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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
February 22-23, 2012
Atlanta, Georgia

Final - February 16, 2012

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)
Centers for Disease Control and Prevention
1600 Clifton Road, NE, Tom Harkin Global Communications Center (Building 19), Kent "Oz" Nelson Auditorium
Atlanta, Georgia 30333
February 22-23, 2012

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
Wednesday, February 22 2012			
8:00	**Welcome & Introductions**		Dr. Carol Baker (ACIP Chair) Dr. Larry Pickering (ACIP Executive Secretary; CDC)
8:30	**Tetanus, Diphtheria and Acellular Pertussis (Tdap) Vaccine**		
	· Introduction		Dr. Mark Sawyer (ACIP, WG Chair)
	· Update: resurgence of pertussis disease in the United States		Dr. Thomas Clark (CDC/NCIRD)
	· Pertussis in older adults in the United States		Dr. Anna Acosta (CDC/NCIRD)
	· Cost effectiveness of Tdap substitution for Td in prevention of pertussis in adults 65 years and older	Information & Discussion	Dr. Anna Acosta (CDC/NCIRD)
	· Cost effectiveness analysis for Boostrix in adults 65 years of age and older		Ms. Shanthy Krishnarajah (Head, US Health Outcomes, GSK)
	· Safety and immunogenicity of Tdap in persons 65 years of age and older		Dr. Jennifer Liang (CDC/NCIRD)
	· Public comment		
	· Proposed recommendation for use of Tdap in persons 65 years and older	Vote	Dr. Jennifer Liang (CDC/NCIRD)
10:30	***Break***		
11:00	**Influenza**		
	· Introduction		Dr. Wendy Keitel (ACIP, WG Chair)
	· Update: Influenza activity and vaccines		Dr. Lisa Grohskopf (CDC/NCIRD)
	· Antiviral medications	Information & Discussion	Dr. Timothy Uyeki (CDC/NCIRD)
	· Future activities		Dr. Lisa Grohskopf (CDC/NCIRD)
	· Recommendations (reiteration of recommendation for annual vaccination for all 6 months of age and older)		Dr. Lisa Grohskopf (CDC/NCIRD)
12:00	***Lunch***		
1:30	**13-valent Pneumococcal Conjugate Vaccine (PCV13)**		
	· Introduction		Dr. Nancy Bennett (ACIP, WG Chair)
	· Pneumococcal conjugate vaccine for adults 50 years of age or older: background review of data, and GRADE	Information & Discussion	Dr. Tamara Pilishvili (CDC/NCIRD)
	· Pneumococcal conjugate vaccine for adults with immunocompromising conditions: background, review of data and GRADE		Dr. Kathleen Dooling (CDC/NCIRD)
3:30	***Break***		
4:00	**Hepatitis B Vaccine**		
	· Introduction		Dr. Mark Sawyer (ACIP, WG Chair)
	· Ensuring hepatitis B protection for remotely vaccinated health-care personnel; overview of issues; ACIP requests for information	Information & Discussion	Dr. Sarah Schillie (CDC/NCHHSTP)
4:30	**Vaccine Supply**	Information	Dr. Jeanne Santoli (CDC/NCIRD)
4:45	**Public Comment**		
5:00	**Adjourn**		

Thursday, February 23, 2012

8:00	**Unfinished Business**		Dr. Carol Baker (Chair, ACIP)
8:15	**Agency Updates**		
	CDC, CMS, DoD, DVA, FDA, HRSA, IHS, NVPO, NIH	Information	CDC and *Ex officio* members
8:30	**Meningococcal Vaccines**		
	· Introduction	Information & Discussion	Dr. Cody Meissner (ACIP, WG Chair)
	· GRADE (Grading of Evidence) assessment for MenACWY-D (Menactra) in children 9-23 months of age		Dr. Elizabeth Briere (CDC/NCIRD)
	· Updates to the Meningococcal Vaccines Statement		Dr. Amanda Cohn (CDC/NCIRD)
10:00	***Break***		
10:30	**Measles, Mumps, Rubella (MMR) Vaccine**		
	· Introduction	Information & Discussion	Dr. Jon Temte (ACIP, WG Chair)
	· Update: measles/rubella elimination consultation and documentation		Dr. Mark Papania (CDC/NCIRD)
	· Epidemiology of mumps in the United States		Mr. Albert Barskey (CDC/NCIRD)
	· Impact of a third dose of MMR vaccine on the course of a mumps outbreak in an orthodox Jewish community		Dr. Preeta Kutty (CDC/NCIRD)
	· Impact of a third dose of MMR vaccine on mumps outbreak in Guam and economic impact of the outbreak		Ms. Amy Parker Fiebelkorn (CDC/NCIRD)
	· Summary of issues and discussion		Dr. Huong McLean (CDC/NCIRD)
12:15	**Public Comment**		
12:30	**Adjourn**		

Acronyms

GRADE	Grading of Recommendations Assessment, Development and Evaluation
MenACWY-D	Meningococcal Polysaccharide (Serogroups A, C, Y and W-135) Diphtheria Toxoid Conjugate Vaccine
NCCDPHP	National Center for Chronic Disease Prevention and Health Promotion
NCEZID	National Center for Emerging and Zoonotic Infectious
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCIRD	National Center for Immunization and Respiratory Diseases
TBD	To be determined
Tdap	Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
WG	Work Group

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core Surveillance
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
AEs	Adverse Events
AFP	American Family Physicians
AI/AN	American Indians/Alaska Natives
AIM	Association of Immunization Managers
AMA	American Medical Association
ANA	American Nurses Association
Anti-HBs	Antibody to Hepatitis B Surface Antigen
Anti-HBc	Antibody to Hepatitis B Core Antigen
ASH	American Society of Hematology
ASTHO	Association of State and Territorial Health Officials
BMI	Body Mass Index
BRFSS	Behavioral Risk Factor Surveillance System
CAP	Community-Acquired Pneumonia
CBER	Center for Biologics Evaluation and Research / FDA
CDC	Centers for Disease Control and Prevention
CeNSIA	National Center for Child and Adolescent Health
CID	*Clinical Infectious Diseases*
CMS	Centers for Medicare and Medicaid Services
COI	Conflict of Interest
COPD	Chronic Obstructive Pulmonary Disease
CRS	Congenital Rubella Syndrome
CSTE	Council of State and Territorial Epidemiologists
DoD	Department of Defense
DSMBs	Data Safety Monitoring Boards
DTaP	Diphtheria, Tetanus, and Pertussis
DVA	Department of Veterans Affairs
EIS	Epidemic Intelligence Service
ELISA	Enzyme-Linked Immunosorbent Assay
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GAO	General Accounting Office
GMCs	Geometric Mean Concentrations
GMTs	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HBIG	Hepatitis B Immune Globulin
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCMV	Human Cytomegalovirus
HCP	Health Care Personnel
HepB	Hepatitis B
HHS	(Department of) Health and Human Services
Hib	*Haemophilus influenzae B*
HPV	Human Papillomavirus
HMO	Health Maintenance Organization
HRSA	Health Resources and Services Administration
IAC	Immunization Action Coalition
IDSA	Infectious Disease Society of America
IgG	Immunoglobulin G
ILI	Influenza-Like Illness
ILINet	Influenza-Like Illness Surveillance Network
IOM	Institute of Medicine
IPD	Invasive Pneumococcal Disease
ISD	Immunization Services Division

JAMA	*Journal of the American Medical Association*
JID	*Journal of Infectious Diseases*
MCO	Managed Care Organization
MMR	Measles, Mumps, Rubella
MMWR	*Morbidity and Mortality Weekly Report*
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
NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
NFID	National Foundation for Infectious Diseases
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIS	National Immunization Survey
NMA	National Medical Association
NNDSS	National Notifiable Diseases Surveillance System
NNV	Number Needed to Vaccinate
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
OGA	Office of Global Affairs / HHS
OPA	Opsonophagocytic
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PPACA	Patient Protection and Affordable Care Act
PPE	Personal Protective Equipment
PPV23	23-Valent Polysaccharide Vaccine
QALY	Quality-Adjusted Life Year
RCT	Randomized Controlled Trial
RSB	Reparatory Diseases Branch
SAEs	Serious Adverse Events
SARS	Severe Acute Respiratory Syndrome
SBA	Serum Bactericidal Antibody
SME	Subject Matter Expert
Tdap	Tetanus and Reduced Diphtheria Toxoids
TIV	Trivalent Inactivated Influenza Vaccines
UK	United Kingdom
US	United States
VAERS	Vaccine Adverse Event Reporting System
VFC	Vaccines for Children
VICP	Vaccine Injury Compensation Program
VNA	Visiting Nurse Association
VRBPAC	Vaccine and Related Biologic Products Advisory Committee (FDA)
VSD	Vaccine Safety Datalink
WHO	World Health Organization

February 22, 2012

Welcome and Introductions

Dr. Carol Baker
Chair, ACIP

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

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

Dr. Pickering welcomed everyone to the February 2012 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, Natalie Greene, Cindy Fowler, and Tanya Lennon. Dr. Pickering recognized that without these individuals it would be very difficult to conduct these meetings, and personally thanked each of them. Those with any questions were instructed to see him or any of these individuals.

Dr. Pickering noted that handouts of the presentations were distributed to the ACIP members and were made available for others on the tables outside of the auditorium. Slides presented at this meeting will be posted on the ACIP website approximately one to two weeks after the meeting concludes, the live webcast will be posted within three weeks following the meeting, and meeting minutes will be available on the website three months or 90 days following this meeting.

He emphasized that they had a full agenda for the next day and a half, and indicated that boxed lunches would be available for both days in the hallway outside the auditorium. Members of the press interested in conducting interviews with ACIP members were instructed to contact Tom Skinner, who was in attendance, for assistance in arranging the interviews.

Dr. Pickering recognized several visitors from the World Health Organization's (WHO's) Pan American Health Organization (PAHO) office in Washington, DC, and from Ministries of Health of PAHO member countries, including Argentina, Chile, and Peru. He requested that they stand to be acknowledged. Also in attendance was a visitor from WHO headquarters in Geneva, Switzerland, Ms. Mikiko Kanda, BSN, RN, PHN. Ms. Kanda currently is enrolled in the Department of Global Health Policy, Graduate School of Medicine, University of Tokyo, Japan and works in the Immunization, Vaccines, and Biologicals Department of WHO. Dr. Pickering noted that this meeting would be translated into Spanish, and that this was the second ACIP meeting that was simultaneously translated into Spanish.

He then recognized the following *ex officio* members and liaison representatives:

Ex Officio Members

- Ms. Amy Groom is the new *ex officio* representative for the Indian Health Service (IHS) replacing Dr. James Cheek who has retired. Dr. Cheek and all of the work he put into his service as an *ex officio* member are appreciated.

Liaison Representatives

- Dr. Laura Riley, Associate Professor, Obstetrics, Gynecology and Reproductive Medicine, Harvard Medical School Maternal Fetal Medicine, is the new liaison for the American College of Obstetricians and Gynecologists (ACOG). For many years, Dr. Stan Gall was the representative from ACOG, and his years of effort and wisdom are appreciated.

- Dr. Patricia Whitley-Williams, liaison representative for the National Medical Association (NMA) was unable to attend, and Dr. Winston Price attended on her behalf.

- Dr. Vesta Richardson, liaison representative for the National Immunization Council and Child Health Program in Mexico was unable to attend. Attending on her behalf was Dr. María Teresa Murguía Peniche, Infancy Branch, Director, National Center for Child and Adolescent Health (CeNSIA), Mexico.

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. He reminded members that the annual ACIP group photo would be taken in the auditorium before lunch.

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.

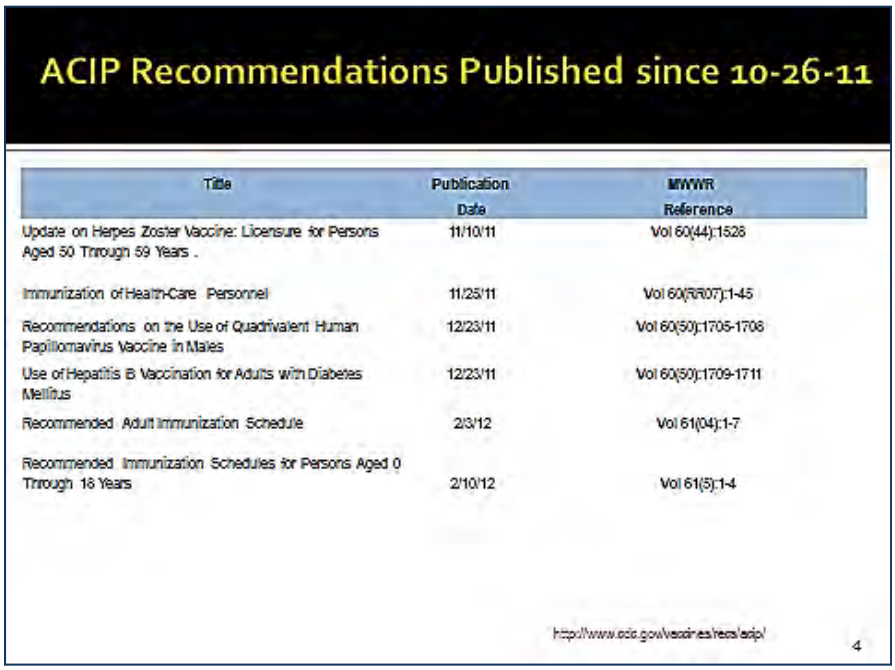
The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) process was implemented during the October 2011 ACIP meeting to formulate recommendations for HPV vaccine use in males and hepatitis B vaccine for use in adults with diabetes mellitus. Since GRADE is a new process to ACIP, educational materials have been placed on the ACIP website. In addition to the information shown on the slide, the GRADE technical document has been cleared and soon will be posted to the website.

Applications for ACIP membership are due no later than November 16, 2012 for the term beginning July 2013. Requirements include: current CV, at least one recommendation letter from a non-federal government employee, and complete contact information. This information may be submitted as email attachments to Stephanie Thomas SThomas5@cdc.gov. 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/reg-nominate.htm

Dr. Pickering noted that at every meeting, an update is provided on the status of ACIP recommendations. Links to these recommendations and schedules can be found on the ACIP web site. A listing of recommendations that have been published since the ACIP meeting of October 2011 follows:



Publication of these recommendations and schedules is sometimes highly complex due to timeframes and would not be possible without the excellent assistance of the *Morbidity and Mortality Weekly Report (MMWR)* editors and staff, including Dr. Ron Moolenaar, Dr. John Moran, Dr. Chris Casey, Douglas Weatherwax, and David Johnson.

The following resource information was shared pertaining to ACIP:

E-mail: acip@cdc.gov **Web homepage:** www.cdc.gov/vaccines/recs/acip/

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

Next ACIP meeting: Wednesday – Thursday, June 20-21, 2012
Registration Deadline: Non-U.S. Citizens *and* US Citizens Wednesday, June 6, 2012

Vaccine Safety: www.cdc.gov/vaccinesafety/

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

Childhood Vaccine Scheduler (interactive):
https://www.vacscheduler.org

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

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

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

Dr. Pickering requested that William (Bill) Atkinson, MD, MPH come to the podium for recognition on the occasion of his retirement. He reported that following training in psychology, medicine, and epidemiology and receiving Board certification in internal medicine and preventive medicine, Dr. Atkinson arrived at CDC as an Epidemic Intelligence Service (EIS) Officer in 1983. During that time, he served in the Louisiana State Health Department in New Orleans until 1989 when he moved to CDC in Atlanta. Dr. Pickering shared 10 highlights of Dr. Atkinson's CDC career.

Dr. Atkinson's first ACIP statement was the 1989 famous publication in the *MMWR* recommending a 2-dose measles immunization schedule. He has had major input into numerous other ACIP statements published over the years. Beginning in 1990, Dr. Atkinson assumed the lead in writing of the *General Recommendations on Immunization*. This document has been critically important as a reference and teaching guide on the techniques and concepts behind immunization. He helped to prepare the 1994 revision of the *General Recommendations on Immunization* and helped in the creation of the first "minimum interval" table, which appeared in this edition as did the 4-day rule. Dr. Atkinson was the lead author on the 2002 edition of the *General Recommendations on Immunization*, which was the first to appear in the expanded form published in the *MMWR Recommendations and Reports* series. He continued to serve as an author on subsequent editions, including the 2010 version.

In 1993, Dr. Atkinson pioneered the use of satellite and broadcast technology for bringing immunization education to thousands of immunization providers simultaneously. Since 2001, over 138,000 people have registered for continuing education credit for the various courses Dr. Atkinson has presented. He also has been immensely helpful in initiation of the ACIP meeting satellite broadcasts.

In 1995, Dr. Atkinson conceived, developed, and led the writing of one of the most widely sought books that CDC has ever produced: *Epidemiology and Prevention of Vaccine Preventable Diseases*, commonly known as the "Pink Book." This book is in its 12th edition, requiring constant updating due to the increasing number of vaccines used in the United States (US). More than 320,000 copies have been distributed, with 37,000 of these being distributed in 2011 alone.

Dr. Atkinson is also a talented speaker who is in constant demand. From 2004 through 2011, he presented 199 talks to a total of 46,293 registered attendees in locations all over the US. The audiences were comprised of nurses, health educators, and other clinicians. He developed NIPINFO, a vaccine telephone and email hotline staffed by himself and other medical educators in CDC's Immunization Services Division (ISD). Between 2004 and 2011, NIPINFO answered 5000 to 10,000 queries per year. Dr. Atkinson is also the recipient of many awards, including CDC's highest immunization award, the Phil Horne Award.

Over the past 15 years, Dr. Atkinson has served as a member of almost every ACIP working group, of which there are generally 12 to 14 in existence at any given time. He has always believed that his extensive interaction with frontline clinicians provides useful input for working groups as they strive to formulate draft recommendations for presentation to ACIP. With only two or three exceptions, he has attended every ACIP meeting, which number approximately 60 over the last 23 years. His attendance dates back to October 1989 to the days when the ACIP meeting was held in the Director's Conference Room #207 in Building 1 when meeting participation typically included less than 30 people.

Dr. Pickering concluded that Dr. Atkinson is a gentle giant. He is unassuming, has a dynamic personality, and has exceptional teaching abilities. His numerous accomplishments serve as an inspiration to all. As he prepares to retire, ACIP recognized the incredible career effort of Dr. Atkinson with a token of appreciation and a standing ovation.

Dr. Atkinson expressed his gratitude. He said that he was very happy to be at CDC long enough to see universal influenza vaccine recommendations, that he was sorry not to be there long enough to witness the revision of the HIB statement, and that he would watch as ACIP tried to deal with infant meningococcal vaccination.

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

- Dr. Tamera Coyne-Beasley: Research support is allocated to the University of North Carolina by Merck Pharmaceuticals.

- Dr. Cody Meissner: Payments are made to Tufts University Medical Center by Pfizer and AstraZeneca for participation in multi-center clinical trials.

- The remainder of the ACIP members declared no conflicts.

Tetanus, Diphtheria, and Acellular Pertussis (Tdap) Vaccine

Introduction

Dr. Mark Sawyer
Chair, ACIP Pertussis Vaccine Working Group

Dr. Sawyer introduced the Pertussis Vaccine Working Group, acknowledging the membership and noting that this working group has been convened for nearly three years. The terms of reference under which this working group initially was convened include the following:

1. Review all existing statements relative to pertussis for infants and young children (1997), adolescents (2006), adults (2006), and pregnant and postpartum women and their infants (2008) and consolidate into a single statement.

2. Review new data on Tdap including
    - Effectiveness of ACIP recommendations
    - Interval between Td booster and Tdap
    - Use of Tdap in adults 65 years of age and older (to be concluded during this session)
    - Vaccinated health-care personnel and need for post-exposure prophylaxis
    - Pregnant and breastfeeding women
        - Use of Tdap
        - Cocooning strategies
    - Revaccination (this is the next topic the working group will consider)

3. Review updated epidemiology of tetanus and diphtheria

This session included the following topics:

- ❑ Update and discussion on the resurgence of pertussis in the United States
- ❑ Pertussis in older adults in the United States
- ❑ Cost effectiveness
    - → Tdap substitution for Td in prevention of pertussis in adults 65 years and older (CDC)
    - → Boostrix® in adults 65 years of age and older (GSK)
- ❑ Safety and immunogenicity of Boostrix® in adults aged 65 years and older, given that this vaccine has now been FDA-approved for use in this age group
- ❑ ACIP recommendation for vote
- ❑ Guidance for use of Adacel™ in adults aged 65 years and older (not yet approved for use at age 65 and older)

Boostrix® is licensed for those aged 10 years and older and Adacel™ is licensed for those 11 through 64 years of age. Both vaccines are recommended as an active booster immunization for prevention of tetanus, diphtheria, and pertussis as a single dose. Tdap vaccine is covered by Medicare Part D, which is relevant to use in those aged 65 years and older

The current ACIP recommendations for adults are as follows:

Adults aged 19 through 64 years

- For adults aged 19 through 64 years who previously have not received a dose of Tdap, a single dose of Tdap should replace a single decennial Td booster dose.

Adults aged 65 years and older

- Adults aged 65 years and older (e.g., grandparents, child-care providers, and health care practitioners) who have or who anticipate having close contact with an infant less than 12 months of age and who previously have not received Tdap should receive a single dose of Tdap.
- For other adults aged 65 years and older, a single dose of Tdap vaccine may be given instead of Td vaccine, in persons who previously have not received Tdap.
- Either Tdap vaccine product may be used.

The working group plans to update / consolidate the ACIP Pertussis Vaccines statement, which it hopes to have completed by the end of 2012; the WG will then address Tdap revaccination and the revaccination interval that might be recommended.

Update: Resurgence of Pertussis Disease in the United States

Thomas Clark, MD, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Clark reminded everyone that pertussis is nationally notifiable. The case definition combines a clinical case (cough ≥2 weeks AND one or more of the following: paroxysms, whoop, post-tussive vomiting) and a confirmed case (culture OR clinical case and PCR positive OR clinical case and epidemiology-linked to confirmed case). Since its incorporation into the case definition in 1997, PCR has become the primary method of confirmation and surveillance reporting. The schedule of vaccination in the US included 5 doses by school entry for children. In 1992, there was a move to acelluar vaccination doses for boosters and in 1997 an all-acellular schedule was introduced. In 2005, Tdap was preferred for adolescents with a catch-up for adults. For many years there has been high vaccination coverage with the childhood series of DTaP. At 19 through 35 months, 95% or more children have received 3 doses and about 85% have received 4 doses, with some catch-up by school entry.

During the pre-vaccine era, the number of pertussis cases culminated to about 270,000 in the mid-1930s, with more than 10,000 deaths. Since introduction of whole cell vaccine, DP, in the late 1940s, the number of reported pertussis cases has decreased dramatically. Despite this decrease, pertussis continues to be endemic. Since 1980, there has been an increase in the number of reported cases from approximately 2,000 cases per year to over 10,000 cases per year. The most recent peak years were 2004 and 2005 in which 25,000 cases were reported in each year [CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System and 1922-1949, passive reports to the Public Health Service].

Infants are most impacted by pertussis. They experience the highest rates of disease nationwide. All other age groups tended to group closely together during the 1990s. During the mid-2000s, however, incidence among adolescents and adults began to increase. Interestingly, 2009 and 2010 have yielded another emerging trend. In children aged 7 through 10 years, rates have been increasing since 2007. There also has been emergence of disease in 1

through 6 year olds [CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System].

There is variability of pertussis from state-to-state. The 2009 incidence was 5.5 per hundred thousand (n=16,858 cases reported). In that year, California was in the lowest quartile of incidence [CDC National Notifiable Disease Surveillance System, 2009 CDC Wonder Population Estimates (Vintage 2009)]. In 2010, California moved into the highest quartile of incidence (19.47/100,000). There were 27,555 cases reported overall nationwide. A significant amount of attention was paid to the outbreak in California in which there were about 10,000 cases. However, Iowa and Minnesota had higher incidence rates at 23.17/100,000 and 21.65/100,000, respectively [CDC National Notifiable Disease Surveillance System, 2010 data accessed July 22, 2011; CDC Wonder Population Estimates (Vintage 2009)]. In 2011, there was an incidence of 5.0/100,000 (n=15,216 cases). However, these data are preliminary. Once datasets are finalized, there typically are 20% to 25% more cases.

Between the late 1990s and early 2000s, the increase in pertussis overall largely was driven by an increase in adolescents and young adults. Tdap products became available in 2005. Pre-licensure evaluation suggested that effectiveness would be approximately 90%. Post-licensure evaluation suggested approximately 65% to 80%. By 2010, there was almost 70% coverage among adolescents. Thus, the program gradually is achieving good coverage in that age group. The program was implemented at the end of the last cyclic epidemic or peak in disease, so it is somewhat difficult to evaluate. To assess the impact of Tdap in adolescents, rate ratios of pertussis incidence among adolescents 11 through 18 years of age were calculated for 1990-2008 (e.g., the rate in adolescents relative to all other age groups. For the 1990s, there was a steady increase in adolescent disease relative to other age groups. With the implementation of the adolescent program in 2005-2006, there was not just a statistically significant change in slope, but there was a decreasing slope. This suggests that Tdap is working in reducing the burden of adolescent disease [Skoff et al. Arch Pediatr Adolesc Med. 2012 Jan 11. [ePub ahead of print].

Indirect effects also were assessed. While the Tdap program was recommended to reduce the burden of adolescent disease, it was hoped that there would be a herd effect in reducing transmission and disease in infants. Comparing the rate of infant pertussis prior to 2004-2005 and subsequently, the rates are unchanged. Thus, there does not appear to be a substantial herd effect in that age group. While the increase in adolescent disease recently has been tamped by the Tdap program, the second highest incidence group that has taken over is children 7 through 10 years of age. The proportion of pertussis cases contributed by this age group over time was 5% to 10%, but this quickly became 20% to 25%.

In terms of the number of reported cases by year of life over time, in general the number of cases decline from infancy to around 9 years of age when they gradually started to increase. In 2005, an increase occurred in 7 year olds. In 2006, this increase progressed with an increasing number of cases over time with increasing year of life. A stair step pattern developed until there was a substantial increase in 2009 in number of cases by year of life, and then declined in 11 year olds consistent with receipt of Tdap in 2009. This is the first cohort of children who largely are exclusive recipients of acellular vaccines.

Given the concern in observing the data in national surveillance as well as in the California outbreak, attention quickly turned to performance of the DTaP vaccination program and the effectiveness of DTaP vaccines. A case-control study was implemented in California. All 4 through 10 year old children with pertussis in 2010 were eligible in the 15 counties in California

that chose to participate. An unmatched design was used with 3 controls per case, and vaccination receipt was verified from provider medical records. In terms of the vaccination characteristics of the subjects, just under 1% of the controls had zero vaccination confirmed for pertussis, suggesting that under-vaccination or vaccine refusal was not a substantial problem in this outbreak or a substantial finding in the study. About two-thirds of the children in California received their 5th dose at age 4, with fewer at age 5 and 6. Comparing receipt of 5 doses overall to zero doses, vaccine effectiveness was 88.7%. The goal of the study was really to assess time since vaccination and yearly vaccine effectiveness. It was very high at 98% within a year of receipt of the 5th dose and declined to about 71% 5 or more years after the 5th dose.

To identify the magnitude of waning immunity from the acellular vaccines, which previously had not been done, in two states registry data were combined for receipt of 5 doses in children and surveillance data for pertussis cases to assess risk of pertussis by time since 5th dose. From Minnesota there were 224,378 subjects and 521 cases, and from Oregon there were 179,011 subjects and 99 cases. The comparison was rates of disease by time since 5th dose and relative risk. There was some variability of rates of disease by increasing age between Minnesota and Oregon, but the relative risks were similar. Rates were higher in Minnesota at about 7 for pertussis by year 5 or more after vaccination, but the confidence intervals overlap.

In summary, the Tdap program has reduced the burden of pertussis in adolescents. Unfortunately, there is no evidence for herd protection of infants. The initial DTaP vaccine effectiveness is excellent, but there is a modest but essentially immediate waning of immunity from DTaP following receipt of vaccination. Pertussis burden in children under age 10 years appears to be a “cohort effect” from change to all acellular pertussis vaccines (e.g., a problem of susceptibility despite vaccination).

Dr. Clark’s group is working to maximize the benefits of the current vaccination program and to look to the future of pertussis control. Efforts are underway to reduce barriers to Tdap uptake, expand Tdap recommendations, and evaluate and refining current vaccination policy. The trend of increasing incidence of pertussis likely will continue, with disease in children aged 7through10 years being more a symptom of the problem. It is unlikely that changes to the timing of vaccination will result in substantial changes in the burden of disease. Chemoprophylaxis works to prevent exposed persons from developing pertussis, but it is an ineffective strategy to reduce transmission in outbreaks, including the staggering number of doses that must be given.

Current and future activities include enhancing diagnostic testing to improve surveillance; enhancing the 6 pertussis surveillance sites (e.g., enhanced case ascertainment and improved data quality; platform for analyses and studies); evaluating cocooning / maternal vaccination effectiveness; evaluating Tdap duration of protection; assessing temporal trends in susceptibility/infection (serosurvey; modeling); and increasing the evidence base for new vaccines or strategies.

Discussion Points

Dr. Duchin inquired as to whether the investigators were able to assess differences according to the vaccine formulation a child received.

Dr. Clark responded that they did try to collect vaccine formulation, but it has proven difficult to confirm product brand and formulation for every child for every dose. They are still collecting these data, and this is an important future analysis for the case-control study in California. Other ways to determine this information also are being explored. For example, they might be

better able to assess this question if they evaluated a managed care organization (MCO) that has used one product longitudinally over time. However, there is not a sense that this is a problem with a product, brand, or vaccine type.

Dr. Duchin wondered whether the differential in the risk ratio studies in Minnesota and Oregon could be related to the difference in the incidence of disease occurring at the time in those states.

Dr. Clark replied that an attempt was made to enroll a cohort of children over time, so they would have moved through some cycles of disease. However, the cycles differed in different places. Minnesota was also one of the enhanced sites over time, so they have engaged in better case ascertainment and testing. In general, this results in additional cases identified in adolescents and older age groups more so than younger children. That may account for the absolute differences.

Dr. Marcy noted that 15,000 to 27,000 cases is really an extremely small tip of a very large iceberg. The estimate of 1 million to 3 million cases annually in the US is far more realistic and puts whatever ACIP may decide into perspective.

Dr. Clark agreed that there are problems in testing and confirmation of pertussis and even in suspecting pertussis. Inquiries have been posed about what is occurring in other countries with similar programs. Some countries have similar programs, but very few have similar programs with similar surveillance. The age-specific incidence in Australia is 10 to 100 times what it is in the US, but in Canada not so much. More must be done globally to assess the burden of pertussis.

Dr. Keitel noted that the duration of protection following a case of pertussis is estimated to be approximately 10 to 12 years, though data shown suggested waning after 7 years. She wondered whether there were any differences observed with respect to race / ethnicity, status of medical care, and other criteria that differed from that which was observed with whole cell vaccines.

Dr. Clark responded that this is the key question. There are considerable data on effectiveness of whole cell vaccines, but very few were conducted with vaccines that were used just before shifting to acellular, which probably were different from the original vaccines. Very few studies included the same kind of case finding, ascertainment, confirmation and the same kind of design. Therefore, it is difficult to know whether this is different. However, even small differences in the initial effectiveness or waning over time can result in large differences in susceptibility. Very small attack rates among susceptibles drive large outbreaks. The 12-year duration of protection came from the observance from the increase in disease, not from vaccine effectiveness studies. There are differences in the immune response from acelluar and whole cell vaccines. There are many unanswered questions pertaining to immunology and vaccinology regarding pertussis vaccines. The proportion of cases and controls did not really differ in terms of coverage of VFC. The analysis was done to account for potential clustering in the individual provider offices, so that it is considered in the analysis. There was some ethnicity/race difference in Hispanics, but that difference resolves with increase age. The highest incidence overall is in whites, and females are somewhat more likely to get disease. However, it is not clear why. It does not appear that individual risk factors, even non-modifiable ones, are driving this observation.

Dr. Baker added that pertussis requires a major uptake of vaccine to result in any herd immunity. She wondered whether there were any plans to evaluate this point, and whether there was a strategy to increase immunization among the recommended groups above 90%.

Dr. Clark responded that this pertained to the concept of non-transmissibility of infection requiring high levels of protection. With modeling susceptibility can be changed, so analyses are being done to assess whether susceptibility predicts the burden of disease. The investigators will continue to assess the impact in infant disease with increasing pertussis vaccine coverage. Some countries would say they have good pertussis control with some degree of adolescent or adult coverage, but it is not clear this is accurate. This observation may be a surveillance bias in many cases.

Dr. Baker emphasized that there would be continuing challenges for adult programs.

Dr. Schaffner (NFID) noted that investigators in Europe, particularly investigators at the Institut Pasteur have been interested in changes in the organism. He wondered whether Dr. Clark could comment on this from the US perspective.

Dr. Clark responded that they have assessed molecular typing of isolates to determine whether the vaccine-related antigens are matched to the vaccine strains. The majority of isolates are mismatched on the vaccine antigens. That is true in most countries that have evaluated this. The changes over time seem to be antigenic drift rather than vaccine pressure, because the changes do not correlate with any changes in the epidemiology. There are no data linking the presence of different antigens or increased production of different antigens to any clinical outcomes. Some authors have posed that as a risk, but others are not convinced about this. In general, it would be beneficial to have broad protection across the variability in antigens. Denmark uses a Pertussis Toxin only vaccine, and the epidemiology in Denmark has not changed substantially. One might expect a region that uses one antigen to be the "canary in the coal mine," but that does not seem to have occurred. It is difficult to acquire strains, and the CDC group does not have a population-based sample of isolates—they have a collection.

Pertussis In Older Adults in the United States

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Dr. Acosta provided an overview on pertussis disease in adults 65 years of age or older. The literature and surveillance focused on this population are lacking. Therefore, where possible, she focused on adults 65 and older and otherwise focused on literature from the general adult population. She discussed the under-recognition of adult disease, clinical presentation and disease severity, and incidence and disease burden.

There are challenges in recognizing pertussis across all age groups. In adults, particularly problematic factors include atypical symptoms and a low index of suspicion among providers. Clinical presentation in adults may not include the typical pediatric symptoms, such as inspiratory whoop or post-tussive emesis, which are most easily recognized as pertussis. Among providers, there is a low suspicion for pertussis in adults given its often non-specific presentation.

The Council of State and Territorial Epidemiologists (CSTE) pertussis clinical case definitions used by the National Notifiable Disease Surveillance System (NNDSS) includes "cough illness lasting ≥2 weeks AND paroxysms, inspiratory whoop, or post-tussive vomiting." The case definition is complex and, as mentioned, the non-specific an atypical presentation of pertussis in adults may result in unreported cases because they are not captured by the case definition.

With regard to the demographics of reported pertussis cases in adults, across the three age ranges (18-39 years, 40-64 years, and ≥65 years) sex and race are similar. About one-third of the cases occur in males and almost 75% are white. The symptoms that have been reported in adults include cough, paroxysm, whoop, apnea, post-tussive emesis, and cyanosis. Cough and paroxysm are common across all age groups. Whoop, apnea, and post-tussive emesis are reported less frequently in adults 65 years of age and older than in infants and children. This suggests that there is a difference in presentation between children and older adults [CDC, National Notifiable Diseases Surveillance System].

In a review of the literature focusing on characteristic symptoms of adult pertussis, the most commonly investigated symptoms included cough, paroxysm, inspiratory whoop, and post-tussive vomiting. Paroxysm is commonly reported. Inspiratory whoop and post-tussive vomiting were reported less frequently, but results varied. This review of the literature of adult pertussis symptoms reflects what is reported by surveillance [Lasserre A et al. Euro Surveill 2011;16(5):1-5; de Serres G et al. JID 2000;182:174–9; Strebel P et al. JID 2001;183:1353–9; Schmitt-Grohe S et al. CID 1995;21:860-6; Wirsing von Konig CH et al. Lancet 1995; 1326-29].

Several proxies for disease severity include encephalopathy, seizure, pneumonia, hospitalization, and death. Most sequelae are rare across all ages. However, the rates of pneumonia and hospitalization increase with age, with 10% of the 65 and older group requiring hospitalization. This suggests that serious pertussis disease does occur in this population [CDC, National Notifiable Diseases Surveillance System 2000-2010].

In summary, the clinical presentation of pertussis in adults ages 65 years and older may lack typical symptoms such as inspiratory whoop and post-tussive vomiting. Pertussis disease severity in adults increases with age, demonstrated by rising rates of hospitalization and pneumonia.

Regarding incidence of reported pertussis in adults from 2000-2010 separated in three age groups (18-39, 40-64, ≥65), there is a peak of incidence from 2004 to 2006 as well as an emerging peak in 2009 to 2010. All age groups followed the same curve, but the ≥65 age group had substantially lower reported incidence rates. There are several limitations to the surveillance. NNMDS is a passive surveillance system with incomplete data retrieval from source sites. These factors may result in under-reporting of pertussis disease in a population of adults ≥ age 65.

Pertussis is one of the few bacterial diseases for which reported incidence does not increase substantially with age, such as *Haemophilus influenzae* and *Streptococcus pneumoniae*. This is another indication that pertussis disease burden may be under-reported in older adults [CDC, National Notifiable Diseases Surveillance System; CDC Active Bacterial Core Surveillance].

To explore the extent of under-reporting, data were examined from other countries with similar vaccine schedules and surveillance systems. Reported disease incidence in the US for adults age 65 and older is comparable to Canada; however, reported incidence in Australia is substantially higher. Incidence there is 60 to 85 times higher than reported in the US. Reasons

for this large difference are unclear, but may be related to Australia's improved reporting practices and the inclusion of serology in the case definition. These data suggest again that pertussis incidence in the US may be higher than reported [Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada; CDC, National Notifiable Diseases Surveillance System; National Notifiable Diseases Surveillance System; Department of Health and Aging, Australian Government].

A review of the current literature of pertussis disease burden found a range in incidence. The 4 prospective studies presented by Dr. Acosta included a broad age range of subjects and were not powered to determine estimates of disease incidence for adults aged ≥65 years. Although inclusion criteria varied among the investigations, all were reflective of current CSTE case definitions and included cough duration or cough symptom criteria. Diagnostic testing also varied across the studies, but most incorporated tests currently included in the case definition. Calculated incidence ranged from 66 to 500 cases per 100,000. For comparison, NNDSS reported pertussis incidence as 1 case per 100,000 for the same timeframe and age group as that of the APERT study, which estimated an incidence of 370 to 450 per 100,000. Reported incidence is at least 70- to 100-fold less than found in the literature, suggesting that true incidence is much higher than reported [Lasserre A et al. Euro Surveill 2011;16(5):1-5; Strebel P et al. JID 2001;183:1353–9; Ward (APERT) JI et al. NEJM 2005;353:1555-63; Nennig ME et al. JAMA 1996;275:1672-167].

To summarize, pertussis disease is under-recognized as a cause of cough illness. The epidemiology of adult pertussis is not well-understood. Surveillance data in the US and abroad have identified a range of incidence. There are few prospective studies focused on adults. Instead, subject age ranges also include older children and adolescents. There are no prospective studies focused specifically on adults ≥65 years of age. Available literature that includes adult populations demonstrates a very wide incidence range between 66 to 500 per 100,000 population.

In conclusion, the literature and surveillance data presented suggest that pertussis disease in the US is higher than reported. Based on this review, the ACIP working group's interpretation is that the true burden of disease in the population of adults aged ≥65 years is likely at least 100-fold higher than reported.

Cost-Effectiveness of Tdap Substitution for Td in Prevention of Pertussis in Adults 65 Years and Older

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Dr. Acosta indicated that the objective of her study was to evaluate the cost-effectiveness of a one-time substitution of Tdap for Td in healthy adults 65 years of age and older to prevent adult disease and complications. The analysis was completed from both a health system (medical cost) and societal (productivity loss) perspective. The cost-effectiveness model compared a one-time Tdap substitution for Td versus no substitution at 65 years of age 65. One cohort population was examined in the model that was comprised of healthy 65 year olds. An analytic time frame of 10 years was chosen given age-related mortality and probable duration of protection offered by Tdap. The health outcomes examined included number of cases,

outpatient illnesses, hospitalizations, pneumonias, and deaths. The economic outcomes examined included cost per case averted and cost per quality adjusted life year (QALY) saved. In terms of the decision analytic model, the cohort was divided into two groups. One group received Tdap and the other did not. The health outcomes were measured in each group in those who experienced pertussis. The general parameters of the model incorporated disease incidence and disease outcomes. Base case estimates and ranges for sensitivity analyses were determined. Based on a literature review, surveillance data, and ACIP workgroup input, a disease incidence for the base case was chosen of 100 times the reported mean surveillance incidence over the last 10 years, which was approximately 104 cases per 100,000. One healthy cohort population 65 years of age and older was examined. A healthy cohort was chosen given the difficulty of including comorbidities in the model. The population size was based on the 2010 US Census and incorporated current age-based mortality rates. The four main outcomes of the model included outpatient illness, hospitalization, pneumonia, and death. The probabilities of these outcomes were based on the main percentage of cases with these outcomes. Because not all adults with moderate pertussis may seek medical care, it was assumed that only 50% of non-hospitalized cases or outpatient cases would seek care.

Important parameters of the model related to vaccination include efficacy, waning immunity, immunosenescence, coverage, and adverse events. Base case estimates and ranges for sensitivity analyses were determined. Vaccine efficacy in adults 65 years of age and older is unknown. The 70% efficacy used in the model was based on efficacy rates of adolescents from field studies, as well as immunogenicity data across pediatric and adult populations. Waning of vaccine induced immunity affects efficacy in an unclear fashion in this population. Based on the literature and ACIP working group input, waning of immunity was accounted for by incorporating a 5% reduction of efficacy each year post vaccination in a base case. Because the age of the population in this model is older, immunosenescence is another factor for consideration. Immunosenescence is the gradual deterioration of the immune system brought about by the natural aging process. Given the relative uncertainty of its effect on vaccine efficacy, immunosenescence was not incorporated into the base case. It indirectly was incorporated into the sensitivity analyses by comparing a range of efficacy rates and waning. Vaccine coverage in the base case was assumed to be 50% based on current Td coverage in this population. In the sensitivity analyses, coverage varied from 10% to 70%, reflecting current zoster and influenza coverage levels. A probability of vaccine adverse event was included in the model, including local, systemic, and anaphylaxis reactions.

Important parameters in the model related to cost include disease and vaccine cost presented in 2010 US dollars. Direct costs or medical costs encompassed outpatient, hospitalization, and pneumonia costs. These were based on a Thomson Reuters MarketScan dataset for average pertussis reimbursement costs from 2000-2009 for adults 60 through 64 years of age. It was assumed that pneumonia would require hospitalization. Adverse event costs were weighted by probability of occurrence. Program costs included incremental cost increase of Tdap vaccine relative to Td, and were estimated at $17.00. The administration fee was not included in the base case analysis because it was assumed that Tdap and Td would have similar fees. The discount rate in the base case was 3%.

Health utilities or values representing preferences for different health outcomes used to estimate QALYs were derived from the literature. Because there are no studies addressing utilities for pertussis in the population of adults 65 years of age and older, it was assumed that the younger adult utilities for pertussis would be applicable to this model, that the utility for moderate cough was the equivalent to outpatient illness, and that the utility for severe cough would be the

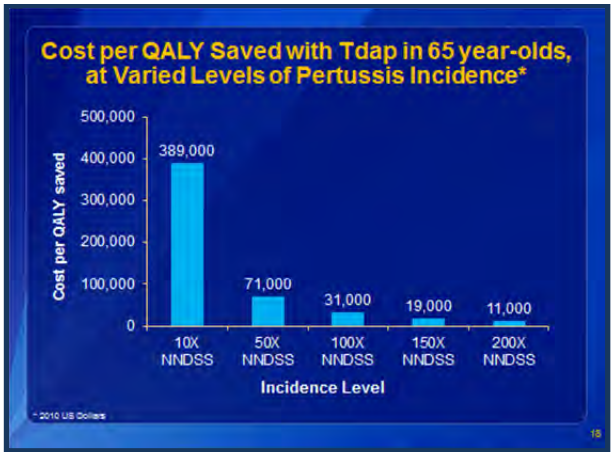
equivalent to hospitalization. The estimate of pertussis disease duration of 56 days was based upon current literature.

One-way sensitivity analyses were performed to examine the effect of incidence, efficacy, immune waning, and coverage on model outcomes. Multi-way sensitivity analyses were performed to examine most cost-effective and least cost-effective scenarios. Each scenario reflected the highest or lowest values for key model inputs, including incidence, efficacy, and waning immunity.

With regard to results, following vaccination at age 65 years, there was a substantial decline in cases. However, with time, the difference between the two groups decreased due to immune waning. In terms of the reduction in the number and percentage of outcomes following a one-time Tdap substitution over a 10-year time period, of note, there was a reduction of approximately 5000 (25%) pertussis cases with the Tdap substitution at age 65. With all outcomes, there was a moderate decline of about 25%. Regarding the cost-effectiveness ratios associated with Tdap substitution in the 65 year old cohort, of note, the cost per QALY averted in the base case scenario was approximately $3,200 and the cost per QALY saved was $31,000.

In one-way sensitivity analyses, when single parameters are changed from that of the base case, all parameters except the one change remained at base case levels. As incidence rose from 10 times the NNDSS value to 200, cost per QALY decreased substantially. Raising efficacy from 60% to 90% also decreased cost per QALY saved. Changing the degree of waning immunity from 5% points per year post-vaccination to 20% increased cost per QALY saved, but not to such a dramatic extent as incidence. Other variables examined in the one-way sensitivity analyses included coverage and percentage of non-hospitalized cases treated. Variation of either of these parameters did not substantially affect the cost per QALY saved.

Data regarding pertussis incidence in adults 65 years and older are limited. However, the working group strongly feels that the true incidence is substantially higher than reported. Cost per QALY saved does vary greatly as incidence changes. Therefore, the range of incidences in the model was presented. As incidence increases, the cost per QALY saved declines. Although presented with a range of incidence levels, the working group feels that the true incidence is closer to 100 times rather than 10 times the reported level, consistent with the literature presented earlier. The following graph illustrates the importance of incidence as a key model input:



Multi-way sensitivity analyses were also performed to evaluate most and least cost-effective scenarios. The most cost-effective scenario showed a significant decline in the number of cases, hospitalizations, pneumonias, and deaths following immunization at age 65 years. The cost per QALY saved was $5,000. In the least cost-effective scenario, there was minimal reduction in a number of outcomes following immunization. The intervention was somewhat costly in this scenario, with the cost per case averted of about $70,000 more than that of Td intervention. The cost per QALY saved was $650,000 in this scenario.

Regarding the assumptions of the analyses (e.g., incidence and under-reporting, efficacy and immune-waning, health utilities, costs, and comorbidities), the over-riding factor is the lack of empiric data for each of these variables in the model. These assumptions were addressed with the available literature and expert opinion from the working group, and the estimation for these parameters is believed to be reasonable.

The main conclusions that can be drawn from this analysis are that substituting Tdap for Td in an age 65 year old cohort results in a moderate decrease in the number of cases and other outcomes. This may represent a cost-effective intervention robust to a range of assumptions. Incidence level is the primary driver of cost-effectiveness. As incidence level increases, the cost-effectiveness of Tdap vaccination increases.

Cost-Effectiveness Analysis for Boostrix® In Adults 65 Years of Age and Older

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GlaxoSmithKline

On behalf of GSK, Ms. Krishnarajah thanked the Pertussis Working Group, ACIP, and CDC for the opportunity to present the cost-effectiveness data for BOOSTRIX® in adults aged 65 years and older. This work was done in collaboration with GSK, OptumInsight colleagues, Dr. Stephen Phelton from Boston University, and Dr. Milton Weinstien from Harvard School of public Health.

The cost-effectiveness model was built to assess the public health and cost implications of administering GSK's Tdap vaccine, BOOSTRIX®, to adults age 65 years and older. This study evaluated the incremental cost of vaccinating adults 65 years and older and the health outcomes. Direct vaccine effects of preventing pertussis only in the individual vaccinated are considered in these analyses. Indirect benefits of preventing transmission of pertussis from infected adults were not considered. Therefore, this direct effect model is a conservative assessment of the benefits of BOOSTRIX® in vaccinating adults age 65 years and older. The model compares a baseline strategy to an intervention strategy. The baseline strategy is the vaccination practice recommendations of vaccinating those aged 65 and older with Td. The intervention strategy is vaccination of eligible adults age 65 years and older with BOOSTRIX®.

Other specifics of this model are that a time horizon of 35 years is considered, and the incidence is adjusted for age-specific mortality rate for this population. Given the uncertainty in the incidence of pertussis in this age group, a range of incidences was used varying from 25 to 200 cases per 100,000. The cases of pertussis were stratified by their severity of symptoms into severe, moderate, or mild. A societal perspective was considered for the analysis. Results were presented in terms of total costs / savings, which included direct medical costs and direct non-medical cost of patient and caregiver productivity losses due to acute illness. Also shown were results for cost per case averted and cost per quality adjusted life-year (QALY) gained.

The probability tree describes the possible pertussis case pathways. A case reported or unreported can vary by severity. The conservative assumption was made that death and encephalopathy were possible only among severe hospitalized cases. It was assumed that all moderate cases were treated and that only a proportion of mild cases are treated. In the baseline scenario, vaccine coverage of 10% was used. A number of sensitivity analyses were done varying vaccine coverage from 5% to 50%. Tdap efficacy was not directly measured, but was estimated via immunobridging to an infant DTaP efficacy study. In the study used for efficacy bridging, vaccine efficacy was shown to be 89%, which was used in the baseline scenario. Additionally in this study, the lower limit of the 95% confidence interval for vaccine efficacy was 77%. Sensitivity analyses were performed based on this number.

In the baseline analysis, the proportion of severity of cases was constant at different levels of incidence. However, in the sensitivity analyses, the proportion of severity of cases was varied at different incidence levels. At low levels of incidence, there will be more reporting of severe and moderate cases via passive surveillance. However, as the incidence of the disease increases, the proportion of mild cases reported will increase and the proportion of severe cases would decrease. Duration of protection was assumed to be 8 years, but this parameter value was varied from 6 to 10 years in the sensitivity analyses. The waning of protective efficacy during this time frame is exponential each year.

In terms of the cost and utilities used in the model, incremental vaccine cost included the cost of the incremental price of Tdap and Td and adverse event. In the baseline analysis, the incremental price difference of Tdap versus Td in the private market is $18.10. Sensitivity analyses were done using public price increments, as well as a mix of public and private prices. QALY values are attached to each health status. On a scale of 0-1, by convention, 0 represents death and 1 represents perfect health. The source of the pertussis utility data used to calculate the disutility data comes from a 2010 publication by Devires et al. Sensitivity analyses were done reducing this disutility by 10% and 20% among those 65 years of age and older.

With regard to the model-predicted costs and cost savings for Tdap vaccination of adults 65 years of age and older stratified by incidence, the net societal cost of the vaccination program is estimated to range from $1.37 million to $4.3 million depending on the incidence level. Costs include $4.7 million in vaccination cost. The following table illustrates the various costs and cost savings predicted by the model:

Cost Item	Incidence 25/100,000	Incidence 50/100,000	Incidence 100/100,000	Incidence 150/100,000	Incidence 200/100,000
Total Direct Medical	($362,639)	($725,277)	($1,450,554)	($2,175,832)	($2,901,109)
Direct Non-Medical Cost	($53,173)	($106,346)	($212,693)	($319,039)	($425,385)
Direct Medical and Non-Medical	($415,812)	($831,624)	($1,663,247)	($2,494,871)	($3,326,494)
Vaccination Cost	$4,691,839	$4,691,839	$4,691,839	$4,691,839	$4,691,839
Net Costs					
Net Costs including Lost Productivity	**$4,276,027**	**$3,860,215**	**$3,028,591**	**$2,196,968**	**$1,365,344**

The model predicts that by vaccinating 10% of those age 65 years and older, when the pertussis incidence is 100 cases per 100,000, the cost per case averted is approximately $1,800. The incremental cost-effectiveness ratio is about $58,000 per QALY at an assumed incidence of 100 cases per 100,000, and is about $13,000 per QALY at an incidence of 200 cases per 100,000. When vaccination efficacy is set at 77% in the sensitivity analysis, the cost per cases averted varies from to $638 to $12,000 depending upon the incidence level. At an assumed incidence of 100 cases per 100,000 the incremental cost-effectiveness ratio is about $73,000 per QALY.

A comparison of results from the two BOOSTRIX® efficacy assumptions shows that the results of the analyses in adults age 65 years and older, and the Lee results in adults age 20 to 64 years, are similar in cost per case averted and in cost per QALY gained. For example, at an incidence of 100 per 100,000 cases, the GSK model predicts a cost per QALY of $58,000 at 89% efficacy and $73,000 at 77% efficacy. The published cost-effective analysis of Tdap vaccination among those 20 to 64 years of age at the same incidence shows a cost per QALY of $65,000 [Lee GM, Murphy TV, Lett S, Cortese MM, Kretsinger K, Schauer S, Lieu TA. Cost effectiveness of pertussis vaccination in adults. Am J Prev Med. 2007 Mar;32(3):186-193].

As the Tdap coverage rate increases, the number of cases averted increases and proportionately, the discounted incremental cost increases. The cost per QALY gained does not change when varying the vaccination coverage rate. This is because transmission of disease is not taken into account in the GSK model. For example, at an incidence of 100 pertussis cases per 100,000, the GSK model predicts a cost-effectiveness ratio of $58,000 per QALY. At an incidence of 200 cases per 100,000, the GSK model predicts a cost-effectiveness ratio of $13,000 per QALY.

Various sensitivity analyses were performed for cost per QALY, varying the proportion of encephalopathy cases, proportion of severity of cases depending on incidence, duration of protection, incremental price of the vaccine, and QALY decrement. For example, when the incidence is 100 per 100,000, the cost per QALY gained ranges between $76,000 per QALY to $48,000 per QALY when varying various input assumptions. These results indicate that not one particular input is driving the model results, as the results are quite stable given the variation in inputs.

As with any cost-effectiveness model, this model has some limitation and model assumptions. Given the uncertainty regarding the pertussis incidence level, five different scenarios were assessed by varying incidence from 25 to 200 cases per 100,000. BOOSTRIX® vaccine efficacy in persons 65 and older has not been directly assessed. The estimates of efficacy in persons 65 and older are based on bridging to infant DTaP efficacy results via immunogenicity data. Data used to estimate vaccine effectiveness and outcomes were derived and synthesized from a variety of sources. Given the underlying methodological assumptions of the static model, the model does not account for long-term medical costs associated with disease outcomes, family or household dynamics, or transmission of disease. A model that captures these factors will result in a lower cost per QALY gained.

In conclusion, the GSK model shows that BOOSTRIX®, a Tdap vaccine licensed for individuals 65 years of age and older, is cost-effective at an incremental cost-effectiveness ratio of $50,000 per QALY when pertussis incidence is greater than 110 cases per 100000. Cost-effectiveness ratios in this age group are of similar magnitude as those that have been modeled in adults age 20 through 64 years. Additionally, the GSK results align with the CDC results presented by Dr. Acosta.

Working Group's Conclusions About the Cost-Effectiveness Analyses

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Dr. Liang reported that the working group's interpretation of the cost-effectiveness of Tdap in adults aged 65 years and older was that there is a modest cost per case averted and cost per QALY saved. The incidence estimates accounting for under-reporting are reasonable based on limited data and expert opinion. There is reassuring concordance between the two different cost-effectiveness models.

Discussion Points

Dr. Keitel corrected a statement she made earlier regarding duration of protection being 12 years, which was after whole cell vaccination. Regarding the comparison of the efficacy in older adults with that in younger adults, she wondered what percent efficacy was estimated in the Lee article. She also inquired as to whether, since no serologic correlates of protection against pertussis have been established, it would be a more direct calculation to use observed levels of efficacy in younger adults and then test lower levels, assuming that there is waning, in the older population.

Dr. Krishnarajah replied that for the Lee model of ages 20 through 64 years, the vaccine efficacy used was in the 80% range. Several internal discussions have occurred about what the correct efficacy estimate is for the adult population aged 65 years and older. After lengthy discussion, the decision was made to use efficacy values that were consistent with all prescribing information. Several sensitivity analyses were performed and noted that this specific parameter is not very specific in the model. The cost-effectiveness ratio was $58,000 per QALY when 89% efficacy was used; $73,000 per QALY when 77% efficacy was used; and $83,000 per QALY when 70% efficacy was used.

Dr. Temte reported that the previous week, his department saw about 4000 patients, of whom about 15% had a respiratory infection coded. It is known from surveillance being conducted in their clinics that for about 50% of those illnesses, a viral cause can be confirmed by multiplex PCR. Of people who present, about 86% have a cough illness. There is a huge sea of patients for whom there is no confirmation to identify cause. In fact, there is really no surveillance system to identify bacterial causes of acute respiratory tract infections and cough illness.

Dr. Duchin said he was deeply troubled by the efficacy estimates in the cost-effectiveness models, which he found to be extremely high. With a generalization of efficacy from 70% to 90% in a cohort of patients 65 years of age and older, he did not find the outcomes to be convincing.

Dr. Acosta replied that in their sensitivity analyses, they examined a rate as low as 60%. However, this was not the key input in the model. When efficacy was varied from 60% to 90%, the cost per QALY saved ranged from $19,000 to only $40,000. It is true that this is an unknown factor. The investigators made the best estimation possible with the data available.

Dr. Bennett expressed similar concerns. While the investigators pointed out that efficacy was not a key element in the models, she would submit that this was because it had not been varied that much. She wondered whether any effort was made to vary efficacy to a much lower rate. There certainly have been vaccines that do not work in the elderly, so she was concerned that the same may be true with Tdap.

Dr. Clark responded that these points were well-taken. Initial effectiveness was based on field evaluations, and immune waning of at least 5% per year was built in over the horizon of the vaccination to as much as 20% waning. While the model is somewhat robust to that, incidence is really the primary driver.

Ms. Ehresmann requested further clarification about the immune waning that was built in.

Dr. Acosta clarified that each year post-vaccination, the initial effectiveness value used would decrease by 5%. In the sensitivity analysis, each year post-vaccination waned by 20%.

Dr. Clark added that GSK's input is based on their antibody responses bridged to infant trials. There are data suggesting higher effectiveness, at least very short-term after vaccination.

Dr. Sawyer pointed out that they would hear immunogenicity data in this age group by antibody measure, which may help everyone digest how likely these vaccines are to be effective in the age 65 years and older population.

Dr. Duchin requested further clarity about the GSK model.

Dr. Krishnarajah responded that the GSK model evaluated 10% of vaccinating a single cohort of adults aged 65 and older.

Dr. Acosta indicated that their model included waning each year and followed a 10-year timeframe. At 75 years of age, vaccine efficacy was 20% in the base case.

Dr. Keitel noted that current policy was targeted at recommending that adults 65 and older be vaccinated if they have close contact with young infants. She wondered if it was known what proportion of that population actually has close contact with young infants.

Dr. Liang responded that there is not an accurate estimate of this.

Safety and Immunogenicty of BOOSTRIX® in Persons 65 Years of Age and Older

Dr. Jennifer Liang
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Liang reminded everyone that two Tdap products are licensed for use in the US: Adacel™ (sanofi pasteur) and Boostrix® (GSK). The vaccines differ in composition and approved age for use. BOOSTRIX® currently is licensed for people aged 10 years and older and Adacel™ is licensed for those 11 through 64 years of age. Both are for use as an active booster immunization for prevention of tetanus, diphtheria, and pertussis as a single dose. Tdap vaccine is covered by Medicare Part D, which is relevant to use in people aged 65 and above.

As previously mentioned, in October 2010 ACIP reviewed the safety and immunogenicity data of both Adacel™ and BOOSTRIX® in adults aged 65 years and older. At that time, both vaccine products were not approved for use in this population. In July 2011, the FDA approved the expanded age indication for BOOSTRIX® to include adults aged 65 years and older. With the availability of an approved Tdap product in this age group, the working group reviewed the data again and considered revising the current Tdap recommendation.

GSK provided information and allowed Dr. Liang to present data on their behalf to expedite the presentation and allow for more time for discussion. Because these data were presented during the October 2010 ACIP meeting, Dr. Liang summarized only the major points.

Data from subjects aged 65 and older are from two clinical trials that are primarily from the pivotal study 011 comparing BOOSTRIX® to Td vaccine in which 887 subjects received BOOSTRIX®. The mean age was 72 years, with a range from 65 to 93 years. There were no apparent differences in the subject characteristics between vaccine groups. With respect to local reaction, BOOSTRIX® appears to be similar to Td vaccine. For reported general symptoms, BOOSTRIX® also is comparable to Td vaccine. Few serious adverse events were report, and none were attributed to receipt of BOOSTRIX®.

For any Tdap vaccine, pertussis immunogenicity has been determined by bridging to a 3-dose DTaP infant series. BOOSTRIX® was bridged to three doses of Infanrix®. Comparing the GMT concentrations of the 3-dose Infanrix® series to BOOSTRIX® in adults aged 65 years and older, BOOSTRIX® met the pre-defined non-inferior criteria. The immune responses to diphtheria and tetanus toxoids were similar to BOOSTRIX® and Td, and also satisfied non-inferiority criteria. For the three pertussis antigens contained in BOOSTRIX®, increases were observed the GMT concentrations for PT, FHA, PRN. As previously stated, this satisfied non-inferiority criteria. Post-marketing safety data from the Vaccine Adverse Event Reporting System (VAERS) was also previously reviewed by the working group. During 2005 through 2010, there were 243 reports in adults 65 years of age and older given Tdap vaccine. Of these, 95.5% were non-serious reports. The most frequent adverse events after Tdap were local reactions. There were 11 serious reports, included 2 deaths among individuals with multiple underlying conditions. Clinical descriptions of the two deaths made it unlikely to attribute to receipt of Tdap. Post-marketing data suggest that the safety profile of Tdap vaccine in adults 65 years of age and older is as safe as Td vaccine [Moro PL, et al. Adverse events after Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis (Tdap) Vaccine administered to adults 65 years of age and older reported to the Vaccine Adverse Event Reporting System (VAERS), 2005–2010. Vaccine 29 (2011) 9404– 9408].
After a review of the data, the working group conclusions were that BOOSTRIX® for adults aged 65 years and older is safe and immunogenic. Older adults boost, which likely provides protection, but the absolute efficacy is unknown for Tdap for all ages. Also unknown is what proportion of people are protected and for how long.

Discussion Points

Dr. Baker noted that this immunogenicity data like most data ACIP sees are one month post-immunization, and she assumed at this point there was no further follow-up information for further duration of protection.

Dr. Liang requested that GSK respond to this question.

Dr. Wayde Weston (GSK) replied that in the 65 years of age and older population, GSK does not have any follow-up data and is not conducting any follow-up studies. They do have follow-up data on younger adults aged 19 to 64, some of which has been published, and they are continuing to collect those data.

Dr. Temte asked for clarification regarding whether the individuals 65 years of age and older had multiple morbidities or were considered to be healthy. Increasingly, the patients he sees tend to have multiple conditions that all may affect immunogenicity.

Dr. Liang replied that for the clinical trial, the population was comprised of healthy people.

Dr. Weston confirmed that they were generally healthy subjects 65 years of age and older. Some co-morbidities were expected, and subject were excluded who had any immunosuppressant conditions or who were taking any type of immunosuppressive therapy, such as those with rheumatoid arthritis.

Dr. Marcy inquired as to why data were not being collected on those 65 years of age and older. It seemed to him that they had been circling this question repeatedly.

Dr. Weston responded that he would take this back to GSK as a topic for discussion.

Dr. Marcy emphasized that this should be taken back as a topic for action. GSK seems to be the only group that can give ACIP this answer.

Proposed Recommendation for Use of Tdap in Persons 65 Years and Older

Dr. Jennifer Liang
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Liang reminded everyone that as presented to ACIP, the working group has interpreted data on disease burden, safety and immunogenicity, and cost-effectiveness of the one Tdap product approved for use in persons aged 65 and older. As outlined by Dr. Sawyer at the beginning of the session, if ACIP approved of the proposed recommendation, the working group would provide guidance on the use of the other Tdap product not approved for use in this age group.

The current Tdap ACIP recommendations for adults are as follows:

- **Adults aged 19 through 64 years**
  - For adults aged 19 through 64 years who previously have not received a dose of Tdap, a single dose of Tdap should replace a single decennial Td booster dose.

- **Adults aged 65 years and older**
  - Adults aged 65 years and older (e.g., grandparents, child-care providers, and health care practitioners) who have or who anticipate having close contact with an infant less than 12 months of age and who previously have not received Tdap should receive a single dose of Tdap.
  - For other adults aged 65 years and older, a single dose of Tdap vaccine may be given instead of Td vaccine, in persons who have not previously received Tdap.
  - Either Tdap vaccine product may be used [Note: No vaccine was approved for use in this age group at the time of this recommendation].

The rationale for the proposed changes to the recommendations is that there is now one Tdap product approved for use in adults aged 65 and older; data on the safety of BOOSTRIX® in this population are reassuring; and the proposed recommendation is consistent with existing Tdap recommendations.

Before presenting the proposed language for ACIP's consideration, Dr. Liang listed the ACIP Tdap recommendations that would remain unchanged:

- ❑ General adolescent Tdap recommendation
- ❑ Tdap administration regardless of interval since last Td
- ❑ After receipt of Tdap, persons should continue to receive Td for routine booster vaccination
- ❑ Adolescents and adults having close contact with an infant should receive Tdap (cocooning)

The working group proposed the following changes to the general adult Tdap recommendations for a vote:

- ❑ Expand the age range to include adults aged 65 years and older
- ❑ Remove the phrase ". . . a single dose of Tdap should replace a single decennial Td booster dose"

Though the working group discussions have focused on adults aged 65 and older, the members wanted to take the opportunity to update the entire adult Tdap recommendation. To be consistent with the ACIP's past removal of language regarding minimal interval, the working group proposed removal of the phrase regarding replacement of a single decennial Td booster dose. This also would be consistent with the overall goal of removing barriers to Tdap uptake.

The working group unanimously agreed to the following proposed language:

- ❑ For adults aged 19 years and older who previously have not received a dose of Tdap, a single dose of Tdap should be given.

The proposed change would replace the current cocooning and permissive Tdap recommendations for those aged 65 years and older with a universal adult Tdap recommendation.

Discussion Points

In moving forward with evidence-based recommendations, Dr. Keitel wondered whether Dr. Liang could reflect upon how the recommendation might look for the younger versus the older age group. That is, how would the working group grade the recommendation for younger adults versus older adults.

Dr. Liang responded that the working group had not been approached to grade this. While she was aware of the grading system, she would not be able to address that without additional guidance.

As a member of the working group, Dr. Baker said that given the amount of evidence, the grading would be significantly different for older versus younger people because there are significantly more data for the younger population.

Dr. Schuchat added that the two pieces of evidence available are immunogenicity, which does not look that different, and incidence, which has many unanswered questions for all age groups and for which there may be a particular bias for some under-detection versus substantial under-detection. It is very indirect to bridge with other bacterial and viral vaccines with poorer efficacy in the older population. Regarding the grading for this particular vote, it was decided that since most of the updated Tdap recommendations preceded the implementation of grading, that they would forgo moving backwards to grade everything for the new statement. In 5 years when an update is done, ACIP will grade everything as per protocol. Perhaps there will be even more data at that time.

Dr. Baker expressed her hope that the vaccine manufacturers heard the comment that more evidence would be very useful in moving forward.

Dr. Temte indicated that for his patients over the age of 65 on Medicare, he wondered what the implications would be in terms of coverage.

Ms. Rosenbaum responded that the instruction is for adults who previously have not received a dose of Tdap to receive a dose. However, the US healthcare system is not good enough to indicate longitudinally whether an individual has received a previous dose of Td. This raises the default question. The default appears to be that if someone has not received a dose or there is no verification of whether they have received a dose, a dose is recommended. She thought that because of the coverage implications, unless they really meant only to give a vaccine when there was affirmative evidence of no prior receipt, ACIP should clearly state that a dose should be administered to those who have not received the vaccine and those for which receipt cannot be confirmed. That is, a clear message should be sent that this should be routine in either case. Regarding the over 65 year old population, any recommended vaccine would be covered as a Part D benefit if it is not specified as a Part B benefit, which it is not. She wondered whether more was known from the on-going discussion about Part D coverage of vaccine coverage how effective Part D has been in realizing access to the vaccine because of the rather clumsy way in which Part D works. Because there is not a direct payment to the provider, unless one is in an integrated delivery system, the vaccine has to be transported from a dispensing site to the provider.

Dr. Baker indicated that the default would be to immunize if immunization status is unknown, which is how pediatric medicine works. She requested that Dr. Hance, the CMS liaison, comment on the question pertaining to Medicare coverage.

Dr. Hance (CMS) responded that, as was noted, Tdap vaccine is part of the formulary for Medicare Part D, so patients with Part D will have access to the vaccine. Given that she is on the Medicaid side, she was unable to offer further details. However, she said she would follow up with her colleagues for further information.

Dr. Poland inquired as to whether Td vaccine fell under Part B. He also wondered why in the recommendations they did not formally signal research that will be needed in order to make valid recommendations in the future. For example, they were just shown that an immunologically vigorous adolescent who receives a booster dose has a 30% plus drop in efficacy 5 years later. Now they were considering recommending a dose to 50 year olds who

will be exposed to children 12 months or younger 15 years later when they are beginning the slide into immunoscenescence. It is unknown what the efficacy is 15 years after receipt of the vaccine. These seemed to be significant provisos that should be signaled and incorporated into the recommendation to motivate the collection of the data.

Regarding Dr. Poland's Part B questions, Dr. Hance (CMS) responded that Td vaccine falls under Part B if it is indicated for a room contamination or a previously existing condition.

Dr. Baker added that the working group would address duration in all age groups as its next major job.

Dr. Schmader (AGS) echoed Dr. Poland's comments. Because elders are often excluded from clinical trials, including vaccine trials, geriatricians have to act on the absence of evidence a lot of times. If they have to wait for the perfect randomized controlled trial, they will never do anything. Weighing the pros and cons, the American Geriatric Association (AGS) agreed with the working groups' conclusions and completely supported this recommendation.

Dr. Tan (AMA) indicated that in November 2011, the General Accounting Office (GAO) released a publication on vaccine access for Medicare Part D versus Medicare Part B, which highlights a lot of the concerns that were raised by ACIP that there is a dramatic decrease in access as a result of vaccines being included in Part D.

Regarding implementation, Ms. Groom (IHS) reported that IHS has a high proportion of grandparents who are primary caregivers in the American Indian / Alaska Native populations. The recommendation to target those with infant contact has been very challenging for their providers to tease out. IHS went ahead and routinely forecast this for adults, including those 65 years of age and older. Acceptance of the proposed recommendation would help to support that.

Ms. Ehresmann made a motion to approve the recommendation as proposed, which was seconded by Dr. Jenkins. Further discussion ensued.

Ms. Rosenbaum inquired as to whether the language should be amended. It was unclear to her whether they would have to think about this each time because of the coverage implications. That is, if it is common practice when information is not known or cannot be verified to immunize routinely, ACIP needs to be clear that this is its recommendation. With that in mind, she suggested the following revision to the proposed language, "For adults aged 19 years and older who previously have not received a dose of Tdap or for whom prior receipt of a dose cannot be verified, a single dose of Tdap should be given."

Dr. Schuchat responded that the guidance language in the draft statement says that. It is fairly standard for adult vaccines in addition to pediatric vaccines. The pneumococcal polysaccharide vaccine is the one for which an enormous amount of change was implemented in the 90s. It was not about provider coverage. It was just provider caution about what to do when they could not find a record. At this point, it is standard when vaccine history is unknown to administer it.

Dr. Jenkins pointed out that it would be beneficial for those who had not served for very long to be provided with a history of how they reached this point, and whether they were waiting for something particular before moving forward.

Dr. Liang replied that when the original recommendation was approved in October 2010, neither Tdap product was approved for adults 65 and older. Given that no product was available at that time for that age group, the working group thought it was important to provide protection to infants through grandparents who were primary caregivers and to provide the additional permissive recommendation. In July 2011, BOOSTRIX® was approved for that age group. Now that a product has been approved in that age group, the working group wanted to revisit and update the language.

Dr. Baker added that ACIP attempts to stay within the FDA label, but there are situations like infant pertussis in which recommendations are made without aligning with the FDA label.

In the finessing of the language in the proposed recommendation, Dr. Temte requested that the working group consider adding language in terms of future data to better understand immunogenicity and waning of immunity over time, and efforts to improve surveillance of pertussis in all age groups.

Dr. Baker said she thought that was planned for the statement.

Vote: Recommendation for Use of Tdap in Persons 65 Years of Age and Older

Ms. Ehresmann made a motion to approve the draft language as presented. Dr. Jenkins seconded the motion. The motion carried with 14 affirmative votes, 1 negative votes, and 0 abstention. The motion passed by a majority vote. The disposition of the vote was as follows:

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

Guidance for Use of Tdap in Adults Aged 65 Years and Older

Dr. Jennifer Liang
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Before providing guidance for the use of Adacel™, which is not approved for use in adults 65 years of age and older, Dr. Liang presented a brief summary of the safety and immunogenicity data for Adacel™ in this age group. She thanked sanofi pasteur for providing data and permitting her to present on their behalf. As a reminder, these data originally were presented to ACIP during the October 2010 meeting. For the past three months, the working group has reviewed these data in detail.

Sanofi pasteur conducted a clinical trial, Td515, for Adacel™ in persons 65 years of age and older. For this study, 1170 participants were vaccinated with Adacel™ and 391 were vaccinated with Td. One-third of the subjects were 75 years of age and older. The safety data showed that the proportion of local and systemic reactions did not differ from Td. For tetanus and diphtheria immunogenicity, antibody responses were similar to Td and met non-inferiority criteria.

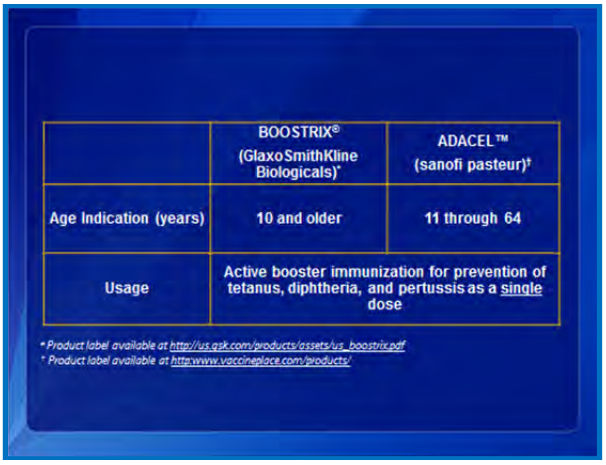
The major question with which the working group grappled pertained to how to interpret the pertussis immunogenicity data when Adacel™ is not approved for use in this age group. In a comparison of the GMC of infants who received either a 3- or 4-dose DAPTACEL® and adults aged 65 years and older who received Adacel™, sanofi pasteur no longer had data to bridge to PT from the 3-dose DAPTACEL® infant series and, therefore, bridged to the 4-dose series. The three antibodies (e.g., PT, PRN, and FIM) have lower GMC concentrations when compared to infants who received DTaP and do not meet non-inferiority criteria. Although Adacel™ did not meet the non-inferiority criteria, it has been shown to be immunogenic in adults aged 65 and older. There is a 4-fold to 15-fold increase in pertussis antibodies 28 weeks post-vaccination depending upon the pertussis antigen.

As mentioned previously, both Tdap products differ in antigen content and responses to each antigen. The working group felt that it was important to assess the pre- and post-vaccination GMC levels for each vaccine type side-by-side, although this assessment was not intended to directly compare the immunogenicity of Adacel™ and BOOSTRIX®. The gestalt of immune response for each vaccine is that both result in boosted antibody responses, and it is known that antibodies provide some level of protection.

The ACIP WG's conclusions were that Adacel™ has an acceptable safety profile in adults aged 65 years and older. Regarding pertussis, Adacel™ is immunogenic in adults 65 years and older and would likely provide protection. Because Adacel™ is not approved for use in adults in this age group, the working group considered guidance for use because there are providers who stock this product. She reminded everyone that in the previous recommendation of cocooning and permissive vaccination for adults aged 65 years and older, ACIP stated that either Tdap product may be used.

Multiple other countries have a broader approved age range for Adacel™. In Canada, licensure for Adacel™ recently was broadened to include older adults following a review of the same data that were presented to the working group and ACIP. In the European Union (EU), the German licensure is for those 4 years of age and up. This is also true of 28 EU member states. In Australia and New Zealand, licensure is for ages 10 years and up. Most Latin American and Asian countries follow license in the country of origin, Canada.

As the working group prepared the language, a review of comparable language from other vaccines was conducted. Guidance will include the following table that notes the approved age indication for BOOSTRIX® and Adacel™:



	BOOSTRIX® (GlaxoSmithKline Biologicals)*	ADACEL™ (sanofi pasteur)†
Age Indication (years)	10 and older	11 through 64
Usage	Active booster immunization for prevention of tetanus, diphtheria, and pertussis as a single dose	

* Product label available at http://us.gsk.com/products/assets/us_boostrix.pdf
† Product label available at http:www.vaccineplace.com/products/

After several working group discussions and input from FDA, the working group favored practical guidance for vaccinating this population. The following specific points were agreed upon by the working group:

- When feasible, the approved Tdap vaccine for adults aged 65 years and older should be used.
- A dose of Adacel™ administered to a person aged 65 years and older is considered valid.
- Providers should not miss an opportunity to vaccinate persons aged 65 years and older with Tdap, and may administer the vaccine that they have available [Phrasing from the General Recommendations Interchangeability language].

Discussion Points

Ms. Ehresmann wondered whether there was a reason they referred to the approved Tdap vaccine and then specifically mentioned Adacel™. She thought they should say the brand or not, but should be consistent.

Dr. Liang indicated that the first bullet could be revised to read, "When feasible, BOOSTRIX® vaccine should be used for adults aged 65 years and older.

Dr. Baker requested an interpretation of how the recommendation is considered valid in terms of Medicare. This seems like a subtle preference and "is considered valid" is unusual language. Stating the "approved vaccine" gives a preference, and suggesting a preference is always going to result in missed opportunities. She requested input regarding how practitioners will understand this in terms of the two available vaccines.

Dr. Liang responded that with regard to the guidance, the reason for providing this in the way that it was presented was so that providers would not miss an opportunity to vaccinate, but recognizing at the same time that there is one vaccine that is approved for use in this age group. The goal was to provide some guidance that would permit providers to use Adacel™ if they had that in stock rather than defer vaccine and miss an opportunity to vaccinate.

Dr. Baker said it should be "FDA-licensed" not "approved."

Dr. Fryhofer (ACP) pointed out that as a practicing physician, she found the language to be very confusing and thought that it would limit access to vaccines. It seems to suggest that the FDA-approved vaccine should be administered. During the last ACIP meeting, data were presented that addressed the safety of both vaccines and during this session, it was shown that other countries have safety information. Therefore, it was unclear to her why Adacel™ had not been FDA-approved.

Dr. Tan (AMA) agreed with Dr. Fryhofer and suggested deleting the first two bullets and leaving the third to achieve the objective.

Dr. Sawyer clarified that an attempt was made to model previous language or general recommendations language, including the statement that vaccination is "considered valid" if

used when not FDA-approved. The statement in the second bullet, "may administer the vaccine they have available" is taken from the general recommendations language.

Dr. Sun (FDA) responded to the questions raised about why Adacel™ had not been FDA-approved in this age group. The basis upon which FDA approves indications is the use of adequate, well-controlled studies. The two studies, one on BOOSTRIX® and one on Adacel™, were very similar in design and pre-specified serological endpoints. BOOSTRIX® met the criteria and Adacel™ did not, which was the reason the FDA did not approve both.

Dr. Coyne-Beasley acknowledged that the working group puts a lot of thought and energy into formulation of recommendations. She expressed interest in hearing from working group members about whether they would be comfortable with the recommendation that was put forth by one of the liaisons regarding the inclusion of just the third bullet.

Ms. Ehresmann commented that part of the motivation for asking the question about why the language "approved Tdap" was used for the first bullet and the trade name was used in the third bullet, was that there is significance to the fact that a vaccine is licensed. While she wanted to acknowledge and completely support the idea of missed opportunities, there is a situation in which there is a licensed vaccine and use of the other vaccine is off-label. She thought it was important for the recommendations to recognize that difference, and that the proposed language did this in a very nice way that continues to promote vaccination but acknowledges that there is a process for licensure.

Dr. Sawyer agreed that part of the impetus behind the language was to address that there are two products, one that is approved by FDA and one that is not. Some members of the working group who have reviewed the immunogenicity data in detail do not believe these are equivalent vaccines in this population. This is how the working group arrived at this compromised position to avoid missed opportunities by basically stating that if Adacel™ is given, that is considered valid and it should be given if it is what an office has in stock. However, they wanted also to state a slight preference for the FDA-approved product.

Dr. Bennett thought the language was very complex for a practitioner and actually would interfere with administration of these vaccines. She wondered whether it would be possible to make a general recommendation about Tdap and then in the description of how to give Tdap include the considerations, including the differences in immunogenicity. As a physician, she would never think about whether she gave a valid vaccine. This is not the language physicians use or the way they think about this.

Dr. Liang clarified that this language is not part of the recommendation. It is guidance that would be included within the statement. The language of the actual recommendation would be what ACIP just voted on for adults. The guidance would be included within the body of the statement to explain the rationale behind the guidance.

Dr. Marcy pointed out that sanofi pasteur now has 1200 immunosenescence individuals they could follow to assess decay. He wondered whether they planned to follow this cohort.

Dr. Hahn (CSTE) indicated that she serves on the working group and helped to craft this language. She suggested reversing the sequence of the bullets to move the third bullet to the first bullet, possibly this might make people more comfortable that this is the main point being made.

Dr. Loehr (AAFP) said that as a practicing physician, he would like to know that BOOSTRIX® is approved and Adacel™ is not, but that he could use Adacel™ if necessary. That should be the clear point if that is what ACIP wants. If ACIP does not really care about approved or not, then the third bullet is all that is needed. He was also curious about the difference between "approved" and "licensed" and which word should be used. It was his understanding that the vaccine was licensed and then approved for this indication.

Dr. Baker replied that the FDA licenses vaccines and approves drugs, and ACIP recommends.

Dr. Clark added that the working group was directed by FDA in these discussions. He clarified that both vaccines are licensed; however, BOOSTRIX® is the only one approved by the FDA for use in those 65 years of age and older. He liked the suggestion to flip the language, and suggested modifying the second bullet to state that "a dose of either vaccine is immunogenic and valid."

Dr. Moore (AIM) asked for clarification regarding whether the recommendation was to administer Tdap at the next visit to anyone who has not yet had a Tdap, or if it was akin to the 19 through 64 year old recommendation in that it would replace the decennial Td vaccine unless there is a specific need to administer Tdap earlier.

Dr. Liang clarified that with the vote ACIP just passed, the phrase about the decennial Td booster for all adults was removed.

Dr. Moore (AIM) emphasized that thinking programmatically, it is important to tell people who have not had it that they need it.

Dr. Netoskie (AHIP) suggested revision of the first bullet to read, "When feasible, the approved Tdap vaccine or a dose of Adacel™ for adults aged 65 and older" and elimination of the second point. That would be clearer for physicians and payers.

Dr. Baker assured everyone that they would try to make everyone happy with the final language, and make it clear to the practitioner. She thought a strong point that had been made was that the recommendation upon which ACIP voted was very clear, but the guidance language needs to take into consideration some of the issues that would confuse practitioners.

Dr. Jenkins stressed that there are no data on the older population; however, the demographic curve is shifting in the sense that there are more well people in this age group. She expressed her hope that the discussion highlighted the point that more data should be collected in this population as more people shift into this age group.

Dr. Friedland (GSK) reinforced that GSK is following immune duration and antibody persistence across all ages for 10 years following vaccination. Those vaccines were licensed in 2005, so they are approaching that timeframe. All adults from the clinical trial program who are 19 through 64 years of age are being followed for 1-, 3-, 5-, and 10-year for antibody persistence studies. The over 65 group was just licensed for BOOSTRIX® in July 2011, so there has not yet been time for these people to age into the duration studies. Nevertheless, GSK takes these comments seriously and is interested in generating as must data as possible that can help guide policy discussions.

Influenza

Introduction

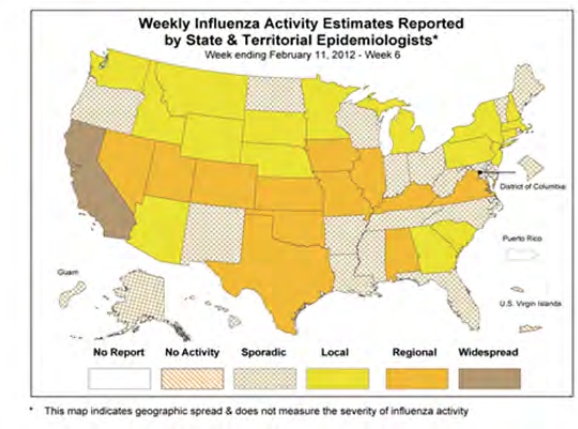
Wendy A. Keitel, MD
Chair, Influenza Working Group

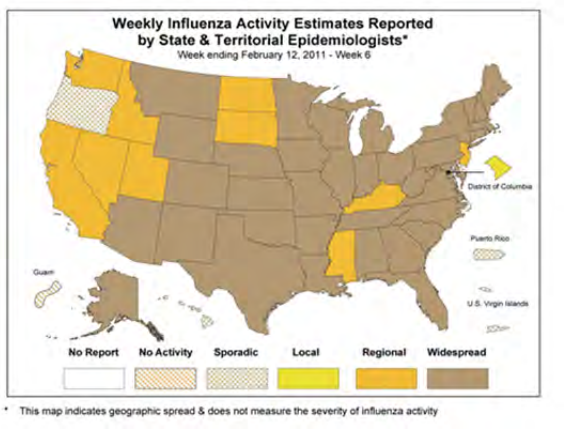
Dr. Keitel reported that the activities of the Influenza Working Group over the last few months included discussions of vaccine products currently under development; discussion of recent epidemiology, including influenza A(H3N2)v; and initiation of review of the evidence base using GRADE.

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. She shared the most recent available FluView data, which was for Calendar Week 6 ending February 11, 2012. These maps depict weekly influenza activity estimates reported by state and territorial epidemiologists, and are intended to illustrate geographic spread over the course of time to provide a snapshot rather than to reflect influenza season severity or intensity. For the week ending February 11, 2012, virtually all reporting states and territories reported at least sporadic influenza activity. Notably, only California was reporting widespread activity at this time. Dr. Grohskopf compared this to Calendar Week 6 ending February 12, 2011 of the previous season which showed a fair amount of contrast in terms of widespread activity. The current season seems to have gotten off to a somewhat slow start. It is not possible to determine where the peak will occur until it has already been passed.





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 primarily hospitals. In terms of the results of influenza positive tests reported to CDC by the WHO / NREVSS collaborating laboratories, it was only in the previous couple of weeks that were 10% or more positive specimens. Among specimens that have been typed thus for, there has been a predominance of H3. Within the sample, there is a relatively low number (~5%) of B isolates.

In terms of the characteristics of recent influenza virus isolates that have been submitted to and tested at CDC, since the season officially started on October 1, 2011, there have been 369 US isolates tested. Among those, 58 (16%) were Influenza A (H1N1), 56 (97%) were A/California/7/2009-like; and 263 (71%) were Influenza A (H3N2), of which 257 (97%) were A/Perth/16/2009-like. These two strains are those represented in the current 2011-2012 seasonal vaccine. There has been a relative dearth of Influenza B specimens. Only 48 specimens have been received, representing 13% of the total tested. Of these, 22 (46%) were of Victoria lineage, 198 (99%) were B/Brisbane/60/2008-like, and 26 (54%) were of Yamagata lineage. This is quite a small sample of viruses. Worldwide, most isolates have been similar to the 2011-2012 vaccine strain.

In terms of the percentage of outpatient visits for influenza-like illness (ILI) reported by the US Outpatient Influenza-like Illness Surveillance Network (ILINet), ILINet is a network of over 3000 healthcare providers throughout the 50 states who report data to CDC on a weekly basis. The epidemic threshold, or national baseline, is calculated based on the mean percent of visits for ILI averaged over the last three years of non-influenza season weeks. The baseline is currently about 2.4%. The percentage of illnesses due to ILI remained below epidemic threshold at this time.

In terms of the number of influenza-associated pediatric deaths reported from the 2008-2009 influenza season to the present season. For 2010-2011 that total number of pediatric deaths reported was 122. This is a slight increase over the figure presented in October 2011, as there were some late reports for 2010-2011 that came in since then. Notably, for 2011-2012, since October 1, 2011, only 3 pediatric deaths have been reported. Compared to this time period last year, this represents quite a few fewer deaths. It is important to keep in mind that the season is not over, the peak will not be known until it has occurred, and there is a reporting lag.

Dr. Grohskopf then described human infections with swine influenza A viruses in the US, some of which have been observed this past season. A total of 35 human cases of swine influenza A virus infection were identified from December 2005 through November 2011. These viruses are known to circulate in swine and do not typically circulate to humans, but CDC does receive periodic reports of cases observed in humans. Previously about 1 case is reported every 1 to 2 years, but better diagnostics and testing at state health departments and greater awareness of occurrence may be contributing to why more cases have been observed in the last couple of years. These are all triple reassortant swine-origin viruses, meaning that they contain genetic material that has its origin in avian, swine, and human viruses. Included within the 35 instances that have been observed, there has been representation of H1N1 (n=13), H3N2 (n=20), and H1N2 (n=2) infections.

The 12 cases of swine-origin influenza A(H3N2) variant that were observed between July 2011 through November 2011 were reported from 5 states (Maine, Iowa, Indiana, West Virginia,

Pennsylvania). These cases were of swine origin H3N2 with the matrix (M) gene from A(H1N1) pandemic 2009 strain. Most of the cases were in children. The median age was 3 years, with a range of 11 months to 58 years. The illnesses were primarily characterized by mild to moderate influenza-like illness. Three persons were hospitalized, but all recovered. The estimated incubation period was about 2 to 4 days, with a range of 1 to 7 days. Exposures are interesting to consider. As with most of these instances, typically there is exposure to swine either directly or indirectly, although there are occasionally cases in which this is not observed. In this particular group of cases, 4 individuals had direct exposure to pigs, 2 had indirect exposure, and 6 had no discernible exposures and represent potential human-to-human transmission. There has been no sustained human-to-human transmission, however, which is important to consider. The hemagglutinin genes in this virus are related to H3N2 viruses that circulated during the 1990s, so as a result adults and some older children may have some limited immunity to these viruses. However, the current seasonal vaccine is not anticipated to provide significant protection. At present, there is not a vaccine specifically for these strains. Vaccine candidate strains have been distributed to manufacturers, but sustained spread is not being observed. The last case was reported in November 2011, but monitoring for new cases continues.

With regard to influenza vaccine safety monitoring for the 2011-2012 season, the formulation is unchanged from 2010-2011 seasonal influenza vaccine. This is the first season of use for intradermal trivalent inactivated influenza vaccine (TIV), and it is the second season of use for high-dose TIV. Monitoring is in place for these vaccines as well as the other influenza vaccines in the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD). To data, no unexpected or new safety concerns have been detected.

Discussion Points

Regarding the map that shows the estimated activity by state, Dr. Meissner pointed out that sometimes there is considerable variation from one state to another. He wondered whether this depicted an accurate reflection of the amount of influenza in a state, or if it was reflective of differences in surveillance by state.

Dr. Grohskopf replied that there is some variation within jurisdictions in terms of how a region is different. The definitions for “no activity, sporadic, local, regional, and widespread” involve several different parameters and can be somewhat complicated. One aspect of this is the number of regions within a state that a considered to be having influenza activity. This may vary from state-to-state as they define “local.”

Dr. Bresee (SME) added that in general, while there are state-to-state variations, the proportion of states that show widespread or regional disease correlates quite well with other surveillance systems.

Regarding the H3N2 data and the suggestion that the M gene came from the pandemic H1N1, Dr. Duchin requested clarification regarding whether it came from the human virus or if it was possible that it shares the same gene as another precursor that was common to both viruses. Given the level of influenza activity, he also wondered whether there would be data about the effectiveness of the high dose vaccine in the population for which it is indicated.

Dr. Grohskopf responded that regarding the M matrix gene, it is susceptible to influenza viruses that infect swine, avian, and humans. The term that is used is that they make good mixing vessels. The M gene is similar to the one that is in the pandemic H1N1 strain, so theoretically of this virus had spread to swine at some point that would allow for some kind of

recombination. The working group expects to receive an update on the high dose vaccination sometime in the near future. She requested that a sanofi pasteur representative comment on the timeline for that update.

Dr. Greenberg (sanofi pasteur) responded that the post-licensure efficacy trial is on-going and results are anticipated within the next two years, depending upon the number of cases ascertained each season, the strains, and the match with the vaccine.

Dr. Temte thought the lack of childhood deaths observed this season was stunning. He knew the influenza branch tended to be very conservative and holds their comments "close to the hip," but he had to assume that there must be incredible effects of universal vaccine policy, recurrence of the same strains, and the likelihood that there will be little influenza this year. He has been amazed in Wisconsin in terms of influenza surveillance and general morbidity and mortality with hospitalized older patients. He was on a teaching service the first two weeks of January and had virtually no admission for chronic obstructive pulmonary disease (COPD) or congestive heart failure exacerbations. He wondered whether there were any guesses about current population immunity.

Dr. Grohskopf replied that there was nothing as far as a broad population-based evidence-base.

Dr. Bresee (SME) added that while the hope is that there will be little influenza this year, CDC's take on it is that there could be more influenza so it is not too late to get vaccinated.

Dr. Schuchat added that there is year-to-year variability in terms of when the influenza season starts. In recent years, it has been very early. It has been a long time since it has been late like this. It would be premature to conclude that there is not going to be an influenza season. Instead, it appears that the influenza season will have a really late start.

Dr. Bennett requested information about immunization rates across the age span.

Dr. Grohskopf responded that for the current season, this could not yet be done.

Dr. Baker congratulated CDC and the liaison organization for the intensity of messaging to the public through a variety of media, which has been impressive. She was also impressed by the incredible job pharmacies were doing as an alternative venue for vaccines. She would like to be optimistic along with Dr. Temte regarding the combination of increasing immunization rates, some communities with herd immunity, and a low influenza season being responsible. She reminded everyone that the first thing that was observed with rotavirus vaccines was a delay in the rotavirus season.

Dr. Duchin noted that some research had been published to suggest that H1N1 produced a very broad spectrum cross-reactive immunity against other influenza viruses. That has some interesting implications about vaccine formulations and the impact of epidemiology on subsequent viruses that might appear. He wondered if any thought had been given to whether the broad pandemic with H1N1 had generated some sort of protective effective in the population for the current season and perhaps subsequent seasons.

Dr. Grohskopf responded that it has been interesting that the same vaccine has been used essentially for two seasons. It is known from other studies that immunity declines, but the degree and the rate to which it declines occur depends on the population. There is an anomaly

in that H1N1 2009 vaccine has been used for two seasons plus the pandemic season, so it does make for somewhat unique circumstances.

Dr. Bridges indicated that final coverage data would not be available until Spring, but in November internet panel surveys were conducted of pregnant women and healthcare workers, and in the national influenza survey data people are asked about receipt of vaccine and if individuals definitely intend to be vaccinated. Those two numbers combined tend to correlate fairly well with the end of season coverage. The November data indicate that this year is on track with last year, with similar coverage rates.

Dr. Pickering wondered whether Dr. Bridges or Dr. Foster had any information on the rates of increase, decrease, or steadiness of influenza immunizations given in pharmacies.

Dr. Foster (APhA) responded that according to CDC numbers, last year was 18% and the previous year was 10%. He expected this to be higher this year.

Dr. Jenkins observed that it is super markets as well as pharmacies. Some super markets are offering a 10% discount on groceries with receipt of an influenza vaccine. They are aggressively marketing influenza vaccine.

Dr. Foster (APhA) clarified that super markets and stores are all pharmacies.

Dr. Baker pointed out that a license was required to inject someone.

Dr. Bridges added that many people do not know when they go to a grocery store whether they were vaccinated by a visiting nurse or pharmacists, which is why it is lumped into retail locations. That proportion has increased for adults to 20% to 21%.

Dr. Poland (ACP) emphasized that in many grocery stores, Sam's Clubs, et cetera, it is the Visiting Nurse Association (VNA) and other nursing associations that go there to administered vaccines. The VNA has done a wonderful job with this.

Antiviral Medications

Tim Uyeki MD, MPH, MPP
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Uyeki emphasized that antiviral agents are an important adjunct to influenza vaccination in terms of the prevention and control of influenza. There is a very high prevalence of resistance to the adamantane class of antivirals among circulating influenza A viruses worldwide, so there is a tendency to focus on the neuraminidase inhibitors, oseltamivir and zanamivir, for prevention and control. As Dr. Grohskopf indicated, more of the viruses tested so far this year are influenza A H3N2. Among all of the H3N2 viruses, B viruses, and the 2009 H1N1 viruses, no resistance has been observed to oseltamivir and zanamivir, which is very good news. In July and August of last year, there was local transmission of oseltamivir-resistant 2009 H1N1 virus in Southeastern Australia. That raised an alarm, but there is no evidence of that so far in the US. Oseltamivir or zanamivir is recommended for treatment of influenza A or influenza B virus infections. Treatment is recommended as soon as possible for any patient who has confirmed influenza is suspected to have influenza, especially those who have severe, complicated, or progressive illness; people who require hospitalization; or outpatients who are at higher risk for

influenza complications. The administration of antiviral drugs should not be delayed while waiting for results of diagnostic testing if clinically indicated. Otherwise healthy patients who present early (e.g., within 48 hours of illness onset) with uncomplicated confirmed or suspected influenza can be treated based upon clinical judgment [ACIP Guidance for Use Antiviral Agents http://www.cdc.gov/flu/professionals/antivirals/guidance/; Updates on antiviral resistance can be found at: http://www.cdc.gov/flu/weekly/].

The groups at higher risk for influenza complications include the following:

- ❑ Persons <2 or ≥65 years of age

- ❑ Persons with the following conditions:
  - → chronic pulmonary (including asthma)
  - → cardiovascular (except hypertension)
  - → renal, hepatic, hematological (including sickle cell) disease
  - → neurological, neuromuscular, or metabolic disorders (including diabetes mellitus)

- ❑ Immunosuppression, including that caused by medications or by HIV infection

- ❑ Women who are pregnant or post-partum (2 weeks)

- ❑ Persons younger than 19 years of age who are receiving long-term aspirin therapy

- ❑ American Indians and Alaskan Natives

- ❑ Persons who are morbidly obese (body-mass index ≥40)

- ❑ Residents of nursing homes and other chronic-care facilities

In terms of inhaled zanamivir dosing, zanamivir is approved for those aged 7 years and older for the treatment influenza A and B. The dosage is 10 mg (two inhalations) twice daily. It is not approved for treatment in those under the age of 7 years. For chemoprophylaxis, zanamivir is approved for influenza A and B for those aged 5 years and older at 10 mg (two inhalations) once daily. It is not recommended for persons with underlying airways disease. Administration requires correct use of inhalation device.

Oral oseltamivir is FDA-approved for treatment of influenza A and B for persons 13 years of age and older. There are differences in the dosing in terms of pediatric ages. The dosage is 75 mg twice daily for those 13 years of age and older. For those ages 1 through 12 years, dosage is determined by weight. Those who are over 40 kg receive adult dose. It is also approved for chemoprophylaxis for influenza A and B in persons 1 year of age and older. It is not FDA-approved for children aged less than 1 year. This drug was used for this age group during the pandemic through an Emergency Use Authorization (EUA), which expired in June 2010. There was extensive use of the drug, there are observational data, and there is a randomized clinical trial that would include this age group that has been presented at meetings, but has not yet been published. ACIP and CDC recommend that this drug be used in children of this age for a number of reasons, given that this age group is at very high risk of severe influenza complications, there have been pediatric influenza-associated deaths, and children less than 6 months of age are not approved to receive influenza vaccination.

With regard to duration of treatment, for therapy the standard course is 5 days. Longer courses may be considered for persons who remain severely ill after 5 days of treatment, especially hospitalized patients. For chemoprophylaxis, the recommended course is 10 days following household exposures and 7 days after most recent exposure in other situations. For control of outbreaks in long-term care facilities and hospitals, prophylaxis for a minimum of 2 weeks and up to 1 week following last exposure is recommended. Other groups who may be considered for receipt of chemoprophylaxis are those who are immunosuppressed and for those for whom vaccine is contraindicated [*MMWR* 2011, Volume 60 (#RR-1), p.7, Table 2].

Discussion Points

Ms. Rosenbaum noted that one of the background documents the ACIP members were sent in preparation for this meeting was what she considered to be an extremely disturbing CDC review of an outbreak in a nursing home in Ohio. This was a long-term residential facility housing only 130 of the most disabled children and adults. Apparently, they were immunized and yet, influenza struck approximately 80 of the 130 residents. Reading between the lines, one of the findings was that the nursing facility did not move fast enough at the first signs of illness to recognize the symptoms of influenza and begin antiretroviral treatment. It was unclear why the failure rate on the vaccine was so high. She wondered what CDC and CMS might do jointly on a letter to all state Medicaid agencies drawing their attention to this outbreak and the CDC and local health agency findings. As much as they would like to think so, the average state Medicaid director probably does not have access to and does not read *MMWR*. The speed with which a nursing facility or other institution introduces antiretroviral agents is a basic patient safety matter. There were 7 or 8 deaths, and these were the most vulnerable people in society. Knowing that this information is not going to get cross-walked to state Medicaid programs without some nudging on the part of the two federal agencies, Ms. Rosenbaum urged that ACIP recommend this kind of action.

Dr. Wharton (SME) thanked Ms. Rosenbaum for the suggestion.

While Dr. Poland had no issues with the recommendations and recognized that they were consistent with the current data, he felt compelled to mention something that he raised as an issue in a working group and published as a commentary in *Clinical Infectious Disease* two years earlier—the idea that there is no RNA virus that would be treated with a single drug. This principle is used for a good reason, which is that those drugs provide mutational pressure and as yet unclear, instances in which it seems to drive resistance. This was observed a couple of years ago with the pandemic with a rising rate of Tamifu® resistance, which fortunately has resolved. The adamantane drugs were used for years until suddenly, inside of a year, there was almost complete resistance. As a research need, he raised the idea that it is in the long-term interest to better understand the effects of using a single antiviral drug in the case of RNA viruses.

Future Activities

Lisa Grohskopf, MD, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Grohskopf reported that upcoming working group activities prior to the June 2012 ACIP meeting include the following:

- On-going review and discussion of vaccine products in development, as indicated and appropriate;
- Discussion of vaccine virus strain selection for 2012-2013 season, and the potential impact this may have on recommendations (e.g., dose recommendations for children 6 months through 8 years of age); and
- Review of the evidence using GRADE, with Dr. M. Hassan Murad of the Mayo Clinic to perform the analyses.

Regarding vaccine strain selection for 2012-2013, the WHO Consultation and Information Meeting on the Composition of Influenza Virus Vaccines for the Northern Hemisphere 2012-2013 ran from February 20-22, 2012 and will conclude the 22nd, meaning that something should be known by the next day or soon afterward. Once WHO makes its recommendations, the individual countries that will be producing vaccines and their regulatory bodies decide what they are going to recommend. In the US case, this is the FDA. FDA Vaccine and Related Biologic Products Advisory Committee (VRBPAC) is scheduled for February 28-29, 2012 at which time the WHO recommendations will be considered.

Recommendations: Reiteration of Recommendations for Annual Vaccination for all Persons 6 Months of Age and Older

Lisa Grohskopf, MD, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Grohskopf indicated that currently, no new language, changes, or recommendations were being proposed to put to vote. The current recommendation will be reiterated for the time being, which is that annual influenza vaccination is recommended for all persons aged 6 months and older. No changes to the groups recommended for annual influenza vaccination are proposed at this time. Any proposed changes will be presented for discussion and vote and the June, 2012 ACIP meeting.

Discussion Points

Dr. Pickering asked how many times the Northern and Southern Hemisphere selection of vaccine strains had been similar. He also wondered whether there was any follow-up information on uptake and implementation of immunizing patients with egg allergies, and how successful that had been.

Dr. Grohskopf responded that she did not know how often the Northern and Southern Hemisphere strains had been similar, but it does occur. Regarding egg allergies, she did not

yet have any information on uptake. CDC is still in communication with its allergist colleagues, and understand that additional study data will probably be coming out over the next year or so regarding vaccination with egg-produced vaccines in allergic patients.

Dr. Baker thought that for patients with egg allergy, pediatricians and family practitioners would be much more likely to administer influenza vaccine. She wondered if those practitioners would be queried as well as the allergists.

Dr. Grohskopf replied that pediatricians and family practitioners would be included as well.

Dr. Bresee (SME) indicated that in the last 12 years, the recommendations from the Northern Hemisphere to Southern Hemisphere have changed maybe 3 or 4 times. Otherwise, at least one strain has changed.

Dr. Vasquez inquired as to whether any thought had been given to recommendations for protection of infants 0 to 6 months of age who currently cannot receive the vaccine themselves, but knowing that there is mounting data to show that if their mother is immunized, that is a way of protecting the infant.

Dr. Grohskopf responded that the current guidance is that the best way to protect these children is for their parents, caregivers, and others who have contact with them to be vaccinated. Given the current age indications for influenza vaccines, ACIP would not be able to make a recommendation for vaccination from a regulatory perspective. However, they will continue to follow the research. Currently, the advice in communications materials is to promote vaccination of caregivers for those in this age group as an important means of preventing them from getting infected.

Dr. Baker added that, similar to pertussis, pregnant women are immunized with influenza vaccine to prevent their enhanced morbidity. As far as protecting the newborn, she did not think there was a clear picture of whether it extended to age 5 and 6 months. Overall, it induces protection. The problem with immunizing infants after immunizing the mother is the issue of potential interference of maternal antibody. There has been considerable discussion about this with regard to pertussis.

Dr. Price (NMA) noted that many years were spent blasting the lack of penetration of adequate supplies of influenza vaccine into communities of need. He commended the unified efforts of many organizations, including ACIP, CDC, and CMS. After a somewhat late start, there were ultimately adequate supplies in communities of need. He expressed his hope that an effort would be made to have adequate supplies of the intranasal influenza vaccine in the coming season, given that it seemed to be taken up by clients much better because of the lack of using a needle. This is also true with the intradermal vaccine.

Dr. Keitel inquired as to whether uptake of the intranasal product was across all age groups that are recommended.

Dr. Price (NMA) replied that the Cobb Institute for NMA is involved along with CMS and CDC in an influenza education program. They do find that there is better acceptance among people who are covered fiscally for the vaccine. One of the problems with the adult population, even though they can be educated about the importance of a vaccine and the option of having intranasal, non-painful administration of vaccine, if they cannot pay for it, they get no vaccine at all. He expressed his hope that ACIP would address this moving forward.

13-Valent Pneumococcal Conjugate Vaccine (PCV13)

Introduction

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

Dr. Bennett introduced the pneumococcal session, noting that she had recently taken over as chair of the Pneumococcal Vaccines Working Group. As a reminder, 13-valent pneumococcal conjugate vaccine (PCV13) was licensed on December 30, 2011 for use among adults 50 years of age and older. The FDA approved this indication under the Accelerated Approval Pathway, which is a pathway that is used for products that address serious and life-threatening conditions. The licensure was based on non-inferior immunogenicity compared to PPSV23. In this case, immunogenicity is not a correlate of protection, but is rather a surrogate for assessing whether a vaccine works well. The indications are prevention of pneumococcal disease, including pneumonia and invasive disease, in adults 50 years of age and older; and prevention of disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. This approval was given with the caveat that there be a post-licensure randomized controlled trial of PCV13 against pneumococcal pneumonia among adults 65 years of age and older, and this trial is ongoing in the Netherlands.

The Pneumococcal Vaccines Working Group terms of reference are to:

- Review data on 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 determined that one including PCV13 recommendations for adults is necessary.

The working group has been presented with quite a bit of data on PCV13 for adults, including immunogenicity results from Phase III studies from Pfizer; immunogenicity data for PCV from published literature; and cost-effectiveness and public health impact of different adult pneumococcal vaccination strategies. Evidence that will not be available to help with decision-making, which has been very worrisome to the committee, includes efficacy against pneumonia, which will come from the Netherlands trial in approximately 2013; or the indirect herd effects of PCV13 use in children. Tremendous effects were observed from introduction of PCV7 in the child population on the elderly, and it is anticipated that similar effects will occur from PCV13, but it is too early to tell.

The working group has been engaged in applying the GRADE process to the PCV13 data, and decided to provide the GRADE evidence during this session for those over the age of 65 and for adults with immunocompromising conditions. The working group hopes by June 2012 to have a recommendation and potentially a vote on the use of PCV13 in immunocompromised adults, as well as an update on the indirect effects of PCV13 on adults from its administration in children.

In October 2012, the working group hopes to have an additional update on the indirect effects of PCV13 use in children, and by February 2013 to see a report on the CAPITA trial results as well as an update on the indirect effects of PCV13 use in children. By June 2013, the working group believes that there should be sufficient data to be able to make a recommendation about the use of this vaccine in those over the age of 65 years.

Considerations for Age-Based Recommendations for Pneumococcal Conjugate Vaccine for Adults: GRADE of Evidence

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Centers for Disease Control and Prevention

Dr. Pilishvili's presentation focused on considerations for age-based recommendations for 13-valent pneumococcal conjugate vaccine among adults. Invasive pneumococcal disease rates in adults have declined dramatically through indirect effects of the 7-valent conjugate vaccine use in children following 10 years of conjugate vaccine use among children. The incidence rate increases with increasing age and ranges from 8 cases per 100,000 among young adults to 68 cases per 100,000 among adults 85 years of age and older [CDC, ABCs, unpublished, 2012]. Currently, 23-valent pneumococcal polysaccharide vaccine is recommended by ACIP for all adults 65 years of age or older and adults 19 through 64 years of age with chronic and immunocompromising conditions [Advisory Committee on Immunization Practices, *MMWR* 2010].

The remainder of this session focused on reviewing the evidence to consider recommendations for the newly licensed 13-valent pneumococcal conjugate vaccine for adults. The working group applied the GRADE system to consider PCV13 recommendations for adults. The following steps were included in the process of evaluating a body of evidence and moving from evidence to recommendations:

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

First, the working group formulated a specific question to be answered by a recommendation, "Should PCV13 be administered routinely to all adults 65 years of age or older?" The target population was defined as adults 65 year of age or older, the intervention was a 13-valent pneumococcal conjugate vaccine (PCV13) administered as a single dose injection, and the control group was 23-valent pneumococcal polysaccharide vaccine (PPSV23). The rationale for focusing the key question on adults 65 years or older was that the disease burden remains in this age group with 1.4 million hospital days due to pneumococcal pneumonia[1] and pneumococcal pneumonia contributes to 15,000 invasive pneumococcal disease cases and 2,600 deaths[2]; current ACIP universal recommendations target this age group; and a clinical trial evaluating the efficacy of PCV13 against pneumococcal pneumonia currently is on-going in

the Netherlands that targets this age group [[1]Huang et al . Vaccine 2011; [2]Active Bacterial Core Surveillance, 2010].

The working group next identified and ranked the relative importance of health outcomes. In the selection of outcomes, the following questions were considered:

- Which outcomes are important or critical for making a recommendation?
- How important is each outcome to prevent?
- Are data available to evaluate each outcome?

Pneumococcal working members were queried and their responses were summarized. The working group members were asked to list relevant health outcomes, including both desirable and undesirable effects. Each member was asked to score the importance of each outcome. The average score for each outcome was used to determine the relative importance of each outcome. The possible options for summary ranking were:

- Critical outcome: should be included in the evidence profile
- Important but not critical: can be included in the evidence table if evidence for critical outcomes is missing
- Not important for decision making: should not be included in evidence base

The following outcomes were ranked as critical: invasive pneumococcal disease (IPD), pneumococcal pneumonia, hospitalizations, deaths, serious adverse events, and systemic adverse events. All critical outcomes were included in the evidence profile. Immunogenicity, office visits, local adverse reactions, and cost-effectiveness were ranked as important but not critical outcomes. From important outcomes, immunogenicity outcomes were included in the evidence profile because it was a criterion used for licensure and because data were missing for 3 out of 4 critical outcomes.

The working group next summarized relevant evidence for each outcome, including the number needed to vaccinate where possible, and assessed the quality of evidence for each outcome. For each outcome included in evidence profile, Dr. Pilishvili summarized the available evidence and assessed the quality of evidence. For the critical outcome of IPD, there was one double-blind, randomized, placebo-controlled. This was an efficacy trial among HIV-infected adults in Malawi (N=496). All enrolled subjects had recovered from documented IPD. In this trial, the intervention was 2 doses of PCV7 given 4 weeks apart. The vaccine efficacy against PCV7-serotype IPD was estimated at 74%. This estimate was statistically significant [French N, et.al. *N Engl J Med* 2010;362:812-22].

To answer the question regarding what effect might be expected based on these data among persons >65 years old in the US, the number of persons 65 years and older needed to vaccinate in order to prevent a single case of PCV13-type IPD was estimated. The rates of PCV13-type IPD were acquired from Active Bacterial Core surveillance data, which was the $Rate_{unvaccinated}$ (14 cases per 100,000 population[1]). Efficacy against PCV13-type IPD was assumed to be 74% (30%, 90%)[2] based on the trial in Malawi, and the upper and lower 95% confidence intervals were applied to the unvaccinated rate in order to estimate the rate among vaccinated, and to estimate the number needed to vaccinate. According to these estimates, over 9600 people 65 years of age or older would need to be vaccinated in order to prevent a single case of PCV13-type IPD. [[1]PCV13-type IPD rate among adults $\geq$65 years old in the US. CDC, ABCs, 2010; [2]French N, et.al. *N Engl J Med* 2010;362:812-22]. The caveat in this estimation is that the number needed to vaccinate is estimated based on efficacy versus

placebo. In the trial in Malawi, the comparison was a placebo. The number needed to vaccinate would be higher if compared to PPSV23. The results of the sensitivity analyses that were conducted using the 95% confidence intervals addressed some of these caveats.

The body of evidence for each outcome was categorized into four types / four levels of quality which reflect the confidence in the estimated effect of vaccination on each health outcome:

1. Randomized controlled trials, or overwhelming evidence from observational studies.
2. Randomized controlled trials with important limitations, or exceptionally strong evidence from observational studies.
3. Observational studies or randomized controlled trials with notable limitations.
4. Observational studies with important limitations, or randomized controlled trials with several major limitations, or clinical experience and observations.

RCTs initially are classified as evidence type 1, and observational studies as evidence type 3. Five GRADE criteria are used for moving down the quality of evidence: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Indirectness was a major factor for moving down the quality of evidence for all outcomes included in this evidence profile. For the critical outcome of invasive pneumococcal disease, one RCT was included, which was downgraded from type 1 to type 3 due to indirectness. Evidence can be considered indirect in the following four situations: 1) the population that participated in studies may differ from the population of interest, 2) the vaccine that was evaluated may differ from the vaccine of interest; 3) the outcome that was assessed may differ from that of primary interest; or 4) the primary interest is head-to-head comparisons of the 2 vaccines, but instead one vaccine was compared with placebo. For the IPD outcome and one RCT included in the evidence profile, the limitation due to indirectness was considered "very serious" due to the fact that the study was conducted in HIV+ adults in Malawi[1]; the efficacy of 2 doses of PCV7 were evaluated when given 4 weeks apart; and, most importantly, the study included as a comparison group a placebo and not PPSV as in the policy question under consideration. Given that the efficacy of PPSV among older immunocompetent adults ranges from 50% to 80%[2] according to studies, the efficacy estimate of 74% would be an overestimate if it was employed as a comparison a group vaccinated with PPSV [[1]French N, et.al. *N Engl J Med* 2010;362:812-22; [2]ACIP Recommendations for PPSV23, 2010].

For the critical outcomes of pneumococcal pneumonia, hospitalizations, and deaths due pneumococcal disease, no data were available. The missing data on a critical outcome of pneumococcal pneumonia did not contribute to estimation of the overall quality of evidence, but was considered in decision making. Though there are no data available on the clinical efficacy of PCV13 against pneumonia in adults, the trial currently being conducted in the Netherlands is a randomized, placebo controlled trial in 85,000 community-dwelling, pneumococcal vaccine naïve adults ≥65 years. The primary objective of the study is to determine the efficacy against the first episode of vaccine serotype community-acquired pneumonia (CAP). The secondary objectives include efficacy against non-bacteraemic VT CAP and VT IPD, all pneumococcal CAP, and death. The results of this study are expected in 2013.

Next, the working group reviewed evidence for the critical outcome of serious adverse events. The results of safety studies were included from PCV13 Phase III trials. Overall incidence of reported SAEs was low, ranging between 0.2% and 1.1%, with no differences reported between the treatment groups among both PPSV23 naïve and pre-immunized subjects. Death occurred in 16 subjects in the 8 studies, with more than 6000 subjects enrolled. None of the deaths were considered vaccine-related. Significant differences in the incidence of systemic adverse events

between the 2 treatment groups were reported in 2 out of 3 Phase III studies, for the outcomes of fatigue, rash, new generalized muscle pain, and use of medications to treat fever. A significantly lower proportion of these events occurred following PCV13 receipt compared to post-PPSV23 [Presented by Pfizer during the February 2011 ACIP meeting]. For the critical outcome of serious and adverse events, the evidence quality was judged to be type 1 because no serious concerns were noted due to biases, inconsistency, indirectness, or other considerations.

Antibody response to PCV or immunogenicity was ranked as an important outcome. While demonstration of non-inferior immunogenicity was a major criterion for licensure, the lack of a correlate of protection in adults was an important limitation of the available studies to be able to use this outcome as a substitute for clinical outcomes. The studies included in the evidence base utilized different assays (ELISA versus. OPA) and analytic methods; and differed in populations studied by age group, presence of comorbidities, and previous vaccination status.

In the evidence for immunogenicity outcome, 2 Phase III immunogenicity studies of PCV13 and 4 published PCV7 studies were included. The detailed results of these studies were presented to ACIP by Pfizer during the February and October 2011 meetings. The first study (004) included 740 pneumococcal vaccine naïve adults 60 to 64 years of age. Comparisons between the treatment groups after a single dose of PCV13 versus a single dose of PPSV23 showed that PCV13 resulted in a statistically superior response compared to PPSV23 for 9/13 serotypes, and a response as good as that of a PPSV23 for 4/13 serotypes. The second study (3005) included 924 adults 70 years old or older who received PPSV23 >5 years prior. Comparisons between the treatment groups after a dose of PCV13 versus a dose of PPSV23 showed that response post-PCV13 was superior compared to PPSV23 for 11/13 serotypes, and response was as good as post-PPSV23 for 2/13 serotypes.

Regarding the 4 published immunogenicity studies of PCV7 included in the evidence profile, in the studies by Goldblatt (2009) and deRoux (2008), comparisons between the treatment groups after a single dose of PCV7 versus a single dose of PPSV23 showed that PCV7 resulted in a statistically superior response compared to PPSV23 for some or most serotypes, and the response was as good as that of a PPSV23 for some serotypes. The studies by Ridda (2009) and Miernyk (2009) showed that response post-PCV13 was similar to PPSV23 for 4 out of 4 serotypes evaluated. Comparisons for the remaining 3 serotypes were not done in these studies. For the outcome of immunogenicity, which included Phase III PCV13 studies and published immunogenicity studies of PCV7, the evidence quality was judged to be type 2. Lack of defined correlates of protection and the lack of clearly superior immunogenicity prevented the working group from extrapolating individual benefits used for licensure to population benefits needed for recommendations.

The working group next determined the overall quality of evidence across all outcomes. The overall evidence type is a combined evidence type across all outcomes considered critical for a recommendation. Because only critical outcomes should be considered, in this case, quality of evidence for a single outcome of IPD determined the overall evidence quality. Data were not available for the three other critical outcomes, so the overall evidence type defaulted to the quality of evidence type for the IPD outcome, which is based on one study with limitations when applied to the key question under consideration. In spite of the vast amount of immunogenicity data evaluated, immunogenicity outcome was not considered to be critical, so the overall quality of evidence had to be based on one study and one critical outcome and the low quality of evidence for that outcome, so the overall evidence was judged to be type 3.

The working group then reviewed results of health economic studies. There were two independent models that evaluated the cost-effectiveness and public health impact of PCV13 for adults[1,2]. Both of these studies previously were presented to ACIP. These models showed that PCV13 in adults could be highly cost-effective. Both models relied heavily on assumptions about the indirect effects of PCV13 on non-bacteremic pneumonia and PCV13 efficacy against pneumonia. The current PPSV strategy is favored if PCV13 effectiveness is low against non-bacteremic pneumonia. The results were sensitive to assumptions regarding PCV13 effectiveness against non-invasive pneumonia, PPSV effectiveness against IPD and herd immunity effects on the likelihood of PCV13-type disease [[1]Smith et al. JAMA 2012 in press; [2]Weycker et al. Manuscript in preparation].

Next, the working group assessed the balance of risks and benefits and determined the recommendation category. The answers to the following 4 questions were considered to determine the recommendation category, and the working group members reached a general consensus on the answers to each of these questions:

1. Is the quality of available evidence considered to be lower? The working group concluded that the evidence is of low quality due to limited data on efficacy against IPD (only one RCT in HIV+ in Malawi, and placebo-controlled) and missing data on PCV efficacy against other critical outcomes, in particular against non-invasive pneumonia.
2. Is there uncertainty about the balance of benefits versus harms? The working group concluded that uncertainty existed because indirect effects of PCV13 use in children may reduce the potential net benefits of PCV13 use in adults, and there is uncertainty about PCV13 effectiveness against non-invasive pneumonia in adults.
3. Is there high variability or uncertainty in relative importance assigned to outcomes? There was low variability and no uncertainty in relative importance assigned to health outcomes. The working group members assigned high values to all the critical outcomes, and there was a consensus reached on which outcomes were considered critical to prevent.
4. Is there uncertainty about whether the net benefits are worth the costs? The working group felt that there was an uncertainty about whether the net benefits are worth the costs.

After considering the answers to the above questions, the working group reached a consensus that no recommendation would be issued at this time for routine PCV13 use among older adults because critical data to help with decision making are not yet available.

In addition to the outcomes evaluated, the working group also considered an additional and very important key factor that is not clearly accounted for by GRADE process; that is, the indirect effects of pediatric PCV13 program may reduce the proportion of adult IPD caused by PCV13 types, and that the net benefits of PCV13 use among adults would be reduced.

With regard to trends in incidence of IPD among adults 65 years of age and older, introduction of the 7–valent conjugate vaccine in children in the late 2000 has led to near elimination of IPD caused by PCV7 types among adults. Incidence of IPD caused by 6 serotypes has increased. The 13-valent vaccine replaced the 7-valent for use in children in mid-2009. This raises the question regarding what should be expected in terms of the potential indirect effects of PCV13 use. The early effects of pediatric use of PCV13 on rates of IPD among young children are already being observed. 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 beginning of 2011, statistically significant reductions were already observed in the incidence of PCV13-type IPD. These data demonstrate that the 13-valent conjugate vaccine is working as expected in children [Active Bacterial Core surveillance (ABCs), unpublished].

The early impact of pediatric PCV13 program on disease rates among adults was also examined among adults by age group. Although it may still be early to expect significant reductions in adult IPD, among adults 65 years of age and older for most calendar quarters in 2010-2011, compared to the same quarters before PCV13 introduction (2006-2008), some reductions were observed. However, these changes were not statistically significant. Among adults 18 through 49 years of age, more consistent reductions are being observed for all quarters by late 2010 and for all quarters in 2011. This was expected, given that the earliest reductions post-PCV7 implementation were observed among adults in this age group.

In summary of what should be expected in terms of the indirect effects of PCV13 on invasive disease, it is known that PCV7 introduction led to near elimination of PCV7-type IPD among adults of all age groups. There were significant declines in PCV13-type IPD in children within the first year post-PCV13 introduction. There is possible early evidence of declines in PCV13-type IPD in adults. Recent data show that PCV13 prevents colonization with PCV13 serotypes[1,2]. A key point is that indirect effects of PCV13 on adult IPD are likely to be observed [[1]R. Cohen, ICAAC 2011; [2]A. Desai, ISPPD 2012].

The working group concluded that at this time, the available evidence is insufficient to recommend routine use of PCV13 among older adults, and that the critical data elements needed to make a recommendation are not available at this time. The impact of indirect effects of PCV13 use in children on serotype distribution of adult pneumococcal disease is unknown and there are no data on the clinical efficacy of PCV13 against non-invasive pneumonia in adults. Despite the vast number of immunogenicity studies showing that PCV13 is immunogenic in adults, the clinical relevance of these data is not clear without defined correlates of protection. Cost-effectiveness studies show that PCV13 may be cost-effective when used among adults; however, the studies rely heavily on assumptions of efficacy against pneumonia and potential herd effects of the pediatric PCV13 program.

In terms of next steps, the Pneumococcal Working Group will continue to evaluate the relevant data as these become available, and will continue updating the committee during the upcoming ACIP meetings. Within the next month, the working group will publish a brief note in the *MMWR* to inform readers about the licensure of the vaccine for adults 50 years of age and older; summarize the available evidence which led to the licensure of the vaccine; outline the working group decision to wait with universal adult recommendations until more evidence is available; and outline plans for future ACIP deliberations. The working group will revisit the question of age-based recommendations as additional data become available.

Discussion Points

Dr. Keitel called attention to steps 7 and 8 for determining the recommended category, “Is there uncertainty about the benefits versus harms and burdens?” She wondered whether the working groups should view this in the context of PCV13 versus PCV23. One way to look at this is that if PCV13 is used, adults may be left unprotected against serotypes that are not contained in another vaccine that has shown efficacy against invasive pneumococcal disease. She also requested that Dr. Pilishvili comment on the CAPTA trial for the US where children are routinely immunized for PCV13.

Dr. Pilishvili replied that the CAPITA trial would offer key information regarding the efficacy of 13-valent vaccine against non-invasive pneumonia. There is more consensus that the currently licensed 23-valent polysaccharide vaccine is effective in preventing invasive disease, but there

is definitely less consensus that the vaccine is effective against non-invasive pneumonia. Non-invasive pneumonia accounts for a higher burden of disease, especially in the age groups of interest. This is where the effect on the net benefits came into play in the working group's decision making, that if efficacy is shown against non-invasive pneumonia, the net benefits would clearly be larger and would outweigh the harms and burdens.

Dr. Sawyer asked whether the level of evidence would need to be downgraded based on the indirectness of the evidence in the Netherlands to the population in the US.

Dr. Pilishvili responded that one of the strongest points for downgrading evidence with respect to the Malawi trial was the comparison group for the outcome of invasive disease. The working group believed that the comparison group of a placebo would clearly over-estimate the efficacy if it was compared to PPSV23. That is because there is evidence to suggest that PPSV23 may be as effective as 50% to 80% against invasive disease. There is less consensus that PPSV23 will be efficacious against non-invasive pneumonia. So, having that placebo comparison in a trial with a pneumonia endpoint would be less of a limitation and would not lead to downgrading of the evidence.

Dr. Baker inquired as to whether the Netherlands has the same schedule as the US for PCV13 for children. This could be confounding.

Dr. Whitney from the Reparatory Diseases Branch (RDB) replied that the Netherlands has good vaccine coverage of children, and they have been switching from vaccine to vaccine. They began with PCV7 and were now on PCV10. The situation would be somewhat similar in that they use a 2+1 schedule, and they have good coverage with even the third dose, so it is a similar population.

Dr. Poland (ACP) noted that one other factor to consider is that the studies referenced for efficacy were in relatively short time periods after immunization. The problem suffered in adult medicine with use of the polysaccharide vaccine is that with few exceptions, adults receive the vaccine one time. If they live to 85 years of age, this leaves 20 years of hoping that a polysaccharide vaccine is going to protect them. This is not modeled in the data presented by Pilishvili and was not likely to be addressed by the study mentioned.

Dr. Pilishvili said she presumed Dr. Poland was referring to the immunogenicity studies that were included with the comparisons of one vaccine to the other. The follow-up period is 4 to 6 weeks, which is a relatively short period of time. The data from the Phase III trials of PCV13, which also had comparisons between the 13-valent vaccine and PPSV23, show that the antibodies do come down following each vaccine, more so for one than the other. It remains unknown how the antibody level translates into clinical protection, and whether one is more likely than the other to continue to offer protection.

Given the complicated issues, Dr. Duchin emphasized the need to continue to conduct studies after vaccines are licensed. For example, he could imagine that a vaccine like PCV13 may protect against invasive disease and, with luck, against non-invasive pneumococcal pneumonia in the first few years after vaccination. Subsequently, susceptibility to non-invasive pneumococcal pneumonia may return. Therefore, following these patients out for a number of years is desirable.

Dr. Tan (AMA) emphasized that one way the evidence is developed is when a vaccine is used. Therein lies a certain amount of paradox. He asked Dr. Pilishvili to comment on any other studies that would shed light on the age group 50 years and older with regard to PCV13. He also requested that she comment on the data that the working group reviewed versus what the FDA reviewed with regard to their approval of the indication of 50 years of age and older. There does not seem to be a clear timeline. There is an FDA-approved vaccine for 50 years of age and older that physicians are beginning to hear about, but there is no ACIP recommendation that is clearly visible coming down the pipeline. It would be helpful to inform physicians.

Dr. Pilishvili replied that data the FDA used to license the vaccine is the same that the working group has been evaluating over the past year, and is the same data that was included in the evidence base. For the particular key question the working group was considering for GRADE, only a subset of data was extracted to address a single dose of one versus the other. That is, while only a subset of the data was used for GRADE, the working group did review all of the data that was presented to FDA for licensure. The working group is aware of the fact that the vaccine is licensed, but at the same time feels that ACIP's role is to use the evidence in order to develop the best recommendations for use of the vaccine that will result in the maximum public health impact. The working group does not feel at this time that there is sufficient evidence to recommend the vaccine. Regarding the question about forthcoming data on the 50 and older age group, the studies presented to the working group from the FDA included this age group. The rationale was presented for why the working group focused on 65 years of age and older, but even if they had evaluated the same question for those 50 years of age and older, the same evidence base would have been used and that would not have changed the conclusion of the working group in terms of the age-based recommendations. Regarding on-going studies, the two key pieces of evidence that are missing are the CAPITA trials in the Netherlands for which there should be data in 2013, and the herd effects data that will continue to be evaluated through ABCs data. This is more or less real-time data from which the impact of the pediatric PCV13 program can be observed on the change in distribution on the serotypes causing adult disease.

Dr. Baker requested clarification about whether by "non-invasive pneumonia" Dr. Pilishvili meant pneumonia that is not accompanied by bacteremia, given that pneumonia by definition is invasive. Dr. Pilishvili answered affirmatively.

Dr. Paradiso (Pfizer) reported that the Netherlands uses the PCV10 vaccine from GSK. They began with PCV7 and transitioned to PCV10. It is an infant program, but it is not with Prevnar 13®, so there would be less herd effect in that population. Regarding the issue of placebo control trials in some of these populations, the trial that was conducted in Malawi by Dr. French was a follow-up to a trial that was conducted in Uganda with the polysaccharide vaccine, also in an HIV-positive adult population, 5 or 6 years prior to that. The Uganda trial actually showed negative efficacy of the polysaccharide vaccine; that is, it was worse to receive the polysaccharide vaccine than to not. When Dr. French decided to conduct the trial with PCV7, it was not possible to use a polysaccharide control in that group because it was considered unethical by the ethics committee, so it had to be a placebo controlled trial. While there is not a direct comparator in that trial, it was conducted by the same investigator and was fairly comparable to that. In those 65 years of age and older, morbidity from pneumonia and hospitalizations and invasive disease is quite substantial. The majority of people in that age group already have been vaccinated with a polysaccharide vaccine, and there is currently no recommendation for them to be revaccinated. Dr. Paradiso suspects that at least 50% of disease in that population is in that group, because it includes many of people who were vaccinated at some point. The data from the 3005 trial shows the immunogenicity, both priming

and boosting, of the conjugate of vaccine in this population of people over 65 years for which there is not currently a recommendation. He was interested in knowing whether the working group considered this to be a high risk population. Because there is not a recommendation, there is not a comparator since that group is at risk. The data Pfizer presented during the last ACIP meeting pertained not only to the quantity of immunogenicity following a dose, but also to the quality of that response. The quality of the response observed with the conjugate vaccine has been demonstrated repeatedly in terms of protection against invasive disease and pneumonia, with response that are quite comparable to what is observed in children and adults with efficacy.

Dr. Pilishvili responded that the working group considered all adults and assessed those at highest risk. Among the general population of adults, those 65 and older and even 85 and older are at higher risk. However, in terms of the herd effects of PCV7 use, those 65 and older and 85 and older have benefitted as well. In terms of the gaps, the next presentation by Dr. Dooling would show the rationale as to why, based on the burden of disease and the potential herd effects that are expected in various groups, adults with immunocompromising conditions are clearly at a much higher risk. Those 65 years of age and older do benefit from herd effects, and are at medium risk compared to those with immunocompromising conditions. Adults with immunocompromising conditions will be the next focus of the working group.

Dr. Paradiso (Pfizer) said his point was that this was the only group that would benefit from the herd effect over time, even though the burden is current.
Dr. Pilishvili replied that those 65 years of age and older are expected to benefit from herd effect, but that is not the only consideration for waiting. The other consideration for waiting is lack of data on efficacy against pneumonia.

Regarding Dr. Paradiso's comments about the quantity and quality of the antibody response, Dr. Baker requested clarity regarding whether he was assuming functionality measured by OPA.

Dr. Paradiso (Pfizer) replied that it was all based on functionality measured by OPA. The response to the first dose wanes over time and then boosts either by a second dose of the conjugate or a dose of polysaccharide. Giving conjugate vaccine before PPS23 results in a much better response to the polysaccharide vaccine.

Dr. Keitel added that the data appeared to show that the boost with the polysaccharide results in a significantly better response than with a second dose of conjugate.

Dr. Paradiso (Pfizer) responded that a first dose is given of the conjugate followed by a dose of either the conjugate or the polysaccharide 3 or 4 years later. With a second dose of conjugate, the response was at least as good as the first dose and for the majority was higher. With a second dose of polysaccharide, the response was the same only it was even higher than the booster response to the conjugate vaccine for half a dozen or so subjects. This is probably because the first dose primed for memory cells and booster response, which was then followed by 25 mg of polysaccharide, which is a large bolus that really boosts the immune response to 5 to 10 times more than would have been achieved with the polysaccharide and much more than two doses of polysaccharide.

Following up on what Dr. Tan said, Dr. Decker noted that the working group has been very thorough and very careful, which is commendable. However, he was struck by the fact that nevertheless, life goes on in medical practices in which people present at age 65 every day and are given polysaccharide vaccines which are known to exhaust the B-cell component, will provide short-term protection, and will render them incapable of boosting. Meanwhile, there is a conjugate vaccine in the marketplace. Although the conjugate covers only 13 of the 23 serotypes, with respect to at least those 13 serotypes, it will amplify rather than destroy the B-cell component and will enable them to be boosted. He was very troubled by not giving clear-cut guidance as early as possible about this, because the polysaccharide vaccines are wonderful when that is all there is, but once the conjugates became available, he did not think they should be using the polysaccharides.

Dr. Baker requested that Dr. Sun comment on the presentation on pneumococcal conjugate vaccine and accelerated approval through the FDA for licensure or approval.

Dr. Sun (FDA) indicated that there are really only three ways that vaccines are approved in the US: 1) traditional approval, 2) accelerated approval, and 3) an animal rule. No vaccines have been approved by animal rule yet. A number of vaccines have been approved through accelerated approval, all of which were influenza vaccines. During the shortage, this mechanism supported the increase of the number of available vaccines on the market. Approval of Prevnar 13® in those 50 years of age and older is the first bacterial vaccine to be approved under the accelerated mechanism. In order to apply for accelerated approval, a vaccine has to address a serious and life-threatening illness, which pneumococcal pneumonia and invasive disease in the elderly are. It also has to offer a meaningful therapeutic benefit over existing treatment. The existing treatment in this case is Pneumovax 23®, and its effectiveness against bacteremia pneumonia is controversial. The study conducted must be adequate and well-controlled study demonstrating safety and effectiveness based on a surrogate. This is a departure from what has been done with previous bacterial vaccines. In this case, the surrogate is an immunologic assay, which is a functional assay. The FDA has determined that this is relatively likely to predict clinical benefit. It is not an absolutely correlated. As part of the approval, the manufacturer is required to conduct a clinical endpoint study with due diligence. Usually, these studies are already on-going at the time of the approval, which is true in this case. The overall point is that if a vaccine is approved under this mechanism, in the GRADE system, it will not have the typical clinical data that shows prevention of disease. This may be an issue for ACIP.

Dr. Schaffner (NFID) requested information about what would occur if a clinical trial cannot be completed for some reason or does not demonstrate efficacy.

Dr. Sun (FDA) replied that the FDA has the authority to withdraw the approval.

Dr. Pickering asked whether this approval pathway would ever be used for a vaccine that does not have clinical data in a population.

Dr. Sun (FDA) replied that this would depend upon the surrogate. This is a mechanism to approve vaccines for which there are no clinical endpoint data.

13-Valent Pneumococcal Conjugate Vaccine Use in Adults With Immunocompromising Conditions: GRADE of Evidence

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Dr. Dooling's presentation focused on considerations for use of 13-valent pneumococcal conjugate vaccine among adults with immunocompromising conditions. The policy question considered by the working group was, "Should ACIP recommend 13-valent pneumococcal conjugate vaccine (PCV13) for immunocompromised adults?" Given that the working group consensus was to wait for additional evidence before making an age-based recommendation, a question regarding why a risk-based recommendation might be made at this time might arise.

There are three reasons to consider a recommendation for PCV13 for immunocompromised persons at this time. The first reason is the very high incidence of invasive pneumococcal disease in adults with immunocompromising conditions. 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. The second reason to consider a risk-based recommendation is that these data demonstrate high rates of disease for immunocompromised persons despite the indirect effects of PCV7. Rates of PCV7-type IPD in this population are several-fold higher than those among immunocompetent persons. Finally, in contrast to the age-based policy question for which a clinical trial is pending, in HIV-infected patients there is already a published clinical trial and no additional data are expected in the near future.

The GRADE process followed by the working group to evaluate evidence for this question was the same as that presented in the previous presentation. To reiterate, first, the working group formulated a specific policy question and then identified and ranked the relative importance of the outcomes. Next, summarized all evidence for critical and important outcomes was summarized, including number needed to vaccinate where possible, and assessed the quality of evidence for each outcome. Once that was complete, the working group summarized the quality of evidence across all outcomes. After a review of health economic data, the next step was to assess the balance of risks and benefits and determine the recommendation category.

As previously noted, the policy question to be GRADED was, "Should PCV13 be administered routinely to adults with immunocompromising conditions?" The population under consideration was adults 18 years of age and older with immunocompromising conditions. The intervention the working group evaluated was PCV13 administered as a single dose. The control or comparison group was PPSV23 recipients.

The next step was to decide which disease outcomes should be considered and the relative importance of preventing each of them. The working group agreed that IPD, pneumococcal pneumonia, hospitalizations, deaths, and serious and systemic adverse events were all outcomes of critical importance. Unfortunately, as with the previous presentation, there were no data available to evaluate pneumococcal pneumonia, hospitalizations, or deaths. Although immunogenicity was deemed by the working group to be important, but not critically important, it was included in the evidence profile.

The next steps in the GRADE process were to summarize all existing evidence for critical and important outcomes, including number needed to vaccinate where possible, and then to assess the quality of evidence for each outcome. Dr. Dooling repeated these steps for each of the four outcomes considered.

As previously indicated, there was only one study that evaluated the critical outcome of IPD defined by isolation of pneumococcus from a normally sterile site. This was a double-blind randomized placebo-controlled trial among HIV-infected adults in Malawi. All 496 enrolled subjects had recovered from documented IPD. Study participants were given 2 doses of PCV7 4 weeks apart as opposed to the GRADE intervention of 1 dose of PCV13. The vaccine efficacy against PCV7 serotype IPD was 74%, and this was statistically significant [French N, et.al. *N Engl J Med* 2010;362:812-22].

In order to calculate the number needed to vaccinate, the working group applied the efficacy of PCV7 from the Malawi RCT to the US incidence of IPD in HIV-infected adults. An estimated rate of 64 IPD cases with HIV/100,000 persons with AIDS was used based on 2007 data. Assuming 74% efficacy and 100% coverage, the working group estimated a rate of 17 cases per 100,000 in vaccinated HIV-infected people. Therefore, the estimated number needed to vaccinate to prevent one IPD case would be 2011.

The fourth step in the GRADE process is to assess the quality of evidence for each outcome. RCTs or overwhelming evidence from observational studies are considered the highest level of evidence and are scored as a 1. RCTs with important limitations or exceptionally strong evidence from observational studies are scored as a 2. RCTs with notable limitations or observational studies are given a 3. RCTs with several major limitations, observational studies with important limitations, or clinical experience and observations are given the lowest grade of 4.

In order to grade the evidence type for the critical outcome of IPD, several factors were considered. There were no serious concerns with study design, bias, or imprecision. The working group felt that there were very serious concerns, however, with indirectness or generalizability of the results because the population studied was in Malawi, only IPD survivors were recruited for the study, and only 13% of the participants were on anti-retroviral therapy. Additionally, PCV13 is licensed for a single dose in adults in the US and the intervention used in the study was 2 doses of PCV7. Recall that the initial policy question concerned all immunocompromised adults; therefore, the working group had additional concerns with extrapolation of the Malawi trial results to HIV negative immunocompromised population.

The next critical outcome evaluated was serious adverse events. As presented in the previous presentation, Phase III studies found only 0.2 to 1.1% serious adverse events, with no difference between treatment arms and no deaths considered to be vaccine-related. These results are also from Phase III trials presented previously, and there was no increased incidence of systemic adverse effects in PCV13 recipients. In fact, there was a significantly reduced risk of fatigue, rash, generalized muscle pain, and treated fever in PCV13 recipients compared to PPSV23 recipients [Phase III studies, presented at February 2011 ACIP].

In addition to the Phase III trials, immunogenicity and adverse events of the 7-valent conjugate vaccine have been evaluated in published RCTs. The three studies considered (e.g., Penaranda, Lesprit, and Feikin) showed no statistically significant difference in systemic adverse events following immunization.

To evaluate the quality of evidence for the critical outcome of serious and systemic adverse Events, 6 RCTs were considered in total. The only serious concerns involved indirectness because the Phase III clinical trials were not done in an immunocompromised population and the published studies were done using the 7-valent conjugate vaccine as opposed to the 13-valent vaccine.

The working group next went on to grade the important outcome of immunogenicity. Four published studies in HIV-positive subjects were considered. All studies were conducted in high income countries with subjects who had CD4 counts of at least 200. Response to a single dose of PCV7 was non-inferior or superior to PPSV23 at all time points studied [Feikin 2004, USA; Lesprit 2007, France; Penaranda 2010, Spain; Crum 2010, USA].

The randomized controlled trials of immunogenicity were used for FDA licensure and were presented in the previous talk (e.g., 004 and 3005). They show that in the HIV-uninfected adults over 60 years old, PCV13 is equal to or better than PPSV23 in generating antibodies to the serotypes they share [Presented by Pfizer at February 2011 ACIP].

Thus, the quality of evidence for the important outcome of immunogenicity varied based on the population under study. The 4 published immunogenicity studies used PCV7 instead of PCV13; therefore, the working group had serious concerns regarding the indirectness of the intervention. The Phase III trials were not carried out in an immunocompromised population; therefore, the working group had very serious concerns about the indirectness of the study to the population of interest. All studies suffered from the absence of an established clinical correlate of protection. Ultimately, the evidence type assigned by the working group for this outcome was 2 and 3.

Having considered the quality of the evidence for each outcome, the working group next summarized the quality of evidence across all outcomes. The quality of evidence for all outcomes considered ranged from 2 to 3. For the critical outcome of IPD, the evidence type was 2 / 3. Therefore, the working group assessed the overall evidence type to be 2 / 3.

The next step in the GRADE process was to review the health economic data. As presented previously, the economic models demonstrate that PCV13 could be cost-effective, but the models are sensitive to assumptions regarding PCV13 effectiveness against non-invasive pneumonia, PPSV effectiveness against IPD, and indirect effects. No models have considered the immunocompromised population specifically.

The final steps the working group completed included an assessment of the balance of risks and benefits of vaccination and a determination of the recommendation category. In order to determine the recommendation category, the working group considered 4 questions:

1. Is the evidence quality “Lower“? Yes. The working group thought that the very serious concerns with indirectness, as well as a lack of evidence for critical outcomes, meant that the overall level of evidence was low.

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

3. Is there variability or uncertainty in what is important? No. The working group reached consensus regarding critical outcomes.

4. Is there uncertainty about whether the net benefits are worth the costs? Yes. In this case, there is still uncertainty regarding the cost-effectiveness of PV13 relative to PPSV23.

Ultimately, these considerations led the working group to propose a Category B recommendation meaning that the desirable consequences probably outweigh the undesirable consequences.

The working group concluded that there remains an extremely high burden of pneumococcal disease among immuocompromised adults. The GRADE process led the working group to conclude that PCV13 is effective in this group and that benefits likely outweigh harms. Unlike age-based recommendations, no additional RCT data is expected to influence GRADE conclusions for the immunocompromised group. Finally, the indirect effects of PCV13 use in children are unlikely to eliminate PCV13 serotypes from the immunocompromised adult population.

The next steps for the working group include grading of the evidence for PCV13 followed by PPSV23 compared to PPSV23 alone. They must also address the issues of timing and interval, as well as the optimal sequence, if two pneumococcal vaccines are to be recommended for this population. Additionally, the working group must reach consensus regarding exactly which conditions shall be considered immunocompromising. Before the next ACIP meeting in June 2012, the Pneumococcal Working Group plans to draft recommendation language for a possible vote.

Dr. Dooling concluded with the following questions for ACIP members:

- ❑ Do ACIP members agree with the working group's GRADE evaluation of the evidence supporting a recommendation for use of PCV13 in immunocompromised adults?

- ❑ What additional issues should the working group consider before bringing a recommendation for a vote?

Discussion Points

Dr. Baker inquired as to whether a cost-effectiveness analysis had been done for this group, and if not whether there was a plan to do so by the June 2012 ACIP meeting.

Dr. Dooling replied that a cost-effectiveness analysis had not been undertaken for the immunocompromised population specifically. One thing that would vary in this group would be the increased incidence of disease, but the model would likely still be sensitive to several factors, including PCV13 effectiveness against non-invasive pneumococcal pneumonia; PPSV23 effectiveness against IPD, which has certainly had mixed results in the literature; and the indirect effects that are likely to have some effect in reducing disease in the immunocomprised population, but certainly not in eliminating disease. There is no plan to conduct a cost-effectiveness analysis before the June 2012 ACIP meeting, but this could be taken into consideration.

Regarding the critical outcome of IPD and vaccine efficacy of 74%, Dr. Coyne-Beasley pointed out that the confidence interval for vaccine efficacy was between 30% to 90%, which is quite large. She wondered whether the working group varied its assumptions based on what the efficacy could be, and whether this would change their final recommendation.

Dr. Dooling replied that the confidence interval does vary from 30% to 90% around the point estimate of 74%. There were only 493 participants in the trial; therefore, the power effects led to a large confidence interval. The number needed to treat on the two broad ends of the confidence interval were not presented, but the range was shown on Slide 11: NNV = 2,011 (1,736 to 5,208). The recommendation did not change based on the range.

Dr. Sawyer asked Dr. Dooling to help him understand the expected impact of indirect effect in the immunocompromised adult population compared to the 65 and older population, and whether that was based on the observations with PCV7 indirect effect or if it was a theoretical consideration.

Dr. Dooling responded that there was a study by Cohen et al that shed light on that particular question. This study compared adults with HIV infection to adults without HIV infection following the introduction of PCV7 in 2000. There was a fairly precipitous decrease in all serotype disease, but primarily in the conjugate vaccine serotype disease in adults with and without HIV infection [Cohen, AIDS 2010;24(14):2253-62]. In 2007, after the indirect effects are presumed to have been fully realized, the incidence in HIV-infected individuals was still 64 / 100,000; whereas, in the adult population without HIV infection, the incidence had decreases to nearly non-existent for vaccine serotype disease.

Regarding whether there were other considerations for the working group, Dr. Poland (ACP) indicated that the American Society of Hematology (ASH) has a group that issues bone marrow transplant guidelines; that group already has recommended PCV13. Most tertiary care medical centers that are doing high volume solid organ transplants already have this as part of their protocols. There is at least one professional society that will soon release some recommendations. At a minimum before June 2012, it would be helpful for ACIP to offer some interim guidance with a layout of the data and evidence, even if it is to acknowledge that a decision will be made in the June timeframe.

Dr. Middleman (SAHM) wondered whether the population was ≥18 or ≥19, because there is already a recommendation for those through the age of 18.

Dr. Dooling replied that the pediatric recommendations include high risk people up to 19 years of age. The working group will make sure that this is clear and is not overlapping.

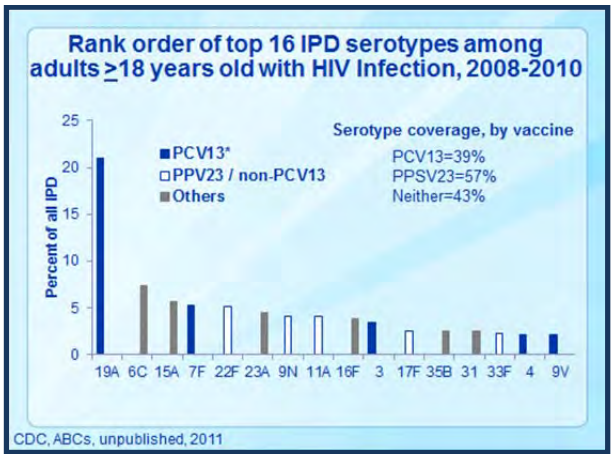
Dr. Keitel asked Dr. Poland whether the groups he mentioned made any comments about the use of 23-valent vaccine relative to the PCV13 vaccine.

Dr. Poland (ACP) responded that while he could not speak to all of them, ASH did. ASH has a series, following a bone marrow transplant, of PCV13 and PPSV23.

Dr. Baker added that her understanding was similar, but that there were differences between centers.

Dr. Foster (APhA) said he was not getting a clear picture of the serotypes that cause disease in the over 64 year old age group.

Dr. Dooling replied that the serotype distribution is slightly different for the HIV-infected and non-HIV-infected groups. 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 PCV13 is about 39%, while disease due to all PPV23 serotypes accounts for approximately 57%. Disease caused by a serotype not in either vaccine is about 43%. 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. Therefore, it is possible that PCV13 could provide protection against an additional 8% or if cross-coverage is good [Cooper, Vaccine 2011;29(41):7207-11)]. The following represents the rank order serotype distribution of the top 16 serotypes:



Dr. Foster (APhA) said his assumption was that they were talking about using this in addition to rather than in place of 23-valent PPSV.

Dr. Dooling replied that those options are up for consideration.

Dr. Baker said that given that final recommendations had not been made, she assumed the working group was talking about the use of PCV13 followed by PPSV23 vaccine.

Dr. Dooling replied that one of the next steps is to grade the evidence for PCV13 plus PPSV23 versus PPSV23.

If feasible, Dr. Baker said that it would be nice with the recommendation to see some influence on cost-effectiveness for this population. For example, for meningococcal vaccine in 2 to 10 year olds, the number of 2 to 10 year olds at risk for a very terrible disease is quite small; however, the benefit is quite great. Therefore, the cost is quite reasonable because the population is so small.

Dr. Bennett was curious about the cost-effectiveness analyses that have been done and whether sub-group analyses were included within those to address the immunocompromised population.

Dr. Dooling said she was not aware of any sub-group analyses that had been done for the immunocompromised group.

Dr. Loehr (AAFP) asked for clarification regarding whether the number needed to vaccinate in Dr. Dooling's presentation of 2011 was a sub-group of the 10,000 indicated in Dr. Pilishvili's presentation.

Dr. Dooling replied that it was not. Those were both number needed to vaccinate evaluations for which the efficacy was based on the Malawi trial, and the underlying rates of disease were both independently ascertained from the surveillance data and studies.

Dr. Loehr (AAFP) said for himself and others who recently have joined ACIP, he would be interested in knowing the number needed to vaccinate for other common vaccines and whether this was comparable to give him some reference points.

Dr. Baker emphasized that the cost-effectiveness analysis would also help everyone better understand comparability to other vaccines. The population at risk may be such that it is quite reasonable to bear the costs.

Dr. Zimmerman reported that he and his colleagues had a study published that day titled "Cost-Effectiveness of Adult Vaccination Strategies Using Pneumococcal Conjugate Vaccine Compared With Pneumococcal Polysaccharide Vaccine." This study is of a cohort of 50 year olds that was followed to death. Within this cohort, subjects developed immunocompromising conditions. While a sub-group analysis was not done only of immunocompromised persons, the cohort includes them as they age, develop immunocompromising conditions, and often pass away [Kenneth J. Smith; Angela R. Wateska; Mary Patricia Nowalk; Mahlon Raymund; J. Pekka Nuorti; Richard K. Zimmerman *JAMA* 2012;307 804-812].

Dr. Middleman (SAHM) did not remember all of the GRADE information for the younger populations, but it sounded as though people were thinking about recommending this for immunocompromised adults. It is worded as a clinical permissive for younger adolescents, so she wondered whether there were plans to assess younger adolescents to determine whether a unified recommendation could be made to make this easier for providers.

Dr. Dooling thought this was a great suggestion, pointing out that there is an off-label permissive recommendation for the pediatric population aged 6 to 18 years of age. The working group will find as many commonalities as possible to make the recommendation easier for providers.

Hepatitis B Vaccine

Introduction

Mark Sawyer, MD, Chairman
Hepatitis Vaccine Working Group

Dr. Sawyer indicated that having completed the work that was voted upon during the last ACIP meeting regarding Hepatitis B (HepB) vaccination of adults with diabetes mellitus, the Hepatitis Vaccine Working Group has begun to address a new term of reference, which is to ensure hepatitis B protection for healthcare personnel (HCP), including trainees, who may have received hepatitis B vaccination in the remote past, without having had post-vaccination serologic testing. This term of reference will not cover the overall long-term protection by

Hepatitis B vaccine, except as related to waning hepatitis B surface antibody levels among healthcare personnel. It also will not cover management of healthcare personnel who are known to be hepatitis B surface antigen positive (e.g., those with chronic infection), as management of known hepatitis B surface antigen-positive healthcare personnel does not involve an immunization question.

A couple of case scenarios may be useful to define the term of reference. Scenario Number 1 is an 18 year old female entering nursing school. She has documentation of receiving the complete Hepatitis B vaccine series in infancy as part of universal recommendations. However, she has never received post-vaccination serologic testing, as post-vaccination serologic testing is not recommended following routine infant or child Hepatitis B vaccination. Scenario Number 2 is a 48 year old hospital laboratory technician who has documentation of the complete Hepatitis B vaccine series, which was provided by his employer 18 years ago. He is unaware of whether any post-vaccination serologic testing was performed, and is now working in a different healthcare system.

The history of this issue dates back at least a couple of years. In February 2011, ACIP approved a consolidated statement of existing recommendations for immunization of healthcare personnel.

Three options were presented for ensuring hepatitis B protection of vaccinated healthcare personnel without post-vaccination serologic testing. These options, although not formal recommendations, had not been previously considered by ACIP. ACIP requested that the Hepatitis Working Group deliberate prior to voting on the options. The three options consist of: 1) No action unless exposed; 2) Pre-exposure hepatitis B surface antibody measurement, and 3) Administration of a challenge dose of hepatitis B vaccine, which would be followed by antibody measurement 1 to 2 months later.

During this meeting, the working group planned to define the term of reference and ask ACIP members for specific questions they may have about this term of reference. In June, the working group will present the cost-effectiveness analysis and proposed wording for ACIP policy. In October, the proposed policy options will be reviewed and the working group will ask whether ACIP is ready to vote.

Ensuring Hepatitis B Protection for Remotely Vaccinated Healthcare Personnel

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

Dr. Schillie reported that an increasing proportion of healthcare personnel have received a documented hepatitis B virus (HBV) vaccination series in infancy, or as catch-up in adolescence. There is no recommendation for post-vaccination serologic testing after routine infant or adolescent vaccination. Experienced healthcare personnel may change employers and lack post-vaccination serologic testing results that were obtained earlier in their careers. Healthcare schools and institutions are seeking guidance to ensure that these healthcare personnel and trainees are protected against Hepatitis B infection. As noted by Dr. Sawyer, the term of reference for the Hepatitis Working Group is to ensure hepatitis B protection for HCP, including trainees, who received Hepatitis B vaccination in the remote past without post-vaccination serologic testing.

Dr. Schillie reviewed the 2011 ACIP hepatitis B vaccination recommendations for HCP. These recommendations were made when most hepatitis B vaccination occurred upon matriculation or employment, both allowing for post-vaccination serologic testing soon after vaccination. The following key points of the recommendations are either copied or paraphrased as follows [*MMWR* 2011;60 (RR-7)]:

- All unvaccinated persons whose work- and training-related activities involve reasonably anticipated risk for exposure to blood or other infectious body fluids should be vaccinated with the complete ≥3-dose HepB vaccine series.
- Because higher exposure risk has been reported during the professional training period, the vaccination series should be completed before trainees have contact with blood.
- To determine the need for revaccination and to guide post-exposure prophylaxis, post-vaccination serologic testing should be performed for all HCP at continuing high risk for occupational percutaneous or mucosal exposure to blood or body fluids.
- Post-vaccination serologic testing should be performed 1-2 months after administration of the last dose.
- Persons determined to have anti-HBs concentrations <10mIU/mL soon after receipt of the primary series should be revaccinated.
- Administration of a second complete 3-dose series on an appropriate schedule followed by post-vaccination serologic testing 1 to 2 months after the 3rd dose is usually more practical than antibody testing after each additional dose of vaccine.
- Persons determined to have hepatitis B surface antibody levels <10mIU/mL after revaccination should be tested to determine infection status.

The Occupational Exposure to Bloodborne Pathogens Standard was published by OSHA in 1991. It requires that employers provide Hepatitis B vaccination to employees, ensure use of personal protective equipment (PPE), and describe how engineering and work practice controls would be used. The Needlestick Safety and Prevention Act became effective in 2001 and established in greater detail requirements that employers identify and use effective and safer medical devices [http://www.osha.gov/needlesticks/needlefact.htm].

Long-term protection after a HepB vaccine series correlates with anti-HBs ≥10mIU/mL measured 1 to 2 months after series completion. Vaccine-induced protection lasts 22 years or longer. Anti-HBs after primary HepB vaccine series wanes over time. Breakthrough HBV infections resulting in disease are uncommon among immunocompetent vaccine responders, even when surface antibody levels wane [Leuridan E. Clin Infect Dis 2011;53:68-75]. Because surface antibody levels wane over time, an antibody level <10mIU/mL years after the primary HepB vaccine series does not differentiate those healthcare personnel who are protected from those who are delayed responders or those who are non-responders [Tohme R. Infect Control Hosp Epidemiol 2011; 32:818-21; McMahon B. J Infect Dis 2009;200:1390-6]. Hepatitis B virus remains viable for 7 or more days on environmental surfaces[1] and occupationally-infected HCP may not be aware of, or report an exposure[2]. A literature review indicated that approximately 54% (38%-67%) of percutaneous injuries are reported[3-7] and approximately 17% (7%-44%) of mucosal exposures are reported[3-7] [[1]Bond W. Lancet 1981;1:550-1; [2]MMWR 2001;50 (RR-11);

[3]Boal W. Am J Ind Med 2008;51:213-22; [4]Gershon R. Ind Health 2007;45:695-704; [5]Gershon R. Am J Infect Control 2009;37:525-33; [6]Kessler C. Am J Infect Control 2011;39:129-34; [7]Trinkoff A. Infect Control Hosp Epidemiol 2007;28:156-64].

During its deliberations, the Hepatitis Working Group will consider the changing epidemiology of occupational HBV infection. Fewer HCP may be at risk because of sharps with engineered sharps injury protections, as well as increases in vaccination coverage. Hepatitis B infection may have decreased among source patients due to the declining incidence of acute hepatitis B and possible changes in the prevalence of chronic HBV [http://www.osha.gov/SLTC/bloodbornepathogens/standards.html; Viral Hepatitis Surveillance, 2009, http://www.cdc.gov/hepatitis/statistics/2009surveillance/; Wasley A. J Infect Dis 2010;202:192-201].

As presented by Dr. Sawyer, the options under consideration by the Hepatitis Working Group include 1) No action unless exposed, 2) Pre-exposure anti-HBs, and 3) Challenge dose of HepB vaccine. Note that all three options are used by healthcare systems in the US. Dr. Schillie briefly explained these.

In Draft Option 1, matriculating or newly hired healthcare personnel who provide documentation of the complete Hepatitis B vaccine series would not be evaluated for Hepatitis B protection unless exposed to blood or body fluids. Healthcare personnel who report percutaneous or mucosal exposure to blood or body fluids to occupational health would be assessed for anti-HBs and the vaccination history would be reviewed. The source patient would be tested for HBsAg. Based on these results, the healthcare personnel may receive Hepatitis B vaccine and/or Hepatitis B immune globulin (HBIG). Draft Option 1 relies upon recognition of the exposure and timely reporting.

In Draft Option 2, healthcare personnel would receive a pre-exposure surface antibody measurement upon matriculation or hire. If anti-HBs are ≥10mIU/mL, no further action would be required. If anti-HBs are <10mIU/mL, 1 additional dose of HepB vaccine would be administered, followed by surface antibody testing 1 to 2 months later. If anti-HBs remains <10mIU/mL, current recommendations would be followed to revaccinate and measure anti-HBs.

In Draft Option 3, the healthcare personnel would receive a challenge dose of Hepatitis B vaccine upon matriculation or hire. Anti-HBs would be measured 1 to 2 months later. If anti-HBs are ≥10 mIU/mL, no further action would be taken. If anti-HBs were <10mIU/mL, current recommendations would be followed to revaccinate and re-measure anti-HBs.

The working group looks forward to presentations of additional data and a cost-effectiveness analysis of these options at the June ACIP meeting. Dr. Schillie invited input from ACIP members in terms of any other relevant options or considerations, as well as questions to consider.

Discussion Points

Dr. Coyne-Beasley wondered where she fit in. There seemed to be a focus on matriculation or hire. She had hepatitis B vaccine over 22 years ago, does not know her titers, and does not plan to matriculate or transfer anywhere. However, it was unclear whether she was at risk of exposure and should be revaccinated.

Dr. Schillie responded that there is no current recommendation for someone in Dr. Coyne-Beasley's situation to have pre-exposure surface antibody testing or a challenge dose of Hepatitis B vaccine.

Dr. Foster (APhA) pointed at that many hospitals and facilities are instituting their own recommendations.

Dr. Schillie replied that they have confirmation that all three of the options presented are in use in healthcare systems in the US.

Dr. Brewer (ANA) said that while there is the 2001 Needlestick Act and there are data to show that nurses are still concerned about needlesticks because employers and other health facilities are not supplying safety devices, ANA believes there is gross under-estimation of needlesticks as Dr. Schillie pointed out. While the act is important, it still has not fixed the problem.

Regarding the three options being practiced, Dr. Jenkins wondered whether there was any knowledge about outcomes, satisfaction, or measures of how successful these approaches are.

Dr. Schillie replied that they do not have any outcomes comparing the three approaches. There are some data from different healthcare systems regarding the risk of exposure and risk of source patients being Hepatitis B surface antigen positive.

Given the data presented regarding the frequency of reporting exposure, it was unclear to Dr. Bennett why Option 1 was even being considered.

Dr. Schillie explained that it is included for baseline purposes.

Ms. Stinchfield (NAPNAP) reported that Children's Hospital in Minnesota where she works uses Option 1, which is based on reliance on education and making sure that healthcare providers know the risks. While there is a concern about any hospital that does not offer safety devices, the reverse is true when they are offered and people choose not to use them because they learned on the non-safety devices. Healthcare workers have secret stashes and sometimes do not use what they are provided. People are concerned when they receive a needlestick. They want to take action, they do it quickly, and it is really about making sure they know what to do when that happens. From a practical standpoint, Options 2 and 3 would be quite expensive and onerous on the employer.

It seemed to Dr. Zahn (NACCHO) that the utility of getting an anti-Hepatitis B surface antigen study would depend upon how long it had been since they received their vaccine. He assumed that how long a vaccine would be useful and what the cutoff should be would be part of the conversation.

Dr. Schillie replied that the working group is considering this issue and plans to present additional data during the June 2012 ACIP meeting.

Dr. Schaffner (NFID) expressed interest in the magnitude of the problem, and noted that no data had been presented on occupationally-acquired Hepatitis B. That is, there was no discussion regarding how many people fall into the category of having been immunized but not serologically tested who turn out after an exposure to have acquired Hepatitis B.

Dr. Schillie responded that every day in US hospitals, there are approximately 1000 percutaneous injuries. Their data of about 7000 injuries indicate that source patient positivity for Hepatitis B surface antigen is approximately 1%. With regard to case reports in the literature of actual infection among healthcare personnel who have been vaccinated, there was a case report of a nurse in the Netherlands who was a delayed responder to vaccine, but ultimately was a vaccine responder who did acquire symptomatic acute Hepatitis B infection. He was also MSM, so it is difficult to determine whether his infection was acquired as a result of an occupational exposure or as a result of his MSM behavior. Also, the 2009 CDC surveillance data indicate that among approximately 1500 case reports of acute Hepatitis B infection with information on occupation, 13 indicated that the person who acquired infection was employed in a medical or dental system. However, it cannot be said whether that infection was acquired as a result of occupational exposure.

Dr. Moore (AIM) raised an issue about which she often receives questions, and suggested that it be addressed in the recommendation. That is, there is a tendency to want to use a challenge dose to check anti-HBs as a way to confirm a history of vaccination when documentation of 3 doses of vaccination cannot be found. She and Dr. Andrew Kroger have had this issue arise in other work groups in terms of whether this is a meaningful way to check.

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, MMR-V vaccine, and zoster vaccine.

With regard to hepatitis A vaccine, Merck anticipates availability of its adult hepatitis A vaccine by late 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.

MMR-V combination vaccine remains unavailable. Merck is committed to returning ProQuad® to the market. Details on timing and availability will be provided at a later date. Merck has an adequate supply of both M-M-R II® and VARIVAX® to meet current demand.

With respect to zoster vaccine, in December 2011, Merck cleared all backorders for ZOSTAVAX® and resumed routine 2-day shipping.

CDC's Vaccine Supply/Shortage Webpage is available at:

http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm

Day 1: Public Comment

Michael Royals, DVM
Chief Scientific Officer
Global Head of Applications Development
PharmaJet, USA

I am the Chief Science Officer for PharmaJet, and clearly I am conflicted because of my employment in this company. Last October, the FDA issued a statement that recommended against the use of jet injectors to deliver influenza vaccine. The statement indicated that this is based on the observation that no data on safety or efficacy had been submitted by vaccine manufacturers on the delivery of their vaccines with jet injection. On January 9, 2012, advocates for the use of the technology held a meeting with the FDA to identify approximately 30 members from all branches of the FDA, representatives of jet injection companies, and users of the technologies from various public health sectors, including those from state level public health immunization programs, US corrections institutions, and US retail pharmacies. The content of the meeting covered historical and current use of jet injectors to deliver a wide range of vaccines, including influenza. Speakers pointed to the fact that the *MMWR* and "Pink Book" both have references to the use of jet injectors as an alternative to needles for delivery of vaccines. Since 1958, 22 controlled studies have been published on the use of jet injectors to deliver influenza, none of which indicated inferiority between delivery methods. The Navy and Coast Guard have, for the past several decades and up to the present, used jet injectors to vaccinate both soldiers and their dependents. The various stakeholders urged the FDA to reassess the October statement and to find a way forward that would permit users to re-establish influenza vaccine delivery using needle-free jet injection. We recently heard from the FDA Office of the Commissioner the stated quote, "We are taking this seriously and will be getting back to you. We did not want you to think the issue had gone into a 'black hole.'" Additionally, we are in discussions with three of the companies that have US licensed influenza vaccine. While we do not have definitive direction from FDA on the matter, there appears to be some progress. Thank you.

February 23, 2012

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Schuchat indicated that CDC traditionally has had an annual immunization conference. In concert with budget cutting efforts, the agency is alternating an in-person physical meeting with a virtual on-line meeting. A fantastic program has been developed for the first national conference on-line, which is March 26-28, 2012. The www.cdc.gov/vaccines contains a lot of information about this meeting. There will be three afternoons of sessions that will also be archived. Those who watch the broadcast live will be able to participate in discussions. Poster sessions will also be available. Next year's conference will be in-person in Atlanta in early June 2013.

April 21-28, 2012 is National Infant Immunization Week. A number of local, state, national, and international activities have been planned. There is a new family of communications materials, including public service announcements (PSAs) for radio and television that will be launched that week and will be available for others to pay for for placement. These are very creative and build on an enormous amount of research focusing on vaccination of young children and the issues that parents find important. These materials are very clever, as well as evidence-based. Related to this, there is a series of materials that are also available on-line. These are vaccine resources for clinicians that were developed in conjunction with the American Academy of Family Physicians (AAFP), the American Academy of Pediatrics (APA), and CDC. These materials address the many issues that parents have, include "war stories" from families who have experienced these diseases, address the rights and responsibilities people have if they refuse vaccines, include a vaccine safety series, and have very cute associated materials. In keeping with budget cutting, millions of copies have not been printed, but they are available for free download or printing locally. CDC encouraged others to sponsor printing in their communities.

On a bittersweet note, Immunization Services Division (ISD) Director Lance Rodewald will be moving to an international position in China where he will be working on WHO immunization. This is a fantastic opportunity for Dr. Rodewald and his family, and the people of China, but a major loss for CDC. CDC will be recruiting for this position, and she requested input to help them find a fantastic new applicant.

Centers for Medicare and Medicaid Services (CMS)

Dr. Hance indicated that CMS is close to publishing an update to administration fees for the Vaccines for Children Program (VFC).

Department of Defense (DoD)

Dr. Geibe commented on jet injectors, indicating that the Navy and Marine Corps have been using these safely and effectively. This is known based on DoD's surveillance on the effectiveness of the vaccine when delivered with the jet injections. However, they also are adhering to the FDA recommendation until further guidance is provided.

Department of Veterans Affairs (DVA)

Dr. Kinsinger reported that DVA continues to work on a policy for deploying influenza vaccination, and have set a goal this season for 85% coverage. At the agency level, DVA is beginning to work closely with the DoD to create a joint electronic medical record (EMR). This is an enormous undertaking that is expected to take many years. One of the first components that will be developed for that joint EMR is an immunization package. She also announced that Dr. Andrew Kroger would be a guest speaker on two national VA calls in March 2012 to review the 2012 Adult Immunization Schedule.

Food and Drug Administration (FDA)

Dr. Sun reported that Dr. Norman Baylor retired after 20 years at Center for Biologics Evaluation and Research (CBER). Currently, Dr. Marion Gruber is serving as Acting Director. Since the October 2011 ACIP meeting, PREVNAR 13® was approved for adults 50 years and older. On February 16, 2012 the Adacel® label was updated to include the Td515 study discussed the previous day. A Vaccine Advisory Committee meeting will be convened on February 28-29,

2012, the topics of which will be the season's influenza strain selection and a discussion of licensure pathways for pandemic influenza. On January 10-11, 2012 CBER convened a public workshop on the development and evaluation of human cytomegalovirus (HCMV) vaccines that focused on the status of the knowledge of HCMV biology, epidemiology, and vaccine development strategies. This information should be posted on the web soon.

Health Resources and Services Administration (HRSA)

Dr. Evans reported that in December 2011, the Advisory Commission on Childhood Vaccines (ACCV) voted to approve the Secretary's proposal to add intussusception to the Vaccine Injury Table for the two currently licensed rotavirus vaccines and approved language in the Now in addition, the proposed paragraph for Qualifications and Aids to Interpretation (QAI), which defines the conditions in the table. When RotaShield® was licensed in 1998, there was a general category of rotavirus vaccine. Once it became determined that intussusception was associated with that, a second category was included with intussusception with live attenuated Rhesus-based rotavirus vaccines. The program adjudicated a number of claims under that category. After many years passed, the category was removed. With the licensure in 2006 and 2008 of RotaTeq® and ROTARIX®, these were covered under the general category of rotavirus vaccines with no specific conditions. Over the past two years, published studies from South America and Australia show a small but attributable risk of intussusception after the first and second dose of both vaccines, with more data supported for ROTARIX®. Therefore, the program went ahead with the proposal to add intussusception to the general table category of rotavirus vaccines to allow a presumption of causation with an onset interval of 0 to 21 days. The ACCV also approved wording to the QAI section of the table to define intussusception and to specify alternative causes of intussusception that if present in a case would render the injury not to be considered vaccine-related. The ACCV approved these proposals, and under the act there must be a *Federal Register* Notice of Proposed Rulemaking with 180 days of public comment before a Final Rule is published. About 15 rotavirus claims have been received since 2006. Dr. Evans will report during the June 2012 ACIP meeting on other proposals to change the table based on the August 2011 IOM report.

Indian Health Services (IHS)

Ms. Groom reported that IHS continues to put a lot of effort into influenza vaccination. IHS healthcare personnel coverage is approximately 74%, which is about the same as the last 4 years. Strategies are being assessed to improve and increase that percentage to reach the Healthy People 2020 goal of 90%. IHS has also been monitoring coverage among its patients, and continues to encourage its providers to vaccinate. However, with little influenza virus in communities this has been somewhat challenging because of the lack of pressure. A significant amount of focus is being placed on adult immunization. One of the first efforts was to have all of the adult vaccines automatically added to the IHS core formulary as they are approved and recommended by ACIP. A survey is being conducted among IHS sites to determine how many facilities are actually providing adults vaccinations. The preliminary data show that funding for HPV and zoster is a major challenge for providing those vaccines to IHS patients, so the agency is assessing ways to address this.

National Vaccine Program Office (NVPO)

Dr. Gellen reported on two Institute of Medicine (IOM) committees that NVPO supports, one of which is assessing vaccine development priorities as part of NVPO's priorities within the National Vaccine Plan (NVP). An initial phase of this, which is a model, will be released in April 2012. The second IOM committee that is being supported by NVPO and CDC is one that was established at the recommendation of the National Vaccine Advisory Committee (NVAC) as part of their vaccine safety review. This committee has met once and plans two more meetings in the near future, the next of which will be in Seattle on March 8, 2012. This committee is assessing the health outcomes related to the schedule. This arose from concerns pertaining to the health outcomes of children who are vaccinated according to schedule versus those who are vaccinated following other schedules. Within HHS, for the past two years the Assistant Secretary for Health has led an Interagency Task Force on Seasonal Influenza Vaccine. Following the pandemic, there was an opportunity to determine what could be done to improve seasonal vaccine use that would help with pandemic preparedness and also emphasize some of the department's priorities, particularly with regard to reducing or eliminating health disparities. That is about to morph into a focus more broadly than just influenza into adult vaccines, which fits in with the Adult Immunization Summit that is also coupled with the Influenza Summit.

National Vaccine Advisory Committee (NVAC)

Dr. Orenstein highlighted two items from the February 7-8, 2012 NVAC meeting. Dr. Melinda Wharton presented on the expanse of the immunization system as it goes beyond vaccines for vaccine purchase. In light of this presentation and the potential impact that the Affordable Care Act will have on immunization systems and vaccine availability, the NVAC charged a working group with the task of identifying and describing critical functions of immunization programs at the national, state, and local levels to ensure their preservation and improvement. Dr. L.J. Tan is co-chairing that working group. The second day of that NVAC meeting was devoted almost exclusively to global immunization and the impact on diseases that make their way to the US, as well as diseases within global populations. There were presentations from Dr. Nils Daulaire who is the Director of the Office of Global Affairs (OGA) within HHS; and several presentations from CDC, FDA, NIH, USAID, and others. Afterwards, NVAC charged the working group with the task of reviewing the role of HHS in global vaccination, the impact of such vaccination on the US and global populations, and to recommend how HHS can best contribute to reducing global disease and the threat of that global disease coming to the US as with many of the outbreaks currently being observed. That working group is being chaired by Phil LaRussa.

National Institutes of Health (NIH)

Dr. Gorman reported that NIH has established a new center called the National Center for Advancing Translational Science (NCATS). The mission of this new center is to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions. On November 28, 2011, NIH and CDC renewed two vaccine safety program announcements. The purpose of these funding opportunities is to support research that will contribute to the overall understanding of vaccine safety. This research opportunity invites studies to address scientific areas potentially relevant to vaccine safety. The National Institute of Allergy and Infectious Diseases (NIAID) has published announcements for 6 leadership group applications. They are being sent out concurrently and are for clinical research networks in the following areas: HIV/AIDS and HIV-Associated Infections in Pediatric and Maternal

Populations; Integrated Strategies for the Prevention of HIV Infection; Microbicides to Prevent HIV Infection; Therapeutics for HIV/AIDS and HIV-Associated Infections in Adults; Vaccines to Prevent HIV Infection; and Antibacterial Resistance. The 2012 Jordon Report, a publication that reports on the state of science and provides valuable information about vaccine research and development for researchers, policy makers, and legislators, is presently public. It was supposed to post to the web within the next couple of days. NIAID is the lead institute at NIH that supports research on infectious disease. Within NIAID, the Division of Microbiology and the Division of Acquired Immunodeficiency Syndromes support extramural research to control and prevent diseases causes by virtually all human infectious agents. Both divisions provide funding opportunities and a comprehensive set of resources for researchers that support basic research, pre-clinical development, and clinical evaluation. Current vaccine trials currently supported by one or both of these divisions include: Anthrax, Cytomegalovirus, Dengue, Enterotoxigenic E-coli, Hepatitis B, Hepatitis C, Herpes Simplex, Herpes Zoster, HIV, Hospital Acquired Infections (HAIs), Human Papillomavirus (HPV), Human Parainfluenza Virus, Influenza, Leishmaniasis, Malaria, Meningococcous, Pertussis, Plague, Poliovirus, Rift Valley Fever, Rotavirus, Severe Acute Respiratory Syndrome (SARS), Salmonella, Septicemia, Shigellosis, Small Pox, Group A Strep, Group B Strep, Tetanus, Tuberculosis, Tularemia, and Typhoid.

Meningococcal Vaccines

Introduction

H. Cody Meissner, M.D.
Chair, Meningococcal Working Group
Advisory Committee on Immunization Practices

Dr. Meissner acknowledged the considerable time and effort the Meningococcal Working Group members have spent on a number of difficult issues. In particular, he recognized the careful attention of Dr. Cohn in guiding the working group through a number of difficult issues.

He then reviewed the four meningococcal vaccines to be addressed during this session. The quadrivalent polysaccharide vaccine (MPSV4: Menomune®, sanofi pasteur) consists of capsular polysaccharide from four serogroups: A, C, Y, and W135. It was licensed in 1991 for persons 2 years of age or older. Currently, this vaccine is recommended for persons older than 55 years of age or for use when meningococcal conjugate vaccine is either not available or cannot be used. Two meningococcal conjugate vaccines are available: 1) MenACWY-D (Menactra®, sanofi pasteur), which is approved for 9 months through 55 years; and 2) MenACWY-CRM (Menveo®, Novartis), which is approved for 2 through 55 years. Both consist of capsular polysaccharide from four serogroups: A, C, Y, and W135 conjugated to a carrier protein. In the case of Menactra®, the carrier protein is a chemically altered diphtheria toxin. The carrier protein for Menveo® is a naturally occurring non-toxic form of diphtheria toxin. Two investigational vaccines are under review by the FDA for use infants as a 4-dose series at 2, 4, 6, and 12 months of age: 1) HibMenCY-TT (MenHibrix®, GlaxoSmithKline) consists of poly-ribosyl phosphate from a capsule of Hemophilus Influenzae type B conjugated to tetanus toxoid plus meningococcal polysaccharide from serogroups C and Y conjugated tetanus toxoid; and 2) MenACWY-CRM.

In April 2011, the FDA licensed Menactra® as a two dose primary series for children 9 through 23 months of age. The pure polysaccharide meningococcal vaccine is not recommended for children less than two years of age because of low immunogenicity in this age group. Menactra® is the first meningococcal vaccine licensed for children <24 months of age. In June 2011, after review of data from clinical studies on safety and immunogenicity, ACIP recommended that children 2 through 10 years of age with certain risk factors for meningococcal disease receive a 2-dose series 3 months apart. Routine vaccination of children 2 through 10 years of age who are not at increased risk of meningococcal disease is not recommended. This is because currently the rates of meningococcal disease due to vaccine containing serogroups is low in this age group. In addition, antibody concentrations wane quickly after the primary dose and most children may not be protected by 3 to 5 years after vaccination.

As mentioned, two investigational vaccines are under investigation by the FDA for use in infants. For more than two years, the working group has discussed the question regarding whether the 4.1 million infants born each year in the US should be vaccinated routinely against meningococcal disease. Discussion has focused on a number of factors, including the burden of meningococcal disease and the relatively small amount of vaccine-preventable disease in this age group; the limited public health impact of routine immunization in this age group; the programmatic difficulties associated with implementation of an infant or toddler vaccine schedule; the immunogenicity data which demonstrate declining antibody concentrations 3 years after either a 2-dose or 4-dose schedule, indicating a booster dose would be necessary before the routine 11- or 12-year meningococcal vaccination; and the cost-effectiveness of infant-toddler vaccination.

Because neither infant meningococcal vaccine has been licensed by the FDA, the decision has been made simply to extend the language used for children 2 through 10 years of age down to children 6 through 23 months of age. This language was first published in the May 2, 2008 *MMWR* in an ACIP report entitled, “The Decision Not To Recommend Routine Vaccination of All Children Aged 2 through 10 Years with Quadrivalent Meningococcal Conjugate Vaccine.” Guidance regarding the infant vaccines will be deferred until these vaccines are licensed. The last recommendation and report on meningococcal vaccines was published as an MMWR supplement in May 2005. During the past 7 years, numerous new vaccine recommendations have been made. In addition to the availability of a second conjugate vaccine, a draft of the updated supplement is being reviewed by working group members. The current draft has been provided to ACIP members for comment. Language regarding use of the conjugate vaccine as a 2-dose primary series in children 9 through 23 months of age who are at increased risk of meningococcal disease is contained in the revised statement.

GRADE Assessment for MenACWY-D in Children 9-23 Months of Age

Elizabeth Briere, MD, MPH
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Briere presented the GRADE evaluation for MenACWY-D toddler vaccines. She reviewed the working group’s study question for GRADE, the evaluation of meningococcal disease burden data quality, and the GRADE assessment of evidence for the benefits and harms outcomes. She indicated that while she would conclude with the working group’s determination of overall evidence type for the toddler MenACWY-D vaccine, a vaccine recommendation would not be formulated.

The first step in the GRADE process is to formulate the study question. The working group's initial question was "Should meningococcal vaccines be administered routinely to infants and toddlers for prevention of meningococcal disease?" The meningococcal vaccines included the two infant vaccines, Menveo® and MenHibrix®, and the toddler vaccine, MenACWY-D. Because the infant vaccines are not yet licensed, the working group focused the study question and GRADE evaluation on the toddler vaccine. GRADE will be used to assess the infant vaccines once they are licensed. Therefore, for this presentation, the study question was "Should MenACWY-D be administered to all 9 and 12 month olds for prevention of meningococcal disease?"

Because current low disease incidence has been such an important consideration during working group discussions, the working group wanted to first evaluate the quality of the meningococcal disease burden data. However, because these data are from surveillance and no intervention was tested, they could not be evaluated using the GRADE format. Instead, the working group assessed the disease burden data for representativeness, accuracy, and applicability.
Presentations on the burden of meningococcal disease in children <5 years of age were given during the October 2011 ACIP meeting. A comparison of the incidence of serogroup C, Y, and W135 meningococcal disease during three time frames shows the large declines in incidence of meningococcal disease overall and in children <5 years of age [1993-2009 ABCs data estimated to U.S. population with 18% correction for under reporting; *1993-2005 for adolescents 11-22 years].

US meningococcal incidence data come from two sources: ABCs and NNDSS. The quality of the incidence data depends on these two sources. ABCs is an active laboratory and population-based surveillance system that collects data only on culture-confirmed cases of meningococcal disease in 10 sites. Cases in the ABCs sites can be projected to the US population to estimate incidence. NNDSS is a passive surveillance system. All states and territories report data for nationally notifiable diseases to NNDSS. NNDSS captures information on all cases, including cases confirmed by PCR only and those with clinically compatible illness. However, serogroup information is limited. Because cases identified in ABCs are also reportable to NNDSS, ABCs and NNDSS are not independent surveillance systems.

The representativeness of incidence data was assessed by comparing projected numbers of cases in the US from ABCs to NNDSS reported cases. Since NNDSS is national surveillance, meningococcal incidence rates should be representative of the US. Because ABCs covers a catchment area comprising only about 13% of the US population, rates using ABCs data are standardized by race and age, and projected to the US population. When comparing NNDSS and ABCs meningococcal cases less than 1 year of age, a similar distribution of cases is found. One limitation of these comparisons is the amount of missing data in NNDSS. Serogroup was missing for 50% to 70% of NNDSS cases, so a comparison with ABCs could not be done.

Next, the accuracy of the incidence data was assessed by comparing the annual cases of meningococcal disease for all ages estimated from ABCs to the number of cases for all ages reported in NNDSS. ABCs typically estimates fewer cases compared to NNDSS, mainly because it does not capture cases reported as probable. 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 underestimate of cases by ABCs, a correction factor of 18% is applied to all incidence data used.

Another limitation in the accuracy of ABCs data is that outbreaks of disease outside ABCs catchment areas may be missed. However, based on the data, the total number of outbreak cases rarely increases the overall disease incidence since cases generally make up only 2% to 3% of total cases.

Finally, the applicability of meningococcal incidence data to the study question was assessed. ABCs and NNDSS capture meningococcal disease incidence in toddlers, so the data are applicable to the evaluation of MenACWY-D for use in toddlers. However, incomplete data in NNDSS prevents assessment of the epidemiology of serogroups specific to the toddler vaccine.

To complete the assessment of burden of disease data quality, morbidity and mortality data were assessed. Measuring meningococcal disease morbidity and mortality is challenging. Data are usually combined that are available from ABCs along with data collected from published manuscripts to estimate the severity of meningococcal disease in infants and young children. Published data on morbidity and mortality are often not representative or generalizable because studies often have small numbers and are usually hospital-based. There is also a wide range of estimates of mortality and long-term sequelae among survivors, and many of these studies do not give serogroup-specific estimates. Data, especially neurologic outcomes, are often not directly applicable to the evaluation of toddler vaccines or disease because they may be for all-cause bacterial meningitis, in broad age-groups, or for all serogroups.

Based on the evaluation of the meningococcal disease incidence, mortality, and morbidity data, minor limitations were found. It is not believed that these significantly affect the quality of the burden of disease estimates.

Turning to the GRADE evaluation, Dr. Briere reminded everyone that this GRADE evaluation applied only to evidence for the toddler MenACWY-D schedule. After selecting a study question, the next step in GRADE is to select outcomes that the working group feels are important to answer this question. The quality of the evidence for these outcomes is then evaluated. First, the working group created a list of 5 outcomes to GRADE. Next, non-CDC members of the working group ranked the relative importance of the outcomes on a scale of 1-9 with 1-3 as not important; 4-6 as important, but not critical for answering the question; and 7-9 as critical for answering the question. Only evidence for the critical and important outcomes are graded. Only mild adverse events were ranked as not important. The final outcomes that were graded included the following:

- Benefits: Short-term and long-term efficacy to assess the benefits of vaccination.

- Harms: Occurrence of serious adverse events after vaccination; and interference with other co-administered vaccines.

In compiling evidence to GRADE for each of these outcomes by vaccine, several inclusion criteria were used. US and non-US populations were included as long as the proposed US schedule (9, 12 months) was used for MenACWY-D. Data were compiled for MenACWY-D by outcome and study design type (e.g., Randomized Control Trial or Observational Study). There were a total of 5 studies, 4 observational and 1 Randomized Control Trial. The majority of studies assessed efficacy and safety outcomes. None were published at the time. Drs.

Campos-Outcalt and Briere rated the evidence separately and compared results. Differences in results were discussed with the working group until consensus was reached.

In terms of benefits and harms, due to the low incidence of meningococcal disease, pre-licensure clinical effectiveness studies are not feasible. Serum bactericidal antibody (SBA) titers are used as the immunologic correlate of protection. Multiple studies have shown that human SBA titers of 1:4 correlate with protection against meningococcal disease. While these studies were based on SBA activity against serogroup C disease, human SBA titers >1:8 are accepted as correlates of protection for vaccine licensure for other serogroups. Indirect data adds to the confidence in SBA titers used as a correlate for protection. Effectiveness was demonstrated to correlate with SBA titers in the adolescent MenACWY-D in the US and MenC conjugate vaccines in the UK [Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. J Exp Med. 1969 Jun 1;129(6):1307-26. Andrews N, Borrow R, Miller E. Validation of serological correlate of protection for meningococcal C conjugate vaccine by using efficacy estimates from postlicensure surveillance in England. Clin Diagn Lab Immunol. 2003 Sep;10(5):780-6].

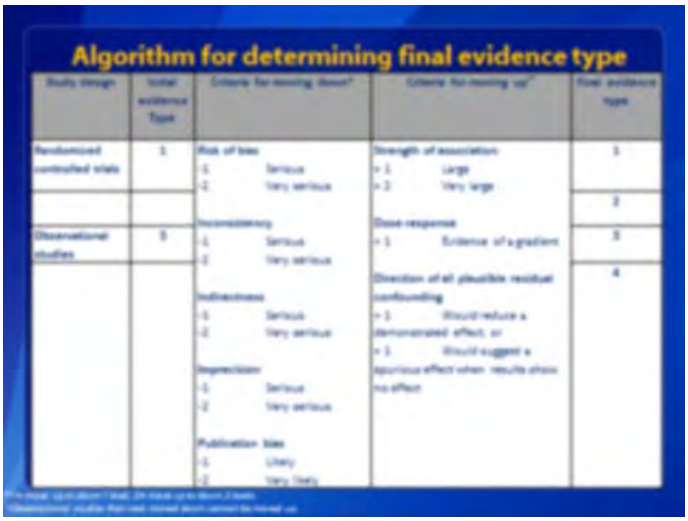
Based on the body of evidence for MenACWY-D, short-term efficacy is achieved for all serogroups after a 2 dose series. However, long-term protection is unlikely given the low percentage of infants with protective titers 3 years after the 2 dose series [Johnson, D.R. Menactra Infant Indication, ACIP June 22, 2011]. A booster dose would likely be necessary to protect children until the 11-12 year vaccination.

In all studies that assessed serious adverse events, events were recorded from the time of vaccination through 6 months post-vaccination^ and were physician-verified. Among the studies for MenACWY-D, at least 1 serious adverse event was reported by 3% to 5% of study participants who received MenACWY-D alone or with concomitant vaccines. At least 1 serious adverse event was reported by 2% to 4% of controls*†. The difference between the intervention and control groups was not statistically significant in any of the studies. Four of the serious adverse events were considered related to MenACWY-D vaccine by non-blinded investigators**. No deaths were reported in any of the studies [^Defined as any medical occurrence that results in death, is life-threatening, requires hospitalization, results in disability/incapacity, is an important medical event. *Menactra package insert 30 Nov 2011 v0.11. †Difference between intervention and control groups not statistically significant. **IDDM, respiratory distress, 2 febrile seizures].

Based on the body of evidence for interference with co-administered vaccines, antibody responses for MMRV and Hib after co-administration with MenACWY-D met the criteria for non-inferiority*. Pneumococcal IgG antibody responses after PCV7 co-administration with MenACWY-D did not meet criteria for non-inferiority for serotype 4, 6B, and 18C. Detectable functional antibody was present, but did not meet non-inferiority for IgG GMC ratio criteria. The clinical relevance of these findings is unclear [*Menactra package insert 30 Nov 2011 v0.11].

Regarding the benefits and harms for a toddler MenACWY-D series, the vaccine is immunogenic in the short-term and is safe. However, low disease burden lowers the overall benefits of vaccination.

In GRADE, all the available data for each outcome are evaluated on these 5 criteria and a final evidence type is assigned. “Other” includes publication bias, strength of association, and dose gradient. The following is the algorithm used to determine the final evidence type for each outcome:



Randomized Controlled Trials start out as an evidence type of 1 and observational studies start out as a type 3. The 5 criteria are assessed to determine whether the overall evidence type is moved down or up. Since the majority of studies for MenACWY-D were observational studies without randomized control groups, an initial evidence type of 3 was used for most outcomes.

The first criterion assessed is risk of bias. Methodological limitations were looked for that may bias the estimates of the effect of vaccination. The majority of studies for MenACWY-D were single-blinded or not blinded at all. It was believed that blinding was likely to introduce more bias for a more subjective outcome, such as severe adverse events, and was less likely to introduce bias for an objective outcome, such as efficacy or interference. Therefore, the evidence for the severe adverse events outcomes was downgraded if there was single or no blinding. However, efficacy outcomes were not downgraded.

As a reminder, for MenACWY-D all outcomes with observational study designs started as an evidence type of 3 and outcomes with randomized controlled trials started as a 1. For risk of bias, serious limitations were found for the serious adverse events outcomes due to single or no blinding, and no serious limitations were found for the remaining outcomes (e.g., short-term efficacy, long-term efficacy, co-administration of vaccines). No serious problems were found with inconsistency for any of the outcomes. As mentioned earlier, it is not feasible to directly measure efficacy, and SBA titers are used as a correlate of protection. Although SBA titers are indirect evidence for efficacy, since they are the accepted measure for vaccine licensure studies, the evidence type was not downgraded. No serious concerns were found with imprecision among the evidence for efficacy outcomes, the observational studies for SAE, or the evidence for interference with co-administered vaccines. The Randomized Controlled Trial for SAE was downgraded for imprecision because the study had a sample size <300 and had a wide confidence interval. No serious concerns were found for “Other.”

In summary, the evidence was downgraded for the serious adverse events outcome, but was not downgraded for any of the other outcomes. Therefore, the overall evidence type was 3. The evidence tables and overall evidence type for MenACWY-D will be published together with the evidence for the infant vaccines once they are licensed.

Updates to the Meningococcal Vaccines Statement

Amanda Cohn, MD
CDR, US Public Health Service
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Cohn reminded everyone that the working group's plan was to evaluate the evidence for the general question, "Should infants and toddlers routinely be vaccinated with meningococcal conjugate vaccines?" However, as there is no licensed infant product, only the evidence grade for the toddler vaccine was presented during this session. At the same time, the ACIP meningococcal statement, published in 2005, needs to be updated so that the most current recommendations are communicated clearly in one document. The updated statement will include language on recommendations for high risk 9 through 23 month olds and language indicating that 2 through 10 year olds are not recommended routinely for meningococcal vaccination. Data on the immunogenicity and safety of the MenACWY-D in 9 through 23 month olds was presented at the June 2011 ACIP meeting, and will also be included in the updated statement.

In June 2011, sanofi pasteur presented data showing that the immunogenicity and antibody persistence of a 2-dose primary series of MenACWY-D in 9 through 23 month olds is similar to a single dose in young children 2 through 5 years old. A high proportion of subjects achieved hSBA titers of greater to or equal to 1:8 after the second dose, and most subjects did not maintain these antibodies 3 years after the primary series. Additionally, current incidence of serogroup C and Y meningococcal disease among 1 year olds is similar to disease incidence among 2 through 4 year-olds. Therefore, including 9 through 23 month olds is simply an extension of the existing recommendations for 2 through 10 year olds.

The language in the statement is on page 33 of the draft given to ACIP members. Background information will include the following information:

- MenACWY-D is licensed for use as a two dose primary series in toddlers 9 through 23 months and a single dose in children 2 through 10 years.

- MenACWY-CRM is licensed for use starting at age 2 years as a single dose.

- These vaccines are safe, immunogenic, and will provide protection against meningococcal disease caused by serogroups A, C, Y and W-135.

- Antibodies wane quickly in this age group and most vaccinated children will not be protected three years after vaccination.

The updated language will read as follows:

- Routine vaccination against meningococcal disease is not recommended for children ages 9 months through 10 years.

- If a child receives MenACWY prior to their 10th birthday, they should also receive the routinely recommended doses at ages 11 through 12 years and age 16 years.

The next steps are to publish the updated ACIP meningococcal vaccines statement as an *MMWR* recommendation and report. It is fully expected that this recommendation will be outdated as soon as it is updated; however, the working group believes that it is important to go ahead and publish the statement this year. The working group will continue to work on grading the evidence for infant vaccines under consideration for licensure. Each vaccine will be graded separately, but recommendations will be formulated for infant vaccination in general. During the October 2011 meeting, a rationale was presented for the working group consensus to not routinely recommend meningococcal vaccines for this age group. However, as language is developed for infant vaccination, the working group will consider harmonizing the 9 month through 10 year old language with the infant recommendation language.

Discussion Points

Dr. Keitel as the Influenza Working Group is considering its broad evidence-based grading of influenza vaccine recommendations, it was interesting to hear that the Meningococcal Working Group did not downgrade the evidence based on a correlate of protection. If that were going to set a precedent for ACIP, that would mean that simple immunogenicity studies could be used for influenza to grade the evidence for likely protection against influenza. She would have imagined that although there is a correlate of protection, it is not an actual demonstration that the vaccine did protect.

Dr. Cohn replied that the Meningococcal Working Group discussed this at length. The primary reason for not giving it a serious downgrade was that, for meningococcal vaccine in particular because the disease incidence is so low, pre-licensure effectiveness trials are not going to be conducted. This was very specific to meningococcal vaccine.

Dr. Baker added that the historical precedent for meningococcal vaccines dated back to the military in 1969 when the efficacy of the Group C outbreaks in the military was shown with the Group C polysaccharide vaccine. Since that time, hSBS titers to Group C has been accepted throughout the world as a correlate of protection, and has been applied to the other serogroups in the vaccines.

Dr. Schuchat said she thought for the time being it would be important to assess this issue in a vaccine-specific manner in terms of the body of evidence underpinning a correlate of protection. As shown the previous day with the pneumococcal work, a correlate in adults is not really agreed upon and the FDA is requiring a post-licensure effectiveness study. This illustrates the challenge many working groups are having with GRADE as originally conceived now being adapted to vaccines. As an agency, CDC is considering learning from this first family of vaccine grading experiences and potentially generating a “Grade 2.0” that might be more user-friendly for the working groups. She noticed the same thing, and imagined the enormous amount of literature for Influenza Vaccine Working Group to be challenging. However, that group would need to consider what is known and knowable and not necessarily bridge from meningococcal.

Dr. Baker asked Dr. Cohn to comment on the data for post-licensure efficacy for adolescents in terms of the reduction observed after recommendation of the quadrivalent conjugate vaccine.

Dr. Cohn replied that the case-control study data had taken 7 years to collect and update because of the low incidence of disease is correlating nicely with antibody titers waning. The first year after vaccination protection appears to be very high as suggested by the SBA titers. Over time, 3 to 5 years after vaccination, vaccine effectiveness is considerably lower. That also correlates with waning group-specific antibodies that have been observed. Meningococcal disease is also very specific in terms of not being able to mount a memory response prior to developing disease. For that reason, it actually correlates even better than perhaps other conjugate vaccines do.

Regarding antibody titers and not downgrading because of indirectness, Dr. Campos-Outcalt pointed out that there are good clinical outcome data showing that those antibody levels are protective.

Peter Paradiso (Pfizer) said that having spent the last 4 to 6 weeks immersed in this evidence-based approach and trying to learn it, he thought Dr. Schuchat's comment about a vaccine-specific grading system was very important because manufacturers' lives depend upon correlates of immunity for licensure of vaccines. There are two important issues to distinguish. For any of the meningococci, the percent of responders seems to be a correlate of immunity. Above a certain level there is efficacy associated with it. However, for many vaccines, it is showing non-inferiority to a vaccine that has proven efficacy and there is really nothing else that can be done besides that for these studies. That is considered a level of evidence that is as high as can be achieved. It is different with vaccines for which the level of evidence is about a response rather than a direct effect. In the consideration of how to adapt GRADE to vaccines, thought should be given not only to correlates, but also surrogates. Often it is the surrogate that can be compared to a vaccine that is proven to be efficacious.

Public Comment

Dr. Deborah Wexler
Executive Director
Immunization Action Coalition

I am Dr. Deborah Wexler, the Executive Director of the Immunization Action Coalition (IAC). IAC is funded by several vaccine companies, in addition to the Centers for Disease Control and Prevention and that public. In the presentation this morning, I noted and was troubled by the language, "Routine vaccination is not recommended." If I had a two-year old child, I would want my child to be vaccinated against meningococcal disease, even though the risk of disease would be low. These vaccines are FDA-licensed for use, they are safe, they are immunogenic, and individual parents may reasonably choose to have their child vaccinated. There is no reason to refuse a parent's request for their child, but the statement, "Routine vaccination is not recommended" is a significant barrier to the child receiving the vaccine, because to a healthcare provider, this language may be interpreted as a prohibition to administering it. An additional permissive statement, "The provider may administer the vaccine to a child if the parent wishes it," should be included in the recommendations to clarify that these FDA-licensed vaccines may be administered in these situations. Thank you.

Frankie Milley
National Director
Meningitis Angels

We do receive money from some pharmaceutical companies and also the public. I also have parents who call me on a daily basis almost, especially from Oklahoma, "I took my child to the doctor. We've had a family member die with this or be left debilitated with this disease. We had an outbreak. I took my 5-year old and the doctor refused to give me the vaccine because he said it's not recommended." Now, my idea for that is to take a piece of paper and make him sign it guaranteeing you your child won't get sick and that he's refusing you the vaccine. Of course, I'm sure all of the doctors in the room are going, "Ahhhh." But, I do agree with Dr. Wexler that there needs to be some wording so that physicians out there in the field understand that if a parent really wants this and they are willing to pay for it, they should have it. There is no reason why that child shouldn't have it. My question, the real reason why I wanted to come up here, too, is I want to make sure that as you proceed with your grading, that you take into consideration the disease outcomes. Because meningococcal, unlike most other diseases, is so severe, so rapid, so deadly, so debilitating, I absolutely believe that when you grade these vaccines you have to take that into consideration. So, if the committee has not done that, I would urge you to please do that for the sake of all of our children. Thank you.

Discussion Points

Dr. Grogg (AOA) reported that a 4-month old died the previous week in Tulsa with meningococcal group Y disease.

Dr. Marcy indicated that the working group has discussed adding language regarding persons wishing to protect themselves or their child against meningococcal disease, so this request has been heard and the working group intends to implement it.

Measles, Mumps, Rubella (MMR) Vaccine

Introduction

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

Dr. Temte indicated that the Measles, Mumps, Rubella (MMR) Vaccine Working Group's terms of reference are to review all available data and discuss potential changes to the current recommendations, which are quite dated. To achieve this, the working group's activities are to review epidemiology of measles, mumps, rubella, and congenital rubella syndrome (CRS); review the existing statements pertaining to MMR vaccine; review new data on MMR vaccine (e.g., safety and immunogenicity among persons with HIV; third dose for mumps outbreak control); and revise/update existing recommendations into a single comprehensive document.

The MMR Vaccine Working Group's recent activities to date have included: 1) reviewing measles vaccination policy, including reviewing immune response to measles vaccination at various ages for first dose and discussing the timing of vaccine dose in relation to measles; 2)

reviewing mumps vaccination policy, including reviewing the US mumps epidemiology and vaccination program; reviewing and discussing data from two studies that assessed the impact of a third dose of MMR vaccine on the course of the outbreak; and 3) reviewing rubella vaccination policy, including a review of the US rubella and CRS epidemiology and vaccination program.

During this session, presentations were delivered on the following topics:

- ❑ Update on the documentation of sustained elimination of endemic measles, rubella and CRS, US, December 2011
- ❑ Background and epidemiology of mumps in the US
- ❑ Impact of a third dose of MMR vaccine on the course of a mumps outbreak in Orange County, New York in 2009-2010
- ❑ Third dose MMR intervention during a mumps outbreak in a highly-vaccinated population in Guam 2010
- ❑ Summary of issues and discussion of options

Dr. Temte referred participants to the February 3, 2012 edition of *MMWR*, which includes an excellent review on the progress of global measles control from 2000 to 2010. One of the highlights is going from an estimated number of deaths worldwide in 2000 of over 800,000 down to about 160,000 by 2008.

Documentation of Sustained Elimination of Endemic Measles, Rubella and CRS, United States, 2011

Dr. Mark Papania
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Papania reviewed US efforts to document the sustained elimination of endemic measles, rubella, and CRS, which is part of the Pan American Health Organization (PAHO) effort to document elimination of these diseases from the entire Western Hemisphere, which if confirmed, is quite an historic achievement.

The goal is the elimination of endemic disease, which is defined as a chain of transmission of measles or rubella lasting 12 months or more. Elimination of endemic diseases does not mean there will be no cases. Imported cases with limited spread and even small outbreaks will continue to occur as long as the diseases are endemic elsewhere in the world. The US verified the elimination of endemic measles in 2000 and of endemic rubella in 2004. External panel reviews were conducted on the evidence of elimination and the extensive data and conclusions were published in a *Journal of Infectious Diseases* (*JID*) supplement for measles and a *Clinical Infectious Diseases* (*CID*) supplement for rubella. Tremendous progress has been made throughout the Americas, with the last endemic case of measles in the Western Hemisphere being reported in 2002 and the last endemic cases of rubella and CRS in 2009. Based on this success, PAHO is organizing formal verification and documentation of elimination of endemic measles, rubella, and CRS from the WHO region of the Americas. Each country in the region is working to assess their elimination status and producing a national report to be reviewed by an International Expert Commission.

As part of this effort, CDC has conducted an assessment to confirm that elimination of endemic measles, rubella, and CRS from the US has been sustained from the time of the initial documentation to the present. The relevant data were compiled into a draft report and the information was reviewed with a panel of external experts in December 2011, including: Drs. Jonathan Temte, Christine Hahn, Alan Hinman, Bonnie Maldonado, and Peter Shulte. On the regional level, the process of documenting and verifying elimination of endemic measles, rubella, and CRS is well-advanced. Fourteen countries have submitted their final reports, and three more including the US, will submit their reports in February 2012. Five other countries are a little further behind.

In terms of the overview of the evidence indicating that the elimination of endemic measles, rubella, and CRS from the US has been sustained, all incidences are extremely low. Reported measles cases have remained consistently below 1 case/million, and reported rubella cases have remained below 1 case/10 million. The majority of reported cases of both measles rubella are associated with importation. This includes internationally imported cases, and cases linked to importation by epidemiologic or virologic information. The remaining cases for which there is not an epidemiologic or virologic link to importation are considered to be unknown source cases. The number of reported unknown source cases of measles and rubella are insufficient to represent endemic chains of transmission. Although outbreaks are observed, they are small and of short duration. The coverage levels for measles, mumps, and rubella vaccine have been sustained at high levels for years. National serosurveys, such as the NHANES studies, have demonstrated high levels of population seropositivity to measles and rubella. Detailed molecular epidemiology has shown no endemic strain of measles or rubella virus in the US, and the surveillance system for measles and rubella is adequate to detect endemic disease if it were occurring. Dr. Papania briefly reviewed most of the lines of evidence of the elimination.

Base on the data reviewed for 2001 through 2011, for measles, 40% of the reported cases were imported and 88% were importation-associated. Internationally imported measles cases occur in persons who were outside of the US during their exposure period. Import-linked cases have a documented epidemiologic link to an imported case. Imported virus cases do not have an epidemiological link to an imported case, but do have genotype information indicating an association to importation. Taken together, imported, import-linked, and imported virus cases are considered importation-associated cases and constituted 88% of reported measles cases from 2001 through 2011. The remaining 12% of cases are unknown source cases. In these cases, measles transmission occurred in the US. However, an epidemiologic link to importation was not detected, and there is no genotype information on these cases. It is possible and even likely that these cases spread from imported measles cases through an undetected link or chain of transmission. However, these unknown source cases must be carefully assessed to determine whether they might represent an endemic chain of transmission. It is important to note that the amount of spread from imported cases was limited, with 84% of imported cases resulting in no reported spread cases and only 7.5% resulting in outbreaks. The same definitions of importation status are used for rubella. From 2004 to 2011 there were extremely low numbers of reported rubella cases, with less than 20 cases reported per year. For rubella, 38% of cases were imported and 53% were importation-associated from 2004-2011. Rubella unknown source cases averaged only 6 cases per year. The very low number of reported rubella cases makes secondary analysis somewhat less critical than for measles; therefore, Dr. Papania focused primarily on measles for the remainder of his presentation.

For the period from 2001 through 2011, a total of 106 unknown source cases of measles were reported. Only 66 counties reported an unknown source case and only 17 counties reported more than 1 unknown source case in this period. In each of these situations, the reports of unknown source cases occurred in a restricted timeframe, with the remainder of the year having no additional reported unknown source cases. Los Angeles County had the most reported unknown source cases, with 9 cases reported total in 5 different years. For measles for this time period, only 16 outbreaks had more than 10 cases and the maximum number of cases was 34 cases. Of these outbreaks, 13 had documented imported sources and 3 had genotype information indicating an imported virus. The longest outbreak lasted 11 weeks. For rubella, there were only 2 outbreaks which included 3 cases, and there were no outbreaks with more than 3 cases.

The National Immunization Survey (NIS) has documented MMR 1-dose coverage of over 90% among children 19 through 35 months of age for the period 2001 to 2011. Adolescent coverage with 2 doses of MMR has been added to the survey since 2008 and runs around 90% [2010 National Immunization Survey for children and teens, available at http://www.cdc.gov/vaccines/stats-surv/imz-coverage.htm]. Serosurveys conducted from 1999 through 2004 as part of NHANES demonstrated an overall measles seropositivity of 95.9% among the non-institutionalized US population aged 6 years and older, with the specific estimates of seropositivity for different birth cohorts shown in the following table:

Birth Year Cohorts	Participants (N)	Seropositive Proportion, % (95% CI)
1949-1966	3360	96.6 (95.5-97.5)
1967-1976	2321	92.4 (90.8-93.9)
1977-1986	5288	96.4 (95.5-97.2)
1987-1998	5080	97.7 (96.4- 98.6)
All Cohorts	16,049	95.9 (95.1-96.5)

The overall seroprevalence of rubella antibody in persons 6 through 49 years of age in the NHANES surveys conducted from 1999 through 2004 was 91.3%.

Much of the evidence for elimination of measles and rubella is based on data from the surveillance system, so it is critical to assess the adequacy of surveillance. It is known that the US surveillance system does not detect all measles or rubella cases, and unfortunately, there are not precise measures of the completeness of reporting. However, the question for this elimination assessment is whether the surveillance system in the US would detect endemic transmission if it were occurring. There is evidence to suggest that the system is adequate. The US system consistently detects imported cases, which can be the most difficult cases to detect because many of the cases occur in foreign visitors who are unfamiliar with the US health care system and may be unlikely to seek care before returning home. The US surveillance system detects isolated cases and small chains of transmission; therefore, it would be unlikely that the system would fail to detect the large chain of transmission which endemic disease would require. Although the surveillance system is passive, waiting for reports from providers, a report of a suspected case activates rapid public health response with active investigation and response through contact tracing. Anecdotally, this active investigation only detects a few unreported cases found retrospectively. The US does not monitor the numbers of suspected cases investigated and discarded or the numbers of IgM tests performed, which would be

measures of surveillance effort. However, there is a substantial IgM testing volume as evidenced by CDC confirmatory testing volume. Very few cases of measles or rubella are confirmed, even in the presence of substantial testing.

Upon review of the draft report, each external expert concluded that elimination of endemic measles, rubella, and CRS from the US has been sustained. The *US National Report on Elimination of Endemic Measles, Rubella, and CRS* has been refined based on suggestions from the expert panel, is currently in CDC clearance, and will be submitted to the PAHO International Commission for review this month.

Discussion Points

Dr. Temte emphasized the fragility of the public health system in the US and the overwhelming importance of surveillance capacity. He keeps hearing at various meetings how budgetary issues are affecting public health, and issued a plea for people to be wise in application of public funds to support efforts that have really had tremendous impacts on health in this country.

Dr. Baker concurred with the need to continue to strengthen, not weaken, the US public health system at the federal, state, and local levels.

Dr. Orenstein noted that this point is exactly why a working group of the National Vaccine Advisory Committee was constituted to determine what is really needed for the non-vaccine side of public health, which would include surveillance.

Mumps in the United States: Background and Epidemiology

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Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Mr. Barskey presented on the background and epidemiology of mumps in the US, discussing the pre-vaccine era (1917-1967), vaccine implementation (1968-1982), mumps resurgence (1983-1992), the first national outbreak (1993-2008), the second national outbreak (2009-2011), and recent mumps vaccine performance.

Mumps is an acute viral illness that can present with classic symptoms, including parotitis (60%-70%), orchitis (30% in post-pubertal males), and fever. Other symptoms include non-specific respiratory symptoms (40%-50%) and other salivary gland swelling (10%). Complications can include deafness (4%), aseptic meningitis (1%-15%), and encephalitis (0.03%). Up to 30% of cases can be asymptomatic.

The mumps vaccine used in the US was licensed in 1967. It is composed of a live, attenuated mumps virus. The Jeryl Lynn strain is used in the US, and that virus is of the Genotype A. The vaccine effectiveness estimates ranges are wide. One dose is approximately 77% effective, and two doses are approximately 88% effective [Schaffzin JK et al. *Pediatrics*. 2007;120:e862-8, Marin M et al. *Vaccine*. 2008;26:3601-7, Cohen C et al. *Emerg Infect Dis*. 2007;13:12-7, Deeks SL et al. *CMAJ*. 2011;183:1014-20, Dominguez A et al. *Vaccine*. 2010;28:3567-70, Sartorius B et al. *Euro Surveill*. 2005;10:191-3, Harling R et al. *Vaccine*. 2005;23:4070-4].

In the pre-vaccine era, peak incidence occurred in 5 to 9 year-olds,' and 90% of children were infected by age 14[1]. Most cases occurred in late winter and spring[2]. There were no remarkable geographic patterns[3]. Most adult disease was associated with outbreaks in the military[2,3]. Mumps was a significant cause of aseptic meningitis[4] [[1]Collins SD. *Pub Health Rep*. 1929; 44:763-826; [2]Gordon JE. *Am J Med Sci*. 1940; 200:412-28; [3]Gordon JE. *Am J Med Sci*. 1949; 218:338-59; [4]USDHEW. Mumps Surveillance: Report No. 1. 1968].

With regard to reported annual incidence of mumps in the pre-vaccine era, epidemic peaks occurred about every three years. In terms of the reported monthly cases of mumps in the US during the vaccine era, during the vaccine implementation period, there was a 97% reduction in reported cases. Notably, there was a remarkable decline in cases even before ACIP made a routine recommendation for 1 dose of mumps vaccine in 1977. A resurgence occurred in the late 1980s and early 1990s. This was marked by an increase in cases in 10 to 19 year olds. In the early 2000s, mumps appeared to be nearly eliminated from the US until a large multi-state outbreak occurred in 2006. The outbreak occurred in a population with high 2-dose vaccine coverage. A few years later, a second multi-state outbreak occurred also in communities with very high 2-dose vaccine coverage.

Taking a closer look at the period of the resurgence from 1983-1992, some late winter and spring seasonality was apparent. The increase in mumps cases occurred in two waves. There was an abrupt rise and fall in incidence in 1986-1987, and a slow return to baseline incidence from 1988-1992. The 1986-1987 resurgence was attributed in an increase in susceptibility among older children who had not been vaccinated, but who had been spared previous disease exposure by declining mumps incidence[1]. During 1988-1992, outbreaks associated with 1-dose vaccine failure were first reported.[2-4] [[1]Cochi SL, *et al*. *Am J Dis Child*. 1988; 142:499-507; [2]Hersh BS, *et al*. *J Pediatr*. 1991; 119:187-93; [3]Cheeck JE, *et al*. *Arch Pediatr Adolesc Med*. 1995; 149:774-8; [4]Briss PA, *et al*. *J Infect Dis*. 1994; 169:77-82].

In December 1989, ACIP recommended a second dose of measles vaccine for improved measles control. ACIP suggested that it be administered as MMR, stating that "Mumps revaccination is particularly important." Effectively, this was a recommendation for a second dose of mumps vaccine [[1]ACIP. *MMWR Morb Mortal Wkly Rep*. 1989; 38(S-9):1-18].

Through the early 2000s, there were signs of elimination. Disease incidence fell to less than 1 per million. Vaccination coverage was higher than the estimated herd immunity threshold. No seasonality was apparent, and there were no locations of sustained transmission. However, in 2006 there was a sharp rise and fall of cases, particularly in the Midwest. This was the first multi-state outbreak attributable to 2-dose vaccine failure. Young adults 18 to 24 years of age were most affected. Most were college students, almost all had had 2 doses of vaccine, most had received vaccines more than 10 years previously, and dormitory living and freshman class status were seen as risk factors. The outbreak was geographically focused, and there was a sudden onset and sudden decline of cases. ACIP issued a formal recommendation in 2006 for 2 doses of a mumps-containing vaccine for school-aged children grades K-12 and adults in high risk groups (e.g., healthcare facility workers, international travelers, and students at post-high school educational institutions [ACIP. *MMWR Morb Mortal Wkly Rep*. 2006; 55(22):629-30].

A second national outbreak occurred between 2009-2010. There was an abrupt epidemic rise and fall of cases during the outbreak period. This was the second multi-state outbreak in communities with high 2-dose vaccine coverage. Of the cases, 97% occurred within an Orthodox Jewish community. Adolescent males 13 to 17 years of age were the most affected demographic group. Approximately 90% had received 2 doses of the vaccine. Unique school

settings and large households were conducive to mumps transmission. Boys attend Yeshiva, or religious schools, where Orthodox Jewish boys study religious texts beginning at approximately age 12 years. School days were long, lasting up to 15 hours per day. Learning was interactive, often involving a Chavrusa, meaning friend or study partner. Partners sit across narrow tables to study texts. The format is close, face-to-face, and often animated. Several pairs sometimes sit at a single table. During the course of a single day, partners may rotate for several different sessions. These unique school settings and large households appeared to be conducive to mumps transmission. It appeared that prolonged, intense exposures likely overcame the protection afforded by the vaccine. Also in 2010, a large mumps outbreak occurred on the island of Guam. Many school children 9 to 14 years of age represented the most affected age group. Kindergarteners through middle school children attending public school had at least 95% coverage with 2 doses of MMR vaccine.

Regarding recent mumps vaccine performance, the effectiveness of 1- and 2-dose mumps vaccine measured in recent outbreaks was compared. For 1 dose, the median effectiveness estimate was 77% and for 2 doses was approximately 88%.

A study was conducted by Cohen et al in the United Kingdom (UK) during 2004-2005. This study took place during a time when over 50,000 mumps cases were reported in the UK in 2005. The overall vaccine estimate was 88% for 1 dose and 95% for 2 doses. However, for the first dose, vaccine effectiveness declined from 96% in 2-year olds to 66% in 11 to 12 year olds. For the second dose, vaccine effectiveness declined from 99% in 5 to 6 year olds to 86% in 11 to 12 year olds [Cohen C et al. *Emerg Infect Dis*. 2007;13:12-17]. If one assumes that age is a reasonable proxy for time since vaccination, then these results suggest waning immunity of full mumps vaccine.

Several biological studies have been conducted to assess the duration of immunity for the mumps vaccine; however, correlates of protection are not well-defined. It has been shown that seropositivity declines over time[1], neutralizing antibody titers decline over time[2], and cellular immunity declines less than seropositivity over time[3] [[1]Davidkin I et al. *J Infect Dis*. 2008;197:950-6; [2]LeBaron CW et al. *J Infect Dis*. 2009;199:552-60; [3]Jokinen S et al. *J Infect Dis*. 2007;196:861-7].

In terms of these outbreaks, more than waning immunity seems to be at play. Waning immunity does not explain certain facets of these outbreaks, including the geographic focal nature of the outbreaks and the fact that in several of these outbreaks, the oldest vaccinated cohorts were not always the most affected. Factoring in intense exposure settings accounts for the focal nature and why some of the oldest cohorts were not the most affected.

In summary, prior to use of the mumps vaccine, mumps was a universal disease of childhood. Use of the mumps vaccine reduced disease levels by more than 95%. The current 2-dose schedule is sufficient for mumps control in the general population, but outbreaks can occur in well-vaccinated communities. Intense exposure settings and waning immunity appear to be risk factors for secondary vaccine failure.

The Impact of a Third Dose of MMR Vaccine on the Course of a Mumps Outbreak: Orange County, New York: 2009–2010

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Centers for Disease Control and Prevention

Dr. Kutty noted that there is no current ACIP recommendation for a routine third dose of mumps vaccine in any setting. Prior to this intervention, the effect of a third MMR vaccine dose in outbreak settings has not been evaluated. In this presentation, Dr. Kutty reviewed the epidemiology of the Orange County outbreak, the third dose MMR vaccine intervention, self-reported adverse events following the receipt of the third dose, and the economic burden of this outbreak on public health.

Of the four locations affected by the 2009-2010 Northeast mumps outbreak, Orange County had approximately 20% of the reported mumps cases. The outbreak was limited to a village in Orange County. As per the 2010 US Census, the affected village in Orange County had a population of 20,363 and a median age of 10.6 years. It is comprised predominantly of an Othrodox Jewish population. The average household size is more than twice the national average of 2.6, which can lead to crowded living conditions. There are 4 main physician practices in the village, of which two see greater than 90% of the residents.

Reporting of mumps is mandatory in New York State [New York State Sanitary Code (10NYCRR 2.10,2.14)]. Active surveillance was instituted by Orange County Health Department after the report of the first case of mumps. They contacted the 4 physician practices as well as the households of the mumps cases. To define a mumps case, the standard CSTE case definition was used. During the outbreak period from September 1, 2009 through June 30, 2010, 790 mumps cases were reported by Orange County to CDC. The median age was 14 years, with 64% being male. Approximately 70% of the reported mumps cases had received two doses of MMR vaccine, and approximately 57% were 11 to 17 years of age. A large percent of the mumps cases reported being exposed in schools and homes. Among the post-pubertal males 6.4% had orchitis, and among those tested for mumps IgM, 18% were positive (n=231). The Genotype was G, similar to the genotype in the UK.

A study was conducted to determine whether administration of a third dose of MMR vaccine in a highly vaccinated population is an effective strategy for controlling mumps outbreaks. IRB approval by CDC and New York was required for this intervention since there was not an ACIP recommendation. Given that the attack rate was highest among 11 to 17 years old, the intervention was conducted among 6th through 12th graders. Inclusion criteria for schools were on-going mumps transmission in preceding 2 weeks and high 2-dose MMR vaccine coverage. The weighted vaccine coverage was 94.3%. Criteria for student eligibility were no previous history of mumps and no previous history of a third MMR vaccine dose. A third dose of MMR vaccine was offered to assenting students who also needed to obtain informed consent from their parent or guardian.

Considering the incubation period of mumps, the analysis used three time periods of 21 days (e.g., pre-vaccination, post-vaccination phase 1, and post-vaccination phase 2). Analyses were conducted at the student level as well as the village level. For the student level analysis, the three time periods were based around each student's vaccination date. At the village level, the time periods were defined around the vaccine intervention period of January 19th through February 2nd. Age specific attack rates/1000 were calculated using the following formula:

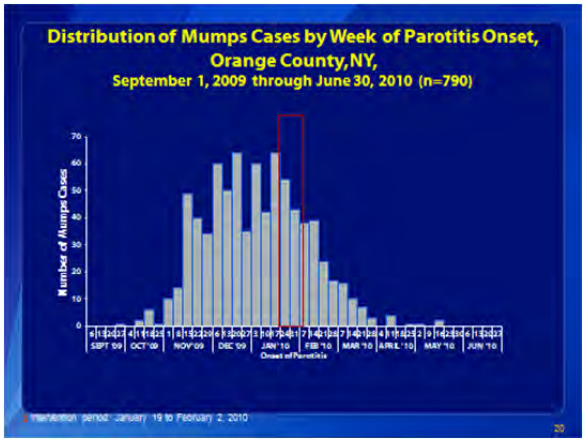
$$\frac{\text{No. of mumps cases in an age-group during a given time period}}{\text{Population at risk [US Census 2010] in that age-group during the same time period}}$$

The intervention was conducted in 3 schools that fit the criteria; schools were provided with the vaccine. Of the children in the village, 98% attended one of these 3 schools. Prior to providing the vaccine to these students, a baseline survey, vaccine information, and informed consents were distributed. The baseline response rate was 94%. Of these, 89% (n=2178) had validated 2 doses of MMR vaccine, and 81% (n=1755) received a third dose. To determine the attack rate among 6th through 12th grade students before and after the third dose MMR vaccine intervention, the pre-vaccination period was compared to the post-vaccination phase 2. The overall attack rate of 4.93% during the pre-vaccination period showed a significant decline during the post-vaccination phase 2 of 0.13%. There were very few cases in post-vaccination phase 2.

Next, students with 2 previous MMR vaccine doses were assessed. The attack rates in the post-vaccination phase 1 and phase 2 periods were compared. The attack rate of students who received a third dose significantly declined from 1.6% to 0.06%. While among those who did not receive a third dose there was a decline from 1.7% to 0.5%, this decline was not significant. However, during the post-vaccination phase 2, the attack rate was 8-fold lower among vaccinated students, although the difference was not statistically significant (0.06% versus 0.48% respectively, RR: 0.12 (95% CI: 0.01, 1.32; P=0.097). This finding may be because of the very low numbers of mumps cases in the two groups. The incremental effectiveness of the third dose of vaccine was 88.0%, with a large confidence interval that included 0 (95% CI: -31.9% to 98.9%).

At the village or population level, the pre-intervention and post-intervention phase 1 period were compared. There was a 76% percent decline in the attack rates when the pre-intervention period was compared to the post-intervention phase 2 period. The attack rate in the targeted age group 11 to 17 years showed 96% decline, the highest among all age groups. The other age group where a decline was observed was among 5 to 10 year olds (73% relative decline). The relative decline in attack rates in the 11 to 17 year age group was significantly greater ($P<0.005$) than that in any of the other 4 age groups. There was a significant decline in the attack rate during and after the intervention. The other age group that showed a significant decline was the age group 5 to 10 years of age, though the decline was more gradual.

To see how the situation looked overall, the following graphic shows the epidemiological curve of the 790 mump cases by week of parotitis onset, reported in Orange County from September 1, 2009 through June 30, 2010. The red box indicates the 2-week period when the 3rd dose of MMR vaccine was offered to eligible 6th through 12th grade students at participating schools. There is a decline of mumps cases during and after the intervention:



The investigators returned to Orange County in April 2010 to conduct a follow-up survey, which also captured information on adverse events. Of the 1755 who received the third dose of MMR vaccine, 91% returned the follow-up survey. Of these, 7.2% (n=115) self-reported at least one adverse event, and 17 reported seeking medical attention. However, on further follow-up, none were related to the vaccine. In addition, a comprehensive search for serious adverse events following MMR vaccination was conducted using physician records, physician billing services, and VAERS. Among the serious adverse events self-reported, 3.6% reported pain, 1.8% arthralgia, 1.7% dizziness, and 1.3% fever. A literature review was then conducted. The proportions of adverse events found in the present study were lower than or within the range of those reported in prior studies of first- and second-dose MMR vaccine studies using Jeryl-Lynn strain, indicating that it is at least as safe as the first and second of MMR vaccine.

To evaluate the economic burden, the outbreak and response activities performed, personnel time/materials allocated, third dose MMR vaccination intervention, laboratory testing, and direct costs incurred in 2010 US dollars by the New York State Health Department and Orange County Health Department were examined. The study period for this assessment was from September 24, 2009 (when the OCHD was first contacted about the mumps outbreak) through June 15, 2010 (when the outbreak ended). Chronological descriptions were obtained from each involved institution. Personnel time was based on the hours allocated to containment obtained from written chronological reports with the personnel in the involved institutions. Personnel time was converted to costs by using the reported gross wage of each individual, plus fringe benefits when available. Overhead costs were based on the number of person-hours and each institution's accounting method. A total of 7736 hours of personnel time were expended, of which 3656 hours (47.3%) were by New York State Health Department and 4080 hours (52.7%) were by Orange County Health Department. The total estimated cost was $463,202, of which 89% was attributable to personnel costs and overhead. The third dose MMR vaccine intervention cost $34,392.

There were several limitations to the study. The mumps outbreak was probably on the decline when the intervention was conducted. There was not a large comparison group due to the high uptake of the vaccine. There was a small number of mumps cases post-intervention. This study is not generalizable, given that it was conducted in a specific population. In addition, the economic survey was done retrospectively.

In summary, further declines in incidence of mumps cases were observed after administration of a third dose of MMR vaccine. Although the decline was seen in many age groups, the most pronounced was in the age group targeted (e.g., 11 to 17 years of age), which showed 96% percent decline. The adverse events reported post-vaccine were found to be lower than or within the range of those reported in prior studies of first- and second-dose MMR vaccine. Use of a third dose of MMR vaccine to control the outbreak as routine control measure may be effective, especially when other routine measures are not effective.

Third Dose MMR Intervention During a Mumps Outbreak In a Highly-Vaccinated Population in Guam: 2009-2010

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CDR Fiebelkorn described the epidemiologic characteristics of the Guam mumps outbreak; the impact and adverse events of a third MMR dose for mumps outbreak control; and the economic impact of the outbreak response on the local public health sector and affected families.

Guam is an organized, unincorporated territory of the US located in the Pacific Ocean. The 2010 population was more than 180,000 persons. The median household size is 3.9 persons compared to the US mainland, which is 2.6 persons. The median household income on Guam is approximately $40,000 compared to nearly $50,000 on the US mainland. Guam follows ACIP recommendations for MMR vaccination [Guam 2008 Statistical Handbook].

Mumps is a reportable disease in Guam. The Guam Department of Public Health and Social Services and CDC implemented active surveillance of schools, daycares, select provider clinics, and laboratories. Cases were reported to the health department on a daily basis. Daily reporting forms were completed, including zero reporting. If these were not received, phone calls were placed to follow up on the information. Educational sessions were held for all those involved in active surveillance.

Once a case was identified using the standard CSTE mumps case definition, a case report form collected basic demographics, diagnostic methods, illness course and complications, and vaccination history. Age-specific attack rates were calculated using projected 2010 Guam population data. For schools, school enrollment data were used. Vaccination coverage was assessed in schools via electronic records of all students enrolled in public schools. For all case-patients, vaccination verification was obtained from health-care providers. Laboratory tests that were used to confirm cases included mumps IgM, RT- PCR, and viral cultures. Mumps viral sequencing and genotyping analyses were performed at CDC.

The outbreak period was defined as December 7, 2009 when the index case imported mumps from Pohnpei through December 31, 2010. During that time period, 505 cases were reported. The epidemic curve shows the peak of the outbreak occurring in April and May of 2010. Of the 505 cases reported, 50% were males; the median age was 12 years, with a range of 2 months to 79 years of age; and 34% self-reported Chamorro ethnicity, the predominant ethnicity on Guam. There were 5 (3.3%) reports of orchitis among post-pubertal males, 2 (0.4%) hospitalizations, and no deaths. Of 312 specimens tested, 60 (19%) were IgM+ and 28 (82%) of 34 specimens sent to CDC were positive by RT-PCR. Genotype G was identified, but was a different lineage than the strain identified in the Northeast outbreak.

When compared with the Guam population, mumps case patients were statistically more likely to be 9 to 14 years of age, with a risk ratio of 16.2 and an attack rate of 8.4. Mumps case patients were also more likely to have reported their ethnicity as Chuukese or Pohnpeian, both of whom are the ethnic minority populations on Guam. Of the total 505 cases, 169 were among the 9 to 14 year old age group.

CDC obtained IRB approval to administer a third dose of MMR vaccine, because a third dose in an outbreak setting is not currently an ACIP recommendation. Schools were eligible for the third dose MMR intervention if they had greater than 90% 2-dose MMR vaccine coverage confirmed by review of school vaccine records, evidence of on-going mumps transmission in the previous two weeks, and a mumps attack rate greater than 5 per 1000. An individual student was eligible for the intervention if he or she had no history of mumps or receipt of a third dose of MMR vaccine. Additionally, consent was required from the parent and assent was required from the child.

A baseline survey was conducted at the time of the intervention in May, and a follow-up survey was administered in October among all students eligible for the third dose. On both surveys, information was collected on demographics, whether the child participated in the third dose intervention, and self-reported mumps and complications. On the follow-up survey, information was also collected about self-reported adverse events following immunization.

The pre-intervention attack rate was highest among children aged 9 to 14 years in 7 schools. There were 4 elementary and 3 middle schools. These 7 schools were selected for participation in the MMR third dose intervention. These 7 schools also had evidence of on-going recent transmission, with attack rates ranging from 8.4 to 31.5 per 1000, as noted in the second to last column in the following table, and evidence of high 2-dose vaccination coverage, as noted in the last column:

Attack Rates and MMR Vaccination Status at the Seven Selected Schools

School	Cases	Enrollment	Attack Rates (cases/1000)	2 Dose MMR Coverage
School A	17	540	31.5	100%
School B*	8	585	13.7	99.3%
School C	3	357	8.4	100%
School D*	10	1189	8.4	99.7%
School E	15	478	31.4	100%
School F	8	598	13.4	100%
School G*	21	1120	18.8	99.8%

*Middle school

There were 3241 eligible students ages 9 through 14 in grades 4through 8 at the 7 selected schools in May 2010. Of these, 1067 (33%) received a third dose of MMR vaccine, and 2447 (75%) eligible students returned a baseline and / or a follow-up survey. There were statistically significant differences between survey respondents who received the third dose and those who did not. Those receiving the third dose were more likely to be female, uninsured, and in the lower grades compared with those who did not receive the third dose.

With respect to mumps by age group and by time, the week of the third dose intervention occurred after the peak of the outbreak on May 14-27. There was an attack rate of 2.4 per 1000 among 2-dose vaccinated students, and 0.9 per 1000 among 3-dose vaccinated students more than one incubation period post-intervention. When any case that occurred more than one incubation period following the intervention was included, 6 students in the intervention schools reported mumps. Of these students, 1 had received a third dose and 5 had not. Students who had 3 doses of MMR vaccine had a 2.6 times lower mumps attack rate compared with students who had 2 doses of MMR vaccine, but the difference was not statistically significant. On the population level, the 9 through 14 year age group had the largest relative percent decline in age-specific mumps attack rates during the second post-intervention period compared with pre-intervention at 84.4%. However, other age groups also showed significant declines. Overall, there was a 70.7% decline among all age groups during the second post-intervention period compared with the pre-intervention period.

Regarding self-reported adverse events among those who received a third dose of MMR vaccine who responded to the survey, the most frequently reported adverse events were dizziness at 2.6% and pain and redness at the injection site and joint ache, both at 2.4%. Of the students responding, 32 (6.0%) indicated any adverse events. There were no life-threatening adverse events reported, and no medical attention was sought related to the vaccination.

The next objective was to describe the economic impact of the outbreak response on the local public health sector and affected families. An economic survey was conducted from a public health perspective. It included all departments and individuals directly involved in the outbreak response, including Guam Department of Public Health and Social Services (DPHSS) and school nurses. The covered activities, from the time of first case reports in February 2010 through October 22, 2010 (the time of the follow-up survey), included in the survey were hours spent, overhead costs, travel, telephone calls, salaries, and vaccine use. For the economic survey from the public health perspective, there were 73 people directly involved in the public health outbreak response. An estimated 8264 hours were spent controlling the outbreak, with DPHSS staff accruing 7484 hours (90% of the total hours). An estimated $281,856 was spent on the outbreak response (DPHSS: $261,798; School Nurses: $20,058).

For the economic survey from the household perspective, telephone questionnaires were administered to persons affected with mumps or their parents/guardian if the affected person was a minor. Participants were taken from the Guam DPHSS outbreak case investigation database. The sample size was 102 persons. The first 20 cases and the last 82 cases of the outbreak were samples to assess change in the cost of the illness over the course of the outbreak. The survey included information on medical consultation fees, transport to a clinic, the number of days the case-patient or parent missed work due to mumps, cost of medications, and any hospitalization related to mumps. Of the responders, 95 (93%) sought treatment from a healthcare provider at a median cost of $20 per case for all visits, 87 (85%) incurred travel expenses for medical consultations at a median cost of $5 per case, 52 (51%) bought medications for their symptoms at a median cost of $10 per case, and 48 (47%) reported missing work an average of 4.6 days. The median cost per family for days lost from work was $601. The total median cost for the household for a typical mumps patient was $636.

This investigation is subject to several limitations. The intervention occurred after the peak of the outbreak. The small numbers of mumps cases in the intervention population make it difficult to draw conclusions on vaccine effectiveness. Although active surveillance increased reporting, there was likely a fair amount of under-reporting of cases, especially when school was not in

session. There were differences between vacinees and non-vaccinees, making the findings non-generalizable. The economic surveys were retrospective.

In summary, this was the largest reported mumps outbreak on Guam in 52 years and the third largest mumps outbreak in the US since 2005. The Guam outbreak occurred primarily in school-aged children despite high two-dose MMR coverage, and disproportionately affected 9 to 14 year olds in seven schools. After the third dose intervention, the relative percent decline of mumps attack rate was 70.7% among all age groups and 84.4% among all 9 through 14 year olds. The post-intervention attack rate was lower for students who received the third dose compared with those who did not, but the intervention occurred after the outbreak peaked and findings were not statistically significant. The mumps outbreak response imposed a large time burden and cost on local staff and affected families. These findings do not provide conclusive evidence on impact of a third dose for outbreak control, but are consistent with potential impact.

Summary of Issues and Discussion

Dr. Huong McLean
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. McLean presented a summary of the issues and the working group considerations for use of a third dose of MMR vaccines for mumps control. The US experienced large mumps outbreaks in 2006 with over 6500 cases reported and in 2009-2010 with approximately 3500 cases among highly 2-dose vaccinated populations. Mumps outbreaks among highly 2-dose vaccinated populations are likely to occur in the future, given the effectiveness of 2 doses of mumps vaccine and the presence of endemic mumps throughout the world. Standard outbreak control measures, such as isolation of cases and vaccination of eligible contacts, have not been completely effective in controlling outbreaks in some situations. Currently, there is no recommendation for use of a third dose of MMR vaccine during mumps outbreaks.

The two studies presented provide common findings with regard to the use of a third dose of MMR vaccine in outbreak settings. First, the target age group had the highest decline in attack rates following intervention compared to other age groups. In Orange County, there was a 96% relative decline among students aged 11 to 17 years. In Guam, there was an 84% decline among students 9 to 14 years of age. However, there were a number of limitations, including the timing of the intervention, which made it difficult to discern the effect of a third dose. A third dose of MMR vaccine appears to be safe. There were very few mild and no serious adverse events reported upon administration of a third dose of MMR vaccine in these studies. These vaccine interventions can be resource intensive. The cost to investigate the outbreak and implement the intervention was estimated to be $463,202 ($586/case) in Orange County and $281,856 ($558/case) in Guam.

Given the limitations of the studies, the working group agreed that there was not enough data to support a firm recommendation for a third dose of MMR vaccine for routine outbreak control of mumps, and that more data are needed. However, the working group discussed the possibility of a statement to allow permissive use of a targeted third dose of MMR vaccine for mumps outbreak control in certain situations with appropriate guidelines. The working group discussed parameters to define the appropriate setting, high 2-dose coverage, and timing, specifically assessing minimum attack rate or number of reported cases and minimum number of generations as guidance for when an intervention would be appropriate. These parameters are meant to provide guidance, and are not strict requirements for intervention.

The first parameter discussed by the working group was the setting in which an intervention would be appropriate. Experience with previous outbreaks suggests the congregate environments with prolonged or repeated, intense exposures are important settings that may facilitate mumps transmission despite high 2-dose coverage and lead to large outbreaks. These settings include schools, colleges, correctional facilities, and residential or institutional settings. Future outbreaks in these closed settings would be appropriate for a third dose vaccine intervention. The working group also thought that targeting personnel in health facilities would be appropriate, given their potential to expose immunocompromised patients, although there have not been large mumps outbreaks in health facilities.

The working group then discussed how high 2-dose coverage should be, and felt that over 90% coverage in the target group would be reasonable. The working group did not want to suggest a third dose if a population needed to catch-up on 2-dose vaccination coverage, because setting the coverage too high may not be practical. The working group considered national 2-dose coverage of MMR vaccine among adolescents aged 13 to 17 years, which is estimated to be 90.5%[1] according to the National Immunization Survey. They also considered the estimated herd immunity threshold, which is about 85% to 92%[2,3], and data showing MMR vaccine uptake in 3 large colleges to be 88% to 89% [[1]MMWR. 2011; 60(33);1117-1123; [2]Anderson RM, et al. *Epidemiol Infect.* Aug 1987;99(1):65-84; [3]Anderson RM, May RM. *Nature.* Nov 28-Dec 4 1985; 318(6044): 323-329].

The last and most difficult issue the working group considered pertained to time in terms of when the intervention should be conducted. The working group preferred using an attack rate which is specific to the target population for vaccination with a minimum number of cases, which may vary depending upon the setting and the number at risk. An attack rate of 5 cases per 1000 population at risk seems to be high enough above the background rate and is a reasonable starting point. Another aspect of timing was the number of generations, or ensuring that there was on-going transmission before initiating the intervention. The working group thought that mobilization of the intervention should start ideally after two generations of spread in the target group, especially since there may be unreported or asymptomatic cases.

The Orange County mumps attack rate in 14-day intervals, which was just short of the median incubation period for mumps, was calculated for the 11 to 17 year old age group. In this case, a third dose of vaccine was administered after 7 generations of spread and over three months after the attack rate reached 5 per 1000. The guidelines presented suggest initiating the third dose after the second generation of spread when the attack rate in this population reached 5 per 1000, which was in October instead of January. During this outbreak, there was sustained transmission for quite some time. In contrast, in the outbreak in Guam the total cases started to decline after several weeks. Because of delays in reporting, identification of the target population, and time to plan the intervention, by the time the third dose was implemented, the outbreak was declining. In a mumps outbreak at a college, the attack rate was over 5 per 1000 with the first generation of cases, and over 5 per 1000 with the second generation as well. According to the guidelines presented, it would have been ideal to initiate a third dose intervention after the second generated had occurred at about mid-March. The last example is of a smaller mumps outbreak at another college. The attack rate almost reaches 5 per 1000 during the first generation of cases, but the attack rates declined thereafter. In this case, a third dose intervention would not be warranted.

In conclusion, Dr. McLean requested that the ACIP members discuss whether permissive use of a targeted third dose for mumps outbreak control in certain situations would be reasonable, based on the guidelines presented (e.g., congregate environments with prolonged or repeated, intense exposure; >90% coverage with 2 doses of MMR in the target population; attack rate of > 5 per1000; and at least 2 generations of spread).

Discussion Points

Dr. Duchin commented that it was remarkable how rapidly the attack rate was decreasing before the intervention, but that some benefit was still found among those who were vaccinated compared to those who were not. He wondered whether those who were not vaccinated were assessed to determine whether they were at higher risk of disease (e.g., larger families).

Dr. Kutty replied that the next step for the New York outbreak would be to assess risk factors for transmission. There are also plans to model the outbreak and apply the intervention at different time periods to determine what the outcomes would be.

Dr. Sawyer observed that the interventions were late in the large outbreaks, and that both presentations emphasized that IRB approval was obtained for that. He requested clarification regarding whether that is really necessary in an outbreak, or whether it was sought simply because there was a research element to these efforts. It seems that this likely delayed the intervention, and people in general should not think IRB approval is required should they decide to administer a third dose since these are licensed products and a physician could choose to use it at their discretion even though it is not approved for this specific use.

Dr. Wallace (SME) responded that IRB approval occurred relatively quickly in both of these cases, and it was done because of the evaluation aspect of understanding what the impact may be. In Guam, there were also delays in reporting. In Orange County, it was unclear whether vaccination was necessary because a number of these outbreaks have burned out on their own, but this one sustained. Once the decision is made to implement the intervention, community buy-in and mobilization and all of the logistics (e.g., acquiring the vaccine) must be put into place. This all takes longer than the IRB process itself.

In the absence of ACIP making a formal recommendation, Dr. Sawyer wondered if it was correct that another jurisdiction could choose to give a third dose without involving an IRB.

Dr. Wallace (SME) replied that there are examples of this. There have been situations that are not always couched as a third dose, because they did not document the first two doses. But groups have been vaccinated that likely have high 2-dose coverage.

Dr. Baker requested a definition for “expedited,” because in her institution it means one month instead of two.

Dr. Wallace (SME) said he thought it was shorter than that. This was CDC’s IRB along with New York or Guam. There were some issues with Guam, but it was very quick in these situations.

Dr. Seward noted that in the Northeast outbreak, it is not so clear that the intervention was well after the peak. The bars were going all the way to the intervention. In some age groups, yes, the 18 to 24 year olds had certainly peaked. In Guam it is very clear in retrospect, but while it was on-going cases were being delayed, et cetera. From the CDC perspective on IRB, if

something is generalizable and an evaluation is being done, it is usually considered to be investigational research. Guidance was sought on that from CDC's IRB.

Dr. Sawyer noted that several studies were presented on vaccine effectiveness estimates, including the Cohen study from the UK in which both 1- and 2-dose vaccine effectiveness appeared to be over 90% at least early on. He wondered whether a conclusion should be drawn from this that the vaccine is less efficacious than some others, and whether there is research of alternative strains in the US.

Dr. Barskey said he thought that Jeryl Lynn is one of the strains used in the UK, which is also used in the US. There have been similar vaccine effectiveness estimates for Jeryl Lynn as well. The study clearly shows that waning immunity is likely associated with the use of the mumps vaccine.

Dr. McLean added that as far as vaccine effectiveness, Jeryl Lynn is the most studied.

Dr. Seward indicated that the UK uses a derivation of the Jeryl Lynn strain, so it is essentially the same.

Dr. Keitel agreed that this seemed to identify a research agenda for a more effective, long-lived vaccine. She was interested to see that some of the immune responses seemed to hold steady, which made her wonder whether anyone was assessing whether the history of vaccination modified the severity of disease.

Dr. Barskey replied that there are preliminary results from the 2009-2010 outbreak in the Northeast, and a low rate of complications has been observed overall compared to estimates from the pre-vaccine era, and there are statistically significant results showing that orchitis was lower in vaccine recipients than in non-vaccine recipients.

In the assessment of cost for the local and state health departments, Dr. Bennett wondered whether the investigators were able to distinguish between outbreak response costs and vaccination program development costs.

Dr. Fiebelkorn (CDR) replied that primarily during the period evaluated, all of the resources were diverted from routine vaccination activities to outbreak response activities. Therefore, efforts that were usually scheduled were delayed until the outbreak response period ended. The costs allocated were categorized (e.g., costs of administering the vaccine, other response activities, et cetera).

Dr. Bennett suggested in the modeling assessing the costs that would have been saved by implementing the intervention sooner, preventing more cases, and having less outbreak management and more vaccination. It seems that this would be important in making a decision.

Considering that and institution may have 80% coverage or 60% coverage, Dr. Marcy suggested dropping the word "third."

Dr. Wallace (SME) replied that this is the way it would be handled. If there was incomplete coverage, the first step would be to catch up 2-dose coverage first. In some interventions, people have been told that if they have any doubt or want to be vaccinated, they could go to the clinics being held. The point is if a group is going to be specifically targeted with a third dose,

there should be high coverage. Trying to raise overall immunity due to incomplete coverage is done routinely.

Dr. Marcy said he was concerned about schools in various parts of the country where vaccine denial is fairly profound, and there may be 25% with no coverage.

Dr. Seward responded that standard guidance already exists to address this type of situation. This is additional guidance to cover the unique outbreaks being observed in situations of high coverage of 2-dose vaccinated populations. In Guam, the major effort initially was to ensure that everyone was being caught up and that this was not an outbreak due to failure to vaccinate.

Regarding the criteria for greater than 90% coverage, Dr. Duchin agreed that clearly an under-immunized population would be vaccinated. However, he would not want this interpreted that a third dose would not be given to people who had 2 doses and were part of a group that was largely under-immunized. He also thought it was remarkable that the rate of complications was very low in this vaccinated cohort.

While Ms. Ehresmann understood that catch-up would be done for those with a lower rate of coverage; however, it was not clear why the 75% who already had 2 doses would not be given a third dose.

Dr. Keitel inquired as to whether the isolates were being assessed for evidence of antigenic variation or other reasons they may be escaping vaccine protection.

Dr. Wallace (SME) replied that this is routinely done. While there is some debate about this, there is no convincing evidence that drift or strain differences are the cause of the efficacy situations. Regarding the comment about high vaccine efficacy in some studies and lower in others, this really is more situation-dependent than vaccine- or strain-dependent. There seems to be something about certain situations that are able to overwhelm in some settings and not others. For instance, in the Northeast outbreak, despite the opportunity to get into the community, it never did.

Dr. Jenkins asked whether lot numbers were assessed to determine whether there was an ineffective lot.

Dr. Wallace (SME) replied that this issue arises, but nothing has ever been identified in terms of lot or storage issues. Orange County, lot numbers, storage records, and handling were assessed. There were no trends to show that there were any issues with this.

Dr. Baker inquired as to whether in the New York outbreak girls and boys were offered the intervention.

Dr. Kutty responded that the intervention was offered to both girls and boys in New York.

Dr. Temte indicated that the working group had engaged in significant discussion regarding what appear to be very high levels of safety for the third dose. In terms of a potential vote in October, the working group will not be able to present clear evidence for efficacy based on the information available. However, they believe they can at least provide reassurance that this type of intervention has a high likelihood of benefit and is very safe.

Ms. Stinchfield (NAPNAP) said she was very happy to see the low degree of adverse events. She was curious after the third dose when the joint pain was reported.

Dr. Kutty responded that in New York, they went through two incubation periods. But, the request to the parents was to report any adverse events within the 14 days post-vaccines. This is one of the limitations. Still, the parents were very aware of what was occurring so the response rates were very good.

Dr. Hahn (CSTE) noted that health departments are always asked to do something when there is an outbreak, and this is obviously the kind of situation for which it is nice to know what the options might be. However, she requested that language be carefully worded to reflect that the evidence is quite weak so that health departments can consider this type of intervention to be a tool versus a mandate.

Dr. Wallace (SME) agreed that there are real costs, even just in vaccine costs. This is why there was a great deal of discussion around these parameters. There are small clusters often, very few of which turn into outbreaks. However, this is very difficult to anticipate ahead of time. He agreed that they would not want to do this every time there were two or three cases, which was the rationale behind listing some parameters.

Dr. Plotkin argued for a stronger recommendation. First, mumps is not measles and rubella. There are several differences, the most important of which is the fact that immunity does not last very long. Second, measles and rubella are being eliminated outside of the US. That is not the case for mumps. Relatively few countries are vaccinating against mumps and their coverage is not great. Therefore, the US is going to have introduction of mumps repeatedly into a situation in which the US vaccination is not going to be completely protective. The overall protective efficacy cited by Dr. Barskey is correct, but that is an overall estimate that does not take into account the interval between vaccination and exposure. As he showed from the British data, and from many other data because these epidemics are occurring elsewhere in the world besides the US and UK, the efficacy wanes with the waning of antibody. There has been discussion regarding the correlate of protection. There are older studies, notably by Frank Enis in a military population, that do show quite a good correlation with neutralizing antibody. The Cortese study also showed a correlation with neutralizing antibody, although there were breakthroughs such that the threshold was not absolute. A related point regards the strain in the vaccine and the circulating strain. It is true that there is a lot of controversy about this, but the facts are that the neutralization of the Iowa strain in vacinees is less than neutralization of the Jeryl Lynn, so when immunity wanes, heterotypic immunity wanes faster than against the vaccine strain. That creates another immunologic susceptibility. That does not mean that the genotypes correlate to serotypes, but nevertheless, there are significant differences in antigenicity between the vaccine strain and the circulating strain. Incidentally, the other mumps vaccine strains also show relatively low efficacy, but there has not been a lot of work following them. He thought it could be said that about 10 years after a first or second dose, there is a distinct drop in efficacy. The additional point is memory. A recently published study, which Dr. Plotkin thought was conducted by CDC, assessed B memory cells for the three different viruses in the MMR in previous vaccinees. Per million B cells, for rubella there were 5000 memory B cells, for measles 3000, and for mumps 300—barely above the threshold, so memory is not good. That does not mean that a booster response is not achieved with a third dose. His recommendation is, considering that there will be many introductions of mumps, third doses should be given at much lower levels than 5 per thousand and consideration should be given to a routine third dose recommendation for adolescents entering collectivity (e.g., college). It seems to Dr. Plotkin that the best way to prevent outbreaks is by administering third doses in

situations in which immunity is known to have waned, youth are collecting, and importation is likely.

Dr. Zucker, Assistant Commissioner for the Bureau of Immunization at the New York City Health Department, had similar epidemiology to what was observed in Orange County. She pointed out that if they overlaid their epi-curve with what was seen in Orange County, it would look essentially identical and they did not implement an intervention. She pointed this out as a caution in how these results are interpreted. They can assess their attack rate before and after the Orange County intervention to determine whether they saw similar declines in the magnitude. New York City would not be the ideal control group, but it may provide some additional evidence for what was occurring with the outbreak and what might be attributable to vaccine or not. Regarding the response of the health department, looking at the Orange County curve and when the 5 per 1000 occurred and when an intervention should be started according to the parameters, she did not think this would have been practical from a health department perspective because where the outbreak is going would be unknown. At that point, for New York City, there would have been a relatively low disease burden. This was all also occurring during H1N1, so it was difficult to mount another vaccine response. New York City had numerous discussions about whether to administer a third dose, and the pressure to do something. By the time they were even able to focus on that, they would have been past the peak of the outbreak. The practical nature of saying when to implement an intervention is always obvious in hindsight, but is not necessarily clear during the situation.

Dr. Seward pointed out that these guidelines are just for consideration. They were not saying that if ACIP issued a permissive recommendation that at 5 per 1000 everyone had to implement the intervention. They absolutely recognize all of the points Dr. Zucker made.

Day 2: Public Comment

No public comments were offered on the second day of the February 2012 meeting.

Attendance Roster

US Citizens

Last	First	Citizenship
Adams	Kimberly	United States
Albright	Karen	United States
Alexa	Pam	United States
Allen	Sandy	United States
ALVARADO	ISABEL	United States
Ambrose	Christopher	United States
Anderson	Marsha	United States
Andrist	Edward	United States
Arthur	Phyllis	United States
Ashley	Don	United States
Aviles-Mendoza	Guillermo	United States
Ba	Amy	United States
Baker	Carol J.	United States
Baldwin	Jennifer	United States
Bandell	Allyn	United States
Barden	Helen	United States
Bardi	Janna	United States
Bargatze	Robert	United States
Barlows	Ted	United States
Bednarczyk	Robert	United States
Bennett	Nancy (Nana)	United States
Berns	Abby	United States
Bhuyan	Prakash	United States
Bobinsky	Marcella	United States
Bocchini	Joeseph	United States
Boone	Christopher	United States
Boone	Heather	United States
Boone	Ethan	United States
Boone	Maggie	United States
Boswell	Alanna	United States
Bousselot	Roger	United States
Bousselot	Roger	United States
Bozof	Lynn	United States
Bradley	Kimberly	United States

Brady	Michael	United States
Braga	Damian	United States
Bravo	Sandra	United States
Bresnitz	Eddy	United States
Brewer	Katherine	United States
Brown	Veronica	United States
Browne	Bonnie	United States
Bryant	Chenoia	United States
Burkard	Rosa	United States
Burkybile	Frank	United States
Burnett	Jeff	United States
BURSTIN	STUART	United States
Cales	Carmen	United States
Callender-Potters	Heather	United States
Campos-Outcalt	Douglas	United States
Cannon	Patricia	United States
Capilouto	Emily	United States
Cappio	Kelly	United States
Cary	Donna	United States
Casias	Maria	United States
Chandra-Puri	Anita	United States
Chaney	Mike	United States
Chen-Rogers	Chia	United States
Chu	Virginia	United States
Chung	Haejin	United States
Clark	Rebekah	United States
Clover	Richard	United States
Coelingh	Kathleen	United States
Cole	Dana	United States
Colwell	Chris	United States
Conis	Elena	United States
Cordell	Laura	United States
Cottone	Melissa	United States
Cox	Kendra	United States
Cox	Chad	United States
Coyne-Beasley	Tamera	United States
Crumlich	Brittani	United States
Csepi	Bela	United States

Cullison	Mark	United States
Cundiff	Kayla	United States
Dachowski	Stephen	United States
Dalrymple	Donald "Dack"	United States
Dana	Adrian	United States
D"Antona	Aida	United States
D"Antona	John	United States
Davis	Victoria	United States
Decker	Michael	United States
Dennis	Sandra	United States
DeNoon	Daniel	United States
Dillard	Reiannon	United States
Dinovitz	Richard	United States
Donnelly	Jessica	United States
Douglas	Andrew	United States
DUCHIN	JEFFREY	United States
Dzierba	Steven	United States
Egge	Steven	United States
Ehresmann	Kristen	United States
Etkind	Paul	United States
Evans	Geoffrey	United States
Farley	Monica	United States
Feltman	Matthew	United States
Fernandez	Carrie	United States
Fish	Rebecca	United States
Foster	Stephan	United States
Foster	Sylvia	United States
Friedland	Leonard	United States
Fryhofer	Sandra	United States
Fye	Jessica	United States
Gaffoglio	Diane	United States
Gargano	Lisa	United States
Geibe	Jesse	United States
Gellin	Bruce	United States
Germano	Geno	United States
Gordon	Lili	United States
Gorman	Richard	United States
Gould	Philip	United States
Goveia	Michelle	United States

Grabenstein	John	United States
Greenberg	David	United States
Grogg	Stanley	United States
Groom	Amy	United States
Gruber	Bill	United States
Gullick	Allison	United States
Hahn	Christine	United States
Hale	Scott	United States
Halsey	Neal	United States
Halstrom	Erik	United States
Hamm	Natalie	United States
Hance	Mary Beth	United States
Hannan	Claire	United States
Hayes	Carol	United States
Henry	Sarah	United States
Henry-Wallace	Stephanie	United States
Hernandez	Alfonso	United States
Herrera-Taracena	Guillermo	United States
Homeier	Barbara	United States
Hosbach	Philip	United States
Houston	Marsha	United States
Howe	Barbara	United States
Hughes	Jim	United States
Hull	Harry	United States
Humiston	Sharon	United States
Humphrey-Franklin	Donelle	United States
Hunt	Matthew	United States
Interis	Evelyn	United States
Jacob-Nara	Juby	United States
Janssen	Robert	United States
Janusz	Cara Bess	United States
Jauragui	Barbara	United States
Jenkins	Renee	United States
Jimenez	Jeanne	United States
Jodhpurkar	Uday	United States
Johnson	Erica	United States
Johnson	David	United States
Jones	Rosemary	United States
Kagan	Stephen	United States

Kalokhe	Ameeta	United States
Keitel	Wendy	United States
Keyes	Danielle	United States
Keyserling	Harry	United States
Kim	Chris	United States
Kimberlin	David	United States
Kinsinger	Linda	United States
Kohlenberg	Katie	United States
Krishnarajah	Girishanthy	United States
Kurtis	Hannah	United States
Kuter	Barbara	United States
Laird	Susan	United States
LaMarca	Lou	United States
Lanphear	John	United States
LaRussa	Philip	United States
Lawson	Wyeth	United States
Le	Luu ly	United States
Lease	Christian	United States
Lee	Julia	United States
Leger	Marie-Michele	United States
Lester	Arlene	United States
Lett	Susan	United States
Lewin	Clement	United States
Liedtka	Patrick	United States
Link-Gelles	Ruth	United States
Linn	Elena	United States
Loehr	Jamie	United States
Long	Deryl	United States
Loynes	Heidi	United States
Lukus	Lori	United States
Lymon	Rufus	United States
Malone	Robert	United States
Manzano	Yecenia	United States
Marcy	S Michael	United States
Martin	Kim	United States
Martin	Maria del Pilar	United States
Matusik	Mark	United States
Mazur	Marie	United States
McGowan	Katherine F.	United States

McGruder	Janet	United States
McGuffin	Colleen	United States
McKinney	Paul	United States
McLaughlin	John	United States
Meigs	Wendy	United States
Meissner	Cody	United States
Merritt	Judy	United States
Middleman	Amy	United States
Milburn	Tarah	United States
Miller	Kimberly	United States
Miller	Jacqueline	United States
Milley	Frankie	United States
Moburg	Christeen	United States
Montero	Jose T	United States
Moore	Kelly	United States
Mukundan	Maya	United States
Mulligan	Mark	United States
Murad	Mohammad Hassan	United States
Narula	Trishna	United States
Narula	Harminder	United States
Narula	Neeta	United States
Nash	kristen	United States
Neese	Kristen	United States
Netoskie	Mark	United States
Neuman	William	United States
Neuzil	Kathleen	United States
NGUNDUE	JEROME	United States
Nicholson	Jennifer	United States
Ochs	Tara	United States
Offit	Paul	United States
Olad	Mohamed	United States
Orenstein	Walter	United States
Ortlieb	David	United States
Owen	Bill	United States
Painter	Julia	United States
Pannemann	Kathryn	United States
Paradiso	Peter	United States
Parker	Rachel	United States
Perry	Robert	United States

Peter	Georges	United States
Peters	Martin	United States
Petersen	Brett	United States
Peterson	Diane	United States
petrofsky	monique	United States
Plotkin	Stanley	United States
Poffenberger	Kimber	United States
Poland	Gregory	United States
Pontani	Dennis	United States
Porter	Travis	United States
Pratt	David	United States
Price	Winston	United States
Pringle	Meridith	United States
ProorHibKitty	ProorHibKitty	United States
Proveaux	Tina	United States
Purdy	Jay	United States
Quinn	Jane	United States
Ramjee	Shilpa	United States
Reeves-Hoche	Mary Kathryn	United States
REISZNER	DONNA	United States
Rha	Brian	United States
Richards	Jennifer	United States
Richmond	Heather	United States
Riley	Laura	United States
Roberts	Clifford Lake	United States
Rogero	Heather	United States
Romano	Kyle	United States
Romano	Kris	United States
Rosenbaum	Sara	United States
Riyals	Michael	United States
Sanchez	Robin	United States
Sanyour	Mark	United States
Sattler	Carlos	United States
Sawyer	Mark	United States
Schaffner	William	United States
Schmader	Kenneth	United States
Senyk	Michele	United States
shahram	shahrooz	United States
Shannon	Ellen	United States

Sharlow	Diana	United States
Shaw	Brian	United States
Sheffield	Tamara	United States
Shelton	Jerry	United States
Sherner	James	United States
SIEVERT	ALAN	United States
Silverstein	Leonard	United States
Singletary	Ivy	United States
Singletary	Brandon	United States
Skjeveland	Eric	United States
Slaughter	Jan	United States
Smith	Jason D.	United States
Smith	Susan	United States
Snow	Vincenza	United States
Spears	Christian	United States
Stephens	David	United States
Stinchfield	Patricia	United States
Strutton	David	United States
Stuerke	Stacy	United States
Sullivan	Gina	United States
Sun	Wellington	United States
Temte	Jonathan	United States
Tennenberg	Alan	United States
Thomas	Michael	United States
Thompson	Brad	United States
Thorne	Christopher	United States
Toback	Seth	United States
Tolene	Anne	United States
Tortorich	Debra	United States
Tubergen	Emily	United States
Tucker	Miriam E.	United States
turner	james	United States
Tyo	Karen	United States
Ulasi	Chijioke	United States
VanOss	Robin	United States
Varan	Aiden	United States
Vaupel	Christine	United States
Vazquez	Marietta	United States
Verma	Bikash	United States

Veselsky	Steven	United States
VierAbefe	VierAbefe	United States
Vigliariolo	Peter	United States
Wallace	Fred	United States
Walsh	margaret	United States
Ward	Michelle	United States
WarreDavid	WarreDavid	United States
Washington	Teneasha	United States
Webster	Angie	United States
Welch	Verna	United States
Wentworth	Marian	United States
Weston	Wayde	United States
Wexler	Deborah	United States
Williams	Michelle	United States
Williams	Mimi	United States
Wolf	Tammy	United States
Wolf	Jesseca	United States
Wood	Laurel	United States
Wornson	Bryon	United States
Worthy	Margaret	United States
Yarn	Sandra	United States
Zahn	Matt	United States
Zavolinsky	Jennifer	United States
Zimmerman	Richard	United States
Zucker	Jane	United States

Non US Citizens

Last	First	Citizenship	Organization
Abdinur A.Olad	Mohamed	Somalia	WHO&H
Acemah	Christian	Uganda	U.S. Institute of Medicine
Arya	Jaya	India	
AVENDANO	Luis Fidel	Chile	UNIVERSIDAD DE CHILE
Baehner	Frank	Germany	Novartis Vaccines
BETSILL	HELEN	MERCK	
biehn	brant	Canada	dynavax
Burga Sánchez	Miriam Madeleine	Peru	Ministerio de Salud
Enyan	Philip	Ghana	Student, University of Ghana
Florez	Jorge	Colombia	Immunoprotection
Gowler	Jeremy	Canada	Novartis Vaccines & Diagnostics Inc.
Ismail	Shainoor	Canada	Public Health Agency of Canada
Jain	Siddharth	India	UAB School of Public Health
Kabore	Lassane	Burkina Faso	UAB
Kanda	Mikiko	Japan	World Health Organization
Khodneva	Yulia	Russia	UAB School of Public Health
Kobayashi	Miwako	Japan	Emory University
Lester-Swindell	Mark	United Kingdom	Pfizer Inc
Liao	Albert	Canada	Novartis Vaccines and Diagnostics
Masseria	Cristina	Italy	GlaxoSmithKline Vaccines
Mendoza Araujo	Maria Ana	Peru	Department of Health
Minaya	Percy	Peru	National Health Institute
Mojica	Jose Alejandro	Colombia	Sanofi Pasteur
Moussa Diouldé	MBOW	Mauritania	Institut ICAD SANTE
Murguia de Sierra	Maria	Mexico	
Ponce	Carmen	Peru	Ministry of Health of Peru
Sasraku	Josephine Naa Deisa	Ghana	Pantang Nursing Training College
Soler Hidalgo	Maria	Argentina	Fighting Infectious Diseases in Emerging Countries
STAMBOULIAN	DANIEL	Argentina	
Suarez	Eduardo	El Salvador	Ministerio de Salud
Suárez	Victor	Peru	Instituto Nacional de Salud, Perú
Tan	Litjen (L.J)	Singapore	American Medical Association
Tende	Frida	Cameroon	UAB School of public Health

Toledo	Washington	Peru	Organización Panamericana de la Salud
Upadhyay	Divvy	India	UAB School of Public Health
VIZZOTTI	CARLA	Argentina	MINISTRY OF HEALTH
Warshawsky	Bryna	Canada	Middlesex-London Health Unit
YORK	Laura Jean	France	PFIZER Inc
Zyambo	Cosmas		UAB