCs, unpublished, 2011]. In addition to age, the incidence of IPD also varies greatly depending on underlying conditions in the host. Regarding the incidence of IPD in adults with and without underlying conditions, the rates of disease are 3- to 7-fold higher in persons with chronic medical diseases compared with the group without these conditions. Recalling that the incidence of IPD was 68 per 100,000 in persons older than 85 years, individuals with hematological cancer and HIV/AIDS have the highest risk for IPD, with over 20-fold increased rates of disease compared to persons without these conditions [CDC, ABCs, unpublished, 2011; based on Kyaw, JID 2005;192:377-86].

Returning to the initial question regarding which groups of adults are at highest risk of invasive pneumococcal disease, the rates of IPD increase with age up to 68 per 100,000 persons in those older than 85. Adults with non-immunocompromising chronic conditions have rates between 25 and 60 per 100,000. Conversely, adults with immunocompromising conditions have rates of IPD of over 170 per 100,000 persons.

The next factor under consideration regards whether the use of PCV13 in children could have indirect effects that benefit immunocompromised adults. To address this issue, it is helpful to know that early effects of pediatric use of PCV13 are already being observed on rates of IPD among young children. Comparing the rates of IPD caused by PCV13 serotypes in the quarters after PCV13 introduction to average rates of IPD before PCV13 introduction, by the end of 2010 and the beginning of 2011, statistically significant reductions had already been observed in the incidence of PCV13-type IPD [Moore, ICAAC 2011]. Although it is still too early to expect significant reductions in IPD among adults, the pediatric data strongly suggest that the vaccine is working as expected in children.

In terms of trends in cases of IPD among adults over a 10 year period, focusing on PCV7 serotypes, rates of IPD have declined dramatically in adults with and without HIV infection since the introduction of PCV7 in 2000. However, the magnitude of the remaining burden remains dramatically different. Among HIV-infected adults, the incidence of PCV7-type IPD is still more than 8 times higher than the pre-vaccine incidence in HIV uninfected adults. In other words, although PCV7 has reduced IPD rates in adults with HIV infection and without HIV infection, a very large disparity in disease rates still remains [Cohen, AIDS 2010;24(14):2253-62].

To summarize, the use of PCV13 in children probably will benefit adults with immunocompromising conditions. PCV13 serotype disease began declining in children less than a year after vaccine introduction; however, the experience with PCV7 suggests that several years of PCV13 use in children may be necessary to observe full benefit in adults. Moreover, rates of PCV13-type IPD could still be substantially higher in immunocompromised persons even after the indirect benefits are realized.

Regarding the policy options ACIP should consider for pneumococcal prevention in immunocompromised adults, there are three general strategies to consider. Option 1 would be to maintain the status quo with PPV23 alone. Option 2 could involve schedules where both PCV13 and PPV23 are given. Option 3 could involve schedules where PCV13 is used and PPV23 is not used. Given that the two vaccines include different serotypes, it is important to consider the proportion of IPD caused by the serotypes in each vaccine. Dr. Dooling noted that the specific schedules for each of the options would be discussed by the working group in future ACIP meetings.

With respect to the proportion of IPD caused by serotypes included in both vaccines, among adults with immunocompromising conditions and adults with no high risk conditions, the proportion of PCV13 serotype disease in immunocompromised is substantial at 50%. The additional serotypes in PPV23 which are not found in PCV13 account for 21% of IPD in immunocompromised adults. Therefore, a PCV13 only schedule would miss the opportunity to vaccinate against serotypes causing 21% of disease in this population. Regarding the rank order of serotypes among adults with HIV infection, as with other populations, 19A has emerged as the most common strain. For people living with HIV, the proportion of IPD due to serotypes in PPV13 is 38% while disease due to all PPV23 serotypes accounts for 57%. Disease caused by a serotype not in either vaccine is 43% [CDC, ABCs, unpublished, 2011].

Importantly, PCV13 has the potential advantage of preventing IPD caused by serotype 6C. The serotype 6A antigen, which is included in PCV13 but not in PPV23, has recently been shown to cross-react with serotype 6C pneumococci [reference is Cooper, Vaccine 2011;29(41):7207-11]. Therefore, it is possible that PCV13 could provide protection against an additional 5% to 10% of IPD among HIV-infected adults. At this time, the burden of disease due to PPV23 serotypes not included in PCV13 makes policy options that would exclude PPV23 suboptimal. In addition, there are no clinical trials which compare the two vaccines directly; therefore, it cannot be said with certainty whether one vaccine works better than the other.

Given the serotype advantages of PPV23 compared to PCV13, consideration was given to how well current use of PPV23 protects immunocompromised adults from pneumococcal disease. The only randomized controlled trial examining PPV23 efficacy in those who are immunocompromised was done in Uganda. Although 44% of the study population had CD4 counts less than 200, 41% of vaccine recipients achieved the immunologic endpoint of a doubling of serotype IgG, proving that the vaccine was immunogenic in some. With respect to clinical endpoints, vaccine serotype IPD was more common in the vaccinated group, although this increased hazard ratio was not statistically significant. All-cause pneumonia did have double the hazard ratio in vaccinated compared to unvaccinated, and this was statistically significant [French, Lancet 2000; 355(9221):2106-11].

In contrast to the Uganda study, observational studies that have been conducted more recently in HIV patients with access to antiretroviral treatment have shown protective effects of PPV23. A retrospective case control study with 184 cases matched with HIV+ hospital controls showed an adjusted odds ratio of 0.44, or in other words, a 56% decreased odds of pneumococcal disease among the vaccinated compared to the unvaccinated¹. A retrospective cohort analysis in the USA with the endpoint of pneumonia or IPD demonstrated a 35% decreased risk of disease in the vaccinated group². Finally, a second cohort study of 60,000 adults and adolescents showed a reduced risk of all-cause pneumonia among PPV23 recipients with viral loads of <100,000³ [¹Penaranda CID 2007;45(7):e82-7; ²Rodriguez-Barradas CID 2008; 46 (7): 1093-1100; ³Teshale, Vaccine 2008;26(46):5830-34].

Returning to the question of whether PPV23 protects immunocompromised adults, there is somewhat conflicting evidence. The only RCT of PPV23 in HIV-infected adults suggests no protection and possibly a harmful effect. However, this study was done in a population very different from HIV-infected adults in the US. Observational studies that have been performed in ARV treated populations suggest that PPV23 is effective, especially when patients are virologically controlled. However, some members of the working group expressed concern that these observational studies may overestimate the vaccine effect due to confounding. In summary, it is thought that PPV23 likely does benefit HIV-infected patients in the US, but the magnitude and duration of that protection are unclear.

The working group also considered some additional limitations of PPV23. These include the lack of effectiveness in reducing nasopharyngeal colonization with pneumococcus; the lack of RCT evidence of efficacy in immunocompromised individuals; the lack of consensus on the effectiveness against non-bacteremic pneumonia; that revaccination is not recommended within the first 5 years; and that only one lifetime revaccination limits the long-term benefits of this vaccine.

Given the limitations of PPV23, the working group then considered whether there were any data to support the idea that PCV13, when used in combination with PPV23, could offer any advantages over PPV23 alone. Although limited data are available to assess efficacy of conjugate vaccine in the immunocompromised adult, we can draw from studies in the immunocompromised child. Klugman et al conducted a randomized controlled trial of PCV9 in almost 40,000 children in South Africa. Among HIV uninfected children the vaccine efficacy was 83%; whereas, in the HIV infected children, the vaccine efficacy was 65%. The vaccine did not demonstrate statistically significant protection against pneumonia among HIV+ children [Klugman *NEJM* 2003;349(14): 1341-8].

An RCT examining the efficacy of PCV7 was conducted among HIV-infected adults in Malawi. The study recruited individuals who had recovered from an episode of IPD. Approximately 13% of the enrolled patients were on antiretrovirals. The study demonstrated a 74% vaccine efficacy in preventing vaccine serotype IPD and 25% efficacy in preventing all-cause pneumonia, which was not statistically significant. Importantly, some of the cases of all-cause pneumonia actually had IPD, so it is not possible to estimate from these data the efficacy of PCV13 against non-bacteremic pneumococcal pneumonia [French *NEJM* 2010;362(9):812-822].

The working group also considered some hypothetical benefits of PCV13 against non-invasive pneumococcal pneumonia, the burden of which is substantially higher than for invasive pneumococcal pneumonia. First, multiple trials of conjugate vaccine in children have documented prevention of non-invasive pneumococcal pneumonia. Conjugate vaccine use in children clearly prevents colonization of vaccine strains, and if PCV use in immunocompromised adults also prevents colonization with vaccine serotypes, then prevention of microaspiration of those serotypes is plausible.

The working group also reviewed data on immunogenicity of pneumococcal conjugate vaccine in immunocompromised adults. PCV does elicit an immune response in HIV+ and cancer patients^{1,2,3,4,5,6}. Response following a single dose of PCV is as good as or better than PPV23 for both vaccine naïve or previously vaccinated^{1,2,3}. Studies with sequential vaccination show similar or improved immune response if PCV is given first^{1,2,3}. Revaccination with PCV shows a similar response compared to the response to the first dose⁴ [¹Feikin *Diag Lab Immunology* 2004, ²Lesprit *AIDS* 2007, ³Penaranda *AIDS* 2010, ⁴Miro *JID*, 2005, ⁵Chan *JID*, 1996, ⁶Crum *JID*, 2010].

The working group did reach consensus on several points, including agreement that the burden of pneumococcal disease is high in the immunocompromised population. Disease due to PCV13 serotypes is likely to decrease in adults due to indirect effects from the pediatric program; however, the magnitude and timing are uncertain. It was felt that opportunities for prevention of pneumococcal disease, beyond that which can be achieved with PPV23, should be sought. There are theoretical benefits of PCV13 regarding mucosal protection with direct vaccination; however, the evidence is pending from an on-going clinical trial in the Netherlands. Finally, it was acknowledged by the working group that providers and expert groups will be looking to ACIP for guidance regarding PCV13 use in adults as soon as it is licensed.

The working group felt that there were several areas that required further discussion. For example, consideration must be given with regard to how to weigh the evidence. RCTs have strong study designs, but have been conducted in vastly different study populations. On the other hand, the observational studies have weaker study design but more comparable study populations. Another issue for further discussion regards whether and how long to await herd effects to prevent disease in immunocompromised groups. Additionally, consideration must be

given to populations with rates of IPD in between those of the general population and those with immunocompromising conditions. There are many unresolved issues regarding a schedule that might recommend 2 pneumococcal vaccines for adults, and considerations for possible revaccination. Given these discussions by the working group, ACIP members were asked to share their thoughts regarding the question, "What are the most important pros and cons of vaccinating immunocompromised adults with PCV13?"

Discussion Points

Dr. Keitel inquired as to whether, in the observational studies of polysaccharide vaccines, the interval before subjects received the vaccine was indicated.

Dr. Dooling replied that most of the observational studies had a study period from 3 to 5 years following receipt of vaccine.

While Dr. Decker (sanofi pasteur) thought the working group's focus on immunocompromised adults was important, he thought it was even more important to remember that the routine recommendation for PPV at age 65 affects a very large group of Americans. The data shown earlier illustrated that the risk of pneumococcal disease begins rising very steeply at age 65. Based on the available clinical trial and immunological data, the conclusion can be made that the current recommendation provides good protection for those ages 65 to 70, but may very well increase risk thereafter during the next two decades when the risk is already rising rapidly. Thus, he urged the working group to consider that the most appropriate way to reduce the risk of IPD in persons 65 years of age and above is to first receive a dose of the broadest spectrum available conjugate vaccine, which is currently PCV13, followed by an appropriate interval of PPV23. This will protect many more people than the groups discussed during this session.

Dr. Grabenstein (Merck) indicated that he was reviewing the 1997 ACIP recommendations for adult pneumococcal vaccination, especially the part about the recommendation for revaccination policy. It fundamentally stated that ACIP was not going to make a recommendation, given that there was limited data. There were a handful of studies with a few dozen patients each, which was not very impressive. However, 14 years have passed and there is other literature that has not yet been discussed. The most relevant study was conducted for the Alaska Department of Health assessing functional antibodies in people receiving their second dose of PPV23, their third or fourth dose of the 23-valent vaccine, and showing comparable responses despite advanced age compared to the first dose of the 23-valent vaccine. In addition, the 10-year kinetics of the antibody response to PPV23 are known. His council is that intervals matter. While ACIP had seen a few intervals (e.g., between doses, for serology) they had not seen a number of other intervals. All of the information should be taken into account while ACIP considers what the right policy would be. His suggestion was to ensure that the whole literature is reviewed before reaching decisions.

Dr. Schuchat reminded everyone that as the working group reviewed the incredibly complex set of issues over the next year or so, the GRADE system would be incorporated into the process. There are a number of older recommendations for a lot of indications, along with numerous questions going forward. Helping the committee understand where the data are strong and not as strong will be beneficial.

General Recommendations: Febrile Seizures

Update on Febrile Seizures and Vaccines

Jeff Duchin MD, Chair General Recommendations Working Group

Dr. Duchin presented an updated analysis on the risk of febrile seizures, reviewed the actions taken to-date by the Febrile Seizures Working Group and ACIP, and discussed future plans. He reminded everyone that an analysis was presented during the June 2011 ACIP meeting from the Vaccine Safety Datalink project that suggested an attributable risk of febrile seizure with TIV + PCV13 in 12 through 23 month age group of 42/100,000 or 1 per 2375 vaccinees. An updated analysis was presented to the Febrile Seizures Subgroup in August 2011 that suggested an attributable risk of febrile seizure peak at 16 months at 45/100,000 or 1 per 2225 vaccinees.

The Febrile Seizures Subgroup concluded that the updated analysis was consistent with previous risk estimates, and no changes in the childhood immunization schedule were recommended. ACIP continues to recommend that both vaccines be given at the same visit, if indicated. Information for health care providers and parents published on CDC vaccine safety website: www.cdc.gov/vaccinesafety/Concerns/FebrileSeizures.htm. The updated vaccination statement for the 2011-2012 season includes a statement about the potential increase of febrile seizures caused by the combination of inactivated influenza vaccine and pneumococcal vaccine.

An additional task for the Febrile Seizures Subgroup was to develop a framework for determining when vaccine-associated febrile seizures should lead to a change in ACIP recommendations. To that end, the following factors were taken into consideration:

- ☐ Confirmation of febrile seizures through review of clinical data and standardized classification
- ☐ Level of certainty vaccine is causing observed increased in seizures
- ☐ Timing of seizures related to vaccine administration
- ☐ Magnitude of effect
- ☐ Additional factors that might influence or confound the association, such as increase in naturally-occurring infection, medications, and underlying medical conditions
- ☐ Age stratified rate and relative risk of vaccine-associated febrile seizures and resulting numbers expected in the population
- ☐ Association with administration of a single vaccine, multiple vaccines, or specific vaccine doses in a series
- ☐ Evidence for potential explanations (e.g., new product, new vaccine ingredient or manufacturing process, adulterant, et cetera)
- ☐ Age stratified benefits of vaccine(s) associated with seizures (key outcomes prevented)
- ☐ Effect of vaccine(s) on preventing febrile seizures
- ☐ Whether the association is expected to be temporary or on-going
- ☐ Potential for change in recommendations to result in missed opportunities to vaccinate or unintended decreased vaccine uptake with resulting increase in naturally-occurring infections

- ☐ Acceptability to healthcare providers and the public of potential options under consideration for change in recommendations
- ☐ Programmatic implications and feasibility of making changes in recommendations

Future General Recommendations Working Group Activities

Andrew Kroger MD, MPH

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

Dr. Kroger indicated that there was an initial set of topics that would be taken forward with the reconstitution of the entire General Recommendations Working Group, moving beyond febrile seizures to assess other issues. First, there will be on-going febrile seizure surveillance. The framework has been developed for the particular issue of TIV and PCV13, it can be used for other vaccines/issues as well. There are many safety issues on the list. Hundreds of updates need to be made to align information in the general recommendations with the vaccine-specific statements that are published. This will be a three- to five-year process.

The working group will have to work through a number of issues pertaining to contraindications and precautions, one of which is chronic moderate/severe illness. Acute moderate/severe illness is considered to be a precaution generally with vaccines. There are various events that may be specific to one vaccine, and the question has been raised in the past regarding whether such illnesses (e.g., Guillain-Barré syndrome, arthus reactions, anaphylaxis to eggs) should be harmonized across all vaccines. There are also administration issues, and it has been quite a while since this issue was raised in the general recommendations, but it was too late to incorporate changes in the most recent publication.

Another issue that has arisen pertains to vaccination under anesthesia, for which there are also safety issues and there may be efficacy issues as well. There are also new data about various vaccination sites, such as the deltoid versus the thigh for school age children. There is also interest in reviewing vaccination records (provider records and personal records taken from the provider) and recording more information in them such as site, route, and dose.

Again, this is just some information regarding on-going topics. The at-large General Recommendations Working Group will be reconstituted. Dr. Kroger thanked the Febrile Seizures Subgroup for the work that they have done. He asked those on the General Recommendations Working Group to be prepared to address the issues he just reviewed, and invited any of those on the Febrile Seizures Subgroup to let him know if they would like to become involved in the broader issues as well.

Discussion Points

Dr. Marcy requested further discussion regarding vaccination under anesthesia, and whether by “efficacy” he meant efficacy of the vaccine or of the anesthesia.

Dr. Kroger replied that he could not expand very much since the issue has not yet been addressed. While the concern regarding efficacy pertained primarily to the vaccine, he thought both vaccine and anesthesia efficacy needed to be studied.

Dr. Pickering added that CDC received several questions about this issue, and the concern regarded whether being under anesthesia when given a vaccine might interfere with vaccine efficacy. There is no pain when vaccine is administered under anesthesia, which is the thought process for this procedure.

Dr. Ehresmann requested information regarding who was utilizing this practice and in what setting.

Dr. Pickering said the articles he had seen and the inquiries they received regarded people who were having surgery and were being immunized at that time. It is a good thought process that practitioners are thinking about the opportunity to immunize people who are having surgery. The question regards whether anesthesia will interfere with vaccine efficacy.

Dr. Turner (ACHA) said that while he was not a proponent of administering vaccine under anesthesia, he vouched for the fact that there is profound needle phobia among some young adults. He knows of several students who refuse to have blood drawn even if they are thought to have mumps, for example. This is quite a remarkable phenomenon, and they had to put special carpet in their vaccine area because so many people pass out. Syncope and phobia are real issues, so vaccinating under anesthesia is an interesting concept.

Dr. Temte said that from his experience, a lot of developmentally delayed young people will go in for a dental examination under anesthesia, which is an ideal time to administer vaccinations. This is especially true for some individuals who respond violently to immunizations or blood draws. Immunization under local anesthetic is fairly common in some practices.

Ms. Stinchfield (NAPNAP) emphasized that it is important to assess whether it is general or local anesthesia. A lot of different medications/technologies are being used, so it is important to clarify what they are. She thought vaccines in the operating room could be challenging, not only with regard to efficacy, but also in terms of the staff being prepared and knowing how to manage vaccines. One issue for hesitant parents is pain, so trying to reduce pain in vaccines may have a tradeoff.

Dr. Coelingh (MedImmune) requested clarification regarding what the relationship would be between the ACIP definitions of “contraindications” and “precautions” versus what is stated on the package inserts.

Dr. Kroger responded that clarifying what constitutes contraindications and precautions is broader than just the work on general immunizations. Package inserts often contain a subheading “warning”, and there is not complete harmony between CDC and FDA on this issue currently. In the context of influenza vaccination, there is a lot of use of the term “hypersensitivity.” Recalling the presentation from the previous day on the adult vaccination schedule, he reminded everyone that the Adult Immunization Schedule Working Group would be publishing a contraindications and precautions table on a yearly basis. The word “hypersensitive” will appear under LAIV as distinct from TIV, which is appropriate to some extent. ACIP is talking about a broader scope of reaction that should be considered, not a contraindication in which TIV should be preferred over LAIV (e.g., hives). The term “hypersensitive” is so broad, perhaps there should be more specificity than use of that term.

Pertussis

Mark Sawyer, MD, Chair ACIP Pertussis Vaccine Working Group

Dr. Sawyer reported that while pertussis is out of the headlines, disease continues to occur. In his community in San Diego, more cases have been observed this year than during the previous peak, not counting last year, which was a very big year. Given that pertussis continues to be an issue, the Pertussis Working Group will continue to meet.

The terms of reference under which the Pertussis Working Group was constituted include the following, most of which were dealt with in the last few years:

- ☐ Review existing statements on infants and young children (1997), adolescent (2006), adults (2006), and pregnant and postpartum women and their infants (2008) and consolidate into a single statement. This term of reference is presently being worked on.
- ☐ Review new data on Tdap including:
 - Effectiveness of ACIP recommendations
 - Interval between Td booster and Tdap
 - Use of Tdap in adults ages 65 years and older
 - Pregnant and breastfeeding women
 - Use of Tdap
 - Cocooning strategies
 - Vaccinated healthcare personnel and need for post-exposure prophylaxis
 - Tdap revaccination
- ☐ Review updated epidemiology of tetanus and diphtheria

Licensure of Boostrix® was extended to persons aged 65 years and older, and announcement of this was published in the September 2011 *MMWR*. The week prior to this ACIP meeting, ACIP's updated use of Tdap in pregnant women and persons anticipating contact with young infants was published. In the future, the working group will review the use of Tdap in all persons aged 65 and older. The previous recommendation was focused only on those with anticipated contact with young children. In light of the FDA licensure of the vaccine, the working group is reviewing the epidemiology and relevant literature about all older individuals. This will include an assessment of cost-effectiveness, as well as a review of the current recommendation. The major topic upon which people are looking forward to advice regards the need for Tdap revaccination. The working group is in the process of reviewing existing data and will update ACIP on this issue during the February 2012 ACIP meeting. There will be an update on the overall ACIP pertussis statement, which will subsequently be published.

Discussion Points

Dr. Plotkin (Vaccine Consultant) inquired as to whether the working group planned to review the recent data regarding the duration of immunity after the initial infant dose, noting that a significant amount of data were presented on this topic during the recent Infectious Disease Society of America (IDSA) meeting.

Dr. Sawyer responded that the working group would include an assessment of duration of immunity after the initial infant dose in the context of whether/when revaccination with either product would be necessary.

Immunization Coverage of Children / Adolescents

Lance E. Rodewald, M.D.

Immunization Services Division

National Center for Immunization and Respiratory Diseases

Centers for Disease Control and Prevention

Dr. Rodewald said he liked to think of the National Immunization Survey as a report on how well the nation is immunizing the community, and how well doctors, nurses, public health professionals, and especially parents are doing at protecting children from vaccine-preventable diseases by following ACIP's recommendations. During this session, he reported on coverage for young children and teenagers; variation by race, ethnicity, poverty, and state; and changes over time.

A comparison between 2009 and 2010 NIS 19-35 month old coverage levels shows that the fourth dose of DTaP vaccine continues to be a struggle. Polio coverage was high. MMR coverage increased by about 2 percentage points. The agency was concerned when it went down to 90%, but it is now back up to 92%. Hepatitis B coverage has stayed high and varicella coverage finally reached 90%. For PCV 4-dose there is a little room to improve. For hepatitis A and rotavirus vaccines the Healthy People objectives are 60% and 80%, respectively. The change has been positive for all of these vaccines, except for hepatitis B vaccine, which stayed steady at above the Healthy People objective of 90% [Source: NIS at www.cdc.gov/vaccines].

In terms of state-by-state coverage, basically coverage is high for all of the vaccines recommended in terms of the national average: MMR 1+ Doses (91.5%), Hib Primary Series (92.2%), Hib Full Series (66.8%), PCV 4+ Doses (83.3%), Rotavirus Series (59.2%). Even during the Hib vaccine shortage, the primary series never decreased below 90%. This was very difficult to do, given that allocation of vaccination was a major challenge to immunization programs and doctors and nurses. There was also a hepatitis B vaccine shortage at the same time, so this was quite an accomplishment on the part of practitioners. The goal of 90% for PCV 4+ doses is anticipated to be reached by 2020. While the rotavirus rate was up approximately 15%, there remained a fair amount of state-by-state variation. This seems to be how the US system work, with each state having a somewhat different pace of uptake of newly-recommended vaccines. There is another 20% to go before rotavirus vaccine uptake reaches the 60% national objective.

Very important to the program is coverage by race and ethnicity. In general, there is little difference by race and ethnicity according to the 2010 NIS. However, there is a statistical difference for 4+PCV and rotavirus between white non-Hispanics and black non-Hispanics. More work needs to be done in this respect. In terms of coverage by poverty level, that same gap is observed for PCV and rotavirus vaccines. However, in general, variation by poverty level is not that great. This may be due to the VFC program, which is designed to help financially vulnerable children have access to vaccines. The long view for young children looks pretty nice. While not perfect, coverage is strongly positive. Rotavirus has only two data points, so it is unclear exactly what will occur with that vaccine [www.cdc.gov/vaccines].

In terms of teen coverage, based on the comparison between 2009 and 2010 NIS-Teen 13-17 year old coverage levels, coverage increased for every vaccine. HPV was disappointing because coverage for this vaccine did not increase nearly as much compared with the other two teen vaccines. Coverage for HPV vaccine for females is plateauing and 3-dose coverage is problematic. National average coverage was as follows for the recommended vaccines: Td/Tdap (81.2%), Tdap (68.7%), Men-ACWY (62.7%), HPV 1st Dose (48.7%), HPV 3-Dose (32%). There is a lot of state-by-state variation for Tdap, which seems to be a common theme with all newer vaccines. Men-ACWY coverage has had a remarkable increase in coverage [NIS-Teen at www.cdc.gov/vaccines].

In terms of race and ethnicity, there are few disparities. White non-Hispanic teenagers are not the highest coverage group with any of these vaccines, and there is very little difference by race and ethnicity. This is perhaps somewhat of a program effect, though this is not known for certain. Just like for young children, coverage by poverty level is similar among teens. As Dr. Schuchat has pointed out before, even though children below the poverty level have somewhat higher coverage with the HPV 1st dose, children above poverty level have somewhat higher completion rate. This is of concern. Taking the long view, the trajectory of teen vaccines is in the positive direction. However, the slope is much less for teen vaccines than for young children vaccines, and there is a plateau of HPV 3-doses [NIS-Teen at www.cdc.gov/vaccines].

In conclusion, coverage for every vaccine has increased. Substantial gains have been made for MenACWY, Tdap, rotavirus, and varicella 2nd dose. Coverage levels for vaccines recommended prior to PCV are above the Healthy People 2020 objectives. Zero-dose children remained below 1%. Coverage with newer vaccines is substantially below Healthy People 2020 objectives, so more work needs to be done in this area. Disparities by race/ethnicity and poverty remained small or decreased with the exception of rotavirus and PCV13, which showed modest disparities. Disparities by state are larger for the newer vaccines.

Discussion Points

Dr. Bennett asked what the prospects were for ever being able to track adult immunizations with the same degree of specificity, and whether there were any plans for validation or whether this would continue to be self-report.

Dr. Rodewald responded that this would be a good topic to bring before ACIP. In terms of coverage, there is a lot of work. Currently, there is information regarding national level coverage through the NHIS, and there is information on influenza and pneumococcal coverage in the BRFSS. Carolyn Bridges and Jim Singleton have been working very hard with BRFSS to make sure that information is obtained about coverage with zoster and other adult vaccines. At this point, it appears that there will be information on one or several of the adult vaccines and basically state-by-state information on at least an alternative year basis for all adult vaccines. It

was his understanding that information would still be obtained from self-reports and that there were no current plans for a validation process.

Dr. Jenkins noted that Dr. Rodewald's first slide showed zero-dose, and wondered whether that referred to children who had never been immunized.

Dr. Rodewald replied that this was correct. This is children who, when they check the records, had not received any vaccinations. The Healthy People 2020 objective is to keep the number of zero dose children below 1%. Currently, it is 0.7%. A *New England Journal of Medicine* (NEJM) article showed that there are sub-state areas in many states that have much lower coverage. So high coverage at a state level or zero-dose coverage can really mask coverage problems in smaller areas. A lot of states are using and tightening up the school immunization laws to make sure that when a parent exempts their child, they really understand the risk of an exemption. Dr. Rodewald thinks that will keep the number of zero-dose children low.

Dr. Jenkins wondered whether Dr. Rodewald had a chart of the state mandates. It seemed to her that there was considerable variation among states, especially with regard to meningococcal vaccine.

Dr. Rodewald replied that some histogram charts were created, one of which has the states with mandates in a different color. These showed that states having mandates had higher coverage levels.

Ms. Rosenbaum asked whether anything was known about children being immunized in the broader settings that are beginning to emerge for adults. Pharmacy-based immunizations are common, but she wondered whether administration was still concentrated in clinical offices and schools for children.

Dr. Rodewald responded that a significant amount of influenza vaccination is occurring outside the doctor's office. CDC is modifying the NIS, especially with respect to influenza vaccination, in order not to miss the various providers. It is believed that a fair amount of influenza vaccine is administered by pharmacists to teenagers. Schools are another setting in which vaccination is being done. They want to ensure that the survey does not miss those children. In general, the US seems to have embraced the idea that immunizations should be woven into the fabric of society and the fabric of the primary care system, and that it is part of keeping children healthy. The primary care system has done a fabulous job of vaccinating young children. There remain challenges with teenagers. Every year, influenza vaccines face additional challenges.

Dr. Marcy wondered whether the lowest three or four states had been assessed to determine the reason for the lower administration levels. He asked Dr. Rodewald to postulate the reason for the failures if was not due to race or poverty.

Dr. Rodewald said he thought someone from the immunization program might be better able to address this. He thought one issue was that there are so many priorities, introducing newer vaccines in adolescents may not be perceived as a priority. This is a new burden on programs. Some of the states that had high coverage talked about their Governor's involvement as a facilitator (e.g., a lot of political will and commitment, and a concerted effort). CDC wants to help states prioritize lagging vaccines.

Ms. Ehresmann indicated that some states have a universal policy through which all vaccines are provided, but some states do not. Some states may have a policy through which they are only able to provide vaccines through the VFC and are not able to augment for under-insured populations. Minnesota had an active group of individuals who have expressed concerns about vaccines, which can influence perceptions within the general population. States like Washington and Oregon are challenged by having highly educated parents who are hesitant about vaccines. All of those factors play a role, so the challenges are multi-factorial. Each state has its own “landscape of speed bumps” to navigate.

Dr. Rodewald thought the new HEDIS measure would be beneficial with regard to HPV vaccine. HEDIS measures went into effect for meningococcal and Tdap vaccines, which will help bring attention to commercial managed care plans and managed Medicaid plans, and will have a strong positive effect. It may have already started to have an effect on the first two adolescent vaccines.

Dr. Bocchini wondered whether it was implementation or the strict time period in which a child can be vaccinated with rotavirus vaccine that was playing a role in the rates of uptake.

Dr. Rodewald replied that one of the Healthy People objectives is 80% uptake because there is no possibility for catch-up once the child is past 8 months of age. While uptake is anticipated to be higher next year, the tight timing is an issue in terms of coverage and objective setting among programs. Rotavirus coverage included which ever vaccine was used (the 2-dose vaccine or the 3-dose vaccine), so it was not an artifact of needing a 2-dose or 3-dose vaccine.

Dr. Kimberlin (AAP) wondered whether the state-by-state variability clustered in certain regions of the country and, if so, what those regions are.

Dr. Rodewald replied that based on the maps, the Northeast tends to be a little higher than the rest of the country and the West tends to be lower. However, there are exceptions. His sense is that it is possible to achieve high coverage, and this does occur over time. Sometimes it is basically a difference in slope. All states are going to reach the goal, but some will just do so faster than others.

Dr. Schuchat indicated that HPV coverage is lower in the Southern states where, of course, cervical cancer rates are higher. That is another distressing statistic. However, uptake of teen vaccines is very dynamic and differs in various areas.

Regarding vaccines for young children outside of the routine settings, Dr. Vazquez indicated that she has been conducting active surveillance for the past three years for influenza hospitalizations in Connecticut. Part of their protocol is to look for documentation of influenza protocol. It is very surprising to her that 5% to 7% of parents and physicians insist that vaccinations were given at Target or Walgreens, but there will be no documentation. There is also no documentation in the Connecticut immunization registry. Therefore, it is unknown what type of vaccines children received or whether they received the vaccine previously and what type of vaccine was received then. She is concerned that lack of documentation will persist and increase.

Dr. Rodewald emphasized the importance of being able to measure changes in the system, and that the surveys and registries should be nimble enough to do this.

Claire Hannan (AIM) stressed that there are additional challenges with adolescents that do not necessarily fall into the formula of success with childhood vaccines, and there are varying priorities in states. The challenges are unique. Some states have vaccine hesitancy, some states have priorities with funding, et cetera. AIM will continue to work with CDC to determine what is working, and will share that with the states that are struggling. This is somewhat of a frontier. Everyone has used a strong formula of infrastructure for childhood, and AIM and CDC are trying to determine what works and what is needed in each state.

Vaccine Supply

Dr. Jeanne Santoli
Vaccine Supply and Assurance Branch
Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Santoli offered an update on the vaccine supply for adult hepatitis A vaccine, and MMR-V vaccine, zoster vaccine.

With regard to hepatitis 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 usage of adult hepatitis A vaccine.

In terms of MMR-V vaccine, Merck is committed to returning ProQuad® to the market. Details on timing and availability will be provided at a later date. This was discussed in the context of the connection between MMR-V and zoster vaccine in other meetings. Merck has adequate supply of both M-M-R II® and VARIVAX® to meet current demand.

With respect to zoster vaccine, Merck has made significant progress in fulfilling customer orders, shipping in every month since February 2011, with increased quantities versus 2010. Customer wait times are currently running approximately 2 to 3 weeks. In June wait times were 2 to 3 months, so this is a significant improvement. Merck expects to maintain the current wait times as they build sufficient inventory to resume normal shipping.

CDC's Vaccine Supply/Shortage Webpage is available at:

<http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm>

Discussion Points

Dr. Gorman (NIH) pointed out that the issue of pediatric drug shortages has gained a great deal of political traction lately. There are several bills presently moving through Congress, which may offer an opportunity to address vaccine shortages at the same time.

Measles

Introduction

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

Dr. Temte reported that the MMR Working Group's recent activities have been directed entirely toward measles vaccination policy, an overview of the US measles vaccine program and epidemiology during the post-elimination era, a review of current recommendations, a review and discussion of measles seroprotection among children with perinatal HIV infection, and a review and discussion of issues regarding immune globulin use as post-exposure prophylaxis for measles. This session addressed the epidemiology of measles in the US, the measles outbreak in Canada, measles prevention activities in Mexico, measles vaccination among children with HIV infection, and a summary of working group considerations.

Epidemiology of Measles in the United States

**Huong McLean, PhD, MPH
Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention**

Dr. McLean presented an overview of the epidemiology of measles in the US, with an emphasis on the period after elimination was declared through 2011. Before vaccine licensure, there were an estimated 3 to 4 million cases of measles each year, which resulted in 400 to 500 deaths; 48,000 hospitalizations; and 4000 cases of encephalitis. Following licensure in 1963 and a 1-dose recommendation, the number of cases of measles declined dramatically, reaching record lows in the 1980s. However, in the late 1980s, there was an increase in the number of cases. A substantial portion of cases occurred in school-aged children who had received one dose of measles vaccine. This prompted ACIP to recommend a second dose for children 4 to 6 years of age in 1989. Before the second dose recommendation was fully implemented, the US experienced a resurgence of measles cases.

During the resurgence from 1989 through 1991, there were more than 55,000 cases of measles. Many of these cases occurred among unvaccinated preschool aged children, particularly among minorities in urban areas. The US had focused control strategies on vaccinating school-aged children, but not on on-time vaccination. Following the resurgence, the VFC was created as a financial mechanism to provide uninsured and under-insured children vaccines at no charge. These efforts to increase coverage resulted in less than 150 cases per year between 1997 and 2000. In 2000, measles transmission was declared eliminated in the US. Since 2001, the number of cases reported averaged about 60 to 70 cases each year.

The US is currently experiencing an increase in the number of cases in 2011. In 2011, incidence is relatively low at 0.7 per million cases, but this is an increase from 0.2 per million cases in 2010. There was also an increased number of cases, and an increased number of outbreaks. In 2011, there have been 16 outbreaks. The previous high was 10 outbreaks. The percentages of cases, importations, hospitalizations, and unvaccinated individuals for 2011 fall within the range of other years. There is little annual difference in the age distribution of cases

among US residents from 2001-2011. There were very few cases among infants less than 6 months of age, who are too young for vaccination (1%). Infants 6 to 11 months of age, who are also too young for routine vaccination, accounted for 13% of cases. Note that approximately one-third of the cases in this age group could have been prevented if they had been vaccinated prior to international travel. Infants 12 to 15 months of age, the age recommended for the first dose of vaccine, accounted for 7% of the cases. Adults 20 to 39 years of age accounted for 26% of the cases.

Pertaining to age-specific incidence over time, without circulation, measles epidemiology is determined by the age of importation and who they expose. In big years, such as 2008 and 2011, there were increases in all age groups. The largest number of cases was in the exposed groups with the most susceptibility, primarily infants 6 to 11 months of age and 12 to 15 months of age. Although these age groups comprise a small proportion of the cases, they do have the highest incidence. The optimal age for first dose is a topic that will be discussed in the working group. Still, the incidence in the young age groups is relatively low at 2 to 4 cases per million in normal years. Also in recent years, incidence in those 16 months to 4 years of age appears to be increasing. About 15% of those in this age group have been vaccinated with 1 dose, so this may also prompt discussion of optimal timing of the second dose in the working group.

In terms of vaccination status in the US between 2001 to 2011 in residents aged 1 to 19 years, most of the cases were in unvaccinated individuals. In more recent years, more than 85% of cases were among unvaccinated children and adolescents or those whose vaccination status was unknown. A substantial number of adults 20 years of age and older have unknown vaccination status. This presents considerable challenges in understanding the role of waning immunity. With regard to reasons for non-vaccination in US residents from 2008 to 2011, among children and adolescents ages 1 to 19 years of age, 74% had a religious or personal exemption to vaccination, and 17% were missed opportunities. That is, they were eligible for vaccination, but for various reasons they remained unvaccinated. Most adults with known status (52%) had philosophical objections. Note that among adults there are less data because most adults have unknown status.

Regarding measles outbreaks in the US from 2001 to 2011, the percentage of cases associated with outbreaks ranged from 22% in 2001 and to 77% in 2008. In 2011, 50% of cases were associated with outbreaks, which is within the range of other years. Although there was an increased number of outbreaks (n=16 in 2011), the outbreak size appears to be limited. The median outbreak size for 2011 is 5.5 cases. With respect to the economic impact of a measles outbreak, although it is difficult to compare and evaluate cost data, four studies offer an idea of how resource-intensive and costly an outbreak can be at a range of \$5,000 to over \$167,000 per case [Dayan et al, *Pediatrics* 2005;116:e1-4. Parker et al, *NEJM* 2006;355:447-455. Sugarman et al, *Pediatrics* 2010;125:747-755. Chen et al, *JID* 2011;203:1517-1525].

With respect to import classification of cases, between 2001 and 2011, 40% of cases were classified as importations and another 48% were classified as import virus-associated (20%) or import-linked (28%). Most of the importations were among US residents who traveled overseas and brought the disease back. In terms of importation status over time, importation varied from year to year. While there has been an increased number of importations in 2011, spread from importation appears to be limited compared to 2008, the last big year, when there were very few importations, but much more spread. Regarding where importations are originating, early in the elimination years many of the importations came from the Western Pacific Regions (e.g., primarily China and Japan). With measles control in that region, there have been fewer importations over time. Importations are consistently observed from Southeast Asia (e.g.,

primarily India). In recent years, the number of importations from the European region have increased. In 2011, half of the importations were from the European region (e.g., mainly France). However, India was the source of 16 importations.

In summary, the epidemiology indicates that elimination status has been maintained in the US. The median number of cases per year is 65 and incidence is still low at less than 1 per million. Many cases were importations or import-associated, and outbreaks were limited. There are challenges to maintaining elimination including the on-going risk of importation, most recently from Western Europe. As long as there are measles elsewhere in the world, the US will continue to have importations. Although measles cases in the US have increased in 2011, the disease remains rare. Many clinicians have never observed a case of measles. A high level of response efforts is needed; however, it is very resource-intensive and costly to control an outbreak.

Measles Outbreak in Quebec, Canada

Gaston De Serres MD, PhD
Institut national de santé publique du Québec

Dr. De Serres reported that Quebec has used a 2-dose MMR vaccination since 1996. The first dose is given at 12 months and the second is given at 18 months. A school-based measles vaccination catch-up campaign was conducted in 1996 during which nearly 90% of children received a second dose. The targeted age group was 18 months to 16 years of age. From 2000 to 2010, 149 measles cases were reported in Quebec, most of which (94%) occurred during the 2007 outbreak that affected primarily unvaccinated individuals in various regions of the province. The measles epidemic in Europe, particularly in France with which Quebec has many connections, led to several importations into the province and probably was the trigger for what occurred in 2011.

National surveillance case definitions are used. Lab-confirmed cases require positive results to viral culture, PCR, or serology (presence of measles-specific IgM). Epi-linked confirmed cases are similar, and clinical cases require a fever of 38.3°C (101°F) and cough or coryza or conjunctivitis and generalized maculopapular rash for at least 3 days. New cases are classified as suspect until more information is obtained.

Before April 3, 2011 there were 12 sporadic cases, 4 of which were travel-related imports, with limited transmission. These occurred primarily in the clinical, medical, and daycare settings. Since that time, sustained transmission began. As of October 19, 2011, there were 750 confirmed cases. Of these, 36% were lab-confirmed and 8 were classified as suspect cases. The overall incidence is 9.4 per 100 000, which is much higher than just reported by Dr. McLean. One region, which is not a central city and is in the middle of the province, had 70% of all cases. Their incidence was 105.6 per 100 000. Imported cases were spread throughout the epidemic. Since the middle of August 2011, cases were still being imported from Europe. However, most of the cases were transmitted in schools. When summer began, transmission occurred in the rest of the community. Overall, 3% of Quebec's cases were imported. Of all cases, 63% were in the age group of 10 to 19 years. The incidence in these two groups of children was higher than in infants, which was 33 per 100,000. In 10 to 14 year olds, incidence was 60 per 100,000. In 15 to 19 year olds, incidence was 44 per 100,000.

In terms of vaccination status, when considering everyone with unknown vaccination status to be unimmunized, most cases were determined to be unimmunized. The proportion of immunized cases in adolescents was the trigger to conduct further investigation. Between September 26, 2011 and October 19, 2011, there were 7 cases and 2 new importations. The outbreak is not over, but the potential evolution remains unknown. The majority of cases occurred in unvaccinated individuals. However, the proportion of cases previously vaccinated with two doses is high at approximately 15% to 20% in adolescents. Vaccination with 2 doses is expected to provide 98% to 99% protection, so this was above what was anticipated and prompted an outbreak investigation.

Of the cases, 70% lived in one of the 18 regions of the province. One high school accounted for nearly 15% of the cases in that region, which suggested that this school's students were under-vaccinated. The objectives of the outbreak investigation were to estimate vaccine coverage, as well as vaccine effectiveness by age at vaccination and interval between the first and second dose. Cases were detected through passive surveillance as well as active surveillance. The school's absenteeism registry was reviewed and a questionnaire was completed by all students in early June 2011. The survey asked questions about symptoms or any measles diagnosis that could have been given to them, because at one point, there were so many cases patients were told not to go to the hospital in order to avoid transmitting to patients in the waiting room. Phone calls were made by a nurse to document symptoms of measles and vaccination status.

The classical national surveillance case definition was used. A few cases had symptoms of measles not fully meeting the case definition. For example, their rash was not generalized, or they may have had a rash and cough but no fever. Therefore, serology was done in early June 2011. That was 7 to 9 weeks after subjects had been sick. Their high levels of IgG were incompatible with antibody titers that would be achieved from vaccination 16 years previously. These were considered to be attenuated cases, and this was found only in 2-dose recipients. Only written proof of vaccination was accepted. Subjects were then classified as unvaccinated, 1-dose, 2-dose, or 3-dose recipients. The dates were required for each dose. A few were vaccinated without written record, but the attack rate in that group was certainly not compatible with the attack rate observed in unvaccinated individuals. However, they were not analyzed in the same way.

In terms of case detection, 98 classical cases and 12 attenuated cases were found. In that school there were 110 cases total. The first case was an adult member of the staff who returned from a trip in the Caribbean, was feverish for a few days, but continued to teach during that time. When the rash began, that person stopped working. Approximately 10 to 14 days later, there were 10 secondary cases followed 15 days later by a major transmission of the majority of cases. By the end of May 2011, the outbreak was over. With regard to vaccination status, 4.7% (n=61) of the students were unvaccinated. That is substantial, but not as high as would be expected given the high attack rate. There were 89 (7%) students who had received 1 dose and 1111 (85%) students who had received 2 doses. In grades 7, 8, and 9 the attack rate was in the range of 10%. In grade 9 the Td booster is given annually, and there is an update of vaccination for those who may lack doses. In grades 10 and 11, the portion of unvaccinated individuals was lower because of that and accordingly, the attack rate was lower.

Overall in that school, 8.5% of students got measles. The attack rate and vaccine effectiveness were calculated, which showed 82% of unvaccinated children and 4.8% of 2-dose recipients got the disease. When using the classical case definition, the number of cases meeting the requirements was 95.9% with a quite tight confidence interval (CI 95% 93.8-96.7). Inclusion of attenuated cases lowered vaccine effectiveness to 94.2% (CI 95% 92.9-95.6). There was a significant effect of the age at first dose, and no effect of the interval between the first and second dose. For students who were vaccinated at 12 months of age with the first dose and exactly 18 months of age with the second dose, the attack rate was 5.4%. If the delay was longer, the attack rate was 7.6% for those who received the second dose 7 to 11 months after their first dose. At 6 months or 12 months or more, the attack rates were similar. If the first dose was administered at 15 months or older, there were cases only among those who had their second dose 12 months after the first dose. There was a significant drop moving from 12 months of age at first dose to 15 months or more at first dose.

Vaccine effectiveness in 2-dose recipients was 93% (95%CI 90.2 - 94.9%) if the first dose was given at 12 months. If the first dose was given at 15 or more months of age, vaccine effectiveness was 97.5% (95% CI 93.5 - 99.1%). The relative risk of measles in 2-dose recipients with the first dose administered at 12 to 14 months versus 15 or greater months was 4.38 (95%CI 1.05-18.3) for classical cases and 2.77 (95%CI 0.99-7.8) for classical plus attenuated cases. Given that this school had 52 individuals who had received 2 doses of vaccine, further investigation was done to determine whether the outbreak was specific to that school or if the same observation was made outside of the school. In the town where this school was located, there were other schools and other cases in twice vaccinated adolescents born between 1993 and 1999. They met the national case definition for classical cases, and age at first and second dose was assessed. These cases were added to the school cases. Only non-cases from the affected high school were used as controls, because there was no possibility to get other controls. When the town cases were combined with the high school cases, the results presented earlier did not change and the relative risk was three times higher and was statistically significant:

	OR	95%CI
High school classical	4.38	1.05- 18.3
High school classical+ attenuated	2.77	0.99-7.8
High school + town cases	3.56	1.42-8.9

In summary, over 8% of students in the affected school were susceptible. There were as many cases in 2-dose recipients as in unvaccinated students. Vaccine effectiveness of 2 doses was 93% (95%CI 90.2-94.9%) if the first dose was administered at 12 months. The risk was three times higher if the first dose was given at exactly 12 months instead of 15 months or older. In the affected school, about 5% of the students were unvaccinated. That is just slightly higher than in provincial vaccine coverage surveys. Based on surveys conducted in various years among children 24 to 28 months old and 14 to 15 years old, MMR vaccine coverage in Quebec is shown in the following table:

Survey Year	24 to 28 Months Old		14-15 Years Old
	At least 1 dose	2 doses or more	2 doses or more
2006	95 %	88 %	91 %
2008	97 %	90 %	92 %
2010	97 %	89 %	92 %

The proportion of unvaccinated overall in the province is probably in the range of 3%. The affected school had a higher percentage of unvaccinated, but not substantially higher.

Regarding the strengths and limitations of the study, in terms of internal validity, it is possible that a few vaccinated attenuated cases were missed. If so, that would have further decreased vaccine effectiveness. It is believed that this is a robust estimate of vaccine effectiveness with the current schedule, given that most participants were vaccinated exactly according to the current schedule at 12 and 18 months. With respect to external validity, in terms of generalizability, it is known that highly affected settings generally underestimate vaccine effectiveness. Sensitivity analyses with town cases confirm that the risk of measles is about 3 times greater with a first dose administered at 12 months versus 15 months or older. The ages at first and second dose do not appear very different in the affected school compared to other regions. Mishandling of the vaccine, batch number, or other factors are unlikely to explain the results, given that several age groups were affected in this outbreak. Since the current schedule does not administer the second dose in school, the results cannot be extrapolated to jurisdictions where the second dose is given at 4 to 6 years of age. This raises the question: Are these children born to vaccinated mothers or mothers who have had measles? The vast majority of the mothers would have been born between 1965 and 1980. The universal program began in 1970. In the first year of the program, there was some catch-up in school children who had not already had measles. Children born in 1965 and later were exposed to the vaccination program, with quite a successful coverage rate of about 90%. Many were vaccinated, but there has been a lot of transmission, so they may have seen the disease nevertheless.

In conclusion, measles elimination requires an overall population susceptibility below 5%, though some would say 6% to 7% would be sufficient. A first dose given at 12 to 14 months leaves 6% to 7% of students susceptible to measles despite a second dose, which could be a serious obstacle to measles elimination. There is clearly a need to replicate this study in particular in jurisdictions where the second dose is given at 4 to 6 years of age. Investigators in the Ukraine were recently contacted to request information about age at first dose among their subjects, given that they recently published nearly identical results pertaining to overall vaccine effectiveness. The Ukraine's first dose is administered at 12 months and the second at 4 to 5 years. It will be interesting to learn whether the Ukraine investigators also observed a difference in protection depending upon age at first dose. If Quebec's results are confirmed, strategic changes to optimize the existing schedule should be considered.

Measles Prevention Activities in Mexico

**Vesta Richardson, MD, Director
National Center for Child and Adolescent Health
Ministry of Health, Mexico**

Dr. Richardson presented a summary of the universal vaccination program in Mexico, pointing out that Mexico has 112 million inhabitants. Through the permanent component of the immunization program, all universal vaccines are available every day in every clinic in the country. The measles schedule follows WHO's recommendation: MMR is administered at 12 months of age, with a second dose at 6 years of age. If a 12 year old does not have proof of a second MMR dose, they receive another dose at that time. Everyone between the ages of 13 to 39 years of age receives a single dose of MR vaccine. MMR coverage rates are acceptable at 93% to 94% among 1 year olds and 89% in the remaining age groups.

The second component of the universal immunization program is an intensive program that uses two basic strategies. One is the National Health Weeks and the other is Special Campaigns recommended by WHO or the country. During National Health Weeks conducted in February, May, and October each year, immunization kiosks and brigades are set up in every town in the country for one week. Several objectives are pursued with National Health Weeks. In a short period of time, an effort is made to update everybody's immunization status, especially children under 5 years of age; cover potential susceptibles, which are calculated to be 3% to 5% of the population at every age; cut the transmission chain for diseases; and remind the population of the importance of vaccines through high media coverage. During the October Health Week, immunization brigades visit elementary schools and update children's immunization status. Nurses give first graders, 6 and 7 years of age, their second MMR dose. Sixth graders receive their Td booster dose and MR if no second dose of MMR is documented on their immunization card. Approximately 70% of all vaccines are given through the permanent program in clinics, and 30% of all vaccines are given during the three National Health Weeks every year.

The second strategy for the intensive program is Special Campaigns. For example, during the 2009 campaign, 28 million doses of influenza A H1N1 vaccine were administered. Two recent special campaigns were aimed at eliminating measles and congenital rubella syndrome. The first was in 2008 in which the target population was 20.7 million young adults ages 19 to 29. In this population, 22 million doses of vaccine were administered in 8 weeks. At the end of 2010 and during the first 3 months of 2011, the entire cohort of children 1 to 4 years of age received an MR vaccine during a 16-week period. This is done every 4 to 5 years as a follow-up campaign in accordance with WHO-PAHO guidelines.

In summary with the measles control and elimination strategies that have been in place since 1994, there have been very few measles cases for the last 15 years. 1990 was a special year during which there was a measles pandemic with 68,000 cases and almost 6,000 deaths. The incidence rate in 1990 was more than 80 cases per 100,000 inhabitants when it had normally been below 20. Because of that, important lessons were learned. In 1991, the current immunization program was created and the first MMR campaign was begun with 14.4 million doses given in all age groups. In 1993, the second dose was added for 6 years olds and the National Health Weeks were reinforced. Also, a complete state and federal laboratories network was started, and in 1999 a strict federal disease surveillance system was put in place. Since 2000, MR has been given to adolescents and adults at 12 years of age in schools and from 13 to 39 years of age, especially among healthcare workers and teachers. There were

campaigns in 2002 and in 2008 aimed at adults 19 to 39 years of age, during which 10.7 million and 22 million doses were given, respectively. Every 5 years during the follow-up campaign, all children ages 1 to 4 years are indiscriminately vaccinated. It is important to note that the last endemic case was reported in 1996, and the last imported case in was December 2006.

In terms of measles control efforts in Mexico during 2011, Federal and State Committees for Epidemiologic Surveillance discussed the worldwide measles situation and the Pan American Health Organization's (PAHO) May 2011 recommendations. There was concern about probable imported measles reintroduction during the summer because of the soccer tournament, summer vacations, and the Pan-American games in Guadalajara in October. An Epidemiologic Alert for possible measles reintroduction was sent in June 2011 by the Federal Epidemiology Surveillance Unit. The National Committee For Health Security sent guidelines to airports, embassies and tourism councils recommending immunization of tourists before traveling to Mexico, and requesting adequate immunization of airport and tourism workers, athletes, and all travelers to the US, Canada, and Europe. The Federal Minister of Health held a National press conference to notify everyone about the measles alert, and followed up with subsequent media conferences and interviews. A social marketing strategy was used to improve immunization coverage. The National Immunization Council decided to purchase 100% additional MR and MMR vaccines to assure adequate coverage rates at all ages up to 40 years old. Measles vaccine was introduced 40 years ago and most seroepidemiologic studies have shown people over this age were in contact with the wild virus and are immune. The Federal Minister of Health discussed actions to be taken with the 32 State Ministers of Health at the National Health Council in June 2011. The agreements were: to complete the MR follow-up campaign in children 1 to 4 years of age, to keep vaccine coverage above 95% in all age groups, and to begin with active surveillance, including early detection of suspicious cases, with immediate notification; and outbreak control measures through 49-block mop-up vaccination campaigns.

MEXICO'S EPIDEMIOLOGY UNIT GUIDELINES FOR MEASLES CONTROL (MODIFIED FROM WHO'S POLIO & CHOLERA GUIDELINES)

- 1) Any case with fever, exanthem, conjunctivitis and URI should be considered suspicious/probable, and studied within 48 hours.
 - a) Immediate notification to the sanitary jurisdiction/ state MOH must be done.
 - b) Urine, pharyngeal exudate + serum should be obtained for viral isolation, PCR, IgM & IgG, done at the State Lab, and sent to the National Lab if positive (days 6 – 20 of rash); positive samples are sent to CDC.
- 2) All close contacts are interviewed and the immunization status is determined.
- 3) Containment measures are started 49 blocks around the patient's home and work, with house-to-house visits (known as the "at risk of exposure area")
 - a) Intentional search for more cases.
 - b) Vaccine coverage data is obtained for the area.
 - c) Vaccination status is determined and vaccines applied: (blockade dose)

6-11 months: MMR Re-apply after 12-15 months old.

1-10 years: MMR

10-39 years: MR

(At least 2 prior doses are needed to consider an immunization schedule complete. Persons 13-39 years need a recent dose as of the year 2000).

- 4) State Epidemiology Surveillance Committees meet and discuss cases and actions taken, and inform the Federal Epidemiology Surveillance Unit.

Yearly, 4000 to 7000 cases of febrile exanthema are studied. There have been no cases of imported measles since 2006. Three cases during the summer of 2011 turned out to be positive for Genotype D4 and were imported cases from Europe. One case was in a 21 month-old unvaccinated French baby girl, the second was in a 16 year old vaccinated teenage girl who traveled to Europe who was a non-responder to 2 doses of MMR, and the third was a 46 year old man who was unvaccinated and had been in London. No secondary cases were reported. The containment strategies used, modified from WHO guidelines, included: 1) Active surveillance for measles cases and tracing their contacts, and establishing measles immunization containment activities within 49 blocks around the cases' households; 2) Active surveillance of febrile exanthematic disease (FED) and measles cases in working places, markets, schools and other places where potential transmission may occur; 3) Verification of the vaccine immunization coverage and immunization of susceptible people; and 4) Health promotion and information to the affected neighborhood and the at-risk communities.

Containment is not an easy activity when a case appears in Mexico City, which has more than 19 million inhabitants. For example, in the case of the 21-month old female from France, 1572 families were interviewed. Only two families refused to participate, so people are generally very cooperative with the epidemiology and immunization teams. People under 44 years of age were surveyed. Out of 822, most had their immunization cards and were able to prove that their vaccination status was up to date. Those who did not have their vaccination card were considered not to be immune. Throughout those 49 blocks, 385 doses of vaccine were administered in this case to achieve 100% coverage after the intervention.

In conclusion, during 2011 there have been 3 imported-measles cases. There have been no secondary cases. The epidemiologic surveillance system and laboratory network had a crucial role for the prompt identification of the cases and establishment of the immediate measles containment actions. There was an adequate risk communication strategy, which promoted the participation of locals and of travelers entering the country. The immunization strategies that have been implemented for the last 21 years have been effective in controlling the reintroduction of measles in the country. Emphasizing the importance of routine immunization, plus the role of supplementary immunization activities among the population, is indispensable.

Discussion Points

Dr. Coyne-Beasley commented that this was a wonderful example of how immunization uptake can be increased. She hoped the US was adopt this strategy in some form, because it truly is a community-based approach that has increased immunizations quite substantially.

Dr. Duchin thanked Drs. De Serres and Richardson for impressive presentations, and commended them on the well-done investigations and outbreak control measures implemented in their respective countries. He wondered whether either country was able to document any secondary cases from their attenuated measles cases.

Dr. De Serres replied that he did not know this, because in the investigated school the attenuated cases were mixed with other cases and it was not possible to know who contaminated who. They did not talk to the families to assess secondary transmission within families.

Dr. Duchin said he was very envious of Mexico's ability to cordon off a 49-block geographic area to focus successfully and contain the outbreak. In US communities, people tend to travel all over the place for work, school, daycare, afterschool activities, and so on. He requested that Dr. Richardson further discuss how they define the geographic area.

Dr. Richardson said this is basically done by very strictly following the city map. The team divides the blocks. Families are normally expected to be out working or elsewhere, so the teams try to go during off hours on the weekends and evenings. They have to achieve this within a 2-week period. Public places within those 49 blocks are also visited and pamphlets are distributed. People are encouraged to get their vaccines, and the success rate is good. In about 10% of the houses, nobody ever opens the door, but very few refuse to participate. Grandparents who are taking care of their grandchildren or other caregivers have to produce their vaccine card to prove vaccine coverage, and if they cannot, they get immunized. They accept this. The teams cross out block-by-block when they achieve their goals, and they are pretty strict about it. The state epidemiology unit has to report to the federal unit, so both teams go over the numbers.

Dr. Meissner requested clarification about whether he understood correctly that there was almost 100% seroconversion after the second dose, regardless of whether a child received the first dose at 12 months or 15 months or beyond. He thought that as long as there was an immune response to the second dose, the child should have similar degrees of protection against measles. He wondered whether this implied that there was less of an antibody response with the second dose, and whether that was the possible explanation. There is a B-cell and T-cell response to the vaccine. He was surprised that even after good seroconversion to the second dose, there was still so much disease.

Dr. De Serres confirmed that Dr. Meissner understood correctly. When Quebec made the recommendation in 1996 to have a second dose at 18 months of age, other jurisdictions chose to administer their second dose at 4 to 5 years of age. Basically, the immunogenicity studies showed that if those who had a first dose and did not respond had a second dose, 80% to 90% would mount an antibody response. Overall, the success of the first and second dose is in the range of 99%, with an antibody response to the 2-dose schedule regardless of how distant the second dose was given from the first. That was the scientific basis for Quebec's recommendation of a second dose at 18 months. The reason for lower protection is unclear. Some would say that with a 1-dose program, it is known that maternal antibodies would interfere with a vaccine. However, the response with a first dose, even in absence of maternal antibodies, is not the same as when vaccine is received at 9, 12, or 15 months. He would not call the problem in Canada a secondary vaccine failure, because people talk about primary vaccine failures when there is an absence of antibodies after one or two doses. While these children could be expected to have had antibodies after the second dose, were they lacking protection initially? Would a third dose fix anything? One case in grade 9 received 2 doses of MMR because he could not find his vaccination record. Even though he was probably vaccinated, he received two doses and got measles a year later. Is there an imprint that remains? Obviously, 2-dose recipients are better protected than 1-dose recipients. The two-dose program works in the majority, but it apparently leaves a proportion that is unprotected,

which is far greater than what would be expected from immunogenicity studies. However, it is unclear whether this has to do with which types of vaccine failures (primary or secondary).

Ms. Ehresmann requested further information regarding vaccinating those who do not have their vaccination card, and whether there is a registry or information system that would show evidence of immunization.

Dr. Richardson replied that the system tries to make immunization weeks simple. There is a very well-developed registration system into which every newborn child is entered and their vaccines are followed in the permanent program. However, these children do not always get into the registration system during Health Weeks because the objective is only to immunize. About 80% of children bring their immunization cards. When they do not bring their immunization cards, mothers receive a small paper that documents the shots they received, but sometimes these are lost. In 2012, an effort will be made to incorporate the doses given during Health Weeks into the formal registration system. This is one reason coverage surveys are conducted each year. Teams go house-to-house to analyze immunization cards. The surveys do not match because they show that the coverage rate is about 80% when it is known through the epidemiological studies and estimated coverage rates that it should be above 90%. So approximately 10% to 20% of children do not get their vaccines registered in their cards during the Health Weeks. If they have a card, they only receive what they need. If they do not, the mother is asked. If she remembers, no vaccine is given. If she does not, it is given according to age.

Dr. Bennett agreed that both presentations were a testament to the value of public health. She was curious as to whether the 49-block approach was supplemented if the case may have exposed people in other settings.

Dr. Richardson replied that this would depend upon the age of the patient. For the infant case, the containment strategy was limited to the 49 blocks around the house. However, for the salesman in Guadalajara, the workplace had to be approached and the 49-blocks were repeated around the workplace. All work and living spaces are approached.

It struck Dr. Bennett that they might not necessarily know whether they actually prevented secondary cases, but at the same time, immunization status is being increased 49 blocks-by-49 blocks.

Dr. Keitel requested clarification about Mexico's registry in terms of every child's vaccinations being entered into the registry, and whether the registry can be accessed during these campaigns. She wondered whether, if someone did not have a card, the registry could be accessed to verify their status.

Dr. Richardson replied that the state representative for the immunization program can access the system anytime. The system will create a report of incomplete schedules for children, and the nurses receive these reports. They can go house-to-house to look for these children. Access is available year round, and it is used during Health Weeks. The problem during health weeks is that the vaccines given are not entered in the registration system, but this will hopefully change in 2012-13.

Recalling that some people with a mild case of measles could be confirmed because they had a high antibody level, Dr. Keitel wondered whether there had been any contact with cases who did not develop disease to determine whether they had any kind of boost or high immune response.

Dr. De Serres responded that they did not perform any studies in the rest of the students who had been in contact and may have boosted their antibody levels. Ideally, blood would have to be collected quite close to the time people become symptomatic. Given the timeline of the investigation (e.g., getting everything together, finding these individuals, deciding what to do) this was all they could do.

While it seemed like ultimately the outbreak ran its course, Dr. Campos-Outcalt inquired as to whether Canada engaged in any outbreak control measures, such as school exclusion of unvaccinated students.

Dr. De Serres noted that there is a different view. Quebec considers measles elimination to be a marathon, and would rather learn earlier than later that there is a major vulnerability in the population. They assume that if they are giving sufficient vaccine at recommended ages, that importation would lead to interruption by itself without intervention. Quebec is implementing interventions targeted at high-risk people such as infants and pregnant women, and cases are aggressively pursued. Obviously, the aggressive approach to try to contain the virus rapidly has advantages in that there are less cases, but this approach has the disadvantage of masking the vulnerability that may exist in the population. The lesson learned in this epidemic was not a pleasant lesson to learn. Despite their efforts, every year in their new birth cohorts, they are leaving 5% to 7% of unprotected twice-vaccinated children. This is creating problems for the future. If this result is confirmed elsewhere, moving the second dose to 15 months would change that vulnerability from 7% to 2.5%. That would be a great achievement. However, a visit at 15 months may be difficult. When the US moved its schedule from 12 months to 15 months in 1976 (one dose program), this improved the effectiveness of the vaccine and there were less susceptible individuals. Thereafter, the US had much less transmission from 1976 to 1990 than Canada. This does not just start in children 12 to 15 months of age. The overall risk occurs in creating three times more susceptible children with the vaccine schedule. There is not only more risk to this 3-month interval, but also there is risk to the whole infant period. It is important to look at the big picture.

Ms. Stinchfield (NAPNAP) was interested in the Canadian description of “classical” and “non-classical.” In 14 recent admissions to Children’s Hospital in Minnesota, this was observed. So much focus is placed on rash as a trigger to test and isolate. Hundreds of children can be quickly exposed in the absence of rash. Absent the rash, measles looks like every other febrile illness. She wondered whether fever plus international travel should be a reason for being sent straight to a negative air room until a diagnosis is determined. She requested further information about the rashes presented in the non-classical children.

Dr. De Serres responded that there is a description of each case, which he said he could show offline to those interested. Some had generalized rash with no fever. Some had facial rash, fever, and a cough, but the rash was not generalized. It was not necessarily that the rash was totally different. There was a mix. When they were tested, they had antibody titers by Enzyme-Linked Immunosorbent Assay (ELISA) that were above 13,000 IU. In consulting with CDC and the Canadian laboratory representatives, they were told that this could not be explained by their vaccination given 10 to 15 years before.

Dr. Plotkin (Vaccine Consultant) said that to answer Dr. Keitel's question, it has been well-documented that individuals with moderate levels of antibody do have boosters when they are exposed to measles, but not with high levels of antibodies. In terms of Dr. De Serres' 5% unvaccinated and 7% with one dose, some of these individuals would have lost antibodies after this. It is not only the absence of response to the first dose. So there are quite a few susceptibles in a sense. In terms of the two doses, it was reasonably explained why some of those individuals in effect have had only one dose of measles vaccine because of the passive antibodies. He agreed that shifting to 15 months for the second dose certainly seemed reasonable. He wondered whether a serologic survey would be conducted in Quebec to determine the actual rate of susceptibles, because they may be quite higher than is thought.

Dr. De Serres replied that this is being discussed. If the intent of the study is to determine the proportion of children who, after two doses, have no antibodies, and they received their first dose at 12 months rather than later, 15 years later 93% of them were protected. It would be expected a large proportion would have antibodies after their second dose. Therefore, it would be difficult to conclude much about the difference. There are certainly different assays that could evaluate a number of variable (e.g., IgG, immune response, et cetera).

Dr. Plotkin (Vaccine Consultant) stressed that the force of infection of measles is extremely high. Even with rates of susceptibility of 7% to 10%, there could be a problem right there when measles is introduced.

Dr. De Serres agreed. He thought the main lesson from the Quebec outbreak was that in the affected school, 5% of individuals were unvaccinated. Average coverage in the population is in the range of 97%. Other provinces in Canada had the same type of vaccine coverage for the first and second doses at 90% plus. If there were 3% unvaccinated overall, other places may have 4% to 5% unvaccinated. Add to that 4% to 6% twice-protected individuals and you are in trouble.

An inquiry was posed regarding whether the general public was aware that there were a number of cases among 2-dose recipients, and whether there had been any decrease in confidence of the vaccine as a result since that is the recommended number of doses.

Dr. De Serres replied that because this outbreak occurred mainly in a rural area rather than the two major city centers, the newspaper relayed poorly the information. There was a press conference by the Provincial Medical Officer of Health. However, there was almost no turmoil surrounding this and there were very few problems. Again, the age group that was affected was not an age group which was less vaccinated because of the fear around the Wakefield issue. This group was born before the Wakefield saga began. The vaccine surveys in 2006, 2008, and 2010 showed that vaccine coverage in infants and toddlers was quite high.

Measles Vaccination among Children with HIV Infection

George K Siberry, MD, MPH

**Eunice Kennedy Shriver National Institutes of Child Health and Human Development
National Institutes of Health**

Dr. Siberry focused on perinatal HIV infection and the use of MMR vaccine in that population. To summarize the current recommendations for persons with HIV infection, MMR vaccine is recommended for all asymptomatic HIV-infected persons who do not have evidence of severe immunosuppression (CD4% <15%). It should be considered for all symptomatic HIV-infected persons who do not have evidence of severe immunosuppression (CD4% <15%). HIV-infected infants without severe immunosuppression should routinely receive MMR vaccine as soon as possible upon reaching the first birthday. Consideration should be given to administering the second dose of MMR vaccine as soon as 28 days after the first dose. MMR Vaccination is not recommended for persons with severe immunosuppression. There is no recommendation for re-immunization beyond 2 doses.

In terms of safety, there have been very few serious adverse events reported from measles vaccine in HIV-infected persons. There is a very well-known case in 1996 of a 21-year old who was not known to have HIV at the time, who received measles-containing vaccine, developed giant-cell pneumonitis 10 months after receiving the MMR vaccine, and died [MMWR 1996]. Since that time, no serious adverse events have been reported after small studies of administering MMR to children on Highly Active Antiretroviral Therapy (HAART) with a past history of immunosuppression [Melvin 2003 USA; Aupibul 2006 Thailand; Farquar 2009 Kenya]. No additional serious adverse events have been reported in the US, nor have any additional serious adverse events been reported worldwide despite immunization of millions of HIV-infected children. WHO states that “measles vaccination is contraindicated in people who are severely immunocompromised due to . . . severe HIV infection.” Otherwise it is recommended.

Regarding immunogenicity, the Moss paper from 2003 offered a nice overall summary. In the pre-HAART era, there were lower response rates, lower titer responses, and faster antibody decay. Factors associated with poorer response to several vaccines (e.g., D/T/P, HBV, PCV, PS23, Hib, measles) included low CD4 counts, high viral loads, and HIV stage. It is important to note that the factors associated with poor response varied across studies and are not entirely consistent.

Most perinatally infected youths living in the US are now adolescents. Antiretroviral therapy was not available to them as infants. It is important to think about impaired response to measles vaccine in HIV-infected infants not on ART. A study from Zambia compared the response to measles vaccines in infants with and without HIV. There was a similar PRN GMT, but significantly lower EIA IgG after measles vaccination at 9 months in HIV-positive infants versus HIV-negative infants, and there was lower avidity in HIV-positive versus HIV-negative infants 3 months after vaccination [Nair JID 2009 Zambia]. This suggests that there is a mixed picture with regard to the level of response, and some concern about the quality of the antibody response after vaccination of infants not receiving ART.

An additional major concern is faster loss of measles antibody in HIV-infected children not on ART. In a study of three groups (e.g., HIV unexposed, HIV exposed but unaffected, and HIV infected not receiving therapy), all children received measles vaccine at 9 months of age. Comparable immunogenicity was initially observed for all three groups at about 3 months after vaccine; however, significantly faster loss of protective antibody was observed in the HIV-positive children [Moss JID 2007].

This raised the question regarding whether administration of HAART after vaccine results in the reappearance of immunity. Dr. Siberry reviewed the most typical sequence for perinatally infected youth in the US. They received routine immunizations in infancy and early childhood, but no HAART therapy. They may experience primary vaccine failure and/or loss of immunity, and then develop a variable degree of immunosuppression. When HAART is initiated, they experience recovery from immunosuppression. Does measles-specific immunity “recover” with HAART-related reversal of immunosuppression?

To help answer this question, Dr. Siberry summarized three studies, one from the US and two international studies that offer evidence that HAART does not likely restore immunity. In the first study from the US, among children 3 to 14 years of age (n=18) who received 1 to 3 measles-containing vaccines prior to starting HAART therapy had been on HAART for 8 to 37 months were shown, only 1 (6%) had detectable measles antibody (EIA IgG). The vast majority, 17 of 18, had no detectable antibodies [Melvin 2003]. A study from Thailand examined a total of 96 children 5 years of age or under who received measles vaccines as infants, many with substantially advanced disease in the past, and all of whom had good CD4 responses on HAART. Only 36% of these children were measles immune (EIA IgG ≥ 320 mIU/mL) and there were no real factors that could be used to predict who, despite immune recovery on HAART, would or would not have measles immunity after being on HAART (e.g., sex, CDC cat, HAART age, duration of severe immune suppression, CD4 or VL before/after HAART) [Aurpibul 2006]. In Kenya, 62 perinatally-infected children were studied whose median age was 4 years, who had CD4 counts of 6%, past severe immunosuppression, and received at least 6 months of HAART. The pre-HAART antibody positivity rate was 31%. Even though these children received vaccines prior to this, giving HAART increased the rate of those with immunity only to 42% [Farquhar 2009].

Most children do seroconvert with re-immunization after HAART. Dr. Siberry summarized three studies that address this issue. In a small study in the US of 3 to 14 year olds, 15 of 18 children (83%) became measles seropositive with a single repeated MMR after HAART [Melvin 2003]. In a US study of 2 to 11 year olds, the rate of immune response was compared in children receiving HAART and children not receiving HAART, with 9 of 14 (64%) on HAART versus 3 of 14 (21%) not on HAART (ART or no ART) becoming measles seropositive [Berkelhamer 2001]. In a study of Thai children over 5 years old with a history of 1 to 2 MMR doses who were seronegative, now on HAART, protective antibody at 4 weeks was 90%, 100%, and 78% respectively for measles, rubella, and mumps. At 24 weeks, the rates were somewhat lower than at 4 weeks (80%, 94%, and 61%, respectively), but measles positivity was still 80% compared to zero at baseline [Aurpibul 2007].

The ability to identify and treat infants and young children with HIV infection has improved, so the story of what will occur over time is likely to change. HIV-infected children who initiate HAART in infancy and then receive their first MMR vaccine at 12-15 months might be expected to respond better than children who are first vaccinated before HAART. For example, in a study of HIV-unexposed, HIV exposed but uninfected, and HIV-infected children (in which all of the infected children initiated HAART in infancy), the overall response to rubella following MMR

vaccine at 15 months was still lower for HIV-infected children. Risk factors include viral load and CD4 counts of less than 25%. However, the response to primary immunization after HAART was similar to HIV-uninfected, if HAART was effective [Lima PIDJ 2004 (Brazil)].

In thinking about the pathophysiology for why there is better preservation of memory B-cells with early HAART, a study by Pensiero does a nice job of showing how early HAART therapy helps preserve memory B-cells. This study assessed the percent of memory B-cells overall and measles-specific memory cells. In both cases, children who were treated with HAART before 12 months of age had B-cell numbers and measles-specific cells similar to the controls (e.g., those without HIV infection), and better than those who started HAART late or started HAART but failed to respond [Pensiero 2009].

The majority of HIV-infected individuals in this country are adolescents and young adults who received one or both doses of MMR prior to effective HAART. The concern is that at this point, they lack protection against measles due to a combination of primary vaccine failure, failure to establish a memory response, and/or waning of response over time. Even if they responded well to HAART, if they did receive additional MMR vaccine after HAART, they are unlikely to have high levels of immunity. There is increasing evidence to support re-immunization with MMR once stable HAART is in place in order to achieve the highest grade of protection in this group. Dr. Siberry shared an article with the committee that supports this [Sutcliffe Lancet ID 2010;10: 630–42].

Summary of Options

Huong McLean, PhD, MPH

Division of Viral Diseases

National Center for Immunization and Respiratory Diseases

Centers for Disease Control and Prevention

Dr. McLean first reviewed the current recommendations for persons with HIV infection are as follows:

- ☐ Recommended for **asymptomatic** HIV-infected persons who do not have evidence of severe immunosuppression (CD4% <15%)
- ☐ Consider for **symptomatic** HIV-infected persons who do not have evidence of severe immunosuppression (CD4% <15%)
- ☐ Routinely administer to HIV-infected infants at 12 months, with consideration to administering the 2nd dose as soon as 28 days after the 1st dose
- ☐ Not recommended for persons with severe immunosuppression

She then reviewed the working group considerations for the use of MMR in those who are HIV-infected, which are as follows:

A. General recommendations for persons with HIV infection:

Option 1 (no change)

- Recommend for **asymptomatic** HIV-infected persons who do not have evidence of severe immunosuppression (CD4% <15%)
- Consider for **symptomatic** HIV-infected persons who do not have evidence of severe immunosuppression (CD4% <15%)

Option 2

- Recommend for HIV-infected persons who do not have evidence of **current** severe immunosuppression (i.e., no CD4<15% in prior 6 months).

B. Children with perinatal HIV infection who are already receiving effective HAART by age 12 – 15 months:

Option 1 (no change)

- Recommend 2 doses of MMR vaccine: age 12 and 13 months

Option 2

- Recommend 2 doses of MMR vaccine: age 12 and 15-18 months, or as early as 28 days after the first dose

Option 3

- Recommend 2 doses of MMR vaccine at ages 12-15 months and 4-6 years

C. Children with perinatal HIV infection who were given MMR vaccine prior to establishment of effective HAART*:

Option 1

- Revaccinate with 2 doses once effective HAART established, **OR** serologically test for evidence of measles immunity and vaccinate those who do not have protective levels of measles antibody

Option 2

- Revaccinate with 2 doses once effective HAART established

Option 3

- [Option 1 OR option 2] PLUS periodic serologic testing (every 3 years) for measles immunity and revaccinate those who do not have protective levels of measles antibody

For Consideration A, the working group favored Option 2. For Consideration B, the working group favored Option 2. For Consideration C the working group favored Option 1.

Discussion Points

Dr. Temte noted that while the handout included discussion regarding immune globulin, there have been changes in terms of the FDA licensure; therefore, this discussion period was to focus only on HIV.

Dr. Duchin noted that the rationale for the CD4 count cutoff of 15% differed from what was shown to them in the data from the previous presentation. He was curious with regard to how this number was selected.

Dr. Siberry clarified that he showed a higher cutoff, but that cutoff was associated with more intact responses in younger children, while the proposed option was focused on children who are potentially older and on HAART for at least 6 months. The goal is to bring them up to the level where the current recommendation could stay. NIH is in the process of collaborating with CDC to assess a large cohort of perinatally infected children and determine whether a more refined cutoff can be used. In assessing children after HAART, 15% seemed to result in the best response.

Dr. Campos-Outcalt inquired as to how many children were included in the cohort of children perinatally infected in the US.

Dr. McLean thought the number was about 8000. Dr. Siberry agreed, adding that many of the children in that cohort are beginning to transition into early adulthood.

Dr. Keitel noticed that the seroprevalence among children who were vaccinated before they received HAART and then revaccinated later was much lower in the US study than observed in the Africa and Thailand studies. She wondered whether there were differences in the measles vaccines that were used.

Dr. Siberry did not believe that there were differences. One other possibility is that the international studies took place where measles were still endemic, so natural exposure may account for higher rates. The US study also involved children who tended to be somewhat older and may have survived despite lower CD4 counts because of the context of not having tuberculosis and other co-morbidities present in the international settings.

Influenza

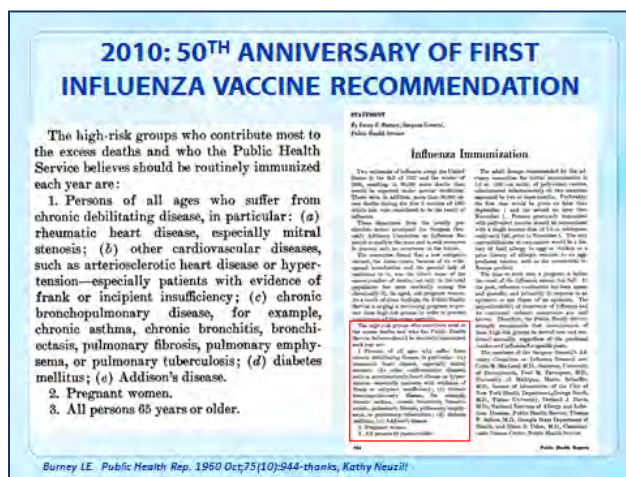
Introduction

Wendy A. Keitel, MD
Chair, Influenza Working Group

Dr. Keitel reviewed the activities of the Influenza Working Group over the last few months. The influenza statement for the 2011-2012 season was published in the *MMWR* with updates related to the vaccine virus strains, dosing for children 6 months through 8 years of age, intradermal TIV, and influenza vaccine for persons with egg allergy.

The working group has been briefed about the recent epidemiology, 2010-2011 seasonal influenza vaccine effectiveness, and influenza vaccine distribution and coverage. In keeping with the commitment to review data and make recommendations within the GRADE framework, an evidence-based review process was begun by the Influenza Vaccine Working Group to conduct a complete evidence-based review of the use of influenza vaccines. With the numbers of vaccines, numbers of age groups, and other considerations, this process is expected to be going on for quite some time. The first step is to address the prevention of influenza in young children with vaccines.

Dr. Keitel thanked Dr. Neuzil, the former Influenza Working Group Chair, who shared the following illustration upon the decision by ACIP to recommend universal influenza vaccine for the people of the US:



2010 marked the 50th anniversary of the Public Health Services' recommendation that individuals with certain high risk conditions should be immunized annually against influenza. It is worth remembering that influenza vaccine was licensed in 1945 based on studies conducted primarily by the military among young recruits in whom the level of vaccine efficacy was shown to be as high as 70% to 90% during seasons in which there was a good match with the vaccine. As risk conditions for deaths and complications from influenza were identified, populations at risk were successively recommended to be immunized against influenza. The database for some of those recommendations is not as robust as it is for younger, healthier individuals. By 2009, individual practitioners and other providers were faced with a daunting list of conditions for which immunization against influenza was recommended. To put that long list into contrast, the decision made in 2010 to recommend annual immunization for all persons at least 6 months of age was a wise one in the context that at least 85% of individuals fall into high risk groups. There were barriers to trying to identify people at high risk, so this is a simpler recommendation. In addition, during the 2009 pandemic it was recognized that there were other conditions associated with high rates of complication, such as obesity, which is epidemic in this country. It is recognized that among certain populations and in certain age groups, vaccines do not perform as well as in other populations and age groups. These are the types of issues the Influenza Working Group plans to assess using the GRADE evidence framework.

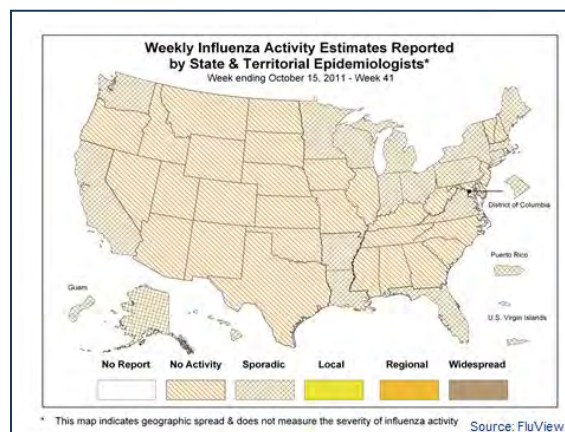
Several weeks prior to this meeting, the working group was contacted by the ACIP CSTE Liaison, Christine Hahn, with a question regarding the use of jet injectors for administration of TIV vaccine. Dr. Keitel saw flyers advertising needle-free injections and made the assumption that they were referring to live attenuated influenza vaccine administered intranasally. As the working group began to investigate this issue, they found that a number of providers in the US were offering an option for receipt of vaccine using a jet gun. These differ from injection guns used in the past on multiple persons that fell to the wayside because of the risk of transmitting infectious diseases. The working group was concerned about the jet injections and many were unaware that this practice was being used, and contacted the FDA. The working group has been communicating with the FDA since that time, and the FDA issued a statement on October 26, 2011 recommending that healthcare professionals use a sterile needle and syringe to administer inactivated influenza vaccines. Based on available information, CDC and FDA believe that it is not necessary for people who received their influenza vaccine via jet injector to be re-vaccinated.

Influenza Activity Update

Lisa Grohskopf, MD, MPH

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

Dr. Grohskopf offered a brief update of domestic influenza surveillance for the season at this point. For the purpose of surveillance, the 2011-2012 season began on October 1, 2011. Data presented during this meeting were collected as of the week ending October 15, 2011, which was 2 weeks into the season or calendar week 41 of the year. The following map illustrates influenza activity reported by state and territorial epidemiologists to CDC:



At the time of this presentation, reports had been received for all 50 states and territories for the week ending October 15, 2011. The majority of states reported no activity, while 18 states, Guam, US Virgin Islands, Puerto Rico and the District of Columbia reported sporadic activities. An update will be presented during the February 2012 meeting.

In terms of the results of influenza positive tests reported to CDC by the WHO / NREVSS collaborating laboratories, for the first two weeks of the season, specimens numbered in the 20s, with only 6 specimens, for the week of October 15th. Although at this time it was rather early in the season, there was representation from A(2009 H1N1), A(H3), and B strains. Note that the results of influenza positive tests are reported to CDC by the 80 WHO organization and 60 respiratory and enteric virus surveillance laboratories that are in all 50 states throughout the US. The WHO collaborating laboratories, all state public health laboratories, some county laboratories, and some tertiary center laboratories participate in this system. The NREVSS laboratories are mostly hospitals.

In terms of the percentage of outpatient visits for influenza-like illness (ILI) reported by the US Outpatient Influenza-like Illness Surveillance Network (ILINet), the percentage of outpatient visits for ILI reported by the system are well below the national baseline. Note that ILINet is a network of over 3000 healthcare providers throughout the 50 states who report data to CDC on a weekly basis. The national baseline of the representative visits for all ILI is calculated from the non-influenza seasons for the previous three years. The baseline is currently 2.4%.

In terms of the number of influenza-associated pediatric deaths reported from the 2009-2009 influenza season to the present, there was limited information since the 2011-2012 season had only just begun on October 1st. There were a total of 116 deaths in 2010-2011, with no deaths reported for the 2011-2012 season at the time of this presentation. The 2010-2011 figure represents a lower figure compared to 2009-2010 in which 282 pediatric deaths were reported. The death of a child under the age of 18 due to laboratory-confirmed influenza has been reportable since 2004.

Vaccine Effectiveness

Mark Thompson, PhD
Epidemiology and Prevention Branch, Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Thompson reported that with last year being the first year of the universal influenza vaccination recommendation, the US Flu VE Network examined influenza vaccine effectiveness at four study sites (e.g., Marshfield, WI; Southeast MI; Rochester, NY; Nashville, TN). The US Flu VE Network was designed to provide estimates of clinical effectiveness of licensed vaccines by age group and by influenza type/subtype. Patients who were evaluated for acute respiratory symptoms in outpatient or inpatient settings were prospectively enrolled and tested for influenza by real-time RT-PCR. The study period was from October 2010 through April 2011. The design was a test negative case-control study in which cases tested positive for influenza and controls tested negative for influenza. Vaccination status was self-report followed by confirmation through record review. A patient was counted as immunized if they had received one or more doses of vaccine at least 14 days before onset of respiratory symptoms. Vaccine effective is the relative reduction in influenza risk with adjustments for potential confounding by age, sex, race, ethnicity; date of symptom onset; days between symptom onset and testing; insurance status; and presence of medical conditions that increase the risk of influenza-related complications.

A little over 1000 cases and about 3800 test negative controls were enrolled last year. Most of these were enrolled in outpatient clinics, and about one in three were in emergency departments or inpatient settings. Overall, the patient characteristics of the cases and controls were largely similar with a few exceptions. There were more non-white participants among cases, and slightly more individuals with high risk conditions among controls. Most enrollees are under the age of 50. This was not unique to last year. There are chronic challenges especially with enrolling adults over the age of 65 for various reasons, including that they are less likely to come in within 7 days of illness onset. In terms of the vaccines received, approximately 70% of the vaccine was sanofi pasteur's Fluzone®. There was only limited high dose vaccine use. In terms of those who were excluded and at what point, controls were excluded at a site prior to enrollment of the first case and controls enrolled after the last case of the season. Patients who were excluded included those with inconclusive influenza testing results, children less than 6 months old, individuals with onset before influenza circulation, individuals with onset after influenza circulation, individuals without confirmation of vaccine status, or individuals with specimen obtained more than 7 days after onset date.

The point estimate for vaccine effectiveness last season was 59% for all ages, 63% for those aged 6 months to 8 years, 51% for those aged 9 to 49 years, 52% for those 50 to 64 years of age, and 39% for those 65 years of age and older. However, low enrollment for those 65 years and older resulted in a wide 95% confidence interval (-15% to 67%). Thus they were rolled into the 50 years and older age group. Of the children ages 6 month to 9 years, 69% were fully immunized and 59% were unimmunized.

The following table shows vaccine effectiveness by vaccine type:

<u>Age group</u>	<u>Cases</u> <u>n immunized / total N (%)</u>	<u>Controls</u> <u>n immunized / total N (%)</u>	<u>VE (95% CI)</u>
Influenza type A infection			
All ages	211/706 (30%)	1959/3718 (53%)	59% (50% to 66%)
6 mo. to 8 years	71/196 (36%)	903/1455 (62%)	63% (50% to 74%)
9 to 49 years	71/359 (20%)	534/1429 (37%)	55% (39% to 66%)
50+ years	69/151 (46%)	522/834 (63%)	47% (22% to 63%)
Influenza type B infection			
All ages	105/330 (32%)	1959/3718 (53%)	60% (47% to 69%)
6 mo. to 8 years	55/169 (33%)	903/1455 (62%)	61% (43% to 73%)
9 to 49 years	33/122 (25%)	534/1429 (37%)	38% (-2% to 59%)
50+ years	17/39 (44%)	522/834 (63%)	52% (4% to 76%)

The following table shows vaccine effectiveness by influenza type:

<u>Age group</u>	<u>Cases</u> <u>n immunized / total N (%)</u>	<u>Controls</u> <u>n immunized / total N (%)</u>	<u>VE (95% CI)</u>
Influenza type A infection			
All ages	211/706 (30%)	1959/3718 (53%)	59% (50% to 66%)
6 mo. to 8 years	71/196 (36%)	903/1455 (62%)	63% (50% to 74%)
9 to 49 years	71/359 (20%)	534/1429 (37%)	55% (39% to 66%)
50+ years	69/151 (46%)	522/834 (63%)	47% (22% to 63%)
Influenza type B infection			
All ages	105/330 (32%)	1959/3718 (53%)	60% (47% to 69%)
6 mo. to 8 years	55/169 (33%)	903/1455 (62%)	61% (43% to 73%)
9 to 49 years	33/122 (25%)	534/1429 (37%)	38% (-2% to 59%)
50+ years	17/39 (44%)	522/834 (63%)	52% (4% to 76%)

The following table shows vaccine effectiveness by influenza subtype:

<u>Age group</u>	<u>Cases</u> <u>n immunized / total N (%)</u>	<u>Controls</u> <u>n immunized / total N (%)</u>	<u>VE (95% CI)</u>
Influenza A (H1N1) infection			
All ages	94/372 (25%)	195/3718 (53%)	61% (50% to 70%)
6 mo. to 8 years	28/74 (38%)	903/1455 (62%)	60% (33% to 76%)
9 to 49 years	34/221 (16%)	534/1429 (37%)	65% (48% to 77%)
50+ years	32/77 (42%)	522/834 (63%)	46% (9% to 67%)
Influenza A (H3N2) infection			
All ages	115/332 (35%)	1959/3718 (53%)	57% (44% to 66%)
6 mo. to 8 years	43/122 (35%)	903/1455 (62%)	65% (49% to 78%)
9 to 49 years	35/136 (27%)	534/815 (37%)	39% (6% to 59%)
50+ years	37/74 (50%)	522/834 (63%)	52% (17% to 71%)

Among the limitations to note, there were slight differences in how patients came to be enrolled across sites. As mentioned, this was a good enrollment year, but there was still insufficient power to do VE for all age groups and by type and subtype with narrow confidence intervals. There was also a lack serologic data, which would have been particularly of interest for the vaccine failures. In addition, the study was limited to the geographic area of enrollment in terms of what circulation was captured and when.

With strong enrollment last season, there were VE estimates by many of the categories of interest in a year with good virus vaccine match. For the most part, similar levels of effectiveness were observed by age groups that could be examined, by influenza type and subtype, and by care setting and by time of season (not presented during this session). These findings will be complemented by the findings from separate studies currently being examined on VE against hospitalizations among adults over age 50 from the EIP Network, and VE in several vulnerable populations, including severely ill children, pregnant women, and healthcare workers.

Fluzone® High Dose Safety Update

Pedro L. Moro, MD, MPH

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

Dr. Moro presented information on the safety review of Fluzone® High-Dose based on the 2010-2011 influenza season, first offering a review of the background information. On December 23, 2009, the FDA licensed a new high dose trivalent inactivated influenza vaccine, Fluzone® High-Dose, vaccine formulation in adults ≥ 65 years. Fluzone® High-Dose contains 4 times the hemagglutinin content as Fluzone® Standard Dose (180 mcg vs 45 mcg) and had superior immunogenicity. ACIP included Fluzone® High-Dose vaccine for adults ≥ 65 years in its recommendations for the influenza season 2010-2011, with no preference stated. Dr. Moro reminded everyone of the strengths and limitations of the VAERS reporting system, and explained that the objective of the safety review was to describe the pattern of adverse events reported to VAERS after Fluzone® High-Dose during the first influenza season after licensure.

The first US VAERS reports were received after Fluzone® High-Dose (TIV-HD) or standard dose influenza vaccine (TIV) from July 1, 2010 through February 28, 2011. This was comprised of individuals who were vaccinated from July 1, 2010 through December 31, 2010. Signs, symptoms, or diagnosis were coded with the Medical Dictionary for Regulatory Activities (MedDRA), and medical records were requested for all non-manufacturer serious reports, and for those suspected of anaphylaxis or Guillain-Barré Syndrome (GBS). All serious reports after TIV-HD and TIV in subjects ≥ 65 years of age were reviewed by medical officers who classified serious non-fatal adverse event reports into one of 12 body system diagnostic categories [Vellozzi C, et al. Vaccine. 2010;28(45):7248-55]. Serious reports after TIV-HD were compared to those after TIV in subjects ≥ 65 years of age. The FDA conducted empirical Bayesian data mining. The Empirical Bayesian data mining was used to detect disproportional reporting in the VAERS database. It ranks event-vaccine pairs based on the lower bound of 90% CI (EB05). If $EB05 > 2$, then the event-vaccine pair is further evaluated. If $EB05 \leq 2$, then there is no need for further evaluation. An $EB05 > 2$ does not demonstrate that the vaccine is associated with increased risk for the adverse event. As background, all inactivated vaccines, including standard dose TIV but not TIV-HD reports, were used. Reports with a live vaccine were excluded.

As of February 28, 2011, there were 622 VAERS reports of Fluzone® High-Dose. Of these, 8.2% were serious reports. The majority of reports were from females, the primary type of reported was the provider, and most of the patients who received Fluzone® High-Dose were recovered by the time the support was submitted. The top 10 MedDRA codes after all reports of Fluzone® High-Dose, in adults ≥ 65 years, included: Chills 156 (25.7); Pyrexia 156 (25.7); Nausea 108 (17.8); Pain 97 (16.0); Vomiting 96 (15.8); Headache 93 (15.3); Dyspnea 85 (14.0); Asthenia 65 (10.7); Dizziness 61 (10.1); and Diarrhea 59 (9.7).

In terms of VAERS serious reports after Fluzone® High-Dose and Standard Dose TIV vaccines in adults ≥ 65 years, for many of the categories, the exposed groups were similar. However, there were some differences. For example, the median onset for adverse events was less than one day for Fluzone® High-Dose and 4 days for Fluzone® Standard Dose. In those 85 years of age and older, there were 15 reports of serious adverse events for Fluzone® Standard Dose compared to 2 for Fluzone® High-Dose. In a comparison of all non-fatal serious reports after Fluzone® High-Dose and Standard Dose influenza vaccines in adults ≥ 65 years by body system category, a high proportion of the reports were in the neurological group following Fluzone® Standard Dose (n=54 reports) compared to Fluzone® High-Dose (n=7 reports). The majority of the neurological reports were GBS, with 39 reports for Fluzone® Standard Dose compared to 5 reports for Fluzone® High-Dose.

There were 5 reports of serious gastrointestinal adverse events following Fluzone® High-Dose, of which 4 were diagnosed as gastroenteritis and 1 of which was diagnosed as multiple digestive symptoms. All were hospitalized, but all recovered. With regard to cardiac diagnoses among serious reports after Fluzone® High-Dose, it is important to note that 41 (83.7%) of the 49 Fluzone® High-dose serious reports with available medical records had one or more pre-existing cardiac conditions. All 9 cardiac patients had cardiac pre-existing conditions. Cardiac diagnoses included 3 reports of atypical chest pain and 1 report each of myocardial infarction, idiopathic pericarditis, acute ischemic cerebrovascular accident, left carotid stenosis, hypertensive emergency, and syncope. No specific cardiac diagnostic pattern of concern was noted among the 9 reports.

Neurological diagnosis among non-fatal serious reports after Fluzone® High-Dose in adults ≥ 65 years (N=48) included Guillain-Barré Syndrome (5), ischemic optic neuropathy (1), and chronic inflammatory demyelinating polyneuropathy (1). Neurological diagnosis among Non-fatal Serious reports after Fluzone® Standard Dose influenza vaccines (N=115) in adults ≥ 65 years included Guillain-Barré Syndrome (39), seizures (3), transverse myelitis (3), chronic inflammatory demyelinating polyneuropathy (2), headache / dizziness (2), dystonic reaction (1), acute disseminated encephalomyelitis (1), left arm neuropathy (1), acute confusional state (1), and encephalopathy (1). Reported causes of death in 3 vaccinees after Fluzone® High-Dose included coronary artery disease (2), and sepsis (1). Reported causes of death in 9 vaccinees after Fluzone® Standard-Dose influenza vaccines included myocardial infarction (2), coronary artery disease (1), small and large bowel ischemic colitis (1), septic shock (1), sepsis (1), viral encephalopathy (1), aspiration pneumonia (1), and respiratory failure (1). These causes of death are based on reports or death certificates.

Regarding the data mining findings, there were two codes for symptoms that exceeded the threshold of EB05>2. One was for 34 cases of ocular hyperemia and the other was for 99 reports of vomiting. In reviewing the reports for ocular hyperemia, 32/34 (94.1%) were non-serious reports, 10 of the 32 (31.3%) non-serious reports had emergency department visits, 28/32 (87.5%) had recovered at the time VAERS report was submitted, and 17 of the 28 (53.1%) had a physician diagnosis of non-anaphylactic allergic type reactions. The diagnoses for the 2 serious cases were syncope and exacerbation of COPD, and both recovered. In reviewing the reports for vomiting, 83/99 (83.8%) were non-serious reports, 19 of the 83 (22.9%) non-serious reports had emergency department visits, and 62 of the 83 (74.7%) had recovered at the time VAERS form was submitted. The main diagnoses for non-serious reports included 36 (36.4%) multiple digestive symptoms, 25 (25.3%) other non-infectious, 14 (14.1%) non-anaphylaxis allergic reactions, 7 (7.1%) respiratory, and 1 local reaction. A clinical review of the 99 cases of vomiting found that 16 (16.2%) were serious reports. The diagnosis for these 16

serious reports included 4 gastroenteritis; 2 non-anaphylaxis allergic reactions, and 1 report each of sepsis, conjunctivitis/UTI, chest pain, renal insufficiency, sepsis/hypotension/gastroenteritis, reactive airway disease, seizures, respiratory insufficiency, anaphylaxis, and febrile illness. Of the 16 serious vomiting cases, 10 (63%) recovered by the time the VAERS form was submitted.

In summary, VAERS received 622 reports following Fluzone® High-dose as of February 28, 2011, most of which (91.8%) were coded as non-serious (e.g., self-limited events). Higher proportions of vomiting and ocular hyperemia (eye redness) were reported after Fluzone® High-dose than after all inactivated vaccines in persons aged ≥ 65 years. Most recovered at the time of submitting the report. Review of serious reports in persons aged ≥ 65 years showed that a higher proportion of reports after Fluzone® High-dose had gastrointestinal diagnoses compared with reports after standard dose influenza vaccines (based on small numbers). A higher proportion of cardiac conditions were observed among serious reports, but no pattern of concern was observed. All had pre-existing cardiac conditions prior to vaccination. CDC/FDA will continue to monitor the safety of Fluzone® High-Dose during 2011-2012.

Influenza Vaccine Distribution and Coverage

James A. Singleton, MS
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Mr. Singleton presented a summary of 2010-2011 vaccine coverage. It is important to note that 2010-2011 was the first post-pandemic season, so there were some challenges. There was concern that given the high seasonal vaccine coverage in 2009-2010 driven by the pandemic, there would be “flu fatigue” that might affect public interest in influenza vaccine. 2010-2011 was also the first season with a universal recommendation, there were new and expanded venues for influenza vaccination (e.g., schools, pharmacies), and there was an unprecedented vaccine supply. During the 2010-2011 season, 158 million doses of vaccine were distributed. Prior to that, the highest level was 214 million in 2009-2010.

In terms of influenza vaccination coverage by month in the 2009-2010 and 2010-2011 seasons, the greatest months of activity are October and November. During the 2010-2011 season, coverage among children reached 51% and coverage among adults reached about 40%. In the 2009-2010 season, coverage among children was lower than in the 2010-2011 season, and for adults was about the same.

Trivalent influenza vaccination coverage by age for the 2008-2009 through 2010-2011 seasons is shown in the following table:

Group	2008-09 (%) ¹	2009-10 (%) ²	2010-11 (%) ³
Overall (persons aged ≥ 6 mo.)	Not Available	41.2	43.0
Children, 6 mos-17 years	29.1	43.7	51.0
Persons ≥ 18 yrs	40.2	40.4	40.5
Persons 18-49 yrs, all	28.2	29.9	30.5
Persons 18-49 yrs, high risk	38.7	38.2	39.0
Persons 50-64 yrs	45.9	45.0	44.5
Persons ≥ 65 yrs	73.6	69.6	66.6

1. BRFSS 2008-09 for adults; child estimate from 2009 NHIS, ages 6 mo. – 18 years, online at:

<http://www.cdc.gov/vaccines/stats-survey/nhis/2009-nhis.htm>.

2. BRFSS and National 2009 H1N1 Flu Survey (NHFS) estimates, 2009-10. Online at:

http://www.cdc.gov/flu/professionals/vaccination/coverage_0910estimates.htm.

3. BRFSS and NIS estimates, 2010-11. Online at:

http://www.cdc.gov/flu/professionals/vaccination/coverage_1011estimates.htm

To assess fully vaccinated coverage, the best that could be done for this season based on the data was to assess receipt of 2-doses of influenza vaccine in children less than 9 years of age. This underestimates fully vaccinated coverage, given that vaccine history was not taken into account. Most 6 to 11 month olds would not have been old enough to have received vaccine for the prior season. There was 33% 2-dose coverage in 6-11 month olds, 22% in 1 year olds, 13% in 2 year olds, 12% in 3 year olds, 12% in 4 year olds, 13% in 5 year olds, 8% in 6 year olds, 10% in 7 year olds, and 10% in 8 year olds. There was quite a difference in the rates of 1-dose coverage among all of the children with 1-dose coverage of 69% in 6-11 month olds, 63% in 1 year olds, 52% in 2 year olds, 62% in 3 year olds, 62% in 4 year olds, 60% in 5 year olds, 57% in 6 year olds, 55% in 7 year olds, and 53% in 8 year olds.

In terms of race/ethnicity, for adults there was substantial disparity, with blacks and Hispanics have lower rates at about 10 percentage points of magnitude compared to whites. In terms of trends, there was a slight increase among Hispanics. For children, comparing just 2009-2010, increases in coverage were observed for each racial/ethnic group, with larger increases among black and Hispanic children. In 2009-2010, there was a lower coverage rate among blacks compared to whites. This was not observed in the 2010-2011 season.

There is quite a bit of variation in state trends, with a range of about 37% coverage to about 58% coverage in children, and about 33% to 46% coverage in adults. In terms of regional distribution, there tend to be higher rates of coverage in the Northeast, and lower rates in the west.

Coverage by state for children in 2010-2011 is shown in the following tables:

	States	n	%...	CI (9)
	Montana	2,044	37.3	(±7.9)
	Florida	2,896	38.9	(±3.7)
	Oregon	1,897	41.6	(±5.8)
	Idaho	2,005	43.1	(±7.8)
	Indiana	1,996	43.7	(±4.6)
	Mississippi	1,826	44.3	(±11.7...)
	Alabama	2,067	45.9	(±5.3)
	Michigan	2,342	45.9	(±4.3)
	Texas	8,476	46.4	(±3.6)

	States	n	%...	CI (9)
	Rhode Island	1,879	79.3	(±4.1)
	Hawaii	2,032	70.0	(±12.5...)
	District of Columbia	1,821	65.4	(±11.2...)
	Massachusetts	1,848	64.9	(±4.7)
	Maryland	2,922	62.7	(±5.2)
	Connecticut	2,116	61.8	(±5.1)
	New Jersey	2,499	60.0	(±4.1)
	Minnesota	1,874	59.3	(±4.9)
	Pennsylvania	3,223	58.3	(±4.6)

Source: National Immunization Survey,

September 2010-June 2011.

Online at:

<http://www.cdc.gov/flu/professionals/vaccination/report1011/report1>

Coverage by state for adults in 2010-2011 is shown in the following tables:

	States	n	%...	CI (9)
	Nevada	2,616	32.7	(±4.1)
	Alaska	2,366	33.7	(±3.3)
	Idaho	4,659	35.1	(±2.5)
	California	13,904	35.1	(±1.4)
	Florida	20,113	35.9	(±2.2)
	Oregon	4,167	36.3	(±2.5)
	Illinois	4,443	36.4	(±4.5)
	New Jersey	11,388	37.6	(±1.8)
	Montana	6,910	37.7	(±2.0)

	States	n	%...	CI (9)
	South Dakota	5,271	56.2	(±4.1)
	Iowa	5,364	49.7	(±2.5)
	Massachusetts	15,104	48.5	(±2.0)
	Virginia	5,081	48.4	(±2.9)
	West Virginia	3,878	47.7	(±2.9)
	Rhode Island	5,629	47.1	(±2.4)
	Maryland	7,700	46.9	(±2.5)
	Minnesota	8,887	46.4	(±2.0)
	Hawaii	5,191	46.1	(±2.9)

Source: Behavioral Risk Factor Surveillance

System, September 2010-June 2011.

Online at:

<http://www.cdc.gov/flu/professionals/vaccination/report1011/report1/>

In terms of coverage of healthcare personnel, the most valid source of data is the NIS as far as representativeness. However, NIS data are not very timely. The estimates available show a gradual increase in coverage among healthcare professionals, with a range of 42% in the 2004-2005 season to 62% in 2009-2010. There is an open question with regard to whether there was an increase in healthcare personnel vaccination, given that there is no “apples-to-apples” comparison at this point. There was basically no significant change in coverage last season [Estimates from the National Health Interview Survey (NHIS), Behavioral Risk Factor Surveillance System (BRFSS), National 2009 H1N1 Flu Survey (NHFS), and internet panel surveys ([MMWR August 19, 2011 / 60\(32\);1073-1077](#))].

With respect to pregnant women, according to BRFSS data there was an observed increase in influenza vaccine among pregnant women. There was a particularly significant increase between the pregnant women and non-pregnant women in the 2009-2010 and 2010-2011 seasons. There was some evidence that there was an increase in influenza vaccine uptake among pregnant women last season and the prior season. Internet panel surveys were conducted in 2010-2011 and will be repeated in 2011-2012, which will offer a more rapid assessment of this population [Behavioral Risk Factor Surveillance (BRFSS) data from December interviews only, for women 18-44 years pregnant or not pregnant when interviewed. Differences in influenza vaccination coverage between pregnant and not pregnant women were statistically significant ($p < 0.05$) only for the 2009-10 and 2010-11 seasons. Other estimates for pregnant women from PRAMS ([MMWR December 3, 2010 / 59\(47\):1541-1545](#)); NHFS (Ding et al. *Am. J. Obstetrics & Gynecology*, June 2011 Supplement); and an internet panel survey ([MMWR August 19, 2011 / 60\(32\):1078-1082](#))].

An *MMWR* article assessed place of influenza vaccination among adults in the 2010-2011 season. The doctor's office was the most prevalent place of vaccination for most age groups (40% for adults overall). About 18% of adults were vaccinated in stores, including supermarkets and drug stores. About 70% received their vaccines in the workplace. There were differences by age. A higher percentage of older adults were vaccinated in doctor's offices, but surprisingly in 2010-2011, 26% of older adults were vaccinated in the store setting. A larger percentage of younger adults were vaccinated in the workplace. Based on these data, the doctor's office is most important medical setting, and the workplace and store represent important non-medical settings. There was an increase in store vaccination (18.4%) compared to 1998-99 (5%) and 2006-07 (7%). There have been increases in persons vaccinated since 2006-07 in doctor's office: 28 million (2006-07) to 37 million (2010-11); and store: 6 million (2006-07) to 17 million (2010-11). The percentage of vaccination in non-medical settings is higher for whites (44%) versus blacks (29%) and Hispanics (34%), and for those who attended college (47%) versus those with less than a high school education (28%) [*MMWR* June 17, 2011;60(23):781-785].

There are some study limitations. This information is primarily based on self-reported vaccination status and was not validated by medical records. Survey estimates may not be representative. BRFSS did not reach households with only cell phones, although it will do so next year. Telephone survey response rates were low. The representativeness of the internet panel survey estimates needs further evaluation. Tracking trends by season are complicated by multiple data sources with different timeliness and possibly validity. Comparisons to 2009-2010 season estimates is complicated by the unique circumstances of the pandemic, and the fact that persons could have received either 2009 H1N1 vaccine only, seasonal vaccine only, or both.

To summarize, 44 million more trivalent seasonal influenza vaccine doses were distributed than in 2009-2010. Coverage levels by Census population estimates can provide estimates of doses administered in the civilian, non-institutionalized population. There were moderate increases in children's coverage in infants since 2009-2010, with large increases since 2008. Coverage for adults was similar to 2009-2010 trivalent coverage. Coverage among adults ≥ 65 years has been declining in the past two seasons, and racial/ ethnic disparities among all adults persist. However, non-Hispanic white adults did have significantly higher levels. Similar disparities were not observed in children. Among children, non-whites did not have higher coverage versus other racial/ethnic groups in 2010-11. There was wide variation among states. Last season's increases were maintained for pregnant women and healthcare personnel. In terms of what was achieved overall in 2010-2011, despite the expected challenge of "flu fatigue," overall vaccine coverage maintained last season's increases. There were significant increases in coverage in Hispanic and non-Hispanic black children. Multiple venues were accessed for

vaccination. The challenges for the coming season are to maintain the gains, improve vaccination coverage among adults with risk conditions and older adults, and improve full vaccination of children recommended for two doses.

In terms of distribution, approximately 115 million doses were distributed by October 7, 2011. In May, the vaccine manufacturers submitted projections about what they may produce, which ranged from 166 to 173 million doses. Based on weekly estimates provided as of October 15, 2011, 22% to 32% of children have been vaccinated, which is higher than the 17% to 20% by this date last season. When children are added whose parents said they intend to have their child vaccinated, the range is about 44% to 56% for this season, which is consistent with the 51% end of season coverage from the end of last season. National Vaccine Week is November 4-10, 2011. Data are being collected through the NIS in November for pregnant women and healthcare personnel, and monthly estimates are being collected for children and adults. Further information is available on the CDC vaccine website at: <http://www.cdc.gov/flu/professionals/vaccination/vaccinecoverage.htm>.

Discussion Points

Dr. Foster (APhA) reported that upon notification of the jet injector issue, APhA immediately contacted the chains involved that they knew of, and within the same day the chains had withdrawn use and got the word out to stop administering influenza vaccine via jet injectors. APhA was surprised to learn that this was a device that was approved by the FDA for use with vaccines and injectable drugs. APhA did not encourage use of this device. He wondered whether the FDA intended to reevaluate that particular statement.

Dr. Sun (FDA) reiterated that the FDA issued an update earlier that morning. The bottom line is that even though the devices were cleared for drugs and vaccines, the regulatory requirements are still such that particular vaccines have to be approved for use with that device, and this has to be reflected in that way when the vaccine was licensed. With the exception of intradermal FluZone® and FluMist®, all current influenza vaccine were studied using a needle and syringe. When they were approved, it was based on the safety and immunogenicity using that method of delivery. That is, there are no data to support administration of current influenza vaccines using jet injectors.

Dr. Marcy said he was disappointed looking at the statement in the *MMWR* of August 26, 2011 regarding this year's influenza vaccine that a stronger statement was not made for immunization of healthcare workers. He felt strongly that a statement should be included every year to emphasize the importance of healthcare workers receiving the vaccine. Regarding Dr. Thompson's presentation, the question Dr. Marcy most often receives from colleagues regards the efficacy of the vaccine if it is received early. He wondered whether there were any data to indicate the status of this issue.

Dr. Grohskopf indicated that the healthcare worker issue was actually the substance of a separate ACIP guideline, which is due to be published shortly. Healthcare personnel are mentioned in the previous 2010-2011 statement.

Regarding Dr. Marcy's question about efficacy, Dr. Thompson indicated that for last season, no changes were observed over the course of the season in terms of efficacy. It was difficult to do a point estimate for the 65 and older age group, so it was hard to estimate for the season as a whole. The issue of length of efficacy when the vaccine is received earlier has been raised, for this season especially. Once the targeted enrollment goals are reached, it should be easier to assess this.

Dr. Meissner asked Dr. Grohskopf to comment on the previous month's *MMWR* in which there was a report of two children who were infected with an avian strain H3N2. One of the children had no history of contact with farm animals.

Dr. Grohskopf replied that the individual child who did not have contact with animals had a relative who did. She deferred to Dr. Bresee, the SME, to share further information.

Dr. Bresee (SME) added that of the 26 cases that have been reported since 2005 to CDC, all except one had either direct or indirect contact with a pig. There has been only one potential human-to-human transmission, and that person had very close contact with pigs as well.

Dr. Jenkins commented that vaccine administration in stores was phenomenal. Some supermarkets are offering discounts on groceries for obtaining an influenza vaccine from them. She would expect to see a lot more of that occurring. In terms of the survey that was conducted, she asked Dr. Singleton to comment on the question posed to parents about intent to vaccinate and whether they got any sense of vaccine refusal. She is surprised by the number of refusals she receives in her population.

Dr. Singleton replied that those who do not intend to have their children vaccinated, and those who do not have them vaccinated by the season, are being monitored to determine the reasons. These data are still being analyzed and could be presented at a later date.

Following up on Dr. Marcy's comments, Dr. Sawyer thought it would be helpful to include more data about waning immunity in the annual statements, including historical data. There was a time when providers were encouraged not to immunize too soon, but now that has changed. At least at the level of the statements, he has never seen the data that led to that change. This continues to be a frequently asked question. Regarding the observation of a decrease in coverage among older adults over the last three seasons, he asked Dr. Singleton whether he felt the estimates were statistically significantly different. If so, he wondered whether there were plans for further evaluation of the reasons for the decrease.

Dr. Singleton responded that the differences were statistically significant and the sample sizes are very large. The BRFSS has an annual sample size of 400,000. One question regards whether they were problematically significant. This is being double-checked with other data sources such as the NHIS, which is an in-person survey with higher response rates, and the results will be assessed over the next couple of months. This will continue to be monitored. It is speculated that the reason may be an after effect of the recommendation in 2009-2010 for H1N1. Coverage in those 65 years of age and over had been increasing until 2004-2005. During the shortage, coverage dropped about 10%, but slowly rebounded to reach 70% in 2008-2009. Then there was another drop.

Dr. Schuchat added that people have requested additional information that they would like to see in the statement that would help with outreach and to clarify frequently asked questions. CDC is trying to focus statements narrowly on the GRADE system and so forth. There are many other communication tools for referenced, scientific support for the answers to the frequently asked questions. For people who are interested, a considerable amount of information on vaccine effectiveness can be found in the CDC vaccine website. For example, the information about waning immunity has been added because they anticipated this question. Such issues can be addressed much more quickly through means other than the annual statement.

Regarding Fluzone® High-Dose and Standard Dose, Dr. Turner (ACHA) was struck by the number of cases of GBS for the Standard Dose. While he realized the number of recipients of the Standard Dose was much higher than High-Dose, that was not mentioned. He asked Dr. Moro to comment on whether that was within the expectations.

Dr. Moro responded that the explanation for the difference is unknown at this point. It is suspected that it is probably due to reporting practice, but this is not really known. There was no signal for GBS with data mining, and no trends of concern have been noted when previous years were assessed. The crude reporting rates are also not greater than background for either High-Dose or Standard Dose.

Dr. Neuzil (IDSA) said she was happy to see the increases in vaccine coverage in the pediatric population, and hoped that with the universal vaccine recommendation, the same would occur among the adult population. She thought it might help to refine the messages if they knew whether the increases in children were seen in healthy children who were not previously recommended to be vaccinated, or if the coverage rates were increasing among high-risk children.

Dr. Singleton responded that while he did not have this information with him, data were collected on the medical conditions of the children, so this information is available.

Ms. Stinchfield (NAPNAP) was disappointed to see that they had reverted to less inclusive language. Regarding the many places that influenza vaccine is being given, ACIP should end its statements with inclusive language for people to contact their healthcare professionals with their concerns. She spoke with Skip Wolf about this and volunteered to work with him on this.

Carol Hayes (ACNM) requested clarification regarding whether the survey regarding immunization rates among pregnant women was an internet-based survey. Her concern was that currently in the US, about 50% of women who deliver children are covered by Medicaid, which means they live very close to the poverty level. It is unclear whether women living at the poverty level are on the internet on a daily basis, so she had concerns about how broadly the data could be applied to the population of pregnant women in the US. It was not clear to her that they could say this reflects all pregnant women.

Dr. Singleton responded that the 2010-2011 data were from an internet panel survey. It was an opt-in general health survey with over 1 million people enrolled. Screening was done to identify women who would be pregnant during this period of influenza vaccination. This is a way to obtain rapid data in a rare population. More evaluation needs to be done with regard to how representative the results are, but it was reassuring when assessing the BRFSS data for women that the estimates were found to be about the same. He said her point was well-taken about women living at the poverty level, but there is a tradeoff for trying to get rapid, cheap, high

quality data. It is difficult to get all three at the same time. The internet survey was a way to obtain a quick and cheap estimate. The next best thing is the Pregnancy Risk Assessment Monitoring System (PRAMS) data, which is a very large sample size from over 30 states. This systems includes women who delivered live births and are followed up, so these data will be available for evaluation later.

Carol Hayes (ACNM) noted that PRAMS is also limited by live births.

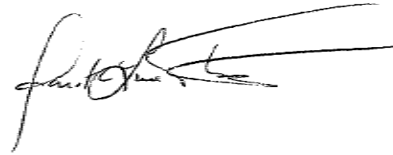
Heather Potters (PharmaJet) My name is Heather Potters. I am the Co-Founder of PharmaJet and Chairman, one of two technology companies in the needle-free injection space affected by the recent comments from the FDA. I'm grateful to have the opportunity to be here today and listen to the briefing and discussion. First, I'd like you to know that we're committed to ensure our family of injection devices are used according to our 510(k) clearance licensure from the FDA, namely general injection of vaccines and liquid medicines for intramuscular, subcutaneous, and intradermal medicines per the specific device involved, but without promoting them for any particular injectable product. Our first license was granted in 2009. We are aware that it was used in New Jersey by state and county health departments for delivery of both seasonal and H1N1 influenza vaccines in mass campaign settings. It was studied for speed and efficiency for utilization by the Department of Homeland Security (DHS). We have received Small Business Innovative Research (SBIR) grants from the CDC for \$850,000 to further the development of our technology for its public health applications, both domestically and for global health. CDC and other experts at Program for Appropriate Technology in Health (PATH) and WHO have advised us that jet injection has been studied clinically and used successfully for more than a half a century for many vaccines, including influenza. WHO, PATH, NIH, and the US Army Medical Research Institute of Infectious Diseases (USAMRIID) are assisting us or financing us and our vaccine partners to conduct domestic and overseas trials and evaluations of our needle-free jet injection systems for various diseases. As a small business with only about 40 employees, the recent announcements by the FDA and CDC about jet injection and influenza have been a major setback for the sales that permit us to keep working to provide safer systems for vaccination that avoid the dangers and drawbacks of needle syringes. We are aware that our customers find utility in the elimination of needlestick and the associated costs of treatment and liability, and also because of the cost-effectiveness and efficiency of our technology, and that our customers and providers like this method of delivery. Last year, we scaled up to provide several hundred thousand syringes, and this season we were expecting to sell several million. Now our domestic sales have virtually come to a halt, with the exception of the investigational trials that I just mentioned. We are making arrangements to meet with the FDA next week or shortly thereafter to discuss the kinds of studies that influenza vaccine manufacturers would need to furnish in order to allow their product inserts for next year's season 2012-2013 to specify jet injection as an alternative to delivery by needle and syringe. But, we're caught in the middle in some sense in the catch-22 gray zone leaving use of jet injection technology to the choice of the provider's discretion if none of the vaccine makers are willing to cooperate with such clinical trials and regulatory submissions in order to modify their product inserts. So, I'm really grateful for your attention and consideration to this very important issue for us, and all of us. Thank you.

Day 2: Public Comment

No public comments were offered on the second day of the October 2011 meeting.

Certification

I hereby certify that to the best of my knowledge, the foregoing Minutes of the October 25-26, 2011 ACIP Meeting are accurate and complete.



____ 23 January 2012 ____
Date

Dr. Jonathan Temte, Acting Chair
Advisory Committee on
Immunization Practices (ACIP)

Participant Roster

U.S. Citizens			
Last	First	Citizenship	Organization
Alameda	Jeannine	United States	Sanofi Pasteur
Armstrong	Jennifer	United States	Glaxosmithkline
Arthur	Phyllis	United States	Biotechnology Industry Organization (BIO)
Ashley	Don	United States	Pfizer Vaccines
Ault	Kevin	United States	Emory University School of Medicine
Auzenne	Angelique	United States	Career and Recovery Resources Inc.
Aviles-Mendoza	Guillermo	United States	HHS/NVPO
Baker	Carol J.	United States	Baylor College of Medicine
Bandell	Allyn	United States	Medimmune
Bardi	Janna	United States	Washington State Department of Health
Bargatze	Robert	United States	LigoCyt Pharmaceuticals, Inc.
Barlows	Theodore	United States	GlaxoSmithKline
Barry	Christopher	United States	American Academy of Physician Assistants
Baxter	Bryan	United States	Novartis
Beaman	Ann	United States	Avalon Catering
Bednarczyk	Robert	United States	Rollins School of Public Health, Emory University
Bennett	Samantha	United States	National Meningitis Association
Bennett	Nancy	United States	U of Rochester, Center for Community Health
Berns	Abby	United States	Emory University Rollins School of Public Health
Blalack	Gary	United States	GlaxoSmithKline
Bobinsky	Marcella	United States	NH Division of Public Health Services
Bocchini, Jr.	Joseph	United States	ACIP - Member
Boomer	Gail	United States	Merck & Co. Inc.
Bozof	Lynn	United States	National Meningitis Association
Brackman	Julian	United States	Avalon Catering
Bradley	Kim	United States	GlaxoSmithKline
Brady	Michael	United States	Nationwide Children's Hospital
Braga	Damian	United States	
Bresnitz	Eddy	United States	Merck & Co, Inc.
Bressler	Lawrence	United States	GlaxoSmithKline
Brewer	Katie	United States	American Nurses Association
Brosseau	Jenny	United States	Emory University
Bryant	Connie	United States	Emory University Hospital

Burnworth	Laura	United States	Children's Healthcare of Atlanta
Burstin	Stuart	United States	GlaxoSmithKline
Campbell-Welsh	Gay	United States	GDPH
Campos-Outcalt	Doug	United States	ACIP
Cannon	Patricia	United States	Allergan
Cappio	Kelly	United States	Biotechnology Industry Organization
Carpico	Annemarie	United States	GlaxoSmithKline
Cary	Donna	United States	Sanofi Pasteur
Castner	Jill	United States	sanofi pasteur
Chaney	Mike	United States	GA Chapter, American Academy of Pediatrics
Chang	Jean	United States	Dynavax Technologies
Cheek	James	United States	IHS DEDP
Chung	Haejin	United States	Novartis
Clark	Liana	United States	Merck
Claxton	Isabelle	United States	GSK
Coelingh	Kathleen	United States	MedImmune
Coen	Lisa	United States	Novartis Vaccines
Colwell	Christopher	United States	Becton Dickinson
Conner	Penny H	United States	Georgia Immunization Program
Conway	Catherine	United States	Avalon Catering
Counard	Catherine	United States	National Assoc of County and City Health Officials
Coyne-Beasley	Tamera	United States	University of North Carolina
Cullison	Mark	United States	Merck and Co., Inc.
Dalrymple	Donald "Dack"	United States	Dalrymple & Associates, LLC
Dana	Adrian	United States	Merck & Co., Inc.
Davis	Carrie	United States	Kalihi Palama health Center
Decker	Michael	United States	Sanofi Pasteur
Decker	Roberta	United States	MD DoH and Mental Hygiene
DiCola	Lauren	United States	Novartis Vaccines & Diagnostics
Dinovitz	Richard	United States	Nuron Biotech, Inc.
Drew	Meghan	United States	Edelman
Duchin	Jeffrey	United States	Public Health - Seattle & King County
Dunham	Holly	United States	
DuVall	Sarah	United States	Rensselaer County Health Department
Egge	Steven	United States	Merck and Co., Inc.
Ehresmann	kristen	United States	Minnesota Department of Health
Eiden	Joseph	United States	Pfizer Inc.
Elliott	Tara	United States	Otto Kaiser Memorial Hospital
Elward	Alexis	United States	Washington University School of Medicine

Epling	John	United States	SUNYUpstate Medical University
Erkman	Brett	United States	Great Point Partners, LLC
Etkind	Paul	United States	National Assoc of County and City Health Officials
Evans	Geoffrey	United States	Division of Vaccine Injury Compensation, HRSA
Facey	Maxine	United States	Paterson Community Health Center, Inc
Feinberg	Mark	United States	Merck & Co., Inc.
Fernandez	Carrie	United States	Pfizer
File	Sarah	United States	Emory University Rollins School of Public Health
Finger	Reginald	United States	independent researcher
Fish	Rebecca	United States	GlaxoSmithKline
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
Gargano	Lisa	United States	Emory University
Gaskins	Diana	United States	retired nurse consultant
Geibe	Jesse	United States	DoD Liason to CDC
Gonzales	Tara	United States	MedImmune LLC
Gordon	Lili	United States	Pfizer
Goveia	Michelle	United States	Merck
Grabenstein	John	United States	Merck & Co., Inc.
Greenberg	David	United States	Sanofi Pasteur
Grogg	Stanley	United States	American Osteopathic Association
Hahn	Christine	United States	Council of State and Territorial Epidemiologists
Hannan	Claire	United States	Association of Immunization Managers
Haupt	Richard	United States	Merck Research Labs
Hayes	Carol	United States	American College of Nurse Midwives
Hazelwood	Kimberley	United States	GDPH
Henry Wallace	Stephanie	United States	Cambridge Communications & Training Institute
Herbert	Natasha	United States	Emory University
Hernandez	Nelina	United States	Mi Doctor
Herrera-Taracena	Guillermo	United States	Janssen
Hewlett	Dial	United States	Pfizer - Medical
Homeier	Barbara	United States	Merck & Company, Inc.
Hoover	Chad	United States	sanofi pasteur
Hosbach	Philip	United States	sanofi pasteur
Howe	Barbara	United States	GlaxoSmithKline

Howell	Kelly	United States	Emory University
Huang	Philip	United States	Merck & Co., Inc.
Hughes	James	United States	Emory University
Hull	Harry	United States	HF Hull & Associates
Humiston	Sharon	United States	Immunization Action Coalition
Humphrey-Franklin	Donelle	United States	Georgia Department of Public Health
Hung	Jeff	United States	Jefferies & Co.
Jacob-Nara	Juby	United States	GlaxoSmithKline
Jacques	Colette	United States	Support Organization For AIDS Prevention
Janssen	Robert	United States	Dynavax Technologies
Jenkins-Woodard	Renee	United States	Howard University
Johnson	Erica	United States	APCO Worldwide
Johnson	David	United States	Sanofi Pasteur
Jones	Eric	United States	sanofi pasteur
Kagan	Stephen	United States	Pfizer
Keitel	Wendy	United States	Baylor College of Medicine
Keyserling	Harry	United States	Society of Healthcare Epidemiology of America
Kim	Chris	United States	Emory University School of Medicine
Kimberlin	David	United States	AAP Red Book
Kinsinger	Linda	United States	Veterans Health Administration
Kozak	Waldemar	United States	Novartis Vaccines and Diagnostics
Kuter	Barbara	United States	Merck
LaBenita	Maribel	United States	Avalon Catering
LaMarca	Lou	United States	Pfizer
LaRussa	Philip	United States	Columbia University
Lawson	Herschel	United States	Retired CDC
Lease	Christian	United States	Novartis Vaccines
Lett	Susan	United States	MA Dept Public Health
Lewin	Clement	United States	Novartis Vaccines
Lewis	Rita	United States	George Washington University
Loehr	Jamie	United States	Cayuga Family Medicine
Long	Deryl	United States	WellStar
Love	Glen	United States	Merck Vaccines
Malingkas	Moody	United States	FEDERAL BUREAU OF PRISON
Malone	Robert	United States	RW Malone MD LLC
Marcy	Stephan Michael	United States	ACIP
MARCY	Lynette	United States	Wife of ACIP member
Martin	Maria	United States	Sanofi Pasteur
Martin	Kim	United States	Association of State & Territorial Health

			Officials
Martin	Tyler	United States	Dynavax Technologies
Mazur	Marie	United States	CSL Biotherapies
McEwen	Karie	United States	Instructor
McGruder	Janet	United States	State Department of Public Health/Immunizations
McGuffin	Colleen	United States	Merck
McKinney	Paul	United States	
Meigs	Wendy	United States	Meningitis Angels
Meissner	Cody	United States	physician
Merriitt	Judy	United States	Scientific Technologies Corporation
Middleman	Amy	United States	Baylor College of Medicine
Miller	Donna	United States	NHC Hawaii
Milley	Frankie	United States	Meningitis Angels
Moburg	Christeen	United States	MedImmune
Montero	Jose	United States	New Hampshire Department of Health
Moore	Kelly	United States	Tennessee Department of Health
Muhammad	Riyadh	United States	SC Dept of Health and Environmental Control
Mullikin	Mark	United States	Novartis Vaccines & Diagnostics
Murphy	Linda	United States	Centers for Medicare & Medicaid Services
Muthulakshimi	Arumugam	United States	Chelsea Skilled Nursing Rehabilitation Center
Myers	Martin	United States	National Network for Immunization Information
Narasimhan	Vasant	United States	Novartis Vaccines & Diagnostics
Netoskie	Mark	United States	America's Health Insurance Plans
Neuman	William Richey	United States	Pfizer Pharmaceuticals
Neuzil	Kathleen	United States	PATH
Ngundue	Jerome	United States	WALDEN UNIVERSITY
Nicholson	Jennifer	United States	Emory University
Oguntei	Grace	United States	Emory University
Orenstein	Walter	United States	Emory University
Owen	Bill	United States	MedImmune
Paradiso	Peter	United States	Pfizer
Parikh	Shefali	United States	Merck and Co.
Perez	John	United States	Pfizer Inc.
Peters	Martin	United States	Novartis Vaccines
Peterson	Diane	United States	Immunization Action Coalition
Pisani	Amy	United States	Every Child By Two
Plotkin	Stanley	United States	Vaxconsult
Poland	Greg	United States	Mayo Clinic
Poore	Linda	United States	NORTH DEKALB Grady Health Sys

Quinn	Jane	United States	GlaxoSmithKline
Reeves-Hoche	Mary Kathryn	United States	Sanofi Pasteur
Reynolds	Megan	United States	Children's Healthcare of Atlanta
Richardson López	Vesta Louise	United States	ACIP Liaison
Richmond	Heather	United States	Medimmune
Riddle	Sally	United States	Pfizer, Inc
Ripley	Millicent	United States	Avalon Catering
Risbeck-Hardin	Karla	United States	St. Benedicts Hospital
Rodriguez	J.	United States	CDC
Rogers	Krystal	United States	Saint Francis Medical Center
Rosenbaum	Sara	United States	GWU/Department of Health Policy
Saah	Alfred	United States	Merck & Co.
Sanyour	Mark	United States	Novartis Vaccines
Saslow	Debbie	United States	American Cancer Society
Sattler	Carlos	United States	Merck & Co., Inc.
Savoy	Margot	United States	Christiana Care Health System
Sawyer	Mark	United States	University of California San Diego
Schaffner	William	United States	Vanderbilt University School of Medicine
Schmader	Kenneth	United States	American Geriatrics Society
Schmidt	Annette	United States	Gerontological Society of America
Schodel	Florian	United States	Philimmune LLC
Schroeder	Steve	United States	Pioneer Health Distributors
Scott	Laura	United States	Families Fighting Flu
Scott-Okerblom	Lorin	United States	Marion County Health Department
Seib	Katy	United States	Emory University
Sheffield	Tamara	United States	Intermountain Healthcare
Shelton	Jerry	United States	Fuld and Co.
Sherner	James	United States	Pfizer
Shin	Tom	United States	Baxter Healthcare Corporation
Sievert	Alan	United States	GA CHAPTER, AAP
Silverstein	Leonard	United States	GlaxoSmithKline Vaccines
Smith	Susan	United States	Medscape
Snow	Vincenza	United States	Pfizer Vaccines
Stier	Jeff	United States	National Center for Public Policy Research
Stinchfield	Patsy	United States	Children's Hospitals and Clinics of Minnesota
Strutton	David	United States	Pfizer Inc.
Stuerke	Stacy	United States	Merck Vaccine Division
Sullivan	Gina	United States	GlaxoSmithKline
Swanson	Robert	United States	Michigan Department of Community Health

Talkington	Kathy	United States	ASTHO
Taylor	Paula	United States	P3S Corporation
Temte	Jonathan	United States	ACIP
Thomas	Michael	United States	GlaxoSmithKline Pharmaceuticals
Titievsky	Lina	United States	Pfizer Inc
Tsai	Theodore	United States	novartis
Tucker	Miriam	United States	Pediatric News
Turner	James	United States	American College Health Association
van Santen	Katharina	United States	Rollins School of Public Health
Vaupel	Christine	United States	GlaxoSmithKline
Vazquez	Marietta	United States	Yale University School of Medicine
Velicer	Christine	United States	Merck
Wallace	Fred	United States	Fuld & Co,
Warner	Amy	United States	Take Care Health
Welsch	Jo Anne	United States	Novartis Vaccines
Weston	Wayde	United States	GlaxoSmithKline
Wexler	Deborah	United States	Immunization Action Coalition
Whitley-Williams	Patricia	United States	Robert Wood Johnson Medical School
Winokur	Jeff	United States	Atlantic Health Partners
Wood	Laurel	United States	Immunization Action Coalition
Woodruff	Jennifer	United States	Merck & Co., Inc.
Wynn	Cynthia	United States	GDPH
Yarn	Sandra	United States	GA-AAP
Zahn	Matt	United States	NACCHO
Zucker	Jane	United States	NYC DOHMH - Bureau of Immunization
Non U.S. Citizens (In VMS)			
Antonova	Jenya	Russia	MedImmune
Biehn	Brant	Canada	Dynavax Technologies
Brakel	Tom	Netherlands	Federated Kaufmann Fund
Chamnan	Nov	Cambodia	nov chamnan
De Serres	Gaston	Canada	Quebec National Institute of Public Health
Dounebaine	Bonheur	Chad	UNICEF
Fernandez	Jovelle	United States	GlaxoSmithKline Biologicals
Florez	Jorge	Colombia	IMMUNOPROTECTION
Gowler	Jeremy	Canada	Novartis Vaccines & Diagnostics
Hollingsworth	Rosalind	United Kingdom	Pfizer Inc
ITO	HIROAKI	Japan	Sotobo Child Clinic
Levy	Jose	Venezuela	Centro Médico Docente la Trinidad

Liao	Albert	Canada	Novartis Vaccines and Diagnostics
Marano	Cinzia	Italy	Glaxo Smith Kline Biologicals
Ozaki	Akio	Japan	MSD K.K.
Petrozzi	Veronica	Peru	Sanofi Pasteur
Reinert	Ralf Rene	Germany	
Rosenberg	John	Ecuador	Sanofi Pasteur
Saddier	Patricia	France	Merck & Co., Inc.
Salisbury	David Maxwell	United Kingdom	Department of Health
Seet	Bruce	Canada	GlaxoSmithKline
Tan	Litjen	Singapore	American Medical Association
Warshawsky	Bryna	Canada	Middlesex-London Health Unit (NACI Chair)
York	Laura Jean	Canada	PFIZER Inc

This document can be found on the CDC website at:

<http://www.cdc.gov/vaccines/recs/acip/downloads/min-oct11.pdf>