

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

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



**Summary Report
October 24-25, 2012
Atlanta, Georgia**

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Final - October 23, 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

October 24-25, 2012

<u>AGENDA ITEM</u>	<u>PURPOSE</u>	<u>PRESIDER/PRESENTER(S)</u>
<u>Wednesday, October 24, 2012</u>		
8:00 <u>Welcome & Introductions</u>		Dr. Jonathan Temte (ACIP Chair) Dr. Larry Pickering (ACIP Executive Secretary; CDC)
8:30 <u>Pertussis Vaccines</u> <ul style="list-style-type: none">· Introduction· Update on the epidemiology of pertussis in the US and Washington state epidemic, 2012· Rationale for vaccinating pregnant women with Tdap· Considerations for updated recommendation on use of Tdap in pregnant women	Information & Discussion <u>Vote, VFC vote</u>	Dr. Mark Sawyer (ACIP, WG Chair) Dr. Sarah Meyer (CDC/NCIRD) Dr. Jennifer Liang (CDC/NCIRD) Dr. Jennifer Liang (CDC/NCIRD)
10:30 <i>Break</i>		
10:45 <u>Meningococcal Vaccines</u> <ul style="list-style-type: none">· Introduction· Immunogenicity and safety of HibMenCY· GRADE evidence for HibMenCY· Considerations for use of HibMenCY in infants· Vaccines for Children	Information & Discussion <u>Vote</u> <u>VFC Vote</u>	Dr. Lorry Rubin (ACIP, WG Chair) Dr. Jackie Miller (GSK Vaccines) Dr. Elizabeth Briere (CDC/NCIRD) Dr. Amanda Cohn (CDC/NCIRD) Dr. Jeanne Santoli (CDC/NCIRD)
1:00 <i>Lunch</i>		
2:15 <u>Measles, Mumps, and Rubella Vaccines</u> <ul style="list-style-type: none">· Introduction<u>Updates to the MMR Statement</u>· Measles post-exposure prophylaxis with IG· Vaccination of HIV-infected persons· Review statement	Information & Discussion <u>Vote</u>	Dr. Jonathan Temte (ACIP, WG Chair) Dr. Huong McLean (CDC/NCIRD)
3:55 <i>Break</i>		
4:10 <u>Child/Adolescent Immunization Schedule, 2013</u> <ul style="list-style-type: none">· Introduction· Child/adolescent schedule - review of changes, presentation of field study results· Discussion and vote on 2013 schedule	Information & Discussion <u>Vote</u>	Dr. Renée Jenkins (ACIP, WG Chair) Dr. Iyabode Beysolow (CDC/NCIRD) Dr. Iyabode Beysolow (CDC/NCIRD)
5:20 <u>Adult Immunization Schedule, 2013</u> <ul style="list-style-type: none">· Introduction· Adult immunization schedule - review of changes· Discussion and vote on 2013 schedule	Information & Discussion <u>Vote</u>	Dr. Tamera Coyne-Beasley (ACIP, WG Chair) Dr. Carolyn Bridges (CDC/NCIRD) Dr. Carolyn Bridges (CDC/NCIRD)
5:50 <u>Public Comment</u>		
6:00 <u>Adjourn</u>		

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ABCs	Active Bacterial Core surveillance
ACA	Affordable Care Act
ACHA	American College Health Association
ACNM	American College of Nurses and Midwives
ACOEM	American College of Occupational and Environmental Medicine
ACOG	American Congress of Obstetricians and Gynecologists
ACP	American College of Physicians
ACIP	Advisory Committee on Immunization Practices
AE	Adverse Events
AFP	American Family Physicians
AHIP	America's Health Insurance Plans
AI/AN	American Indians/Alaska Natives
AIM	Association of Immunization Managers
AMA	American Medical Association
ANA	American Nurses Association
Anti-HBs	Antibody to Hepatitis B Surface Antigen
Anti-HBc	Antibody to Hepatitis B Core Antigen
AP	Acellular Pertussis
APHA	American Public Health Association
ART	Antiretroviral Therapy
ASH	(United States) Assistant Secretary for Health
ASTHO	Association of State and Territorial Health Officials
BBF	Blood and Body Fluid
BLA	Biologics License Application
BRFSS	Behavioral Risk Factor Surveillance System
CBER	Center for Biologics Evaluation and Research
ccIIV	Cell Culture Inactivated Influenza Virus Vaccine
CDC	Centers for Disease Control and Prevention
CDPH	California Department of Public Health
CGH	Center for Global Health
CIN	Cervical Intraepithelial Neoplasia
CISA	Clinical Immunization Safety Assessment Network
CMS	Centers for Medicare and Medicaid Services
COI	Conflict of Interest
COID	Committee of Infectious Disease
CRS	Congenital Rubella Syndrome
CSTE	Council of State and Territorial Epidemiologists
CVT	Costa Rica Vaccine Trial
DAIDS	Division of Acquired Immunodeficiency Syndrome (NIAID, NIH)
DoD	Department of Defense
DMID	Division of Microbiology and Infectious Diseases (NIAID, NIH)
DSMBs	Data Safety Monitoring Boards
DTaP	Diphtheria, Tetanus, and Pertussis
DVA	Department of Veterans Affairs
ECMO	Extracorporeal Membrane Oxygenation
EHR	Electronic Health Record
EIA	Enzyme Immunoassay
EIP	Emerging Infections Program
EIS	Epidemic Intelligence Service
EPINet	Exposure Prevention Information Network
EOC	Emergency Operations Center
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
GFR	Glomerular Filtration Rate

GID	Global Immunization Division
GMCs	Geometric Mean Concentrations
GMTs	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HA	Hemagglutinin
HBIG	Hepatitis B Immune Globulin
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCP	Health Care Personnel
HEDIS	Healthcare Effectiveness Data and Information Set
HepB	Hepatitis B
HHS	(Department of) Health and Human Services
Hib	<i>Haemophilus influenzae type B</i>
HICPAC	Hospital Infection Control Practices Advisory Committee
HPA	Health Protection Agency
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
IAFE	International Association of Fairs and Expositions
ICERs	Incremental Cost-Effectiveness Ratios
IDSA	Infectious Diseases Society of America
IG	Immune Globulin
IgG	Immunoglobulin G
IGIM	Immune Globulin given Intramuscularly
IGIV	Immune Globulin given Intravenously
IGSC	Immune Globulin given Subcutaneously
ILI	Influenza-Like Illness
ILINet	Influenza-Like Illness Surveillance Network
IOM	Institute of Medicine
IPD	Invasive Pneumococcal Disease
IIS	Immunization Information System
IIV	Inactivated Influenza Vaccine
ISO	Immunization Safety Office
JAMA	<i>Journal of the American Medical Association</i>
JE-VC	Vero cell culture-derived JE vaccine
LAIV	Live Attenuated Influenza Vaccine
MCH	Maternal and Child Health
MDCK	Madin Darby Canine Kidney (Novartis proprietary cell line)
MMR	Measles, Mumps, Rubella
MMRV	Measles, Mumps, Rubella, Varicella
MMWR	<i>Morbidity and Mortality Weekly Report</i>
MSM	Men Who Have Sex With Men
MSPB	Meningitis and Special Pathogens Branch
NACCHO	National Association of County and City Health Officials
NACI	National Advisory Committee on Immunization
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
NEJM	<i>New England Journal of Medicine</i>
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)
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
NIS	National Immunization Survey
NIS-Teen	National Immunization Survey-Teen
NMA	National Medical Association
NNDSS	National Notifiable Diseases Surveillance System

NNV	Number Needed to Vaccinate
NPHIC	National Public Health Information Coalition
NREVSS	National Respiratory and Enteric Virus Surveillance System
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
NVSN	New Vaccine Surveillance Network
ORISE	Oak Ridge Institute for Science and Education
OSHA	Occupational Safety and Health Administration
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PEP	Post-Exposure Prophylaxis
PICU	Pediatric Intensive Care Unit
PI	Percutaneous Injury
PPHF	Prevention in Public Health Fund
PCV	Pneumococcal Conjugate Vaccine
PPSV23	Pneumococcal Polysaccharide Vaccine
PRAMS	Pregnancy Risk Assessment Monitoring System
QALY	Quality-Adjusted Life Year
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAEs	Serious Adverse Events
SAGE	Strategic Advisory Group of Experts (WHO)
SBA	Serum Bactericidal Antibody
SES	Socioeconomic
SME	Subject Matter Expert
STFM	Society of Teaching Family Medicine
Td	Tetanus-Diphtheria
Tdap	Tetanus and Reduced Diphtheria Toxoids
TIV	Trivalent Inactivated Influenza Vaccines
TPS	Texas Pediatric Society
UK	United Kingdom
US	United States
VA	Department of Veterans Affairs
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Effectiveness
VFC	Vaccines for Children
VICP	Vaccine Injury Compensation Program
VRBPAC	Vaccine and Related Biologic Products Advisory Committee (FDA)
VSD	Vaccine Safety Datalink
VTE	Venous Thromboembolism Events
WHO	World Health Organization

Welcome and Introductions

Dr. Jonathan Temte
Chair, ACIP

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

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

Dr. Pickering welcomed everyone to the October 2012 Advisory Committee on Immunization Practices (ACIP) meeting. He noted that while this was Dr. Temte's first meeting as chair of ACIP, he is well-experienced both from being a member and from serving as chair for one meeting on behalf of Dr. Baker. As with previous ACIP meetings, Dr. Pickering 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, Reed Walton, and Chris Caraway. Dr. Pickering recognized that without these individuals it would be difficult to convene these meetings, and he personally thanked each of them. Those with any questions were instructed to see him or any of these individuals.

Dr. Pickering emphasized that there would be a full agenda, which would include 5 votes and 3 Vaccines for Children (VFC) votes. He noted that handouts of the presentations were distributed to the ACIP members and were made available for others on the tables outside of the auditorium. Slides presented during this meeting will be posted on the ACIP website approximately one to two weeks after the meeting concludes, the live webcast will be posted within four weeks following the meeting, and the meeting minutes will be available on the website three months or 90 days following this meeting. Minutes of the June meeting consisted of 162 single-spaced pages and are posted on the ACIP website. Members of the press interested in conducting interviews with ACIP members were instructed to contact Tom Skinner, who was in attendance, for assistance in arranging the interviews.

Dr. Pickering recognized a delegation of visitors from the World Health Organization's (WHO's) Pan American Health Organization (PAHO) office in Washington, DC, which is WHO's Regional Office for the Americas. The delegation also included members of Costa Rica's national immunization advisory body, the National Immunization Commission, led by the technical secretary of the committee and accompanied by technical staff from the Washington, DC PAHO office. The previous day, the PAHO group and CDC staff from the Global Immunization Division (GID) held a meeting to share information about ACIP, including its structure and procedures. Costa Rica is seeking to formalize several of its current practices, and is working with PAHO and CDC staff to assist with this process. Dr. Pickering extended appreciation to the Sabin Vaccine Institute, which provides financial and logistic support for participation of National Immunization Committee members from Latin America to attend ACIP meetings.

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

Ex Officio Members

- ❑ Dr. Vito Caserta, Acting Director, Division of Vaccine Injury Compensation, is the new Health Resources and Services Administration (HRSA) *ex officio* member.
- ❑ Dr. Geoff Evans has retired and will be missed. He has been an outstanding resource for and good friend to ACIP during his tenure at HRSA.

Liaison Representatives

- ❑ Dr. Kevin Ault, Department of Obstetrics and Gynecology, Emory University School of Medicine, represented the American Congress of Obstetricians and Gynecologists (ACOG) on behalf of Dr. Laura Riley during this meeting.
- ❑ Dr. Susan Lett, Medical Director, Immunization Program Division of Epidemiology and Immunization, Massachusetts Department of Public Health, represented the Council of State and Territorial Epidemiologists (CSTE) on behalf of Dr. Christine Hahn during this meeting. Dr. Lett is a past ACIP member, having served from July 2006 to June 2010.
- ❑ Dr. Carol Baker, Professor of Pediatrics, Molecular Virology and Microbiology, Baylor College of Medicine, represented the Infectious Diseases Society of America (IDSA) on behalf of Dr. Kathleen Neuzil during this meeting. Dr. Baker served until July 2012 as ACIP Chair.
- ❑ Dr. Susan Even, Chair, Vaccine Preventable Disease Advisory Committee for American College Health Association (ACHA), Executive Director, Student Health Center, University of Missouri-Columbia represented the ACHA on behalf of Dr. James Turner during this meeting.

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

Dr. Pickering explained that topics presented during the ACIP meeting include open discussion with time reserved for public comment. During this meeting, a time for public comment was scheduled following the afternoon sessions during both meeting days. 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 about the process. Those who registered to make public comments were instructed to state their name, organization if applicable, and any conflicts of interest (COIs) prior to making their comments.

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

prohibited from participating in 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.

Applications for ACIP membership are due no later than November 16, 2012 for the 4-year 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: [CDC ACIP Vaccine Recommendations Website](http://www.cdc.gov/vaccines/acip/)

Nominations: [CDC ACIP Website Member Nominations](http://www.cdc.gov/vaccines/acip/)

With regard to the mechanisms and timelines by which ACIP recommendations are published, all ACIP recommendations are not official until approved by the CDC Director and published in the *Morbidity and Mortality Weekly Report (MMWR)*. Three methods are used for information dissemination: Policy Notes, Recommendations and Reports, and Provisional Recommendations. All three documents are posted on the ACIP website. An update is provided during each ACIP meeting regarding 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 June 2012 follows:

ACIP Recommendations Published Since February 2012		
Title	Publication Date	MMWR Reference
Recommended Adult Immunization Schedule — United States, 2012	2/3/12	2012;61:1-7
Recommended Immunization Schedules for Persons Aged 0 Through 18 Years — United States, 2012	2/10/12	2012;61:1-4
New Framework (GRADE) for Development of Evidence-Based Recommendations	5/11/12	2012;61:327
Licensure of 13-Valent Pneumococcal Conjugate Vaccine for Adults Aged 50 Years and Older	6/1/12	2012;61:394-395
Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis (Tdap) Vaccine in Adults Aged 65 Years and Older	6/29/12	2012;61(25):468-470
Prevention and Control of Influenza with Vaccines	8/17/12	2012;61(32):613-618
Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine for Adults with Immunocompromising Conditions	10/12/12	2012; 61(40):816-819

<http://www.cdc.gov/vaccines/acip/> 4

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, February 20-21, 2013

Registration Deadline: Non-U.S. Citizens *and* US Citizens [February 4, 2013](#)

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>

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

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

Dr. Temte welcomed and introduced four new ACIP members. Dr. Kathy Harriman is the Chief of Vaccine Preventable Disease Epidemiology Section at the California Department of Public Health (CDPH). Dr. Harriman has served since 2007 in the CDPH Immunization Branch where she guides outbreak investigations and implementation of vaccine and control measures. Dr. Lee Harrison is Professor of Medicine and Epidemiology in the Infectious Disease Epidemiology Research Unit at the University of Pittsburgh. He is Board Certified in internal medicine and infectious disease, is a graduate of the Epidemic Intelligence Service (EIS), and worked in CDC's Meningitis and Special Pathogens Branch (MSPB). Dr. Ruth Karron is Professor and Director of the Center for Immunization Research, Department of International Health at Johns Hopkins Bloomberg School of Public Health. She is Board Certified in pediatrics and pediatric infectious disease. Since 2007, she has served as the Director of the Center for Immunization Research and the Director of the Johns Hopkins Vaccine Initiative. Dr. Lorry Rubin is the Director of Pediatric Infectious Diseases at the Steven and Alexandra Cohen Children's Medical Center of New York, North Shore Long Island Jewish Health System, and is Professor of Pediatrics at the Hofstra-North Shore LIJ School of Medicine. Dr. Rubin is Board Certified in pediatrics and pediatric infectious disease. He has served on several national committees,

including the Committee on Infectious Disease for the American Academy of Pediatrics (AAP), and chair of the IDSA Guidelines Committee for Immunization of Immunocompromised Hosts.

Dr. Temte then took a few minutes to provide some introductory comments. He said he thought he was the first family physician to serve as the ACIP Chair. He reassured everyone that he sees infants, adolescents, adults, and pregnant patients in his practice and is pretty good about immunizing all of them. Dr. Temte emphasized that it was a great honor and privilege to be part of the US ACIP, and to have been asked to serve as chair. By his reckoning, this was his 25th ACIP meeting. He said he thought what brought everyone to the ACIP meetings was a dedication to provide a wonderful preventive intervention that, in the end, makes a difference. For example, October 24th was World Polio Day. The October 19, 2012 *MMWR* highlighted this. As of October 9, 2012, a total of 162 polio cases had been reported during the year worldwide, with 97% reported from three countries (Nigeria, Afghanistan and Pakistan). This is the lowest number of recorded cases worldwide during a 9-month period ever. Over the years, Dr. Temte has been impressed with the commonality of all ACIP attendees, including the voting members, the liaisons, the dedicated ACIP Secretary, the tireless CDC staff, manufacturers, the Meningitis Angels, Mothers Against Mercury, Families Fighting Flu, and other concerned individuals. This is a venue in which ACIP hopes it uses science wisely so as to touch people and make a difference.

With regard to his background, Dr. Temte is one generation off the farm. His dad spoke only Norwegian until he went to kindergarten in a one-room public school house, and went on to teach Mathematics at the University of Wisconsin. Dr. Temte graduated from the same small liberal arts college as his parents, and went off to study the developmental physiology of seals.



Dr. Temte returned to Wisconsin and received his medical training, and ultimately became a family physician. His interest in seasonality led to seasonal viruses, such as influenza, which eventually led to his interest in vaccines. He currently practices full-spectrum primary care medicine at Wingra Family Medical Center. Whereas Madison, Wisconsin is an affluent community, his patient population tends not to be so. The Wingra Family Medical Center practice is comprised primarily of African American, Latino, Hmong, chronically mentally ill patients, among others. Every day Dr. Temte sees firsthand the incredible disparity that exists within the American medical enterprise. Despite these challenges, however, his center's vaccination rates are high.

Much of this is due to the VFC program. VFC is incredibly successful. As far as Dr. Temte is aware, childhood vaccination in the US is the only part of the US medical system in which there is no disparity. It does not depend upon one's race or ethnicity, and whether one is rich or poor, it works. ACIP is a steward for the VFC program, and as such, the committee must make wise choices in order to assure the future of this program. There remains a challenge to do as well with adolescents, and especially with adults, as the US population demographics change radically in the coming decades. There is a need to enhance attention to older citizens as well. Much has been made of the inclusion of an evidence-based framework in vaccine recommendations. Dr. Temte commended his fellow ACIP members, liaisons, CDC staff, and others who have taken this on. He will continue to be committed to ACIP's approach of the use of the best available scientific information, and applying this information based on patients, values, and preferences in a rational and transparent manner. ACIP tends to care a lot about numbers; however, it is essential to translate these numbers into meaningful outcomes.

Dr. Temte concluded with a brief story about his Freshman year at Luther College. Freshmen usually get the dregs for January terms and, true to form, after all of the good courses were taken, he ended up with one that was low on his list. It was based on the PBS series, *The Ascent of Man*, and featured Dr. Jacob Bronowski, a Mathematician who incidentally went on to become an Associate Director at the Salk Institute. While Dr. Temte did not remember much of the course, there was a brief treatise on the role of science that he wanted to share with everyone. In the interest of time, he was unable to share the clip during this session, but indicated that he would make the YouTube link available.

Pertussis Vaccines

Introduction

Mark Sawyer, MD **Chair, Pertussis Vaccine Working Group**

Dr. Sawyer introduced this important session, which led to a vote on the consideration of repeat Tdap vaccination for pregnant women. The terms of reference under which the Pertussis Working Group is currently constituted are as follows:

- ❑ Review existing statements on infants and young children (1997), adolescent (2006), adults (2006), and pregnant and postpartum women and their infants (2008) and consolidate these into a single statement.
- ❑ Review new data on Tdap including:
 - Effectiveness of ACIP recommendations
 - Interval between Td booster and Tdap
 - Use of Tdap in adults ages 65 years and older
 - Pregnant and breastfeeding women
 - Use of Tdap
 - Cocooning strategies
 - Vaccinated HCP and need for postexposure prophylaxis
 - Tdap revaccination
 - Pregnant Women

- ❑ Review updated epidemiology of tetanus and diphtheria

During this session, the following presentations were delivered:

- ❑ Update on the epidemiology of pertussis in the US and Washington epidemic, 2012
- ❑ Review of evidence considered for pregnancy Tdap recommendation (February and June 2011)
 - Safety of Tdap to mother and fetus
 - Transplacental transfer of maternal antibodies
 - Interference with infant immune response to primary DTaP vaccination
 - Cocooning
 - Decision and cost-effectiveness analysis
- ❑ Considerations for recommendation on Tdap for every pregnancy

The current recommendation for pertussis immunization in the US begins with 5 doses of DTaP in infants and young children (2, 4, 6, 15-18 months, 4-6 years); 1 dose at ages 11 and 12 in adolescents; and 1 dose in adults of all ages, with a special emphasis for health care personnel (HCP), pregnant women, and those in a cocooning situation with young infants.

There are two licensed products of Tdap currently on the market: Adacel[®] from sanofi pasteur, which is approved for use in those 11 through 64 years of age; and Boostrix[®] from GlaxoSmithKline (GSK) for use in those 10 years of age and older. These vaccines are very similar in composition, particularly with regard to diphtheria and tetanus toxoids. This session's discussion pertained to revaccination and potential side effects from repeated doses of diphtheria- and tetanus-containing vaccines.

Currently in the US, 95.5% DTaP coverage has been achieved for 3 or more doses in young children, and 95% coverage at school entry (e.g., Kindergarten). Coverage is not as high with Tdap, although with adolescents there has been a steady increase that has reached 78% as of 2011. However, coverage of the general adult population is only 8% despite the recommendation for everyone to be immunized. In April 2012, CDC conducted an internet panel survey among US women who were pregnant any time during August 2011 through April 2012, a period during which the new pregnancy recommendation was just issued, and asked about Tdap vaccination. The coverage rate based on that survey was only 2.6%, so there remains a long way to go in terms of immunizing the US adult population [CDC. National, State, and Local Area Vaccination Coverage Among Children Aged 19–35 Months — United States, 2011. MMWR. 61(35);689-696; CDC. Vaccination Coverage Reports. 2009-2010. [Vaccination Coverage Reports 2009-2010](#); CDC. National and State Vaccination Coverage Among Adolescents Aged 13–17 Years — United States, 2011. MMWR. 61(34);671-677; CDC. Adult Vaccination Coverage — United States, 2010. MMWR. 61(04);66-72; CDC. Tdap vaccination coverage among U.S. women who were pregnant any time during August 2011 - April 2012, Internet Panel Survey, April 2012. Unpublished].

With regard to reported pertussis incidence by age group from 1990 through 2011, Dr. Sawyer emphasized that the major burden of disease remained in young children under 1 year of age, and a recent peak from 2010 to 2012 included the various outbreaks discussed during ACIP meetings. The recent increase in disease in 7 through 10 year old children raises the question regarding duration of protection from DTaP vaccination [CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System]. Dr. Sawyer stressed

that for this session's discussion, it would be very important to keep in mind reports of pertussis deaths by age group from 2000 through 2012. As of October 2012, there have been 16 deaths in the US from pertussis. Most importantly, almost all of these deaths occurred in the first few months of life, an age at which infants cannot be protected directly through immunization. Indirect efforts are required; hence, the discussion regarding immunization of their mothers before they are born.

The current ACIP Tdap recommendation for pregnant women is as follows [CDC. Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) in Pregnant Women and Persons Who Have or Anticipate Having Close Contact with an Infant Aged <12 Months; Advisory Committee on Immunization Practices (ACIP), 2011. MMWR; 60(41);1424-1426]:

“ACIP recommends that women's health-care personnel implement a Tdap vaccination program for pregnant women who previously have not received Tdap. Health-care personnel should administer Tdap during pregnancy, preferably during the third or late second trimester (after 20 weeks' gestation). If not administered during pregnancy, Tdap should be administered immediately postpartum.”

Under consideration during this session regarded whether to extend this recommendation such that women would be immunized at each pregnancy, as was recently introduced in the United Kingdom (UK) in response to their on-going outbreaks of disease.

The next steps for the Pertussis Vaccines Working Group include consideration of Tdap revaccination for the general population, which the working group hopes to bring to ACIP for further discussion during the February 2013; and development of the updated statement to incorporate all pertussis vaccination recommendations, which should begin by the end of 2012 and hopefully will be finished soon thereafter.

Update on the Epidemiology of Pertussis in the US and The Washington State Epidemic of 2012

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As seen in the headlines recently, Dr. Meyer reported that the US is in the midst of a national pertussis resurgence, with record-breaking numbers of cases reported throughout the nation. As of October 12, 2012, there have been 32,645 cases reported in the US. While no longer seeing the 200,000+ annual cases reported during the pre-vaccine era, pertussis is on the rise after reaching historic lows in the 1970s. By the end of the year, more pertussis cases will have been reported this year than in any year since 1959. Year-to-date case counts for 2012 have already surpassed the number of cases reported for all of 2010, the last record-breaking year, and final 2012 numbers are expected to be much higher given the typical reporting lag. This year, 16 deaths from pertussis have been recorded [2012 NNDSS data are provisional and reflect cases reported to NNDSS as of Week 41; CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System and 1922-1949, passive reports to the Public Health Service].

Based on cases reported to CDC through national surveillance, the incidence of pertussis in the US is 10.6 cases per 100,000 population, but varies considerably by state. Many states are reporting substantially higher rates, such as Wisconsin, with an incidence of 87.6 cases per 100,000 [2012 data are preliminary and subject to change. Data represent cases received at CDC through Week 41; CDC National Notifiable Disease Surveillance System 2012; 2011 Census data used for population estimates; Incidence is per 100,000 population].

Cases increased in 48 states in 2012 compared to this period in 2011, with 32 states reporting at least twice as many cases. Of these 32 states, 8 of these states have reported at least 5 times as many cases. Washington State has been particularly hard-hit in this epidemic, as was reported to ACIP in June 2012 [Data for 2012 are provisional and subject to change; Cases reported through Week 41 in 2011 were compared with cases reported through Week 41 in 2012; fold-changes were calculated for each state]. Over 4300 cases have been reported this year in Washington, which is 8 times higher than this time last year. Notable in this epidemic were the high rates in adolescents [Washington State Department of Health: [Washington State Department of Health Pertussis Link](#)], which the Washington State Department of Health and CDC reported in the July 20, 2012 *MMWR*.

From January 1 through June 16, 2012, high rates of disease were observed in 7 through 10 year olds. In fact, 10 year olds had the highest incidence of pertussis. Disproportionately high rates of pertussis have been observed in 7 through 10 year olds since the mid-2000s, when this trend emerged among the first birth cohorts to receive all acellular pertussis (AP) vaccines, following the switch from DTwP, or whole cell pertussis vaccine, to DTaP in 1997. This raised concerns for early waning of immunity after the 5th dose of AP vaccines [CDC. *MMWR* 2012;61(28);517-522].

This trend was evident in 2010 during a resurgence of disease in the US, when a clear, stepwise increase in pertussis cases was reported in every year of life from 7 to 10 years of age, after the 5th DTaP and before Tdap receipt. Evaluations conducted in California, which reported over 8000 cases in 2010, demonstrated that despite excellent immediate DTaP vaccine effectiveness, immunity waned substantially in the 5 years since receipt of the 5th dose [Misegades, et al. *IDSA* 2011, Boston; Klein et al, *NEJM* 2012; 367:1012-9].

With regard to estimates of vaccine effectiveness at 98.1% in the 1st year since receipt of the 5th dose, by 5 years out, vaccine effectiveness dropped to 71.2%. This leaves nearly 30% of fully vaccinated 7 through 10 year olds susceptible to pertussis until they are eligible to receive Tdap at age 11 [Misegades, et al. *IDSA* 2011, Boston]. This earlier than expected waning of immunity is contributing to emergence of disease in school-aged children. In addition to the continued surveillance trends documenting this increase, Klein et al demonstrated a 1.42 odds of a positive pertussis polymerase chain reaction (PCR) every year since the 5th DTaP dose, and Tartof et al showed a 4.2-7.0-fold increase in risk of pertussis by 6 years after the 5th dose. This raises a question regarding whether immunity from aP vaccines wanes faster than that of whole cell vaccines [Klein et al, *NEJM* 2012; 367:1012-9; 2 Tartof et al, *IDSA* 2011, Boston].

In the first head-to-head comparison, Sheridan et al showed that among children born in 1998, during a transition from whole cell to AP vaccines in Australia, the children who received the primary series as all whole cell vaccines have significantly lower rates of pertussis than those who received all AP vaccines. In addition, children who received a mixed primary series but whose first dose was whole cell had lower rates than both those who received all AP vaccines and those with a mixed course whose first dose was AP. Thus, based on these results, it appears that having at least 1 dose of whole cell vaccines, if given first, provides greater

protection against pertussis than AP vaccines if given first [Sheridan et al, *JAMA* 2012, 308(5):454-456].

Going back to Washington State in the 2012 epidemic, after these high rates peaking in 10 year olds, a relative reduction in incidence in 11 through 12 year olds is observed, presumably due to the immediate effectiveness of Tdap vaccination. But surprisingly, a very high rate of disease is seen in 13 through 14 year olds, despite high coverage with Tdap administered within the past 2 to 3 years. Given that early waning of immunity has been observed after DTaP vaccination, is a similar phenomenon after Tdap administration being observed?

Assessing the age breakdowns according to vaccination type received, AP vaccines replaced whole cell vaccines for the complete childhood series in 1997. Thus, anyone 14 years of age and younger received all AP vaccines. Those aged 15 years were in a transitional period in which they either received all AP vaccines, or received a mix of AP and whole cell vaccines. Adolescents aged 16 and older received a mix of whole cell and AP vaccines. This age-trend adds further evidence to the hypothesis that AP vaccines wane earlier than whole cell vaccines, and that Tdap booster among recipients of AP childhood vaccine may have different effectiveness and duration of protection than among recipients of whole cell childhood vaccines. Results from Washington do not support the hypothesis that strain changes are leading to this resurgence in pertussis, as isolates tested from Washington have substantial variety in PFGE profiles, with the majority among the most common strains identified in the national database for the past 20 years. While this clear age trend was seen in Washington, an effort was made to determine whether this was occurring elsewhere. An assessment of the national epidemiology found the same trend of high rates in 13 through 14 year olds, a trend that persisted even after Washington cases were removed from the analysis [CDC. *MMWR* 2012;61(28);517-522].

Regarding what is known about Tdap effectiveness thus far, in the field studies published to date, Tdap vaccine effectiveness is estimated at 70% within the first few years after administration. However, these studies all involved adolescents who received whole cell vaccines as children, and thus Tdap effectiveness among adolescents who received all AP vaccines in childhood is unknown. Duration of protection of Tdap is also unknown, for recipients of both AP and whole cell childhood vaccines. To address these questions of vaccine effectiveness and duration of protection, evaluations were initiated in Washington State and California and are currently on-going.

In terms of the evaluation in Washington State, the objectives are to evaluate the vaccine effectiveness and duration of protection of Tdap, as well as the impact of the primary series type and the vaccine manufacturer and brand on these estimates. A case-control methodology via chart abstractions is being conducted for 11 through 18 year old Washington residents in the 7 counties that reported greater than 80% of adolescent pertussis cases, which encompasses over 200 clinics and 1000 cases. Primary data collection is complete, and the preliminary analysis is underway, with the goal of presenting initial findings during the February 2013 ACIP meeting.

In conclusion, the recent changes in pertussis epidemiology may be related to the switch from whole cell to acellular vaccines. Although DTaP has excellent initial effectiveness, immunity wanes over time. The evolving epidemiology of early adolescent disease is concerning for a similar early waning of immunity after Tdap administration. However, the immediate priority remains to maximize the current vaccination program, including universal adolescent and adult Tdap vaccination, particularly for pregnant women. Continued support for surveillance and

evaluations of vaccine performance is critical to help guide future pertussis vaccine policy and practice in the US.

Rationale for Vaccinating Pregnant Women with Tdap

Dr. Jennifer L. Liang ACIP Pertussis Vaccine Working Group

Before presenting the working group's proposed update to the 2011 Tdap recommendation for pregnant women, Dr. Liang presented an overview of the data reviewed and conclusions made by ACIP during the February and June 2011 meetings that led ACIP to make this recommendation. At the time, the original recommendation was to vaccinate all close contacts of infants with Tdap, referred to as cocooning. Unvaccinated mothers were recommended to receive Tdap immediately postpartum.

As shown earlier, infants less than one year of age have the highest reported incidence of pertussis compared to other age groups. This does not include the 2012 data which are incomplete. Pertussis incidence in infants ranges from 20 to 100 cases per 100,000 [CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System]. Among infants, those less than 2 months of age have the highest incidence of pertussis cases. This is before they are old enough to receive their first DTaP dose. Incidence declines rapidly after introduction of the DTaP series. These youngest infants also have the highest reported percent of hospitalizations and deaths among all infants. Half of infants less than 4 months of age require hospitalization [CDC, National Notifiable Diseases Surveillance System, 2011]. As previously shown, infants aged 2 months and younger have the highest number of reported pertussis deaths, compared to older infants and all others ages combined [2012 data are provisional and reflect deaths reported to NNDSS as of October 19, 2012; CDC, National Notifiable Diseases Surveillance System, 2012].

Several studies have identified the source of infant pertussis, and among them, the majority show that the source is not the mother. In 2005, the cocooning strategy was recommended to protect infants from pertussis by vaccinating all close contacts with Tdap. Cocooning programs have had success with vaccinating mothers postpartum, but have had difficulty achieving coverage among all family members. The effectiveness of this strategy is unknown and in 2011, ACIP concluded that cocooning was a sub-optimal strategy to prevent infant pertussis [Wendelboe AM, et al. Transmission of *Bordetella pertussis* to Young Infants. *Pediatr Infect Dis J* 2007;26: 293–299; Bisgard KM, et al. Infant pertussis: who was the source? *Pediatr Infect Dis J* 2004; 23(11):985-989; Healy CM, et al. Pertussis immunization in a high-risk postpartum population. *Vaccine*. 2009 Sep 18;27(41):5599-602].

While ACIP continues to recommend Tdap vaccination to all contacts of infants, because of the challenges with cocooning programs, ACIP considered shifting the timing of the mother's Tdap dose from postpartum to pregnancy. This shift would provide earlier protection to a mother and therefore indirect protection to the infant. By vaccinating during pregnancy, high levels of transplacental maternal antibodies would be transferred to infants, which may provide direct protection.

In 2011, ACIP reviewed safety data on use of Tdap in pregnant women. As a reminder, inactivated viral vaccines, bacterial vaccines, and toxoids are considered very safe during pregnancy. The other two vaccines recommended to pregnant women are influenza vaccine to protect pregnant women and young infants, and tetanus toxoid vaccine to protect infants born to women in developing countries from neonatal tetanus. There is no evidence to demonstrate an increased risk of adverse events or outcomes from these vaccines to mother or fetus.

ACIP reviewed published and unpublished Tdap safety data from the Vaccine Adverse Event Reporting System (VAERS), pregnancy registries from sanofi pasteur and GSK, and other small studies [Gall SA, et al. Maternal immunization with tetanus-diphtheria-pertussis vaccine: effect on maternal and neonatal serum antibody levels. *Am J Obstet Gynecol* 2011;204:334.e1-5; Talbot EA, et al. The safety of immunizing with tetanus-diphtheria-acellular pertussis vaccine (Tdap) less than 2 years following previous tetanus vaccination: experience during a mass vaccination campaign of healthcare personnel during a respiratory illness outbreak. *Vaccine* 2010;28:8001-7].

A review of reports from VAERS data of Tdap vaccines in pregnant women showed no unexpected patterns or unusual events. Although not presented during this session, data from pregnancy registries and small studies reviewed by ACIP were consistent with VAERS findings and did not suggest any elevated frequency or unusual patterns of adverse events in pregnant women who received Tdap.

ACIP concluded that Tdap during pregnancy is acceptably safe to woman and fetuses, given that Td and TT have been used extensively in pregnant women and no evidence indicates that administering either vaccine during pregnancy is teratogenic. Any data collected support the safety of Tdap in mother and newborns. Although data are not sufficient to exclude occurrence of a rare adverse event, current data suggest that potential risks, if any, are likely to be small.

Transplacentally transferred maternal antibodies likely provide protection against pertussis in early life and before beginning the primary DTaP series. Several studies provide evidence supporting the existence of efficient transplacental transfer of pertussis antibodies. A study from the Netherlands on unvaccinated mothers measured the maternal antibodies for pertussis in 196 paired maternal delivery and cord blood samples. Although there are low levels of pertussis antibodies in unvaccinated mothers, there is active transport of transplacental antibodies in cord blood [de Voer RM, et al. Seroprevalence and placental transportation of maternal antibodies specific for *Neisseria meningitidis* serogroup C, *Haemophilus influenzae* type B, diphtheria, tetanus, and pertussis. *Clin Infect Dis*. 2009 Jul 1;49(1):58-64].

In a study comparing pregnant women vaccinated with Tdap to pregnant women who were not vaccinated, newborns from mothers vaccinated with Tdap during pregnancy had significantly higher concentrations of pertussis antibodies when compared to newborns from unvaccinated mothers [Gall SA, Myers J, Pichichero M. Maternal immunization with tetanus-diphtheria-pertussis vaccine: effect on maternal and neonatal serum antibody levels. *Am J Obstet Gynecol* 2011;204:x.ex-x.ex].

Geometric mean concentration (GMC) curves showing antibody response after Tdap vaccination of healthy, non-pregnant adults to both licensed Tdap products indicate that antibody response in pregnant women would likely not be much different. After receipt of Tdap, antibody levels peak during the first month after vaccination, with substantial antibody decay after 1 year [Weston W, et. al. Persistence of antibodies 3 years after booster vaccination of adults with combined acellular pertussis, diphtheria and tetanus toxoids vaccine. *Vaccine*. 2011 Nov 3;29(47):8483-6].

One of the concerns with immunizing pregnant women with pertussis vaccines was that maternal antibodies would interfere or inhibit active pertussis-specific antibody production after administration of DTaP vaccine in infants whose mothers were vaccinated during pregnancy. This is also referred to as blunting. Historical data have shown that when vaccinated with whole cell, the immune response was lower in infants with high cord blood anti-PT antibody levels than in infants with a low cord blood level of circulating maternal antibodies. More recent data have shown that when vaccinated with acellular pertussis vaccines, immune response was lower, but was not similarly inhibited by circulating maternal antibody as observed with whole cell. There remains limited data available, but one study suggests that the effects of blunting largely resolve by completion of the 3rd DTaP dose.

ACIP concluded that Tdap during pregnancy may prevent infant pertussis following the same pregnancy because there is efficient maternal-infant antibody transfer after Tdap; for infants, maternal antibodies likely confer protection and modify the severity of pertussis illness; and to optimize the concentration of maternal antibodies to the fetus, unvaccinated women should get Tdap during pregnancy.

To help answer the question regarding the impact on infant pertussis if a women's dose of Tdap was shifted from postpartum to pregnancy, CDC presented a decision analysis that analyzed the impact of Tdap during pregnancy and compared this to the existing recommendation of postpartum Tdap. The analysis also quantified the theoretical risk of infant pertussis infection due to blunting. A simulated birth cohort model was used to follow the 2009 US birth cohort of 4 million infants for 1 year. The direct medical and non-medical costs of pertussis disease were analyzed in infants only over the first year of life, and life years lost were based on a life expectancy of 77.9 years. In the model, the pregnancy dose was given during the 3rd trimester and resulted in increased risk of disease in the infant's 3rd and 4th month of life to simulate blunting. The postpartum dose was given immediately postpartum with a 2-week delay in vaccine effectiveness, and cocooning doses were given to the father and a grandparent before birth.

Both the postpartum Tdap strategy and the Tdap during pregnancy strategy result in a reduction of infant cases, but the reduction is most striking in the first 2 months of life, where most infant morbidity and mortality occur. By protecting the mother earlier, and providing additional direct protection to the infant through maternal antibodies, the model shows that vaccinating during pregnancy offers maximum protection during the months where disease incidence, morbidity, and mortality are highest.

In summary of the mean reduction in infant pertussis morbidity and mortality relative to the base case, a postpartum dose of Tdap can reduce the number of pertussis cases, hospitalizations, and deaths in infants compared to the base case. However, by moving this dose to the 3rd trimester of pregnancy, the mean reduction is greater, reducing cases by 33%, hospitalizations by 38%, and deaths by 49% compared to the base case—all at the same program cost as a postpartum dose.

Based on this decision analysis, ACIP strongly agreed that in every scenario, the impact of vaccinating during pregnancy is favorable; Tdap during pregnancy prevents more infant cases, hospitalizations, and deaths; and vaccination during pregnancy could avert more cases and deaths at no additional cost than postpartum vaccination with or without additional cocooning doses.

After review of the data presented to ACIP in February and June 2011, ACIP concluded that postpartum vaccination is a suboptimal national strategy to prevent infant pertussis morbidity and mortality; vaccinating pregnant women during the late second or third trimester is acceptably safe for both mother and fetus; the programmatic cost of vaccinating with Tdap during pregnancy or postpartum is the same; the theoretical risk of blunting is outweighed by the benefits; and late second or third trimester maternal vaccination may prevent infant pertussis during the same pregnancy.

Based on these conclusions, ACIP recommended that women's health-care personnel implement a Tdap vaccination program for pregnant women who previously have not received Tdap. Health-care personnel should administer Tdap during pregnancy, preferably during the third or late second trimester after 20 weeks' gestation. If not administered during pregnancy, Tdap should be administered immediately postpartum. This was published as an *MMWR* Policy Note in October 2011. From the moment ACIP made this recommendation, questions were raised about subsequent pregnancies or previously vaccinated women.

Discussion Points

Dr. Duchin requested a reminder of the vaccine effectiveness in the decision analysis model for preventing infant pertussis.

Dr. Liang replied that 100% vaccine effectiveness was used for the mother, with 100% of that transplacentally transferred to the infant. The effectiveness included in the model for the infant was approximately 60%.

Dr. Baker thought the estimate included for the father and grandfather was high based on data from various programs that have tried to implement cocooning. If anything, the model overestimates the potential effect of cocooning.

Dr. Temte agreed, emphasizing that it is extremely difficult for hospitals to undertake a cocooning strategy because the fathers and other family are not patients and it is very difficult to get services applied to them. Regarding safety issues, he was curious about the structure of the data collection that is on-going by the manufacturers for safety with Tdap during pregnancy.

Dr. Friedland (GSK) responded that GSK maintains a pregnancy registry for which they have an 800 number for healthcare providers and pregnant women to call to register information prospectively about their pregnancies. There is also a link to the pregnancy registry on the FDA website related to pregnancy registries for all drugs and vaccines. GSK is actively collecting data prospectively on pregnancy, as well as retrospective reports that are submitted from the US and worldwide. GSK has shared its most up-to-date report of the worldwide experience with the pregnancy registry as of August 2012 with Dr. Liang.

Dr. Decker (sanofi pasteur) indicated that his response was identical to Dr. Friedland's.

Regarding the study showing that the women vaccinated during pregnancy had a higher rate of maternal antibodies, Pamela Rockwell (AAFP Vaccine Science Fellow) noted that the recommendation was to only vaccinate women during pregnancy who were previously unvaccinated. She requested clarity about what "previously unvaccinated" meant (e.g., people who never had childhood vaccinations, people who never had one booster, people who had a booster 5 years ago). She thought this language would be very confusing to practitioners and

others who. For example, if someone received her 11-year old Tdap and was pregnant at 17, her feeling would be that they should receive a booster during pregnancy.

Dr. Liang replied that the recommendation was written this way because currently, Tdap is only FDA-approved and recommended by ACIP for a single dose. She indicated that the proposal in her next recommendation would be Tdap immunization for pregnant women during every pregnancy, regardless of vaccine history.

Dr. Temte reminded everyone that there is currently 2.6% coverage rate during pregnancy, which is approximately 100,000 pregnancies per year in the US.

Dr. Salisbury (DOH, UK) reported that the UK observed a rise in pertussis in 2011 that has continued and exacerbated in 2012. The greatest number of cases have been in adolescents and young adults, and not in the same age group as the US has observed. The highest rate was in infants under 3 months of age. Through August of 2012, there were 9 deaths in infants under 3 months of age and subsequently had 1 more. The options were carefully considered, and the conclusion was reached that introducing an adolescent dose would take far too long to have an impact on the highest rates of cases and deaths. Assessment was then made regarding whether compliance was being achieved with the recommended schedule for the first dose to be given at 8 weeks. Compliance is extremely high, so it is not delaying the first dose that is leaving infants at risk. Consideration was then given to whether to bring forward the first dose from 8 weeks to 6 weeks, which would only prevent something on the order of 10% to 20% of cases. Thus, it was felt that there was no alternative but to make a recommendation to vaccinate during pregnancy, with the ideal ages between 28 weeks and 38 weeks, but best between 28 weeks and 32 weeks because that fits with the antenatal visits most appropriately. Also recommended was that women should be vaccinated in each and every subsequent pregnancy, irrespective of when they last had a dose of pertussis vaccine. Those recommendations were made 3 weeks prior to this ACIP meeting. On the day the recommendation was issued, orders for vaccine were received because it is centrally managed and distributed. As of the 22nd of October 200,000 doses were distributed for pregnant women. The media response was extraordinarily supportive, and the response from pregnant women and healthcare professionals was very strongly supportive. It is interesting to compare this situation against influenza, for instance. Perhaps the difference was that they could be very clear how many infants were dying from pertussis, and there was considerable public anxiety about the severity of pertussis. Collection of data regarding coverage will begin in November 2012 to assess the impact on the disease and the immunology on the potential for blunting. This has been described as a provisional program while other initiatives / interventions are evaluated and the epidemiology is evaluated. A number of means of communication have been used (e.g., email, text messages, Twitter, and Facebook), and a scheme where pregnant women can record their details and are sent email, text, Twitter, or Facebook messages according to each stage of their pregnancy.

Dr. Ault (ACOG) said he thought that most practicing obstetricians and gynecologists seek guidance from ACOG on such issues. ACOG's recommendations were published in its official journal, *Obstetrics and Gynecology*, in March 2012. Most obstetricians and gynecologists would not have heard about the new recommendations if they were relying on ACOG for guidance. Provider education and information packets were disseminated during the summer specific to this vaccine, along with another batch of influenza information. The Georgia ACOG group put a lot of effort into convincing hospitals to administer the postpartum dose at their own expense, and convinced hospital administrators that this was the right choice. Given that so much effort was put on the postpartum dose, which is no longer going to be the standard of care, there may

be some resistance. The Pap smear guidelines have been changed at ACOG about every 6 months, so there is some guideline fatigue. Perhaps the same is occurring with the pertussis guidelines.

Noting that Dr. Liang referred to only one personal communication pertaining to blunting, Dr. Poland (ACP) inquired as to how good the data are on blunting, and what is known about blunting in the short- and long-term. In addition, particularly if advocating for a dose of Tdap with every pregnancy, it is important to understand the safety of giving 3 to 5 doses over a 4 to 6 year time period. With less doses than that of Td, serum sickness-like events have been observed.

Dr. Liang responded that she would be addressing the safety of a dose with every pregnancy during the next presentation as part of the discussion and consideration. Regarding blunting, there are very few data about the long-term effects of blunting. At the same time, the clinical implications of blunting are not known. That is, it is unclear how much of an increase in risk blunting presents to a child. Two studies are underway. One is in the US that Dr. Baker might like to summarize. The other is in Canada, which is following infants whose mothers are immunized with Tdap during pregnancy and collecting serum at various time points after DTaP to measure blunting. As mentioned from the Halperin study, by the third dose, the immune response was comparable to children whose mothers were not vaccinated during pregnancy.

Dr. Baker indicated that her study consists of only 32 pregnant women immunized during pregnancy, a crossover of the placebos to postpartum, and some other controls. The data from this study should be available for the February 2013 ACIP meeting. She reminded everyone that Dr. Halperin's study was comprised of 50 women who were immunized during their third trimester. There was no blunting with the third dose, with some implication that there was blunting after the first dose. But there was no problem with priming, which is what the first dose does. The main point is that if blunting is biologically significant, because there is no correlate of protection, it would result in the occurrence of disease at an older age at which time some babies would probably still be hospitalized at similar rates, but deaths would be prevented.

Consideration for Updated Recommendations on the Use of Tdap in Pregnant Women

Dr. Jennifer L. Liang ACIP Pertussis Vaccine Working Group

When the working group began discussions on additional doses of Tdap, they decided to first focus on pregnant women before the general population. Before presenting the data reviewed by the working group, Dr. Liang reported on the 2012 case history of fatal pertussis in an infant born to a mother who received Tdap two years ago, which was recently presented to the working group. A male, Hispanic infant developed illness when he was 8 days old and was hospitalized at 32 days. The infant had apnea, paroxysmal cough, whoop, and cyanosis. On the day of admission, the infant was PCR positive for pertussis. During hospitalization, he was intubated and placed on mechanical ventilation. Extracorporeal membrane oxygenation (ECMO) was started one day after admission. He died 9 days later at age 40 days. The infant's mother had cough illness starting 1 week prior to delivery with paroxysmal cough, whoop, and post-tussive vomiting. No medical attention was sought. She had received Tdap postpartum 2 years prior. The mother had 3 other children. Of the two who were ill, one had illness onset 2 weeks before the infant's birth. In addition to the infant, one of the children was PCR positive

for pertussis. All were treated after the infant died. Although this is one case, they did everything right, but the mother's postpartum Tdap from 2 years before was not enough.

The working group is continuing efforts to remove barriers to improve Tdap uptake. As Dr. Sawyer presented at the beginning of this session, coverage among adolescents has been steadily improving over the years; whereas, only 8% of adults have received Tdap, and among pregnant women only 2.6% were vaccinated with Tdap during pregnancy. There are new data available on the persistence of maternal antibodies, and the working group wants to optimize strategies to prevent infant pertussis morbidity and mortality in light of record-setting increase in pertussis cases.

In terms of background, Tdap is approved by the Food and Drug Administration (FDA) for single use only, and ACIP currently recommends Tdap as a single lifetime dose. Because of this, the current ACIP recommendation for pregnant women is only for women not previously immunized with Tdap. When considering Tdap for every pregnancy, the working group reviewed barriers to vaccinating pregnant women; antibody response and kinetics of Tdap during pregnancy; safety on multiple doses of Tdap; and statistics on births in the US.

There are numerous barriers to vaccinating pregnant women. One specific to Tdap is provider hesitancy to vaccinate if the patient's Tdap history is undocumented or unknown. Because this recommendation is only a year old, many programs are still focused on postpartum Tdap and have yet to shift to Tdap during pregnancy. This is not only about translating the recommendation to programmatic implementation, but also is communicating and educating patients, providers, professional organizations, and public health. There are several initiatives aimed at improving vaccination of pregnant women. As the influenza experience has illustrated, provider recommendation is the best predictor of getting pregnant women vaccinated [Tong A, et al. A cross-sectional study of maternity care providers' and women's knowledge, attitudes, and behaviours towards influenza vaccination during pregnancy. *MJ Obstet Gynaecol Can.* 2008 May;30(5):404-10. Meharry et al. Reasons Why Women Accept or Reject the Trivalent Inactivated Influenza Vaccine (TIV) During Pregnancy *Matern Child Health J.* 2012 Feb 25].

Drawing upon the experience from influenza, it has taken time for coverage in pregnant women to increase. The hope is that by continuing to remove barriers to Tdap uptake, coverage of Tdap among pregnant women will improve as it has with influenza vaccine [Kennedy ED, Ahluwalia IB, Ding H, Lu PJ, Singleton JA, Bridges CB. Monitoring seasonal influenza vaccination coverage among pregnant women in the United States. *Am J Obstet Gynecol.* 2012 Sep;207(3 Suppl):S9-S16. Epub 2012 Jul 9].

Recalling the GMC curves in Dr. Liang's first presentation showing antibody response in healthy, non-pregnant adults to both licensed Tdap products presented earlier, antibody levels peak during the first month after vaccination, followed by a substantial antibody decay after 1 year. Antibody response in pregnant women would likely not be much different. The working group asked: Would a currently pregnant woman provide a high enough concentration of maternal pertussis antibodies to her fetus if she was previously vaccinated?

A study by Dr. Mary Healy assessed the persistence of maternal pertussis-specific antibody concentrations after receipt of Tdap. In this study, 105 maternal delivery and placental cord pairs were collected from women who received Tdap within the prior 2 years. The mean time from Tdap vaccine was 13.7 months. Approximately 70% received Tdap postpartum after the previous baby, and 19 women were immunized during pregnancy; the median at 6 weeks gestation, before they knew they were pregnant. The pertussis specific Immunoglobulin G (IgG)

GMCs were measured, and cord and maternal GMC ratios were calculated. Anti-PT IgG in 2 month old infants was estimated using the accepted half-life of maternal-PT IgG of 36 days. Based on the PT IgG GMC in cord sera and estimated decay with age, by age 2 months, the concentrations of maternal antibodies in these infants declined. Results from the study verified the efficient placental transport of pertussis antibodies, but there was little difference in pertussis antibodies in neonates of women vaccinated pre-conception and those vaccinated in early pregnancy, and both were low. At time of first DTaP, the estimated concentration of PT IgG fell to levels that were likely too low to ensure protection to infants in mothers immunized preconception [Healy C. IDSA 2012, in press].

The working group concluded that a single dose of Tdap at one pregnancy is insufficient to provide protection for subsequent pregnancies. If pregnant women were recommended a dose of Tdap for each pregnancy, the working group had concerns about the safety of multiple doses of Tdap to the mother. The original pregnancy recommendation was predicated on ACIP's conclusion that Tdap was very safe in pregnancy. Therefore, additional data were reviewed on multiple doses.

The working group assessed the risk of adverse events with short intervals between receipt of tetanus containing vaccines. A study by Halperin and colleagues on healthy non-pregnant adolescents supports the safety of an interval as short as approximately 2 years between Td and Tdap. In terms of the percent of reported adverse events in the 14 days after immunization with Tdap, and the intervals by year since the previous tetanus and diphtheria toxoid containing vaccine, as the interval from previous vaccination became shorter, rates of adverse events did not increase. There were with no differences from 2 through 10 year intervals. Severe adverse events, including Arthus reactions, were not observed in the study [Halperin SA, et. al. How soon after a prior tetanus-diphtheria vaccination can one give adult formulation tetanus-diphtheria-acellular pertussis vaccine? *Pediatr Infect Dis J.* 2006 25(3):195-200].

For healthy non-pregnant adults who received Tdap at intervals less than 2 years after Td, the most commonly reported adverse events were pain, redness, and swelling. Systemic adverse events included headache, fever, and myalgia. Serious adverse events related to the receipt of Tdap were not observed or reported. These data are similar to the Halperin study [Beytout J, et. al. Safety of Tdap-IPV given 1 month after Td-IPV booster in healthy young adults: a placebo controlled trial. *Hum Vaccin* 2009;5(5); Talbot EA, et. al. The safety of immunizing with tetanus-diphtheria-acellular pertussis vaccine (Tdap) less than 2 years following previous tetanus vaccination: Experience during a mass vaccination campaign of healthcare personnel during a respiratory illness outbreak. *Vaccine* (2010)].

The working group also reviewed published data on repeat Tdap administration 5 or 10 years after a previous Tdap dose. The second dose of Tdap was well-tolerated, with injection site pain as the most commonly reported adverse event. The frequency of reported adverse events for the second dose was similar to the first dose in this study group, and to those receiving Tdap for the first time. Of the few serious adverse events reported, none were attributed to receipt of vaccine [Knuf M, et al. Repeated administration of a reduced-antigen-content diphtheria-tetanus-acellular pertussis and poliomyelitis vaccine (dTpa-IPV; Boostrix™ IPV). *Hum Vaccin.* 2010 Jul;6(7):554-61; Booy R, et al. A decennial booster dose of reduced antigen content diphtheria, tetanus, acellular pertussis vaccine (Boostrix™) is immunogenic and well tolerated in adults. *Vaccine.* 2010 Dec 10;29(1):45-50; Halperin SA, et al. Tolerability and antibody response in adolescents and adults revaccinated with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed (Tdap) 4-5 years after a previous dose. *Vaccine.* 2011 Oct 26;29(46):8459-65; Halperin SA, et al. Immune responses in adults to revaccination with a

tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine 10 years after a previous dose. *Vaccine*. 2012 Jan 20;30(5):974-82].

The primary concern for working group members was the potential for severe adverse events such as Arthus reactions and whole limb swelling for pregnant women who have multiple pregnancies in a short period of time. Both Arthus reactions and whole limb swelling have been associated with vaccines containing tetanus toxoid, diphtheria toxoid, and/or pertussis antigens. A review of historical data on multiple doses of tetanus toxoid and diphtheria toxoid containing vaccines shows that hypersensitivity is associated with higher levels of pre-existing antibody. The frequency of side effects was dependent on antigen content, product formulation, preexisting levels related to short interval, and the number of doses. One study showed that post second Tdap tetanus GMCs did not differ from post first Tdap with a 5-year interval between doses. Excess risk of serious hypersensitivity is unlikely, even in a small number of pregnant women who might receive several doses [Halperin SA, et al. Tolerability and antibody response in adolescents and adults revaccinated with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed (Tdap) 4-5 years after a previous dose. *Vaccine*. 2011 Oct 26;29(46):8459-65].

For pregnant women, WHO recommends 2 or more doses of tetanus toxoid during pregnancy to complete the primary series to prevent neonatal tetanus. Data on the number of doses administered and adverse events are not systematically collected. However, major studies have not reported clinically significant severe adverse events beyond local redness, swelling, pain and tenderness, and systemic events like fever, body-ache, or lethargy [Schofield FD, et al., Neonatal tetanus in New Guinea. Effect of active immunization in pregnancy. *Br Med J*, 1961. 2(5255): p. 785-9; Newell, K.W., et al., The use of toxoid for the prevention of tetanus neonatorum. Final report of a double-blind controlled field trial. *Bull World Health Organ*, 1966. 35(6): p. 863-71; MacLennan, R., et al., Immunization against neonatal tetanus in New Guinea. Antitoxin response of pregnant women to adjuvant and plain toxoids. *Bull World Health Organ*, 1965. 32(5): p. 683-97; Hardegree, M.C., et al., Immunization against neonatal tetanus in New Guinea: 2. Duration of primary antitoxin responses to adjuvant tetanus toxoids and comparison of booster responses to adjuvant and plain toxoids. *Bulletin of the World Health Organization*, 1970. 43(3): p. 439-51].

There were challenges to reviewing historical data on multiple doses of tetanus-toxoid containing vaccines. There have been changes to adjuvant and toxoid amounts in vaccines, the severity of adverse events by number of doses is difficult to separate, and no data address Tdap in multiple pregnancies. Much of the data are historical, suggesting that the risk has been reduced with current formulations. The working group felt that available data and experience with tetanus toxoid containing vaccines suggests no excess risk of adverse events, but supported the need for prospective safety studies. In essence, the working group wished for more data pertaining to the theoretical concerns on severe adverse events, but felt that this was not a reason to deter them from making a recommendation for Tdap for every pregnancy or to limit the number of doses.

In the US, more than 4 million births occur in a year¹. Of these, 12% are born preterm¹. The mean age of women at first birth is approximately 25 years¹. On average, 2 children are born per woman [¹ [CDC NCHS Website for Birth Statistics](http://www.cdc.gov/nchs/data/br/b12008a01.pdf); ² [<https://www.cia.gov/library/publications/the-world-factbook/geos/us.html>]]. This number is reassuring that most women would potentially be pregnant two times, and would receive two doses of Tdap.

Among women who have 2 births, only 2.5% have an interval of 12 months or less between births. Interval is defined as between deliveries. Pregnancies resulting in multiple births, such as twins, are considered one delivery. There is not much difference with race or ethnicity. The majority of women who have 2 births have an interval of 13 months or more between births [Gladys Martinez G, Daniels K, Chandra A. Fertility of Men and Women Aged 15–44 Years in the United States: National Survey of Family Growth, 2006–2010. National Health Statistics Reports. No. 51, 2012. [CDC NCHS Website National Health Statistics Reports](#)]. For women of lower socioeconomic status, the time between pregnancies is generally 18 months or longer [CDC. Summary of Health Indicators, 2010 Pregnancy Nutrition Surveillance, Pregnancy Nutrition Surveillance System. [Summary of Health Indicators, 2010 Pregnancy Nutrition Surveillance, Pregnancy Nutrition Surveillance System](#)]. In terms of how many women have more than the average number of children, data suggest that around 5% of women have 4 or more babies. Therefore, a small proportion of women would receive more than 2 or 3 doses of Tdap [Fertility of American Women: 2010; June Supplement to the Current Population Survey. [US Census Website Current Population Survey](#)]. The working group concluded that the interval between subsequent pregnancies is likely greater than the persistence of maternal antibodies, and were reassured that a very small proportion of women would receive 4 or more doses of Tdap.

Before presenting the proposed language to ACIP, the working group concluded that although safety data are limited on multiple doses of Tdap, available data and experience with tetanus toxoid vaccines suggest no excess risk of adverse events. The working group was reassured that a very small proportion of women would be recommended 4 or more doses of Tdap. The working group supported on-going safety monitoring and requested that CDC commit to safety studies to address concerns about the potential increase in severe adverse events after Tdap is given during subsequent pregnancies.

CDC's Immunization Safety Office (ISO) plans to oversee safety monitoring in pregnant women vaccinated with Tdap. VAERS will implement enhanced monitoring for adverse events in pregnant women following Tdap. The Vaccine Safety Datalink (VSD) will be implementing studies assessing acute adverse events, adverse pregnancy outcomes affecting the mother, and birth outcomes following receipt of Tdap and other vaccines during pregnancy. The study power for Tdap depends upon uptake and may take a few years.

The working group also concluded that a single dose of Tdap at one pregnancy was insufficient to provide protection for subsequent pregnancies, and that the benefits of vaccination outweigh the theoretical risks of severe adverse events with multiple doses of Tdap. With poor Tdap uptake of 2.6% in pregnant women, the working group is continuing efforts to remove barriers to improve vaccine uptake and optimize strategies to prevent infant pertussis morbidity and mortality. In order to do so, the working group members believe that a more universal recommendation for pregnant women would remove real and/or perceived barriers to vaccination.

As mentioned earlier, several initiatives are aimed at improving Tdap uptake in pregnant women. Both the National Vaccine Advisory Committee (NVAC) and National Foundation for Infectious Diseases (NFID) are working to remove barriers to maternal immunization. CDC is collaborating with ACOG and other professional organizations and immunization partners to provide tools and resources to help implement this recommendation. There are also continued efforts to monitor the coverage in pregnant women through the Pregnancy Risk Assessment Monitoring System (PRAMS) and through the CDC's internet panel survey of pregnant women.

Changes to the 2011 recommendation reflect the working group's conclusions based on their review of available data and expert opinion. These changes included the following:

- Recommending a dose of Tdap irrespective of previous Tdap history
- Recommending Tdap for every pregnancy
- Simplifying the recommendation by moving language on timing of dose to the guidance section
- Expanding the discussion on timing in the guidance section of the updated pertussis vaccines statement

The proposed updated recommendation on use of Tdap for pregnant women read as follows:

“ACIP recommends that providers of prenatal care implement a Tdap immunization program for all pregnant women. Health-care personnel should administer a dose of Tdap during each pregnancy irrespective of the patient's prior history of receiving Tdap. If not administered during pregnancy, Tdap should be administered immediately postpartum.”

In the updated pertussis vaccines statement, which CDC hopes to publish in 2013, there will be an expanded section on guidance for use that will include, among other things, language on optimal timing of Tdap administration and safety.

Discussion Points

While she found the data to be compelling for the proposed recommendation, Dr. Coyne-Beasley inquired as to whether there would be a change to the FDA approval based on those data. Some practitioners prefer to follow what the FDA approves.

Dr. Sun (FDA) responded that labels are changed through submission of data from the manufacturers. The only way to make a change is for manufacturers to provide safety and effectiveness data to support multiple doses during pregnancy for FDA to review.

Ms. Rosenbaum inquired as to whether this meant that ACIP would be making an off-label use recommendation. If so, it would be important to understand how the coverage of immunizations under Medicare, Medicaid, employment-based insurance, and individual plans would be affected as a result of the Affordable Care Act (ACA). She requested that any public and private insurers in the room comment on what would occur if ACIP made a recommendation for an off-label use, and if there was a problem how quickly it could be rectified. While it could be assumed that under existing Medicare / Medicaid and private insurance payment standards, as modified by ACA, it is important to confirm with the Centers for Medicare and Medicaid Services (CMS) that they would instruct Medicaid program insurers to cover ACIP recommendations. Actually, each form of coverage should be checked.

Dr. Doskey (AHIP) disclosed that he is with Humana and was representing America's Health Insurance Plans (AHIP) during this meeting. He reported that most insurance plans almost always follow ACIP recommendations, even when those recommendations are for an off-label use, and there is precedent for this.

Dr. Hance (CMS) responded that for Medicaid, the ACIP recommendations are followed by the exchanges. Medicare does not follow the ACIP recommendations. Under Part D, DTaP is covered.

Dr. Keitel commented that during the development of the acellular pertussis vaccines, some transient consideration and discussion was undertaken to determine whether a standalone acellular vaccine might be of some value. It was anticipated and hoped that the duration of protection of the acellular vaccine would be longer than currently being observed. With that in mind, she wondered whether this was part of a new research agenda or discussion with the manufacturers to consider developing a standalone acellular product that could be used for this circumstance, as well as for outbreak control in populations that are already largely vaccinated against tetanus and diphtheria. She requested an estimate of the number of hospitalizations that would be prevented, how many pregnancies are monitored over the course of each year, and how many people in the UK birth cohort have more than one child in order to estimate how long it would take to compile a robust safety database for this approach. The UK approach is to recommend the vaccine within a more narrow time during pregnancy; whereas, the US is recommending anytime during pregnancy.

Dr. Clark (SME) responded that the recommendation was clarified to state that it is recommended during pregnancy. The guidance for use that will immediately follow that currently states third or late second term. He requested that Dr. Liang show the slide with this information and modify it to state "27 to 36 weeks is optimal" with discussion about why and preferably when not to give it.

Dr. Liang responded that she did not have a specific number of prevention of hospitalizations, and she referred to the decision analysis in terms of the mean reduction compared to the base case. In that decision analysis, if women were vaccinated during pregnancy, the hospitalization mean reduction would be about 38% within the birth cohort of 4 million.

Dr. Keitel wondered whether a "back of the envelope" estimation could be done. That is, if the rate of disease is X per 100,000 in infants of that age, of whom 66% would be hospitalized, with the 38% reduction, a rough estimate could be made.

Dr. Clark (SME) responded that it is hundreds of hospitalizations, so the majority of cases under about 3 or 4 months are hospitalized (e.g., about 50% to 60%). There are a couple of thousand in the youngest age group.

Dr. Liang inquired as to whether anyone was present from ISO to respond to Dr. Keitel's question regarding the VSD.

Claudia Vellozzi (ISO) replied that with regard to the VSD, a study would soon be implemented to monitor Tdap during pregnancy. While it will not necessarily address repetitive doses, at least the safety of one dose during pregnancy will be assessed. Given that coverage is low, uptake is likely to take a couple of years. However, she thought that the VSD reflected better uptake than the 2.6% stated. The rate is currently about 10%, and that is expected to rise with the new ACOG recommendations.

As a segue, Dr. Temte requested that Dr. Salisbury comment on the UK's plans to monitor safety.

Dr. Salisbury (DOH, UK) reported that the birth cohort for England and Wales is 660,000 per year. The average number of children per family is 2.4, though he did not have the details of the spread by numbers per family of 1, 2, and more children. In terms of safety monitoring, the UK's equivalent of the FDA has already started a process by which they will evaluate the adverse events reported in pregnancy for women who are vaccinated, and already has background data on the number of incidents that are likely to be observed against expected in real time as the information is submitted. Clearly, what comes through will depend very much upon coverage. Given that this program began only three weeks prior to this meeting, Dr. Salisbury pointed out that attempting to project uptake in the UK was premature. Tdap uptake will be compared closely with the uptake of seasonal influenza vaccine. The UK's recommendation does not differ significantly from the US. The US recommends 27 weeks to term, while the UK recommends 28 to 38 weeks. The UK stated that the ideal time would be 28 to 32 weeks because that aligns with the antenatal appointments.

Dr. Harrison inquired as to whether there are any data on the likelihood of acceptability among obstetricians of the new recommendation. He also wondered whether there were any data on the individual effectiveness of the vaccines, and whether the Washington case-control study would address effectiveness of the individual vaccines.

Dr. Ault (ACOG) reiterated that obstetricians tend to follow what ACOG states in its guidelines, and ACOG has a pretty robust process for developing practice guidelines. In addition, the lines of communication are pretty good between ACOG and the other parties involved. Therefore, he thought there was an opportunity to present this similarly to the 2009 pandemic influenza recommendation. Vaccine uptake during pregnancy increased two to three years ago. While it is still less than ideal, maternal vaccination is no longer a foreign concept to obstetricians and gynecologists.

Dr. Temte said he thought that about two thirds of deliveries in the US are made by obstetricians, with remainder by midwives and family physicians.

Dr. Brewer (ANA) offered the American Nurses Associations' support of the recommendation as stated, as well as vaccinating pregnant women. It is imperative to work harder to convince hesitant providers to do the right thing.

Dr. Loehr (AAFP) indicated that the American Academy of Family Physicians would also be supportive regardless of whether they were providing the prenatal care, or if they happened to see a women during her pregnancy for other reasons.

Dr. Clark (SME) reported that the Tdap case-control study in Washington State will attempt to assess brand, but there are no data to suggest a preference for one brand over the other. He does not expect to find a strong difference based on immunogenicity. Regarding the questions about blunting, this has been a problem historical with discussions about pregnancy vaccination for pertussis. Data are somewhat mixed, but the working group concluded that there likely is interference based on the presence of maternal antibody. However, the data were reassuring that consistent with the half-life that wanes and probably disappears by the third dose, it is unlikely to have a lasting effect. A large case-control study with several of CDC's state health department partners is assessing the effectiveness of cocooning and pregnancy vaccination, so hopefully there will be some effectiveness data. While this does not address a label change, it does address real-world performance of the vaccines. Thus, product can also be evaluated for this question specifically. The case-control study is powered to assess any change in risk in slightly older children based on blunting. While the clinical relevance is unknown, it was built

into the decision analysis where it was found to have little adverse effect because most of the deaths, hospitalizations, and severe disease are in the youngest children. CDC hopes to obtain some clinical evidence for blunting or not.

Dr. Liang added that for this recommendation, the focus is primarily on a short time from when the mother is vaccinated to her building an immune response and transferring it to her infant. This recommendation is intended to address a much shorter duration of effectiveness versus one or two years out following receipt of vaccine.

Dr. Duchin requested clarification on the predicted benefits of this strategy. The model assessed 72% coverage and found a 49% reduction in deaths and a 38% reduction in hospitalizations. He asked for a reminder of the basis on which those reductions in hospitalizations and deaths were derived.

Dr. Liang responded that these were compared to no Tdap intervention at all. This was based just on the infant cases that were modeled after what was reported in the national data (e.g., comparing postpartum and pregnancy vaccine to the known incidence). CDC feels comfortable in supporting this model because it is known that in general, Tdap coverage is low in the population. The impact of this model is assessing one dose of vaccination in pregnant women.

Dr. Duchin requested clarity regarding whether Dr. Liang was saying that there are studies to show that maternal vaccination results in a decrease in hospitalizations and deaths.

Dr. Liang replied that aside from this model, no studies have addressed this specifically. Based on a historical observational study in women who were vaccinated with whole cell vaccine during pregnancy, there was no pertussis in their infants compared to mothers who were not vaccinated during pregnancy.

Given that these are assumptions from the model rather than actual data, and that 72% coverage seems a long way off, Dr. Duchin thought it would be quite a while before any impact would be observed from this strategy. He wondered whether there was a plan to assess the beneficial impact of this strategy in the absence of 72% coverage, and how it would be determined whether the strategy was working.

Dr. Liang indicated that there were plans in place, as Dr. Clark mentioned. Through CDC's collaborations with the enhanced pertussis surveillance sites, case-control studies are evaluating the effectiveness of maternal vaccination and cocooning. As noted, because coverage is low, it will be several years before there are any data to share.

Dr. Clark (SME) added that an average was taken from 2001 through 2009 data in the decision analysis approach, and there are peak years in 2010 and 2012. It is known that because the case definition requires two weeks of cough in the absence of culture confirmation, many infant deaths do not meet the actual pertussis case definition. Therefore, deaths are under-reported. In the decision analysis, observed incidence was used. Any under-reporting favors the impact of the program substantially.

Among those who were hospitalized and died, Dr. Duchin wondered whether there were some epidemiological features that could help to identify who should be emphasized to receive this vaccine (e.g., socioeconomic, racial, family size, or other factors) in order to target the vaccine to the highest risk persons.

Dr. Clark (SME) responded that there were not. Hispanics are somewhat over-represented among deaths, but it is not clear whether they are over-represented among cases. There is a lot of variability in overall case fatality. The range observed from state to state is from 0 to 1 per 100,000. Therefore, even the differences are consistent with the overall case fatality. There are a couple of clinical studies underway, but by and large the children who die of pertussis have really severe pertussis, so they have pulmonary hypertension, very elevated white counts, and a very poor pathophysiologic profile. This is not related to socioeconomic status or any other type of modifiable risk factor.

Dr. Duchin thought the dilemma of trying to make a recommendation with limited data was partially due to the fact that there is a suboptimal vaccine. He wondered whether the manufacturers could offer some optimism about the eventual production of a more immunogenic, long-lasting pertussis vaccine.

Dr. Friedland (GSK) emphasized that it is important to keep in mind that while there have been outbreaks, vaccination is still the most important strategy to control pertussis in the US. Clearly, more studies and more information are needed to fully understand the situation and to identify the causes and solutions. GSK is committed to working with the public health community to identify the solutions to better control pertussis in the US. In follow up to Dr. Keitel's inquiry regarding a standalone vaccine, an investigational acellular pertussis vaccine was developed by GSK and was studied in an efficacy study in US adolescents and adults that was published in 2005 in the *New England Journal of Medicine (NEJM)*. This study reported a 92% vaccine efficacy on the basis of the primary pertussis case definition. GSK has not registered this standalone acellular pertussis vaccine. If CDC is expressing interest in an acellular pertussis vaccine and altering the immunization schedule in the US, GSK would be interested in further discussions with CDC and with FDA about a potential registration strategy.

Dr. Duchin expressed further interest in better understanding the situation and determining the strategies that would be appropriate with respect to potentially developing better vaccines from the perspective of the manufacturer. The data appear to show that the duration of protection is very short. He wondered what information would be useful to convince manufacturers that vaccines of longer duration are needed.

Dr. Friedland (GSK) responded that clearly the case-control studies being conducted in Washington State by CDC will be very important. Accurate understanding of vaccination history, case ascertainment through review of medical records, complete understanding of prior vaccination history, et cetera are going to be critically important to understand the full situation. That information is preliminary and needs to be determined, understood, and discussed in order to plan appropriately.

Dr. Decker (sanofi pasteur) agreed with Dr. Friedland. Data from throughout the country suggest the same thing. The problem is that the studies are basically measuring the same thing, so it is not surprising that they are reporting the same results. Almost all of the studies are ecological studies; therefore, they are susceptible to significant confounding. For example, there is correlation between age, changes in recommendations, the vaccine received, the trends in pertussis, and other factors. For example, one of the slides shared showed a decline among people ages 16 to 19 who received a mixed schedule. That also correlates with the typical household differences in ages and opportunities to be exposed by younger children who are at higher incidence rates. While Dr. Decker said he was perfectly willing to believe the conclusions he was hearing, he also wanted better evidence about what is occurring. It does not do any good to chase the wrong solution. He did not know whether there was a problem with initial

priming; whether it was the first dose that matters; if there was a problem with durability; or whether there was a problem with DTaP, Tdap, both, or neither. He wondered what ACIP would do about its recommendations if there were still a licensed whole cell vaccine in the US. Would the committee be prepared to abandon its preference recommendation for acellular pertussis vaccine? In a world in which every country recommends infant pertussis vaccine, and in which therefore ethically any study for licensure would have to be active-vaccine controlled, which would require approximately 1 million children given the high efficacy in infancy of these vaccines, it is unclear how any new vaccine would be licensed. How will anyone figure out what changes to make in the vaccines, given that there are no adequate animal models in which hypothetical changes can be tested. Whole cell vaccine has over 3000 antigens. Dr. Decker would like a list of the ones that should be included in a new vaccine.

Dr. Hosbach (sanofi pasteur) pointed out that clearly a standalone acellular pertussis vaccine is something that all manufacturers of pertussis vaccine, particularly those making DTaP vaccines, have contemplated for some time. What drives manufacturers is need and demand, which are really unclear at this point. In terms of outbreaks, clearly there could be a need. However, it is unclear how sustainable that is, or whether it can be prioritized in terms of manufacturing, research, and resources. It is relatively straightforward to develop a new vaccine, but it is important to understand need and demand.

Ms. Rosenbaum was pleased to see that the working group presented not only the evidence for adding the vaccine, but also addressed the issue of access to the vaccine. While a number of experts representing healthcare professionals were heard from, she thought it was important to note that basically 50% of all low income births and 1 in 8 US births are occurring in community health centers. A fair proportion of the remaining low income births are occurring in public hospital and public health system settings. She expressed interest in knowing what HRSA planned to do through the maternal and child health (MCH) and health centers program to try to diffuse this new standard. She was also struck listening to Dr. Salisbury describe how the committee took a vote in the morning, and by the afternoon they were shipping vaccine to clinical practices. The US should live in this kind of nirvana. In the US it is much more complicated because of the multi-payer system. Whether done in the context of the VFC vote or because the working group raised the issue, Ms. Rosenbaum strongly recommended thinking about an additional ACIP recommendation that with respect to coverage, public and private payers be urged to take the most expedited steps available to alter their coverage and payment rules to indicate to providers that this will be a covered and payable service as quickly as possible.

In contemplating what is and is not known about this recommendation, Dr. Campos-Outcalt highlighted Dr. Duchin's observation that there are no direct data to substantiate that the strategy of vaccinating during pregnancy is preventing hospitalizations or deaths in newborns. The data regarding the decline in antibody titers and adverse reactions pertain to one dose. He wondered whether there is any evidence or data regarding those two items in terms of subsequent doses (e.g., two Tdap vaccinations during pregnancy).

Dr. Liang replied that while there may be instances of women who have received more than one dose, there are no data about antibody titers and adverse reactions following two doses.

Dr. Sawyer added that there is a small amount of data on second doses in non-pregnant individual showing that the titers they achieve are not higher than after a first dose. Based on that small amount of data, it does not appear that increasingly higher titers continue to be accumulated, which might predict more adverse events. The titers seem to be the same.

In terms of the guidance for use for optimal timing, Dr. Bocchini thought that Dr. Salisbury's comment about including the higher end of the range of 32 weeks seemed to make better sense because then there would be an opportunity to address some of the late preterm infants that comprise a percentage of premature infants. Waiting until 36 weeks for optimal timing would miss those infants. He suggested changing the recommendation to align with the UK's recommendation.

Dr. Temte inquired as to whether Dr. Ault had any information about late acquisition of prenatal care in the US. Dr. Temte's clinic sees a number of women for the first time between 34 and 36 weeks in their pregnancies.

Dr. Ault (ACOG) responded that this is a less than ideal situation, although he did not readily know the data. The people who are most vulnerable for short pregnancy intervals, lack of prenatal care, et cetera can be concentrated in public hospitals and community health centers. That timeframe would still offer an opportunity to vaccinate and achieve an antibody titer for those who went on to have a term delivery.

Dr. Harrison inquired as to how ACIP could be reassured that there will be a focused effort to collect safety data on women who are receiving multiple doses. There are women who have many pregnancies, so it seems that there should be a concerted effort to assess the subset of women who are receiving multiple doses.

Dr. Pickering indicated that for any vaccine recommended by ACIP, safety data are required to be provided during each meeting afterward. ACIP is very serious about safety data.

Dr. Poland (ACP) acknowledged that the situation is difficult, but that obviously something must be done. They heard some caution from various members that the presentation opened with an anecdote, proceeded to a small study that was extrapolated as if it were a correlate of protection, went on to some modeling that assessed some intervals between childbirth, not pregnancy. Particularly if he was working in an area where access was a problem and he was unsure whether he would see a pregnant patient on a regular basis, he would administer the vaccine as soon as he realized she was pregnant. The actual number of doses and the intervals may be very different in those areas than what has been modeled. Given that ACIP is going to get into the habit of using Grading of Recommendation Assessment, Development and Evaluation (GRADE) and putting an evidence base on recommendations, he was curious as to how this recommendation would be graded in terms of what level of evidence this represents.

Dr. Clark (SME) replied that this was cleaning up the previous recommendation. ACIP recommends Tdap during pregnancy, and that consideration was made before the GRADE implementation. Certainly, the recommendation is predicated on the assumption that antibody protects. There are some data that show that children born to mothers who have had pertussis vaccine were less likely to get pertussis. It is known from observational studies that one dose of DTaP protects against hospitalizations and deaths. As Dr. Plotkin would say, the correlate of protection is antibody. There are just not any absolute numbers. The situation is that children are dying of pertussis in the US, some of them are being missed, and there is a safe vaccine that is likely to be beneficial.

Dr. Poland (ACP) said that while he believed that, it is an assumption that is yet untested. The key issue is the balance between costs, risks, and benefits for which there are some critically missing data. This would meet a very low threshold in terms of GRADE.

Dr. Temte commented that this probably would be included in a very low category of evidence, which basically means that with additional studies, ACIP is likely to be better informed and change the results. In the GRADE process, that does not preclude making a recommendation. It is just predicated on the fact that the evidence is very open to changes as there is more evidence and better studies are conducted.

Dr. Baker commented that she cares for babies who die of pertussis. The number of deaths is small, but that is because that is the number of confirmed pertussis deaths. The first serious symptom of pertussis in a two-month old is apnea, so a large number of infants who are reported as SIDS are probably pertussis cases. This is strictly the “tip of the iceberg.” She reminded everyone on the committee that there are no FDA licensed vaccines for pregnancy. The decay of antibodies to pertussis is known, and they wane very quickly. The young infant, as opposed to older infants, adolescents, and adults, has only antibody for protection; whereas, older people have cell-mediated immunity to help them when they are exposed to pertussis in addition to serum antibody concentrations. Another point is that everybody seemed to be worried about safety, and she agreed with all of the intense plans for safety monitoring. In terms of a second dose, she wondered whether a pregnant woman would opt for a painful or swollen arm or an Arthus phenomenon versus a hospitalized or dead baby. Pregnant women will choose to be vaccinated, even if they are not highly educated. Dr. Baker believes that much of the slow uptake is due to provider hesitancy not pregnant women hesitancy.

Dr. Plotkin expressed his hope that CDC would attempt to evaluate correlates of protection specifically in its studies. There is pretty good evidence to suggest that at least anti-PT and pertactin, and perhaps agglutinogens, are useful, there is just not an absolute level of protection. It is very important to obtain those data because in relation to Dr. Duchin’s question regarding development of a new vaccine, there is a possibility of new adjuvants and components. In order for FDA to license a new vaccine short of a major efficacy trial, which is impractical, a correlate of protection would be very important so that FDA could judge the data to establish what would be a new, licensable vaccine. He highly recommended that this be part of the investigations CDC is currently conducting.

Dr. Decker (sanofi pasteur) noted that the comments might suggest to some that there have not been formal studies of re-administration of Tdap. Multiple formal studies have been conducted by sanofi pasteur of re-administration of Tdap, all of which have been submitted over the course of the years to FDA. There have been studies of re-administration 5 and 10 years following initial administration, and sanofi pasteur is currently engaged in a multi-national study of re-administration 10 years following immunization. All of these studies show that there is a great antibody response similar to initial administration with no more adverse events than with initial administration. That is not directly on point to issue raised, but that offers some guidance.

Dr. Friedland (GSK) indicated that GSK has studies similar to those described by Dr. Decker, and looks forward to having the opportunity to present revaccination and antibody persistence data during the February 2013 ACIP meeting.

Tamara Sheffield (Intermountain Healthcare) noted that there is already an approved strategy of one dose during pregnancy, but she wondered whether the working group had done a cost-effectiveness study of the new strategy.

Dr. Clark (SME) responded that essentially, the decision analysis applied to all settings because no assumptions were made about the history of Tdap receipt in the cohort of women covered at 72% in the entire 4 million birth cohort. It was difficult to sort out one dose versus second doses, but the results of the cost-effectiveness were the same with multiple doses.

Regarding the Vaccine Injury Compensation Program (VICP), Dr. Temte requested reassurance that because Tdap is recommended for adolescents, any vaccine injury would be automatically be covered for a pregnant woman.

Dr. Caserta (HRSA) responded that VICP would cover the person who receives the vaccine, which would be the pregnant woman. Based on the current language in the Childhood Act, the fetus would not be covered. Should there be issues with the baby due to the mother's receipt of the vaccine during pregnancy, it would not be covered under the current language. That would require a legislative change.

Dr. Whitley-Williams (NMA) commented that she recently cared for an infant with pertussis whose mother was offered Tdap during the post-partum period, but refused it because she did not believe in vaccines. The point is that there are not only provider barriers, but there are also public barriers. If the recommendation carries, information should be disseminated to the public about pertussis (e.g., the burden of disease, morbidity and mortality, hospital length of stay, et cetera). This is not as well-recognized a disease as varicella, except in states that have major outbreaks. Especially younger women 20 to 30 years old have never seen pertussis and may not know that much about it. Thus, she urged a focus on provider and public education.

Dr. Loehr (AAFP) inquired as to whether anyone could provide numbers of how many people have been studied for repeat Tdap.

Dr. Decker (sanofi pasteur) replied that ultimately, sanofi pasteur will have studied multiple thousands of people, including the study that is currently underway. It is fairly obvious that the 10-year anniversary of the initial recommendation for Tdap is coming up, and the decennial Td recommendation desperately needs updating. For that to occur gracefully, the products need to be licensed. He felt confident that everyone with a licensed Tdap is working to meet those deadlines, and they will have to provide enough data to make the FDA happy with including that in the label. The obvious inferences can be drawn from that.

While Dr. Temte was certain that everyone would like to be going into this with a well-designed randomized controlled trial (RCT) powered with enough pregnant women to reassure them entirely about safety and clinical efficacy, this is nearly impossible. In the clip Dr. Temte mentioned earlier, Dr. Bronowski talks about in science, always standing in the known and looking for what is hoped for in the scientific process. That is very appropriate in this situation.

Ms. Stinchfield (NAPNAP) thanked Dr. Liang for beginning her presentation with the anecdote. While scientific recommendations are not made based on anecdotes, it is important to share those in ACIP meetings so that everyone does not get lost in rates, confidence intervals, and statistics and lose sight of what they are really there for—keeping their eyes on families and the hazards that can befall them.

Dr. Duchin wondered whether it would be possible to include a statement in the recommendation that would commit them to evaluate the effectiveness of this intervention, and reassess the appropriateness of the recommendation based on those data. He felt very uncomfortable committing to a long-term recommendation for two reasons: 1) because there are not good data currently about the effectiveness, but the case-control studies in progress should provide that information; and 2) pertussis incidence waxes and wanes, but there was no discussion about the threshold at which this recommendation makes sense. How many cases need to occur in the population? With these large naturally occurring outbreaks, he imagines that there will be many years in many communities with very low rates before susceptibility increases again and increased numbers of cases are observed.

Dr. Liang replied that this kind of language would be included in the statement, given that the recommendation is based upon limited data. Reviewing data when it becomes available about the effectiveness of the strategy is part of the larger picture of what is being observed with pertussis vaccines in general, not just with the pregnancy vaccination.

Dr. Duchin noted that there had been a great reluctance to ever change or go back on a recommendation once it is made, so he wanted it to be made explicit that this recommendation would be reassessed when data become available, including the safety data.

Dr. Temte thought that would be within ACIP's purview.

Dr. Kimberlin (AAP) was struck by the lack of specific safety data, including actual numbers and actual results of the second dose of Tdap. It sounded as though GSK and sanofi pasteur have those data, and that they will be presented during the February 2013 ACIP meeting. He wondered if they waited one meeting, those safety data would be on the agenda.

Dr. Liang reported that the Pertussis Vaccines Working Group has begun reviewing data on revaccination of Tdap (e.g., an additional dose of Tdap). The GSK and sanofi pasteur studies are part of that review, but are within healthy non-pregnant persons for which safety data are available. The plan is to begin the discussion with ACIP on revaccination, and those studies would be part of those presentations.

Dr. Clark (SME) added that the working group reviewed the safety data for the pregnancy recommendation, and what is known about Tdap after tetanus-containing vaccines. The specific concern was Arthus reactions, or the severe hypersensitivity reactions, of which there are essentially none in the large databases. Much of what is known about Arthus reactions is from the historical data suggesting that is primarily a phenomenon of older vaccines with more antigen and different formulations.

Dr. Decker (sanofi pasteur) did not recall that they had observed any Arthus reactions in any studies. Antecedent data has long since been provided to the working group. Some studies are still underway, so those data have not yet been provided. However, everything that exists has been provided to the working group.

Dr. Friedland (GSK) that GSK has proactively shared information when it has been requested by the working group. GSK's studies are also on-going. Boostrix[®], GSK's Tdap vaccine, was first licensed in the US in 2005. The adolescent study that was the basis of that licensure was conducted during 2002 and 2003, so those subjects are now about 10 years older. As data continue to be collected in the studies that are underway, GSK will continue to share information

with the working group, and looks forward to being invited to share those data during future ACIP meetings.

Dr. Loehr (AAFP) noted that the decision analysis focused primarily on one pregnancy. He did not see a cost for multiple pregnancies. Also, the decision analysis and the benefits seem to be compared to the base rate, but the Tdap during pregnancy and Tdap postpartum rates are known, so some of the benefits have already been realized. He is concerned that this might be a fairly expensive procedure with multiple Tdaps for fairly minimal benefit. Dr. Keitel asked for a “back of the envelope” calculation earlier. It appears that based on the decision analysis, about 300 cases, 150 hospitalizations, and 7 to 10 deaths would be prevented.

Dr. Liang confirmed that Dr. Loehr was correct in terms of how the decision analysis was made, but it is important to keep in mind that with regard to the effectiveness of the model, the postpartum dose was part of the cocooning strategy. In terms of a cocooning strategy, additional doses would be added for the father and additional close contacts of that family and comparing that cost as well to just the one dose for the pregnant woman.

Dr. Campos-Outcalt was concerned that there were no limits in terms of number of doses, intervals between doses, background prevalence of disease, et cetera. While he was probably comfortable with a dose given for the first and second pregnancies, what if the pregnancies were a year apart? What if it was the third pregnancy within three years? There are families who have had multiple pregnancies that occurred fairly quickly, so he wondered whether the working group considered any limits at all.

Dr. Liang responded that this was part of the working group’s discussions, and the concerns regarded scenarios such as Dr. Campos-Outcalt described. Reassuringly, the statistics available on births in the US show that pregnancy intervals are greater than one year and, on average, a woman has only two children. With regard to placing limits on the number of doses and the safety data, the working group felt that while there are concerns, this should not be a reason to defer this recommendation.

Dr. Sawyer emphasized that this is a bad problem about which something must be done immediately. No doubt, additional data are needed. No doubt, the recommendation will potentially need to be revised over time. However, he did not see an alternative at this point.

In her years on ACIP, Dr. Baker said the one thing she thought the members really took seriously, besides evidence, was risk (and this is “tip of the iceberg” risk for infants under 2 months of age) versus benefit. There is no question that more evidence and hard data are needed, but she expressed her hope that the committee would consider risk versus benefit when voting.

Dr. Pickering requested that Dr. Clark remind everyone of the duration of protection following natural pertussis disease compared to immunization.

Dr. Clark (SME) replied that natural pertussis disease protection is generally considered to be longer, but he did not think it was reasonable to talk in terms of an interval such as 4 to 12 years, because protection wanes immediately over time. There are implications of even a small increase of the rate at which waning occurs, and there can be much more disease.

Dr. Duchin requested a timeframe for which ACIP might be able to anticipate having data to reassess this recommendation.

Dr. Clark (SME) responded that the results of the case-control study will hinge on coverage among the control group. It is powered for 20% coverage. It was assumed that coverage would be low, and it is hundreds of cases needed. The hope is to have results in a year.

Dr. Coyne-Beasley agreed with all of the discussion regarding a mother's choice, but her recollection was that there are no data to suggest that there are any teratogenic effects, which is what truly concerns mothers. That question regarding teratogenic effects is also important because as Dr. Caserta pointed out, the infant would not be covered under the VICP if the mother was vaccinated.

Dr. Friedland (GSK) reported that in September 2012, Boostrix[®] was changed. Its pregnancy category is now a Category B, which states that a developmental toxicity study has been conducted in animals and there was no evidence of harm.

Dr. Duchin requested that specific language be included in the recommendation that this recommendation will be revisited when the safety and effectiveness data are available.

Dr. Liang confirmed that this would be included in the statement.

Ms. Rosenbaum requested clarification about whether Dr. Duchin wanted language in the recommendation itself stating that the recommendation would be revisited. She thought that all of ACIP's recommendations were implicitly subject to the notion that the recommendations will be revisited when the evidence shifts. She could not imagine that such a statement would be included within the actual recommendation.

Dr. Temte responded that this statement would not be part of the recommendation per se, but would be included in the accompanying language.

Dr. Bocchini inquired as to whether language regarding the optimal time of gestation during which vaccination should be given would be included as part of the recommendation.

Dr. Liang responded that language regarding timing would be included in the guidance for use.

Dr. Bennett inquired as to whether there was anticipation that when data become available from the case-control study that a full analysis will be done of cost and cost-effectiveness.

Dr. Clark (SME) replied that cost-effectiveness could be revisited based upon what is known about effectiveness. Again, the decision analysis reflects the cost of 72% coverage in a 4 million birth cohort regardless of birth order.

Vote: Recommendation for Use of Tdap for Pregnant Women

Ms. Rosenbaum made a motion that the proposed language for the recommendation of Tdap use in pregnant women be approved. Dr. Bocchini seconded the motion. The motion carried with 14 affirmative votes, 0 negative votes, and 1 abstention. The disposition of the vote was as follows:

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

Vaccines For Children Program Resolution

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

Dr. Santoli indicated that the purpose of this resolution was to revise the previous resolution to incorporate new recommendations regarding the vaccination of pregnant adolescents. No changes were made to eligible groups, schedule, intervals, footnotes for the schedule and intervals, the table of various products and intervals, recommended dosage and contraindications / precautions, or the statement regarding update based on published documents. The only change was made to the table note (7) to reflect the discussion and vote, and which will read as follows:

(7) Adolescents who are pregnant should receive Tdap, irrespective of past history of Tdap receipt. If not administered during pregnancy, Tdap should be administered immediately postpartum.

Discussion Points

Returning to the previous discussion, Ms. Rosenbaum pointed out that under the ACA, ACIP's scientific recommendations are a direct link, when approved by the CDC director, to coverage. Therefore, she thought it was highly appropriate to vote not only on VFC coverage, but also on any question of coverage, which is now by law, what ACIP does.

VFC Vote: Recommendation for Use of Tdap for Pregnant Women

Dr. Bocchini made a motion that the proposed VFC language for the recommendation of Tdap use in pregnant adolescents be approved. Dr. Keitel seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Meningococcal Vaccines**Introduction**

Lorry Rubin, M.D.
Chair, Meningococcal Working Group
Advisory Committee on Immunization Practices

Dr. Rubin indicated that he is a Pediatrician and Infectious Disease Specialist at a children's hospital in New York, and has cared for a number of adolescents and children with invasive meningococcal disease. Each case seemingly comes out of nowhere, and some end tragically. Fortunately, he has seen fewer of these cases in recent years. He said he knew he spoke for other members of the working group by saying that they are highly motivated to use vaccines to prevent these episodes. The major driving value of the working group is to prevent children from dying or suffering long-term consequences of infectious diseases such as this, and they highly value vaccines as highly effective prevention tools. At the same time, there is a strong value of public health stewardship, and a recognition that the working group is supposed to evaluate the impact of interventions at the population level rather than the individual level. The working group strives to balance these two values in all of its discussions.

Meningococcal vaccines for infants and toddlers include the following:

- MenACWY-D (Menactra[®], sanofi pasteur)
 - Currently licensed and approved for a 2-dose series at 9 through 23 months
- HibMenCY-TT (MenHibrix[®], GlaxoSmithKline)
 - 4-dose series at 2,4,6 and 12 through 15 months of age
 - Licensed in June 2012
- MenACWY-CRM (Menveo[®], Novartis)
 - Licensed for ages 2 and older
 - Investigational for infants

The current recommendation is for high-risk infants 9 through 23 months to receive 2 doses of MenACWY-D. During the October 2011 ACIP meeting, the working group rationale was presented for no routine recommendation for infant meningococcal vaccines. The factors that entered into this included the declining disease rates, which are now at historic lows; the low proportion of infant cases and deaths that are vaccine-preventable, because of both the young age at onset of many infant cases and the high proportion that are due to serogroup B, which is not a component of any current or proposed vaccine; and the multiple doses required, with potential need for booster doses to take infants through to their 11-year old dose.

HibMenCY-TT is immunogenic against serogroups C and Y, but does not protect against serogroups A, B, or W135. There is similar safety and immunogenicity to the *Haemophilus influenzae B* (Hib) component of the vaccine compared to other Hib vaccines. As noted, this vaccine is administered in 0.5 mL doses by intramuscular injection at 2, 4, 6, and 12 through 15 months of age. The first dose may be given as early as 6 weeks of age, and the fourth dose may be given as late as 18 months of age.

During this session, information was presented on the following:

- Immunogenicity and safety of HibMenCY, including the response to two doses, antibody persistence, and GRADE evaluation
- Considerations for use of HibMenCY in infants
- Recommendation for a vote for infants at increased risk for meningococcal disease

In terms of additional activities of the Meningococcal Working Group, an ACIP Meningococcal Vaccines Statement is to be published in the December 2012 *MMWR* Recommendations and Report. This updates the previous 2005 report. In addition, the working group is reviewing an updated Policy Note for Hib vaccines, and expects to present that during the February 2013 ACIP meeting. The working group anticipates licensure of the MenACWY-CRM vaccine as a 4-dose infant series, and is in the process of developing guidance for use. Indeed, there is some early thinking among the working group members regarding the approach to candidate serogroup B vaccines, which are particularly needed in the infant age group and are under development.

Immunogenicity and Safety of HibMenCY

Jacqueline M. Miller, MD, FAAP
Senior Director, Vaccine Discovery and Development
GSK Vaccines

Dr. Miller presented the clinical results from GSK's development program for MenHibrix[®], GSK's combination *Haemophilus influenzae B* and *Neisseria meningitidis* serogroups C and Y conjugate vaccine. Although much of this data has been presented over the past 9 years of development, Dr. Miller said she was pleased to be able to present to the newer members of the committee. She also shared GSK's 5-year persistence data, which was presented the previous week at the IDWeek 2012[™] meeting in San Diego.

GSK's goal in developing MenHibrix[®] was to provide the US with a meningococcal conjugate vaccine for infants and toddlers that targeted serogroups C and Y, the two most important non-B serogroups[†], combined with Hib in order to simplify implementation of the vaccine. GSK chose specifically to focus on serogroups C and Y because in the US, serogroup W135 recently has accounted for approximately 1% to 3% of disease each year, and serogroup A is only

sporadically reported. GSK also wanted to develop a vaccine specifically for infants and toddlers to allow the vaccination regimen to start as early as 4 months of age, which is the time of highest risk, and to provide an additional source of Hib conjugate vaccine for the US. Immune interference for the Hib antigen has not been observed[‡], and non-inferiority has been demonstrated to two US licensed Hib vaccines. Immune interference has also not been observed with pneumococcal conjugate vaccine (PCV7); Pediarix[®]; measles, mumps, rubella (MMR), or varicella vaccines[¶]. GSK's safety profile was evaluated in over 7500 children who received at least one dose of MenHibrix[®], and the safety profile has been consistently similar to other Hib vaccines [[†]Cohn AC, MacNeil JR, Harrison LH, *et al.* Changes in *Neisseria meningitidis* disease epidemiology in the United States, 1998-2007: Implications for prevention of meningococcal disease. *Clin Infect Dis* 2010;50:184-91; [‡]Bryant KA, Marshall GS, Marchant CD, *et al.* Immunogenicity and safety of *H influenzae* type b- *N meningitidis* C/Y conjugate vaccine in infants. *Pediatrics* 2011;127:e1375; [¶]Marshall GS, Marchant CD, Blatter M, *et al.* Co-administration of a novel *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C and Y-tetanus toxoid conjugate vaccine does not interfere with the immune response to antigens contained in the infant series routinely used in the United States. *Human Vaccines* 2011;7(2):258-264].

MenHibrix[®] contains three discrete polysaccharide protein conjugates, which are each individually conjugated to tetanus toxoid: PRP 2.5 µg, MenC 5 µg, and MenY 5 µg. The total tetanus toxoid content is approximately 18 µg, and the vaccine contains no adjuvants or preservatives such as thimerosal or phenoxyethanol. As noted, the clinical development program occurred over the course of 9 years. GSK studied over 11,000 children, of whom 7500 received at least one dose of HibCY. In the early phase developments, the focus was on dose ranging and formulation selection, and also demonstrated the induction of immune memory with the vaccine. Study 005/006 was the first study in the US, and that study was used to refine safety and immunogenicity endpoints for GSK's Phase 3 program. That study was also extended to provide antibody persistence data, and to demonstrate the acceptability of co-administration with PCV7. A second Phase 2 study, 007/008, was conducted in Australia to evaluate non-inferiority to licensed meningococcal serogroup C vaccines outside the US; to evaluate immunogenicity post-dose 2; and contributed to the evaluation of co-administered MMR and varicella. GSK's Pivotal Phase 3 program, 009/010, demonstrated non-inferiority to two US licensed Hib vaccines, and the acceptable immunogenicity to serogroups C and Y. Co-administration with Pediarix[®], MMR, and varicella was evaluated. Lot-to-lot consistency was also evaluated in this study. Study 011/012 is a companion safety study that was designed to increase the database on which GSK could assess rare but serious adverse events.

With regard to the design of the Pivotal Phase 3 study (009/010), subjects were randomized 3:1 to receive either 3 doses of HibCY at 2, 4, and 6 months of age followed by a fourth dose at 12 to 15 months of age, or PRP-TT at 2, 4, and 6 months of age followed by PRP-OMP at 12 to 15 months of age. Both groups received routinely recommended vaccines concomitantly. Serology was performed one month post-dose 3, immediately pre-dose 4, and approximately 6 weeks post-dose 4. Safety follow-up was continued until 6 months after the final vaccination. The study design for the persistence study was similar; however, the randomization ratio was different and the control group in contrast received 4 doses of PRP-TT.

Regarding the immunogenicity data from the Pivotal Phase 3 study (009/010), there were non-inferiority hypotheses for Hib at both the post-dose 3 and post-dose 4 time point and the same hypothesis was used. Non-inferiority was demonstrated if the percentage of children achieving 1.0 µg/mL was within a 10 percentage point difference to the control group. This hypothesis was met at both time points. Furthermore, at the post-dose 3 and pre-dose 4 time points in an exploratory analysis, the rates were statistically significantly higher in the MenHibrix® group. In the second exploratory analysis, the GMCs were higher at each time point as well.

To measure the meningococcal serogroup C responses, a serum bactericidal assay was used with human complement as the exogenous source. The primary endpoint was titers $\geq 1:8$. For both MenC and MenY there was a primary hypothesis after the full 4-dose series that stated that the 95% confidence interval on the percentage of children achieving the threshold would have a lower limit that was greater than 90%. This hypothesis was met for MenC, and 99% of children achieved this threshold after the third dose, with 96% retaining that level of antibody prior to the fourth dose. There was a 12-fold increase in geometric mean titers (GMTs) after the fourth dose was administered. The primary hypothesis was met for serogroup Y, with 96% achieving the threshold of $\geq 1:8$ post-dose 3 and 93% retaining that level of antibody prior to the fourth dose. Again, there was a 12-fold increase in GMTs after the fourth dose.

The Pivotal Phase 3 study also included two secondary hypotheses in terms of fever post-dose 3 and post-dose 4. Both of these hypotheses were met. Furthermore, for each increment of fever over the 4-dose series, the rates were comparable with the Hib control group despite the two additional antigens. Parents recorded solicited symptoms on a diary card. For both local and general solicited symptoms, the rates were comparable between the two groups. Another important facet of GSK's development program was to evaluate whether HibCY could be given concomitantly with other routinely recommended vaccines. For each vaccine studied, the statistical hypotheses were met and no immune interference was observed.

The Phase 2 study, 007/008, was followed for 5 years after the fourth dose, or until children were 6 years of age. An anti-PRP concentration of $\geq 0.15\mu\text{g/mL}$ is accepted as the short-term correlate of protection. At 5 years after the fourth dose, 98% of children in the MenHibrix® group retained this level of antibody. An anti-PRP concentration of $\geq 1.0\mu\text{g/mL}$ is accepted as the long-term correlate of protection. More than half of the MenHibrix® recipients retained this level of antibody. In terms of persistence of hSBA-MenC greater than or equal to a titer of 1:8, over 82% of the MenHibrix® recipients retained this level of antibody until age 6. For MenY, almost 70% of the MenHibrix® recipients retained this level of antibody 5 years after they received their fourth dose.

In summary, the goals of GSK's clinical development program were met. The vaccine was demonstrated to be immunogenic to all three antigens in 99% of children, and the vast majority retained antibody until 5 years after the fourth dose. The anti-PRP responses were non-inferior to two US licensed Hib vaccines after dose 3 and dose 4. There was no immune interference with PCV7, Pediarix®, MMR, or varicella vaccines. The safety profile was consistently comparable to the Hib control vaccines despite the two additional antigens. GSK's data have demonstrated that MenHibrix® has the potential to add protection against MenC and MenY to US infants and toddlers without adding shots or medical office visits.

GRADE Evidence for HibMenCY

Elizabeth Briere, MD, MPH
LCDR, US Public Health Service
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

During this session, Dr. Briere presented the GRADE evaluation for the HibMenCY infant vaccine, described the study question for GRADE, offered a brief review of the quality of disease burden data, presented the GRADE assessment of evidence of the benefits and harms outcomes, outlined the working group's determination of overall evidence type for the infant HibMenCY vaccine, and briefly reviewed of public and provider values and preferences and the economic analysis.

The first step in the GRADE process is to formulate the study question. The 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: MenACWY-CRm (Menveo[®]) and HibMenCY (MenHibrix[®]), and the toddler vaccine MenACWY-D (Menactra[®]). For this session's presentation, the study question was, "Should HibMenCY be administered to all 2,4,6, and 12 month olds for prevention of meningococcal disease?" Since this vaccine also contains a Hib component, an additional question was, "Can HibMenCY be used for Hib vaccination?"

Given that the meningococcal disease burden data were covered in past ACIP meetings and an evaluation of the quality of the disease burden data was presented during the February 2012 ACIP meeting, Dr. Briere only briefly summarized these data during this session. 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 (1997-1999, High Incidence Years; 1993-2009, Base Case; and 2007-2009, Low Incidence Years) showed the large declines in incidence of meningococcal disease overall and in children <5 years of age in the US. During the February 2012 meeting, an evaluation was presented of meningococcal disease incidence, mortality, and morbidity data from National Notifiable Diseases Surveillance System (NNDSS), Active Bacterial Core surveillance (ABCs), and published manuscripts. Only minor limitations were found. For example, for representativeness, one limitation is that ABCs covers a catchment area comprising only about 13% of the US population. To account for this, rates using ABCs data are standardized by race and age and are projected to the US population. For accuracy, it is known that ABCs typically underestimates cases by 15% to 20% compared to NNDSS, mainly because it captures only culture confirmed cases. To account for this underestimate of cases by ABCs, a correction factor of 18% is applied to all incidence data used. For applicability, some of the analyses are limited due to lack of serogroup-specific mortality and morbidity data. However, these limitations are not believed to significantly affect the quality of the burden of disease estimates.

In GRADE, several key factors are evaluated when discussing considerations for vaccine use. First the evidence is GRADEd to determine the balance between benefits and harms and the overall evidence type. The values and preferences of all involved (e.g., general population, patients, health care providers, and policy-makers) are considered, and an economic analysis assessing the number needed to vaccinate and cost-benefit analysis are conducted.

After selecting a study question, the working group selected outcomes that they felt were important to answer the study question. The quality of the evidence for these outcomes was then evaluated. First, the working group created a list of 5 outcomes to GRADE: 1) Short-term efficacy for Hib and MenCY (one month after vaccination), 2) Long-term efficacy for Hib and MenCY (1, 3, and 5 years after vaccination), 3) Occurrence of mild adverse events after vaccination, 4) Occurrence of serious adverse events after vaccination, and 5) Interference with other co-administered vaccines. Next, Non-CDC members of the working group ranked the relative importance of the outcomes on a scale of 1 to 9 with 1 to 3 defined as not important; 4 to 6 defined as important, but not critical for answering the question; and 7 to 9 as critical for answering the question. In GRADE, only evidence for critical and important outcomes are GRADED. Of the five outcomes selected for infant meningococcal vaccines, only mild adverse events were ranked as not important.

The final outcomes that were GRADED included: 1) Short-term efficacy of Hib and MenCY (one month after vaccination), 2) Long-term efficacy of Hib and MenCY (1, 3, and 5 years after vaccination), 3) Occurrence of serious adverse events after vaccination, 4) Interference with other co-administered vaccines. In compiling evidence to GRADE for each of these outcomes, several inclusion criteria were used. US and non-US populations were included as long as the proposed US schedule (2,4, 6, and 12 through 15 months) was used for HibMenCY. Data were compiled for HibMenCY by outcome and study design type (RCT or observational study). There were a total of 9 studies. Of these, 7 were published, 1 was presented at conference, and 1 was unpublished. All of the studies were RCTs. In GRADE, RCTs start with an evidence type of 1 and then can be downgraded to a 2 through 4 if necessary based on several criteria. Dr. Campos-Outcalt and Dr. Briere rated the evidence separately and compared results. Differences in results were discussed with the working group until consensus was reached.

Data regarding the evidence findings for benefits and harms were presented during past ACIP meetings, and earlier in this session by Dr. Miller. 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 being 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. Anti-PRP titers are accepted as the correlate of protection for invasive Hib disease. Studies have suggested that long-term protection from invasive Hib disease is correlated with the presence of anti-PRP levels ≥ 0.15 ug/ml in unvaccinated populations, and anti-PRP levels ≥ 1.0 ug/ml in vaccinated populations.

Based on the body of evidence for HibMenCY, short-term efficacy is achieved for serogroups C and Y after the infant 3-dose series and the full 4-dose series. There is moderate duration of protection against serogroups C and Y 5 years after the fourth dose. A higher percentage of patients had protective titers for serogroup C than serogroup Y post fourth dose. However, waning immunity, especially for serogroup Y, indicates the vaccine is unlikely to provide protection until age 11 through 12 years and a booster dose would likely be necessary. Based on PRP levels, the Hib portion of HibMenCY was found to be non-inferior to monovalent Hib vaccine for the infant and toddler doses and up to 5 years post fourth dose.

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 over 11,000 infants studied, at least 1 serious adverse event was reported by 3% to 14% of study participants who received HibMenCY alone or with concomitant vaccines. At least 1 serious adverse event was reported by 2% to 10% of controls who received monovalent Hib with concomitant vaccines. The difference between the intervention and control groups was not statistically significant in any of the studies. Four serious adverse events were considered related to HibMenCY vaccine by non-blinded investigators. In the control group, no serious adverse events (SAEs) were considered related to vaccination. Mild local and systemic reactions reported following HibMenCY vaccination were similar to those seen after monovalent Hib vaccination, and no deaths were reported in any of the studies.

Based on the body of evidence for interference with co-administered vaccines, antibody responses for Dtap-Hep B-IPV, MMR, and varicella after co-admin with HibMenCY met criteria for non-inferiority. Pneumococcal IgG antibody responses after PCV7 co-administration with HibMenCY met criteria for non-inferiority for all serotypes post-dose 3. Looking at the benefits and harms for an infant HibMenCY series, the vaccine is immunogenic in the short-term and 5 years post-vaccination and is safe. However, low disease burden lowers the overall benefits of vaccination.

Regarding the determination of the evidence type for benefits and harms, in GRADE, all of the available data for each outcome are evaluated on 5 criteria: risk of bias, inconsistency, indirectness, imprecision and other considerations (e.g., publication bias, strength of association, dose gradient) and a final evidence type is assigned. The majority of studies for HibMenCY were single-blinded or not blinded at all. The working group felt that blinding was likely to introduce more bias for a more subjective outcome such as severe adverse events (SAEs), and less likely to introduce bias for an objective outcome such as efficacy or interference. Therefore, the evidence was downgraded for the severe adverse events outcomes if there was single or no blinding, but did not downgrade for efficacy outcomes.

For risk of bias, the working group found serious limitations for the serious adverse events outcomes due to single or no blinding, and no serious limitations for the remaining outcomes. There were no serious limitations for inconsistency, indirectness, or publication bias for any of the outcomes. The RCTs for long-term efficacy 3 and 5 years post-fourth dose were downgraded for imprecision because the sample sizes for each study were less than 300, and the lower limit of the confidence interval showed only a small difference in hSBA titers compared to the control group.

In summary, the working group downgraded the evidence for the serious adverse events outcome and for imprecision for the 3 and 5 year efficacy data, but did not downgrade the evidence for any of the other outcomes. Since the working group had ranked the long-term efficacy and serious adverse events outcomes as critical, and those outcomes had been downgraded to an evidence type of 2, the overall evidence type for benefits and harms was 2.

Dr. Briere then turned to the values and preferences portion of GRADE, explaining that capturing values and preferences of the public and providers can be challenging and that two approaches were used. One approach was a public engagement community meeting, with four meetings convened in cities across the US. A total of 277 people participated. Each meeting included presentations on meningococcal disease clinical course and epidemiology, group discussions, and polling questions. The second approach used was a provider survey

conducted in 2009 among pediatricians and family practitioners recruited from random samples of AAP and AAFP.

The issues raised by the participants in the public engagement sessions included safety, availability, access, affordability, equity, and parental choice to vaccinate or not. Reassuringly, these were the same issues that the working group had considered and discussed during working group meetings. Although the public engagement meetings were not representative of the public since they involved self-selected participants interested in the topic or issue and captured values and views primarily from people at the ends of the continuum (either “for” or “against”), they did provide valuable feedback to state health departments and CDC about how to communicate vaccine issues to the public. In the provider survey, providers were asked if they would use the meningitis vaccine if it was recommended for routine use and if they would use it if it was not recommended for routine use. The overall message was that the majority of providers (80% of pediatricians and 72% of family practitioners) would use the vaccine if it was recommended for routine use. The percent of providers who said they would use the vaccine if it was not recommended for routine use was much lower.

As Dr. Rubin discussed earlier, the Meningococcal Working Group is comprised of a clinicians, nurses, and public health professionals. They are also parents, friends, and neighbors. Over the years, many of them have taken care of children who suffered the devastating consequences of meningococcal disease. A major driving value of the working group is to prevent children from dying or suffering long-term consequences of meningococcal disease, and they value vaccines as highly effective prevention tools. At the same time, there is also a strong value of public health stewardship, and a recognition that one of the working group’s responsibilities is to evaluate the impact of interventions at the population level. Balancing these two values was apparent in all of the working group discussions. Fortunately, fewer and fewer cases of disease are being seen, but that also means there would then be less impact of a vaccine seen on a population level. In summary, for values and preferences, the data suggest that the issues considered by the working group are similar to those raised by the public, and that providers rely on clear vaccine recommendations from the ACIP and other provider organizations.

Economic analysis data have been presented by Dr. Ortega-Sanchez at previous ACIP meetings, which Dr. Briere briefly summarized during this session. Based on information from the vaccine manufacturers, the actual price per dose of HibMenCY is expected to be around \$30. At this price, the estimated annual program cost for the 4-dose series is \$564 million US dollars. This translates into a cost per quality-adjusted life year (QALY) saved of \$647,000. Therefore, vaccinating infants with meningococcal vaccine has a high cost per case prevented, even at a low vaccine price.

In summary, the overall evidence type for the HibMenCY data is 2. The data support the safety and immunogenicity of the vaccine against Hib and serogroups C and Y. However, low meningococcal disease burden lowers the overall benefits of the MenCY components. The assessment of the values and preferences for an infant meningococcal vaccine highlights the importance of clear vaccine recommendations, while the economic analysis found that infant meningococcal vaccines have a high cost per QALY even if the vaccine price is low. These findings were taken into consideration by the working group when creating the proposed vaccine recommendations.

Considerations for Use of HibMenCY In Infants

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

Dr. Cohn reported that the meningococcal working group has been discussing infant meningococcal vaccine issues on working group calls and at ACIP for over 3 years. During this session, she highlighted the key considerations of the working group. She began by summarizing two presentations given during the October 2011 ACIP meeting. The first regarded the burden of meningococcal disease in infants, presented by Jessica MacNeil, and the second pertained to the cost-effectiveness analysis of infant meningococcal vaccination presented by Ismael Ortega-Sanchez. She then reviewed the working group's rationale for proposed use of HibMenCY, and the proposed language for the recommendation and vote.

Historically, meningococcal disease has been cyclical with peaks in disease incidence every 8 to 10 years. Rates of disease were approximately 1 case / 100,000 population through the 1990s, and 10 years ago as disease rates were declining, it was assumed they would peak again. But rates have declined to historic lows, and the US has remained at a nadir of disease incidence for the last 5 to 6 years. The reason for these sustained low rates of disease is not understood, but there is no indication, even reviewing preliminary 2012 data, that rates are increasing.

Rates of disease have declined for all serogroups, including serogroup B, which is not included in currently licensed meningococcal vaccines. Rates of serogroups C and Y declined prior to achieving high adolescent vaccination coverage, but the recent low rates may be attributed in part to the adolescent vaccination program. Incidence has declined in all age groups, not just among adolescents. Rates of disease were too low prior to vaccine implementation to understand if there is an impact of the adolescent vaccination program on other age groups, including infants.

In terms of incidence by age and serogroup, in children <5 years of age a large proportion of disease is caused by serogroup B compared to serogroups C, Y, and W135 combined. The proportion of disease that caused by serogroups C, Y, and W135 increases with increasing age. Only about 1% to 3% of disease is caused by serogroup W135, and even less in younger age groups. If the incidence of disease in children <5 years of age is broken down further, the greatest incidence in this youngest age group is among children <1 year of age. Of disease in this age group, 50% to 60% is caused by serogroup B, which is not prevented by HibMenCY. This remains true throughout the first 5 years of life.

With regard to the estimated annual number of cases caused by each of the three major serogroups for children <5 years of age, 50% of disease occurs in children 0 through 8 months of age. In the 0 through 8 month olds, serogroup Y is more common than serogroup C; whereas, serogroup C is more prevalent in children over 1 year of age. Averaging incidence data from 1993 to 2011, the number of serogroup C and Y cases among children <5 years is about 206 cases annually.

In order to better understand the impact of declining disease burden on the number of cases annually, three time periods were compared: 1997-1999, prior to the decline; 1993-2011, to include the last peak and current nadir in disease incidence; and 2007-2009, to represent current disease. During the peak in the late 1990s, about 475 cases of serogroups C and Y disease occurred each year in children less than 5 years of age. In more recent years, that number has declined to about 77 cases a year. This translates into about 4 to 8 deaths and 8 to 12 serious sequelae occurring in children <5 years annually.

While the data are not as complete in the national reporting system, NNDSS, as they are in the ABCs system, these data provide a good snapshot of the most recent disease trends. In 2011, there were 139 cases of meningococcal disease, caused by any serogroup, reported in children less than 5 years old. Among the 66% for which there is serogroup information, only 25%, or 24 cases, were caused by serogroup C or Y, compared to 60 cases caused by serogroup B. Only 17 of these cases occurred in children less than 6 months of age. Among the 52% for which outcome data are available, all deaths were either serogroup B or unknown serogroup. Disease appears to be continuing to decline in 2012. Among all ages, there are 401 cases reported through week 41 compared to 541 cases reported by week 41 in 2011. Among cases with reported serogroup and outcome, which is likely to be approximately 60% to 70%, there have been 7 cases and 2 deaths caused by serogroup C and Y among children 6 through 59 months.

Far fewer cases of meningococcal disease are being seen in the US compared to 10 to 15 years ago, but this also means that the amount of disease that potentially would be prevented with a routine infant vaccination program is low at this time. Among the cases seen in children < 5 years old, most disease is caused by serogroup B, and a large proportion of disease occurs in the first 6 through 8 months of life. The epidemiology of meningococcal disease is highly dynamic and will need to be monitored frequently for changes in disease patterns, but the working group feels strongly that there is no evidence at this point that disease will increase in the near future.

Turning to key findings from the cost-effectiveness analysis presented by Dr. Ismael Ortega-Sanchez during the October 2011 ACIP meeting, Dr. Cohen reported that a Monte Carlo simulation analysis was done using a hypothetical 4 million birth cohort over 10-year time-frame. For the base analysis, average incidence rates from 1993 through 2009 were used, but high incidence and low incidence years were used in sensitivity analyses. These results were updated to reflect the better than expected 5-year immunogenicity data presented by Dr. Miller during this session showing that at 5 to 7 years after vaccination, an expected 60% of children would still be protected, and that at 7 to 10 years after vaccination, 30% would still be protected. The model uses waning immunity over the 9 years following the fourth dose. Additionally, a vaccine price of \$30 a dose was to be presented during this session, with no additional administration costs because the vaccine is combined with Hib vaccine.

In the base case scenario, 164 cases and 13 deaths would be prevented by a routine infant vaccination program. However, in the sensitivity analyses using 2007 through 2009 incidence data, an estimated 52 cases and 4 deaths would be prevented by a routine infant vaccination program. With the current low disease incidence, over 60,000 infants would need to be vaccinated to prevent a case and over 800,000 infants would need to be vaccinated to prevent a death from meningococcal disease. As one would expect, the cost per QALY saved using HibMenCY is highly dependent upon the disease incidence used. Using an average disease incidence over the last 18 years, the cost of HibMenCY is over \$500,000 per QALY saved. However, in terms of current disease incidence, the cost per QALY saved is well over a million dollars. The high cost per QALY saved for an infant meningococcal vaccination program

reflects the limited impact a vaccination program would have on preventing cases and deaths. However, cost considerations were not a major factor in ACIP working group deliberations.

Dr. Cohen highlighted the key elements of the working group's rationale to propose recommendations for meningococcal vaccine for infants at increased risk of disease. As Drs. Miller and Briere presented, data support the safety and immunogenicity of HibMenCY against Hib and serogroups C and Y *N. meningitidis*. There are supportive data that some children will have protective levels of bactericidal antibody after the second dose given at 4 months, and there was no evidence of immune interference with PCV7. HibMenCY does not protect against serogroup B disease or serogroup A or W135. The price of HibMenCY is \$56.75 per dose. The private sector price for stand-alone Hib vaccines is about \$25 a dose, while the CDC price is about \$10 a dose. Therefore, the private cost of the MenCY component of HibMenCY is considered to be about \$30 a dose.

While multiple options were initially considered by the working group over the last three years, in the end the working group discussed two options: 1) recommending HibMenCY for infants at increased risk for meningococcal disease, or 2) recommending HibMenCY for all infants. The working group used the current landscape and data available as their frame of reference, including recent disease epidemiology data, current data on vaccine durability, and the 2012 immunization schedule. The working group has a strong preference for a recommendation for high-risk infants only to be recommended for meningococcal vaccination. Infants in these risk groups are small, an estimated 5000 infants may be at risk a year, but they are a feasible target for vaccination. These high risk groups include infants born with or having a family history of complement component deficiency, infants with known asplenia, or those with sickle cell disease detected on newborn screening, and infants who are at increased risk due to a community outbreak of serogroup C or Y disease. These recommendations mirror high-risk recommendations for children 9 months through 10 years of age, with the exception of not being able to use HibMenCY as a travel vaccine.

N. meningitidis is primary pathogen in persons with late component complement deficiency, including C3, properdin, factor D, and C5-9 deficiency. Persons with complement deficiency are at a 7,000- to 10,000-fold higher risk for meningococcal disease compared to the healthy population, 43% to 57% will develop disease, and half of these will have recurrent disease. Complement component deficiency is rarely diagnosed during infancy, and is most commonly diagnosed after the first meningococcal infection, which frequently does not occur until adolescence. Infants will only be recognized as being at increased risk for disease in the setting of a family history of complement component deficiency. *N. meningitidis* is the third most common cause of sepsis in persons with asplenia. The data to support an increased risk for meningococcal disease among persons with asplenia are limited. Most studies evaluated increased risk of all-cause sepsis, but there is evidence of increased mortality of up to 40% to 70% among persons with asplenia who develop sepsis. HibMenCY offers an alternative to using MenACWY-D in the second year of life, which is not recommended due to concerns about immune interference with PCV13. Children with sickle cell disease detected on newborn screening could achieve protection prior to developing functional asplenia.

Vaccination may be recommended for target groups during outbreaks of meningococcal disease in communities and organizations such as schools or churches. The need for multiple doses of vaccine required in infants limits the benefit of HibMenCY in this setting. However, availability of HibMenCY for infants less than 9 months who are targeted for vaccination in response to an outbreak is useful. In the last two-three years, CDC is aware of at least two outbreaks where young children were targeted for vaccination.

The primary rationale for the working group recommendation is the low burden of potentially preventable cases, and the low proportion of overall cases in infants that are prevented with HibMenCY. In terms of the incidence by month of life and the timing of when the four-dose schedule occurs, while infants are clearly at increased risk for disease compared to other age groups, it is a short-period of increased risk, declining after the first 6 to 8 months of life and prior to completion of the primary series of HibMenCY. In comparison, infants in high-risk groups, for the most part, will be at life-long increased risk for disease. It is this short and early period of increased risk that contributes to the limited impact an infant meningococcal vaccine would have on non-B disease. Additionally, most disease in infants and young children is caused by serogroup B. Of the estimated 205 cases in children <5 years of age annually during 2007 through 2009, only 44, or 20% to 25%, would potentially be prevented by HibMenCY vaccine.

While the supporting evidence considered by the working group over the last three years was extensive, Dr. Cohen highlighted three considerations: 1) the duration of protection for of the meningococcal component of HibMenCY, 2) the potential for HibMenCY to reduce transmission of *N. meningitidis*, and 3) the programmatic aspects of a routine meningococcal vaccination program.

If infants could be vaccinated against meningococcal disease and they would be protected until adulthood, even at such low disease incidence the impact of vaccination would be greater. However, it is now understood that long-term protection after a complete series of meningococcal vaccine is unlikely. There is evidence of declining antibodies 5 years after vaccination with HibMenCY. However, data on the proportion of infants who maintain protective levels of antibody against serogroups C and Y are reassuring. These data received a lower evidence grade compared to the short-term immunogenicity data, and further study would help support these initial results. Both the US adolescent vaccine effectiveness estimates and the infant vaccine effectiveness estimates from the UK have offered an understanding of waning immunity, and that a booster dose at age 4 to 6 years would be needed to protect children until the 11- to 12-year old meningococcal vaccination.

Unlike Hib and *Streptococcus pneumoniae* in which carriage rates are high in young children, meningococcal carriage rates are higher in adolescents and young adults. Adolescents are considered a reservoir of transmission for *N. meningitidis*. Increased vaccination coverage rates in adolescents and the increased immunity from the booster dose may interrupt transmission to infants and young children. However, vaccinating infants will unlikely protect unvaccinated age groups.

Estimates for three doses of Hib vaccine from the National Immunization Survey (NIS) were included in the analysis of incidence of disease by month of life. This is coverage for infants who did not receive PRP-OMP, for whom only two doses are required. While 3 dose coverage does increase to 86% by 13 months of life, on time coverage for dose 3 at 7 months is lower at 64%. The timing of actual Hib vaccination in association with disease risk makes achieving maximum impact from a routine infant program difficult.

The working group concluded that data do not support routine infant meningococcal vaccination at this time based on the low number of preventable cases and the high proportion of cases caused by serogroup B, which are not prevented with this vaccine. Targeting high-risk infants for vaccination is a feasible approach consistent with current recommendations for 9 month through 10 year olds. The working group is in agreement. It is difficult to accept that there will be cases that are preventable, but this is the judicious approach given the current disease

epidemiology. Risk for serogroup C and Y disease is extremely low even in the absence of vaccination. In terms of additional considerations, HibMenCY is a Hib vaccine, and guidance for use of HibMenCY will be provided. HibMenCY is not a travel vaccine, as it does not contain serogroups A or W135, and quadrivalent vaccination is required for infants traveling to the Hajj or the Meningitis Belt.

Recommending meningococcal vaccine for infants at increased risk for meningococcal disease is an extension of current meningococcal recommendations for children aged 9 months through 10 years of age. The working group had no preference between using HibMenCY starting at 2 months or MenACWY-D starting at 9 months, with two exceptions. HibMenCY is not recommended in infants who are traveling to the Meningitis Belt or Hajj. MenACWY-D is not recommended for infants 9 through 23 months with functional or anatomic asplenia to avoid potential interference with PCV13. Guidance for use of HibMenCY in high-risk infants will be integrated with guidance for MenACWY-D in 9 through 23 month olds. The working group proposed the following recommendations for use of HibMenCY in infants:

- Infants at increased risk for meningococcal disease should be vaccinated with 4 doses of HibMenCY at 2, 4, 6, and 12 through 15 months.
- These include infants with recognized persistent complement pathway deficiencies and infants who have anatomic or functional asplenia including sickle cell disease.
- HibMenCY can be used in infants ages 2 through 18 months who are in communities with serogroup C and Y meningococcal disease outbreaks for which vaccination is recommended.

The work group would include the following guidance for use that discusses use of HibMenCY as a Hib vaccine:

- At this time, ACIP does not recommend routine meningococcal vaccination for infants.
- HibMenCY is safe and immunogenic. HibMenCY may be administered to infants to complete the routine Hib vaccination series.
- If HibMenCY is used to achieve protection against serogroups C and Y, HibMenCY should be used for all four doses of Hib vaccine.

Public Comments

Dr. Leonard Friedland
Physician Scientist
GlaxoSmithKline

Thank you Mr. Chairman for the opportunity to speak to the ACIP. GSK is committed to developing medicines and vaccines of value to patients and society, and then doing everything that we can to ensure that those medicines and vaccines reach the patients who may benefit from them. In 2003, GSK set out to develop a vaccine to prevent meningococcal disease in infants and toddlers. MenHibrix[®] was specifically designed to address the epidemiology of the United States. Meningococcal disease is known to have a cyclical nature. This means the low rates currently observed may not be sustainable long-term. ACIP has already implemented recommendations to address the risk of vaccine-preventable meningococcal disease in

adolescents. This risk is even higher for infants and toddlers. What we are discussing today is ensuring that the most vulnerable among us, infants and toddlers, can begin to receive vaccination earlier than ever before.

Speaking now both as a pediatrician and as a parent, I emphasize that there's a family community, healthcare provider, and a medical home behind every one of the meningococcal cases that occur in young children each year. Giving healthcare providers a clear signal that it's appropriate to discuss meningococcal risks and vaccination with parents is what's at stake here. A high risk only recommendation for meningococcal vaccination sends the opposite messages. GSK respects the ACIP and its recommendation process. Therefore, we ask you to consider providing guidance that: 1) MenHibrix[®] may be used as a Hib vaccine and be available with VFC coverage; 2) that MenHibrix[®] also be assigned a Category B permissive recommendation for meningococcal C and Y vaccination with VFC funding. We appeal to you to consider the message that you will send today. Please do not send an unintended message to parents, healthcare providers, and payers that meningococcal vaccination for healthy infants and toddlers should not be discussed. This is an important medical decision that belongs in the hands of the healthcare providers and parents. I thank ACIP for granting me the time to share my thoughts.

**Tammy Wolf, Parent / Advocate
National Meningitis Association**

Good morning. My name is Tammy Wolf and I am here representing the National Meningitis Association, which is not an organization with or paid for by any pharmaceutical company. I am the mother of 3-year old twins, Addie and Kate. Addie contracted meningococcal disease when she was 6 months old, but Addie's story is a little different than others you've heard. She emerged from her experience relatively unscathed. We had what I call Addie's lifesavers—a series of decisions and events that began shortly after Addie woke us up one morning with the most terrible scream I had ever heard. First, we decided early to take Addie to the ER at Children's Hospital of Philadelphia. She had a high fever, was vomiting, was very lethargic. Second, after receiving treatment, we were actually discharged. As we left the hospital, Addie vomited again. A seasoned ER nurse insisted on holding her for observation. Had we left at that moment, Addie would not be with us today. Third, the ER doctors began antibiotic treatments early. Finally, the pediatric intensive care unit (PICU) staff was skilled and caring, and did everything in their power to give Addie a fighting chance.

We acted quickly, and Addie was in a top hospital with experts who recognized the disease and knew how to care for her. This saved her life. But how many other families can say the same? We've heard devastating stories about misdiagnosis, multiple trips to the doctor or ER, and delayed treatment. Even with the appropriate and fast treatment Addie received, she nearly died. Our family experienced the incredible trauma of watching her fight for her life for over 22 days in the hospital. We spend months helping her recover, and yet, we're the lucky ones. For Halloween this year, I have a little girl whose going to be a beautiful mermaid, and a little boy whose going to be a dinosaur who wants to eat beautiful mermaids, and they are exactly why I am here today advocating for vaccines—for meningococcal vaccines as part of the immunization schedule for infants. Every day we are reminded how very lucky we are. As parents we're the first, last, and only line of defense for our infant children. We must prevent the preventable. Having a meningococcal vaccination as part of the recommendations will help ensure that parents have access to vaccines that can help protect their children. Thank you.

**Lynn Bozof, President
National Meningitis Association**

I'm Lynn Bozof. I'm the President of the National Meningitis Association (NMA), and I have no conflicts of interest. I stood before the ACIP for the first time 12 years ago in the October meeting. I had lost my 20 year old son to meningococcal disease. There was a licensed vaccine, but we were not aware of it. I can't help but think of the families of infants, how they will feel if they lose a child, to then learn that there was a vaccine available that could have possibly saved their child's life. I've been there. So much has been done in the last 12 years to protect our adolescents, and I thank the committee for their efforts. Now we have the opportunity to protect infants. Our organization will continue to do our part in educating parents, but it is only with a recommendation and VFC funding that all parents will be educated and their infants protected. Thank you.

**Clare Hoang, Parent / Advocate
National Meningitis Association**

My name is Claire Hoang. I am recording this message on behalf of the National Meningitis Association. I can't be there in person today. I'm currently 8 months pregnant and unable to travel. Back on February 13th of this year, I lost my beautiful son, Phoenix, at three and a half years old to meningococcal disease. Phoenix was a beautiful, intelligent, healthy, who was loved by us, his parents, his grandparents, his aunts, uncles, cousins, family, community, and most of all his twin brother, Griffin. We miss him every moment of every day. On Thursday, Phoenix woke up, had a mild fever, as the day progressed he got worse, I took him into the ER, once in the ER, no medical staff could identify Phoenix's condition as meningitis. The last time we ever heard Phoenix's little voice was when he sang to us "E I E I O." Around one o'clock on Monday, we held our little Phoenix's hand and watched as his heartbeat slowly died away. As a mother, I feel it is critical for every child to have access to a lifesaving vaccine. Phoenix's twin brother got the vaccine two days after we learned about the vaccine, and I guarantee that this baby will also get the vaccine once he is old enough. I hope that you remember my story and the stories of other mothers and fathers as you consider expanding the meningococcal recommendations. Thank you for your time and your consideration.

**Kyle Dramano, Advocate
Meningococcal Disease Survivor**

My name is Kyle Dramano. I'm an infant meningococcal survivor. I have no industry affiliation, but I'm here with Meningitis Angels. My presence here is a form of advocacy in itself. I stand before you as a way of showing rather than telling, as a demonstration of the violence that meningococemia puts on the body. As bacterial meningitis spreads, it ravishes all that it touches and leaves its victims lives changed forever. At 13 months old, I was stricken with meningococcal meningitis and was given zero percent chance to live. I went from a normal, active, healthy toddler who was able to run, jump, and climb to a child who was fighting for his life. For four weeks at St. Joseph's Hospital in Tampa, Florida I was on life support, during which all of my limbs died and turned black due to gangrene. At this point, the doctors told my parents that they had done everything in their power. I was alive and somewhat stable; however, the gangrene had to be removed from my body, requiring the amputation of all of my limbs along with debriding all of the dead tissue that accumulated on my body. This all took place at Shriners Burn Unit in Cincinnati where they specialize in skin grafts. After all my limbs were amputated, I weighed only 12 pounds and my parents were told that I had very little chance of learning to sit up independently, much less live an active lifestyle.

I endured 27 surgeries from the time of the amputation when I was 14 months old until I was two and a half years old. After finally coming home, I underwent 8 years of physical and occupational therapy, which help me learn to adapt to my disability. The therapist made many different prostheses to simulate the arms and legs that I no longer had, but I found that I am more functional without them. The only adaptive equipment that I use are my wheelchair and a small prosthesis that use to write. Every Saturday morning, my parents drove me to play Challenger League Baseball with other disabled kids that were my age. I also loved the therapy sessions that I attended at Clearwater Marine Science Center, now called the Clearwater Aquarium, where I helped feed and train the rescued sea animals, a few of which were amputees like me. Some of the most difficult times involved being mainstreamed into a typical classroom. My mom fought for a year and a half and finally succeeded. The school board felt that it would have been cruel to allow a child like myself into a classroom filled with typical children. My mom's argument was that we do not live in a disabled world, and that I needed to be allowed the same opportunities as other able bodied students. The rest of my life progressed in much the same way that most people's lives do, but my life has been far from easy. I wasn't able to start driving until I was 20. I had to take extensive driving training that lasted an entire year until I could drive on my own. I had to rely on my younger brother and my parents to drive me if I wanted to hang out with my friends. I am thankful for the family and friends who have supported me throughout the years. If it wasn't for Shriners, who helped with my medical costs, the community which helped to modify my house, and vocational rehabilitation who helped pay for the modifications to my car, I know that my family and I wouldn't have been able to afford these on our own.

Life as a quad-amputee has propelled me toward an interest in disability studies, and I am now a graduate student in communications at the University of South Florida, studying the way that communication impacts our understanding of disability. In this aspect, I've grown to respect disability. But today, I still face challenges while going to college. My own handicap has made me keenly aware of the difference between my own experiences as a student in opposition to that of my able bodied peers. Instead of worrying about whether or not I will have friends in my classes, I'm worried about a plethora of other obstacles I must overcome. Will there be room for my wheelchair in the classroom? Who will help me retrieve my binder from my backpack? Will I have enough time in between classes to make it to a handicap accessible bathroom? What are the odds that it will be occupied? These are only a few things I must consider every day while at school. I have grown accustomed to these challenges, and they aren't as daunting to me now as one might think. But when I look in the mirror, I realize that meningitis could have taken more from me, causing internal or cognitive damage. Meningitis has taken all of my limbs, but I gaze at myself in the mirror and can't help but think, "Damn. I'm one of the lucky ones."

Frankie Milley
Founder / National Director
Meningitis Angels

My name is Frankie Milley. I am the Founder and National Director of Meningitis Angels, and the mother of an only child who died from meningococcal meningitis. My only conflict is that I'm still standing here 14 years later fighting for kids so they don't have to die or end up like Kyle. Summer before last, I was privileged to attend all six of the meetings that CDC held gathering public opinion. Time, after time, after time even those parents who were anti-vaccine, vaccine resistant, voted to recommend this vaccine. No matter how low the case rate, no matter how much the cost, they voted to vaccinate kids against this disease when they wouldn't vote to vaccinate their child for anything else. When you talk about grading, how do you grade the loss

of the child? I mourn Ryan every day. How do you grade a mother holding her baby while they take him off of life support? How do you grade a mother who watches her infant lose their little face, their little arms, their little legs, and an order so bad in the hospital room that no one can stand to walk in there. How do you grade that? How do project costs when you look at the cost of burying a child, or you look at the cost of lifelong care, or even initial hospital care of one child who survives like Kyle? It's millions.

Not one child should have to suffer that life, and no one parent should have to bury their child when it's vaccine-preventable. We give other boosters for other vaccines. Why not this one? It's one of the worst diseases known to man on this Earth. I say to you, if you have a ship that is sinking and you have 50 life vests, are you going to give out those 50 or are you going to let everybody go down with the ship because you don't have enough? Finally, I say to this committee, it has been an honor and a privilege to stand here many years in front of you. I know that you vote on the side of children, and their health, and prevention. I've seen you do it time, after time, after time. I know that all of you are parents and grandparents, and you want what's best for children. I also know that you have that daunting task to look at economics, whether we all want to think about it or not, look at cost-effectiveness. You cannot put a cost on the life of a child. You cannot put a cost on a young man who has to have help to go to the bathroom—to just do the normal things we all take for granted. You cannot grade it. I ask you today, committee, as you vote, vote the right thing for kids. Vote on the side of health and prevention of this deadly, debilitating disease. Again, I thank you, and I'm honored to stand before you.

Discussion Points

Of the handful of deaths that occur in young infants each year from meningococcal disease, Dr. Sawyer wondered how many are occurring in the small subgroup of patients with high risk conditions. Regarding concomitant use of PCV conjugate vaccine, both presentations reassured the committee that there is not interference. The GRADE level conclusion for that was 1, which he thought meant that ACIP would be unlikely to change that over time. That is, how robust are those data compared to the data on the ACWY-D vaccine for which there was interference?

Dr. Cohn replied that it was safe to say that it is very few, and practically none. For most children who are lifelong increased risk, the risk does not develop until later in life. This would be preemptive vaccination for those children. Regarding concomitant use of PCV conjugate vaccine, to clarify, those study were conducted with PCV7 not PCV13. There is evidence to suggest that there is no interference with PCV7. The data did meet non-inferiority for the first three doses by FDA requirements, which the working group felt was robust enough to be considered an evidence grade of 1. Understanding interference in real life is more difficult to assess.

Dr. Keitel requested that Dr. Salisbury discuss the program in the UK, specifically with regard to when the program started and what impact infant immunization has on carriage in adolescents.

Dr. Salisbury (DOH, UK) responded that 13 years ago, the UK ran a national level campaign to introduce vaccines for infants at 2, 3, and 4 months with MenC as a single component vaccine. A catch-up campaign was conducted up to roughly the age of 20, with single doses from age 1 upwards. Since that time, meningococcal C disease has effectively been eliminated and no resurgence has been observed to date of meningococcal disease. The program has been adapted over a number of years, with a change from 3 infant doses to 2 infant doses and

inclusion of a Hib MenC booster at the age of 1. With just those doses in young children, there continues to be no disease. Consideration is being given to whether carriage is increasing, but disease so far is not increasing. The difference between the UK's schedule and the US's schedule relates to the Hib vaccine, because the UK's Hib vaccine is included with the diphtheria, tetanus, and invasive pneumococcal disease (IPD). The UK does not have a standalone Hib vaccine in its primary series. Currently under consideration is whether the doses of MenC can be reduced from 3 doses to 1 dose, eliminating the 3- and 4-month doses and shifting the dose to an adolescent dose that would be delivered through the school program. So there would simply be 1 dose at 3 months, Hib MenC at 12 to 13 months, and then an adolescent dose. Currently, the control of meningococcal disease in the UK remains exemplary.

Dr. Karron wondered whether the 5000 children estimated to be at risk each year could be broken down in terms of the specific risk groups.

Dr. Cohn responded that the majority of the children who would be included in that risk group are children who have sickle cell disease identified at birth. That number is estimated to be about 4000 children per year. The number of people in the US living with complement component deficiencies is probably between 1000 to 2000, but the number of infants who would have a complement component deficiency would be difficult to assess.

Dr. Temte inquired as to whether there is fairly universal neonatal testing for sickle cell across all 50 states.

Dr. Cohn replied that testing is pretty universal at this point, with all 50 states testing at this point.

Dr. Pickering said it seemed from Dr. Salisbury's comments that no other serotypes of meningococcal disease are observed in the UK, which seemed strange because he would expect serotype A with all the travel and people going through the UK. He also wondered whether serotype B is seen in any infants.

Dr. Salisbury (DOH, UK) responded that there have been some relatively small increases in serotype Y, but it is still at pretty low levels. Serotype A has not been a problem since there was an importation of an A strain at the time of the Hajj a number of years ago, and there was no continuation of that. When the UK embarked on its campaign, they had levels of MenC that were at least 10-fold higher than what the US was observing. The circumstances that drove the UK's campaign and continued use of the vaccine were different from the US. It was highly cost effective at the price the UK was being offered the vaccine in 1999 to implement the program, because the burden of disease was so much higher than in the US.

Dr. Baker noted that it is always nice to have more than one vaccine for children in case there are shortages. She heard that there is a standalone Hib conjugate vaccine being developed by GSK, and she requested confirmation about whether that was true and, if so, whether Dr. Miller could predict when that vaccine might be available.

Dr. Miller confirmed that what Dr. Baker heard was true. That vaccine is in the final stages of its Phase 3 study. The vaccine is currently on the market. It was licensed through an accelerated procedure during the last Hib vaccine shortage, but was licensed only for the fourth because at that time that is what ACIP had deferred. GSK continues with development of this vaccine. They children have been vaccinated for the first three doses, and are now receiving their fourth

dose through that program. This has been a challenging study to enroll, given that it is not novel to provide monovalent Hib in the US, but it will perhaps be available sometime in the latter half of 2013.

Vijay Tammara (Nuron Biotech) reported that Nuron Biotech has HibTITER® from Pfizer / Wyeth and is developing a compound to bring back to market as a single mono-component, which was withdrawn from the market in 2006. They discussed this with the FDA last year. Currently, the filing is under discussion and review at the FDA. Nuron Biotech is ready to start a Phase 2 trial.

Dr. Warshawsky (NACI) reported that while Canada has some variability between its provinces, several of the provinces administer 1 serogroup C dose a 1 year of age, and then there is an adolescent dose that varies between the provinces as well. Some provinces use only serogroup C and others use conjugate quadrivalent vaccine. Canada has also realized a significant decline in serogroup C disease because of those strategies. As with the US, Canada's greatest risk is serogroup B, particularly in infants, but also in adolescents.

Dr. Harrison requested a sense of the working group discussions on the issue of a permissive recommendation.

Dr. Cohn replied that the working group has discussed permissive language for these recommendations for two to three years. In fact, the first time the recommendation was presented to ACIP was in February 2010. The working group is in pretty strong agreement that the language used in the guidance just read to the committee that this vaccine can be used as a Hib vaccine is the permissive language that the working group would like to use. The vaccine is licensed and approved by FDA; therefore, the vaccine is implicitly permissive and may be used by clinicians. The working group feels that permissive language in the past has been confusing to providers and to parents. Most providers really rely on ACIP to evaluate the need for the vaccine. Discussing the risk for meningococcal disease is difficult in the limited amount of time that providers have with patients and parents, and because of the number of competing priorities that they have to discuss. It is very hard to make that decision. There are multiple prevention priorities that take precedent in the 10-minute primary care visit. The confusing aspect of this is communicating that the vaccine is really effective against only 25% of cases, and a child's risk is not decreased that much from this vaccine because the greatest risk is from serogroup B. The working group is also concerned about obligating providers to have this discussion with parents, and what that might do in the setting of a provider who chooses not to vaccinate a child who then goes on to develop disease.

Noting that a VFC vote was scheduled after the vote on the recommendation, Dr. Sawyer requested that Dr. Cohn offer clarification of what the VFC vote would allow for patients covered by the VFC program.

Dr. Cohn responded that the VFC vote would mirror the recommendations voted on for meningococcal prevention for high risk infants. The issue of whether this particular vaccine could be considered under the Hib vaccine resolution would be discussed during the February 2013 ACIP meeting during the Hib vaccines session. This vaccine will not be available until mid-2013.

Ms. Rosenbaum emphasized that in probably half of all jurisdictions, clinicians who have knowledge that there is a treatment (e.g., vaccine) for a small but significant risk, and do not inform parents or caregivers about the risk of a condition and a potentially effective treatment, the clinician could face liability for violation of basic standards of informed consent. While she had no quarrel with the notion that this may not be the kind of situation in which a routine addition to the schedule is warranted, but she thought it was a different matter entirely for this committee to not strongly recommend that clinicians always talk to parents about risks, and about potential steps that can be taken against risks. It was not clear how to put that kind of statement to work for ACIP. This is one of the very hard instances where the question of ACIP recommending something for coverage has run headlong into questions about the appropriate standard of care. It was not apparent how to separate out a permissive treatment standard from what is clinically appropriate from a professional practice point of view.

Dr. Brady (AAP) noted that a treatment is potentially different from a non-recommended prophylactic approach because there are many things that a pediatrician could talk to parents about that are creating risks that they just do not have time for—not only related to medicines and vaccines, but also various other activities. Therefore, he did not know whether this was something the committee would want to add to the burden of trying to address vaccines at 2, 4, and 6 months, but all of the other issues that are very important. Currently, a physician has about 8 to 10 minutes to get all of that in. If something else is added that requires a tremendous amount of discussion, such that even the people on the committee have a difficult time addressing (e.g., nadir of disease, serogroups covered, when the vaccine is going to provide adequate immunogenicity to expect protection), it will be impossible.

Dr. Doskey (AHIP) encouraged ACIP in the strongest possible way to either recommend, recommend for certain groups, or not recommend the immunization. Otherwise, the result will be a scatter of coverage across the country as with the human papillomavirus (HPV) vaccine. With FDA approval, there is already a permissive recommendation. Practitioners can use the immunization.

Dr. Temte reminded everyone that within the framework of evidence-based recommendations, ACIP has tried to get away from permissive language per se, and places priority on Category A recommendations. There are some limited circumstances for which a Category B (formerly known as the permissive recommendation) may be appropriate, but ACIP tries to keep those at a minimum for the exact reason Dr. Doskey mentioned.

Dr. Loehr (AAFP) indicated that he was part of the CDC public conversation about meningitis, and as part of that, he actually spoke to some of the Meningitis Angels. As part of that, he promised them that he would go back to his practice and talk to parents about the meningitis vaccine. He did that for several months, and actually had no parents accept the vaccine. The major drawback was that he was offering it for older children, there was not a lot risk, and it was possibly going to be out-of-pocket. His population might be skewed, but they were not willing to accept the vaccine.

Ms. Rosenbaum thought it was admirable that Dr. Loehr did that, and that it was perfectly understandable that parents would make that choice. Her point simply was that regardless of whether ACIP recommends that a vaccine be added to an insurance coverage schedule is quite a different matter from ACIP's broader views about the discussions that occur between healthcare professionals and patients. In many states, the standard for an informed consent does not pertain to what a reasonable professional in practice would do. Instead, it focuses on what a reasonable parent wants to hear, which is a very different matter. Therefore, she was

eager for ACIP not to focus on how burdened health professionals are in talking to their patients. She was more concerned about whether the evidence showed that this vaccine should be routine or routine for certain populations.

Vote: Recommendation for Use of HibMenCY in Infants

Dr. Campos-Outcalt made a motion that the proposed language in the recommendation for HibMenCY in infants be approved. Dr. Duchin seconded the motion. The motion carried with 13 affirmative votes, 1 negative vote, and 1 abstention. The disposition of the vote was as follows:

- 13 Favored:** Bennett, Bocchini, Campos-Outcalt, Duchin, Harrison, Karron, Jenkins, Keitel, Rosenbaum, Rubin, Sawyer, Temte, and Vazquez
- 1 Opposed:** Coyne-Beasley
- 1 Abstained:** Harriman

Vaccines for Children

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

Dr. Santoli indicated that the purpose of this resolution was to update the eligible groups for meningococcal vaccination to include children 2 through 8 months of age at increased risk of meningococcal disease, and to update the recommended vaccine schedule to include another conjugated meningococcal vaccine schedule as an option. The change in the Eligible Groups section is to simply expand the eligible groups to 2 months through 10 years of age for the younger group and 11 through 18 years of age for the older group. The proposed changes to the Recommended Schedule Intervals are shown in yellow in the following tables:

Recommended Schedule, Intervals (1)

Age	Subgroup	Primary Vaccination	Booster Dose
2-18 months of age, with high risk conditions	Infants with complement deficiencies Infants with functional or anatomic asplenia Infants part of a community or organization outbreak Infants traveling to the Hajj or the "meningitis belt"	HibMenCY (four doses at 2, 4, 6, and 12-15 months of age starting at 2 months or catch-up schedule) OR MCV4-D (9 through 18 months, 2 doses 3 months apart) HibMenCY (four doses starting at 2 months or catch-up schedule) MCV4 (3 months apart) MCV4 (3 months apart) (infants receiving the vaccine prior to travel can receive the doses as early as two months apart)	If first dose received at age 9 months through 6 years and remain at increased risk for meningococcal disease, should receive an additional dose of MCV4 three years after primary vaccination. Boosters should be repeated every five years thereafter.

Recommended Schedule, Intervals (2)

Age	Subgroup	Primary Vaccination	Booster Dose
19 months of age, with high risk conditions	Infants with complement deficiencies Children who are traveling to the Meningitis Belt or Hajj, children who are part of a community or organizational outbreak	Two doses of MCV4 (9 months through 6 years and remain at increased risk for meningococcal disease, should receive an additional dose of MCV4 three years after primary vaccination. Boosters should be repeated every five years thereafter.) Two doses of MCV4 (9 months through 6 years and remain at increased risk for meningococcal disease, should receive an additional dose of MCV4 three years after primary vaccination. Boosters should be repeated every five years thereafter.) (infants receiving the vaccine prior to travel can receive the doses as early as two months apart)	If first dose received at age 9 months through 6 years and remain at increased risk for meningococcal disease, should receive an additional dose of MCV4 three years after primary vaccination. Boosters should be repeated every five years thereafter.

For children 2 through 18 months of age, there are four groups of infants. The schedules are consistent with the schedules for the new component, HibMenCY, as well as the use of meningococcal conjugate Menactra[®] vaccine, which is referred to in the table as MCV4-D for those 9 through 18 months of age. For children 19 through 23 months of age with high risk conditions, there are two groups of children and the option is Menactra[®] MCV4-D vaccine. The table notes, which explain all of the products and abbreviations used in the table, were slightly updated to add the HibMenCY product and move the meningococcal polysaccharide vaccine to its own note. It existed previously, but was included in the first table note. The revised notes would read as follows:

- (1) At the time of this resolution, there are currently two licensed MCV4 products and one licensed HibMenCY product. The first MCV 4. One product, Menactra[®], is manufactured by sanofi sanofi pasteur and is licensed for use in persons aged 9 months through 55 years of age. The second MCV4 product, Menveo[®], is manufactured by Novartis Vaccines and Diagnostics, Inc. and is licensed for use in persons aged 2 through 55 years of age. In the table above, the abbreviation MCV4-D is used when the recommendation applies only to Menactra[®] and the abbreviation MCV4 is used when the recommendation applies to either Menactra[®] or Menveo[®],
- (2) At the time of this resolution, there is currently one licensed HibMenCY product, MenHibrix[®], which is manufactured by GlaxoSmithKline Biologicals and is licensed for use in persons 6 weeks through 18 months of age.
- (3) At the time of this resolution, a meningococcal polysaccharide vaccine is also available, Menomune[®], which is manufactured by Sanofi Pasteur and is . This product is licensed for use in persons 2 years of age and older. This vaccine and may be used when meningococcal conjugate vaccine is unavailable or contraindicated.
- (4) Includes children who have complement deficiencies (C3, properidin, factor D, and late component deficiencies), anatomic or functional asplenia, and children with HIV infection; travelers to or residents of countries in which meningococcal disease is hyperendemic or epidemic; and children who are who are part of a community outbreak of a vaccine-preventable serogroup.

No changes were proposed to the recommended dosage and contraindications / precautions, or to the statement regarding updates based on published documents.

Discussion Points

Regarding eligible groups slide, Dr. Keitel noted that the tables delineate the quadrivalent from the bivalent meningococcal vaccines. However, if someone did not go to the table to look specifically, the travelers issue could be a problem (e.g., travelers require the quadrivalent vaccine).

Dr. Santoli clarified that the slide she showed regarding eligibility was only meant to discuss which groups are eligible. She said she could revise it, but the complexity of this made it tricky. That was why they went to the table format; however, she invited further suggestions.

Dr. Keitel suggested that perhaps a footnote could be included that for traveling children less than 9 months of age, the quadrivalent vaccine would be needed.

Dr. Karron requested clarity regarding whether that slide implied that if an infant under 9 months of age was traveling to the Hajj, he or she should receive HibMenCY. That did not seem to make sense.

Dr. Cohn clarified that the 2 through 18 month table would not include language about the Hajj. The 19 through 23 month old table would include the information about the Hajj.

Dr. Santoli clarified that the committee could opt to delete the last row of the 2 through 18 month table regarding the Hajj.

Dr. Rubin pointed out that it is not routinely recommended that HIV-infected children receive meningococcal vaccine. He was confused by that and proposed the deletion of "HIV in children 2 months through 9 years of age."

Dr. Cohn clarified that children with HIV vaccination are not recommended to be vaccinated. That was added to the VFC resolution when there was more permissive language for children with HIV to be vaccinated. It was not removed when it was clear that there was no recommendation for children of that age to be vaccinated.

VFC Vote: Recommendation for Use of HibMenCY in Infants

Dr. Sawyer made a motion that the proposed language in VFC resolution be approved, with the stipulation that the clause pertaining to children 2 months through 9 years of age with HIV infection be stricken from the language. Dr. Keitel seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

15 Favored: Bennett, Bocchini, Campos-Outcalt, Coyne-Beasley, Duchin, Harriman, Harrison, Karron, Jenkins, Keitel, Rosenbaum, Rubin, Sawyer, Temte, and Vazquez

0 Opposed: N/A

0 Abstained: N/A

Dr. Temte acknowledged that the Meningococcal Working Group had an enormous burden of information added to the data to consider, and he commended them for doing a tremendous job of assessing the data and helping to digest it into meaningful information. Speaking for the entire committee, he thought this was incredibly helpful for their understanding.

Measles, Mumps, and Rubella Vaccine

Introduction

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

Dr. Temte reminded everyone that the Measles, Mumps, and Rubella (MMR) Vaccine Working Group's terms of reference were to review all available data and discuss potential changes to the current recommendations. Toward that goal, the working group has engaged in the following activities:

- Review of the epidemiology of measles, mumps, rubella, and congenital rubella syndrome (CRS)
- Review of the existing statements pertaining to MMR vaccine
- Review of new data on MMR vaccine, including safety and immunogenicity among persons with HIV and the possibility of a third dose for mumps outbreak control
- Revise / update the existing recommendations into a single document

The document has been drafted and disseminated to ACIP members, and has been reviewed. Presented during this session were an overview of the 2013 ACIP MMR statement, a review of the working group's deliberations and recommendations, and the 2013 ACIP MMR draft statement.

Overview of the 2013 ACIP MMR Statement

**Huong McLean, PhD, MPH
Division of Viral Diseases,
National Center for Immunizations and Respiratory Diseases
Centers for Disease Control and Prevention**

Dr. McLean explained that the rationale for updating the MMR statement was that the full ACIP MMR statement was last published in 1998¹. Since that time, the epidemiologies of the diseases have changed with the elimination of endemic measles in 2000 and rubella in 2004, and though mumps incidence has been low, there have been large mumps outbreaks among highly vaccinated populations. Monovalent measles, mumps, and rubella vaccines are no longer available in the US, and the measles, mumps, rubella, and varicella (MMRV) vaccine has been licensed. There have been several revisions to the recommendations, including change in the interval for avoiding pregnancy after receiving rubella-containing vaccines (2001)², change in adequate mumps vaccination for school-aged children and adults at high risk* (2006)³, and change in evidence of immunity for health-care personnel and recommendations for personnel born before 1957 (2011)⁴ [i.e., health-care personnel, international travelers, and students at post-high school educational institutions; ¹*MMWR*. May 22 1998;47(RR-8):1-57; ²*MMWR*. Dec 14 2001;50(49):1117; ³*MMWR*. Jun 9 2006;55(22):629-630; ⁴*MMWR*. Nov 25 2011;60(RR-7):1-45].

The background information section of the 2013 MMR statement will include updated epidemiology, information regarding MMRV vaccine and immune globulin products, and expanded section on vaccines (i.e., immune response, vaccine effectiveness, duration of immunity), a summary of the Institute of Medicine (IOM) reports on MMR vaccine safety, a summary of studies of a third dose of MMR vaccine for mumps outbreak control, and a link to CDC's *Manual for the Surveillance of Vaccine-Preventable Diseases*. The 2013 MMR statement recommendations section clarifies policy language; incorporates more recent recommendations; and includes proposed revised recommendations regarding evidence of immunity, use of immune globulin products for measles prevention, and vaccination for persons with HIV infection.

Dr. McLean then reviewed working group deliberations and recommendations regarding the use of a third dose of MMR vaccine for mumps outbreaks in certain settings, acceptable evidence of immunity, use of immune globulin products for post-exposure prophylaxis (PEP) for measles, and vaccination of persons with HIV infection.

Use of a Third Dose of MMR Vaccine during Mumps Outbreaks

Huong McLean, PhD, MPH
Division of Viral Diseases,
National Center for Immunizations and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. McLean reminded everyone that information regarding the use of a third dose of MMR vaccine during a mumps outbreak was previously presented during the February 2012 ACIP meeting by Dr. Preeta Kutty and Ms. Amy Parker Fiebelkorn.

As background, mumps vaccine (Jeryl Lynn strain) was licensed in the US in 1967, and was recommended for routine use in children in 1977. In 1989, children began receiving two doses of mumps-containing vaccine as a result of a two-dose measles vaccination policy using MMR vaccine. By the early 2000s, less than 300 cases of mumps were reported annually. However, large mumps outbreaks among highly 2-dose vaccinated populations occurred in 2006, 2009, and 2010.

With regard to the epidemiology of mumps outbreaks in the US prior to 2006, during the pre-vaccine era outbreaks were common in crowded settings and in populations with a build-up of susceptible persons (e.g., prisons, orphanages, schools, military). By the late 1980s, there were outbreaks among cohorts of unvaccinated older children¹ who were spared from previous disease by declining mumps incidence. Outbreaks associated with 1-dose vaccine failure were also reported during this time²⁻⁴ [¹Cochi SL, et al. *Am J Dis Child*. May 1988;142(5):499-507; ²Hersh BS, et al. *J Pediatr*. Aug 1991;119(2):187-193; ³Cheek JE, et al. *Arch Pediatr Adolesc Med*. Jul 1995;149(7):774-778; ⁴Briss PA, et al. *J Infect Dis*. Jan 1994;169(1):77-82].

In 2006, over 6000 cases were reported in the US¹. Outbreaks occurred on college campuses with 2-dose vaccine coverage of 95% to 99%²⁻³. Vaccine effectiveness estimates during these outbreaks were within the range of other published reports. The median vaccine effectiveness for two doses is approximately 88%, with a range from 66% to 95%. Risk factors for vaccine failure³ included younger age or college freshman, living on versus off campus, female gender, and 10 or more years since the second mumps vaccine dose compared with less than 10 years [¹Dayan GH, et al. *N Engl J Med*. Apr 10 2008;358(15):1580-1589; ²Marin M, et al. *Vaccine*. Jul 4 2008;26(29-30):3601-3607; ³Cortese MM, et al. *Clin Infect Dis*. Apr 15 2008;46(8):1172-1180].

In 2009 and 2010, large mumps outbreaks among 2-dose recipients were reported in the US and Guam. In the US¹ there were over 3500 outbreak-related cases reported from several counties in the Northeast. Of these, 71% were male; 27% were 13 through 17 years of age; 97% occurred among Orthodox Jewish persons; and 76% had received 2 doses of MMR vaccine*. In Guam², 505 cases were reported. Of these, 50% were male; 34% were 9 through 14 years of age; 34% were of Chamorro ethnicity; and 94% of school-aged children had received 2 doses of MMR vaccine [*Among the 72% of case-patient with vaccination status reported; ¹Barskey AE, et al. *N Engl J Med*. 2012 (In press); ²Nelson GE, et al. *Pediatr Infect Dis J* 2013 (In press)].

The key issues are that large mumps outbreaks have occurred despite high 2-dose MMR vaccine coverage; standard outbreak control measures (e.g., isolation of cases and vaccination of eligible contacts) have not been completely effective in some situations; and mumps continue to be endemic in many parts of the world, so mumps outbreaks are likely to occur in the future.

Currently, there are no recommendations for use of a third dose of MMR vaccine during mumps outbreaks. The data on use and effectiveness of a third dose on mumps outbreak control are limited. In a small study among seronegative college students who had two documented doses of MMR vaccine, 82% became seropositive 7 to 10 days after vaccination with a third dose of vaccine. This suggests that these individuals had the capacity to mount a rapid anamnestic response following a third dose that could possibly boost immunity to protective levels [Date AA, et al. *J Infect Dis*. Jun 15 2008;197(12):1662-1668].

In 2010, in collaboration with local health departments, CDC conducted a study to evaluate the impact of a third dose of MMR vaccine during mumps outbreaks in two highly vaccinated populations. The first study was conducted in Orange County, New York. In three schools, children aged 11 through 17 years with high 2-dose MMR vaccine coverage and on-going mumps transmission were offered a third dose of MMR vaccine. Of the eligible students, 1755 (81%) received a third dose of MMR vaccine. Overall, attack rates declined 76% in the village following intervention, with the greatest decline among those who were targeted for vaccination (e.g., those aged 11 through 17 years). The decline in this age group was statistically greater than the other four age groups. However, there were a number of limitations to this study, including the timing of the intervention. When the intervention was conducted, the outbreak was on the decline. Also, because of the high uptake in vaccine, there was not a large comparison group and very few cases occurred post-intervention [Ogbuanu IU et al. *Pediatrics* 2012 Dec;130(6):e1567-74].

The second study was conducted in Guam. Children aged 9 through 14 years of age were selected from 7 schools with high attack rates and high 2-dose vaccination coverage. Of the eligible students, 1067 (33%) received a third dose of MMR vaccine [Nelson GE, et al. *Pediatr Infect Dis J* 2013. (In press)]. More than one incubation period after the third dose intervention, students who received three doses of MMR vaccine had a 2.6-fold lower mumps attack rate compared to students who had two doses of MMR vaccine. However, this was not statistically significant. Again, there were a number of limitations, including the timing of the intervention. In Guam, the intervention occurred after the peak of the outbreak and during the week before the end of the school year, so there was limited ability to evaluate the effectiveness of the intervention. Also, there were very few cases post-intervention and under-reporting of cases was likely.

In terms of safety, although these studies did not have a control group, there were very few adverse events reported following administration of a third dose of MMR vaccine. The percents of adverse events in the third dose studies were lower than or within the range of those reported in prior studies of first and second dose MMR vaccinations. This indicates that the third dose is at least as safe as the first and second doses of MMR vaccine.

In summary, both studies showed an impact in the targeted group. In Orange County, New York there was a 96% decline among those aged 11 through 17 years. In Guam, there was a lower attack rate among 3-dose versus 2-dose recipients. However, there were a number of limitations, including the timing of the interventions. This made it difficult to discern the effect of the third dose. Very few mild and no serious adverse events were reported. Although these studies do not provide conclusive evidence on the impact of a third dose for outbreak control, they are consistent with potential impact.

The working group discussed this topic over several calls and concluded that the data are insufficient to recommend for or against the use of a third dose of MMR vaccine for mumps control. However, they thought that it was still important to provide CDC guidance. Therefore, a link to CDC's *Manual for the Surveillance of Vaccine-Preventable Diseases* chapter on mumps that contains the guidance will be included in the statement. The proposed language for the link to the CDC guidance follows:

“Currently, data are insufficient to recommend for or against the use of a third dose of MMR vaccine for mumps outbreak control.

CDC has issued guidance for considerations for use of a third dose in specifically identified target populations along with criteria for public health departments to consider for decision making (link to CDC website and/or CDC's *Manual for the Surveillance of Vaccine-Preventable Diseases Mumps Chapter*)”

The proposed language for CDC guidance for the use of a third dose of MMR vaccine for mumps outbreaks follows:

“During mumps outbreaks, public health authorities may administer a third dose of MMR vaccine for specifically identified target populations.

Criteria to consider prior to administering a third dose in a target population for mumps outbreak control include:

- high two-dose vaccination coverage (i.e., vaccination coverage >90%);
- intense exposure settings likely to facilitate transmission (e.g., schools, colleges, correctional facilities, congregate living facilities) or healthcare settings;
- high attack rates (i.e., >5 cases per 1,000 population); and
- evidence of on-going transmission for at least two weeks in the target population (i.e., population with the high attack rates).

Additional data on the effectiveness and impact of a third dose of MMR vaccine for mumps outbreak control are needed to guide control strategies in future outbreaks.

Authorities who decide to administer a third dose as part of mumps outbreak control are encouraged to collect data to evaluate the impact of the intervention.

The following data should be collected:

- incidence of mumps in target population (before and after the intervention, by vaccination status),
- incidence of adverse events following vaccination with a third dose, and
- costs associated with the intervention (vaccine, personnel).”

Acceptable Evidence of Immunity

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Dr. McLean reminded everyone that information regarding acceptable evidence of immunity was previously presented during the June 2012 ACIP meeting. The criteria for acceptable evidence of immunity were developed to guide vaccination assessment and administration in clinical and public health settings. These criteria provide presumptive rather than absolute evidence of immunity to measles, rubella, and mumps. Persons who meet the criteria have a very high likelihood of immunity.

The proposed changes for acceptable evidence include “laboratory confirmation of disease” and removal of “physician diagnoses of disease” for measles and mumps. The rationale for the proposed changes is that the validity of history is low, especially over the last 30 years; there have been challenges with documenting history from physician records for adults; and to be consistent with the recommendations for health-care personnel [Immunization of health-care personnel: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011;60(RR-7):1-45].

The current and proposed changes for acceptable evidence of immunity (routine) are shown in the following table:

Acceptable Evidence of Immunity - Routine		
	Current	Proposed
Measles	(1) documentation of adequate vaccination: - preschool-aged children and, adults not at high risk: 1 dose - school-aged children (grades K-12): 2 doses, or (2) laboratory evidence of immunity, or (3) born before 1957, or (4) documentation of physician diagnosed measles	(1) documentation of age-appropriate vaccination with a live measles virus-containing vaccine ⁵ : - preschool-aged children: 1 dose - school-aged children (grades K-12): 2 doses - adults not at high risk ^{6*} : 1 dose, or (2) laboratory evidence of immunity ⁴ , or (3) laboratory confirmation of disease , or (4) born before 1957
Rubella	(1) documented administration of one dose of live rubella virus vaccine, or (2) laboratory evidence of immunity, or (3) born before 1957 (except women of childbearing age who could become pregnant)	(1) documentation of vaccination with 1 dose of live rubella virus-containing vaccine ⁵ , or (2) laboratory evidence of immunity ⁴ , or (3) laboratory confirmation of disease , or (4) born before 1957 (except women of childbearing age who could become pregnant ^{6*})
Mumps	(1) documentation of adequate vaccination with live mumps virus vaccine: - preschool-aged children and, adults not at high risk: 1 dose - school-aged children (grades K-12): 2 doses, or (2) laboratory evidence of immunity, or (3) born before 1957, or (4) documentation of physician diagnosed mumps	(1) documentation of age-appropriate vaccination with a live mumps virus-containing vaccine ⁵ : - preschool-aged children: 1 dose - school-aged children (grades K-12): 2 doses - adults not at high risk ^{6*} : 1 dose, or (2) laboratory evidence of immunity ⁴ , or (3) laboratory confirmation of disease , or (4) born before 1957

⁵The first dose of MMR vaccine should be administered on or after age 12 months; the second dose should be administered no earlier than 28 days after the first dose.

⁴Measles, rubella, or mumps immunoglobulin (IgG) in serum; equivocal results should be considered negative.

^{6*}Women of childbearing age are adolescent girls and premenopausal adult women. Because rubella can occur in some persons born before 1957 and because congenital rubella and congenital rubella syndrome can occur in the offspring of women infected with rubella virus during pregnancy, birth before 1957 is not acceptable evidence of rubella immunity for women who could become pregnant.

^{6*}Adults at high risk include students in post-high school educational institutions, healthcare personnel, and international travelers

The current and proposed changes for acceptable evidence of immunity for students at post-high school educational institutions are shown in the following table:

Acceptable Evidence of Immunity Students at Post-High School Educational Institutions		
	Current	Proposed
Measles	(1) documented administration of 2 doses of live measles virus vaccine, or (2) laboratory evidence of immunity, or (3) born before 1957, or (4) documentation of physician-diagnosed measles	(1) documentation of vaccination with 2 doses of live measles virus-containing vaccine [§] , or (2) laboratory evidence of immunity [¶] , or (3) laboratory confirmation of disease , or (4) born before 1957
Rubella	(1) documented administration of one dose of live rubella virus, vaccine, or (2) laboratory evidence of immunity, or (3) born before 1957 (except women of childbearing age who could become pregnant)	(1) documentation of vaccination with 1 dose of live rubella virus-containing vaccine [§] , or (2) laboratory evidence of immunity [¶] , or (3) laboratory confirmation of disease , or (4) born before 1957 (except women of childbearing age who could become pregnant ^{¶§})
Mumps	(1) documented administration of two doses of live mumps virus vaccine, or (2) laboratory evidence of immunity, or (3) born before 1957, or (4) documentation of physician-diagnosed mumps	(1) documentation of vaccination with 2 doses of live mumps virus-containing vaccine [§] , or (2) laboratory evidence of immunity [¶] , or (3) laboratory confirmation of disease , or (4) born before 1957

[§]The first dose of MMR vaccine should be administered on or after age 12 months; the second dose should be administered no earlier than 28 days after the first dose.
[¶]Measles, rubella, or mumps immunoglobulin (IgG) in serum; equivocal results should be considered negative.
^{¶§}Women of childbearing age are adolescent girls and premenopausal adult women. Because rubella can occur in some persons born before 1957 and because congenital rubella and congenital rubella syndrome can occur in the offspring of women infected with rubella virus during pregnancy, birth before 1957 is not acceptable evidence of rubella immunity for women who could become pregnant.

The current and proposed changes for acceptable evidence of immunity for international travelers are shown in the following table:

Acceptable Evidence of Immunity International Travelers		
	Current	Proposed
Measles	(1) documented administration of 2 doses of live measles virus vaccine, or (2) laboratory evidence of immunity, or (3) born before 1957, or (4) documentation of physician-diagnosed measles	(1) documentation of age-appropriate vaccination with live measles virus-containing vaccine: -infants age 6-11 months ^{††} ; 1 dose -persons age ≥12 months [§] ; 2 doses, or (2) laboratory evidence of immunity [¶] , or (3) laboratory confirmation of disease , or (4) born before 1957
Rubella	(1) documented administration of one dose of live rubella virus, vaccine, or (2) laboratory evidence of immunity, or (3) born before 1957 (except women of childbearing age who could become pregnant)	(1) documentation of vaccination with 1 dose of live rubella virus-containing vaccine [§] , or (2) laboratory evidence of immunity [¶] , or (3) laboratory confirmation of disease , or (4) born before 1957 (except women of childbearing age who could become pregnant ^{¶§})
Mumps	(1) documented administration of two doses of live mumps virus vaccine, or (2) laboratory evidence of immunity, or (3) born before 1957, or (4) documentation of physician-diagnosed mumps	(1) documentation of vaccination with 2 doses of live mumps virus-containing vaccine [§] , or (2) laboratory evidence of immunity [¶] , or (3) laboratory confirmation of disease , or (4) born before 1957

[§]The first dose of MMR vaccine should be administered on or after age 12 months; the second dose should be administered no earlier than 28 days after the first dose.
[¶]Measles, rubella, or mumps immunoglobulin (IgG) in serum; equivocal results should be considered negative.
^{¶§}Women of childbearing age are adolescent girls and premenopausal adult women. Because rubella can occur in some persons born before 1957 and because congenital rubella and congenital rubella syndrome can occur in the offspring of women infected with rubella virus during pregnancy, birth before 1957 is not acceptable evidence of rubella immunity for women who could become pregnant.
^{††}Children who receive a dose of MMR vaccine before age 12 months should be revaccinated with 2 doses of MMR vaccine, the first of which should be administered when the child is aged 12 through 15 months (12 months if the child remains in a high-risk area) and the second at least 28 days later.

Measles Post Exposure Prophylaxis (PEP) with Immune Globulin (IG)

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Dr. McLean indicated that information on measles PEP with immune globulin (IG) was previously presented during the June 2012 ACIP meeting by Dr. Mark Papania. IG is a blood product used to provide antibodies for short-term prevention of some infectious diseases, including measles. IG is prepared from plasma pools derived from thousands of donors. IG products currently available in the US include the following:

- ❑ IGIM: IG given intramuscularly
 - Historically has been the blood product of choice for measles PEP
 - Dose and volume restrictions may limit usefulness as PEP in certain populations

- ❑ IGIV: IG given intravenously
 - Available since 1981
 - Primarily used for patients with primary immunodeficiency disorders
 - High cost and administration requires observation by skilled professional, and hospital admission (The average cost in 2007 was \$55 per gram = \$220 for a 10 kg child and \$1540 for a 70 kg adult for a 400 mg/kg dose [Sorenson R, et al. JMCP 2007])

- ❑ IGSC: IG given subcutaneously
 - Available since 2006
 - Same major indications as IGIV
 - Administration requires a pump and advance training
 - Multiple weekly doses are needed to establish a steady state of protective antibody levels
 - Recommended only for patients who are on IGIV already, but are having difficulty with venous access

Data on the protective effectiveness of IGIM for measles PEP are limited. Studies in the 1940s demonstrated that IGIM can reduce the risk of measles or modify disease if given within 6 days of exposure^{1,2}. However, there are a few studies of PEP effectiveness in the vaccine era. A retrospective study in the US among household contacts conducted during the measles resurgence found IGIM was not effective when given within 6 days of exposure³. The IGIM doses were not recorded in this study. A study in South Wales in 2006 found protective efficacy to be 76% among susceptible contacts⁴, but a very loose definition of “exposure” was used that included being in the same room as a case up to two hours after the case had left. They also defined “susceptibility” by including children over 4 years of age through adults who received one dose of measles vaccine. In another study, 2/15 (13%) seronegative infants became seropositive 48 hours after PEP with IGIM following exposure in a NICU in 1990⁵. The optimal IGIM dose needed for protection is unknown. However, a 1999-2000 Japanese study showed higher anti-measles titer provided greater protection⁶. In this study, neutralizing antibody titer concentrations were determined in IGIM lots that were used for PEP. Protected children received a mean dose of 10.9 IU/kg (SD 3.4) compared to 5.7 IU/kg (SD 1.6) for whom PEP failed [¹Janeway CA. *Bull N Y Acad Med* 1945;21(4):202-222; ²Ordman CW, et al. *J Clin Invest*. Jul 1944;23(4):541-549; ³King GE, et al. *Pediatr Infect Dis J*. Dec 1991;10(12):883-888;

⁴Sheppard V, et al. *N S W Public Health Bull.* May-Jun 2009;20(5-6):81-85; ⁵Subbarao EK, et al. *J Pediatr.* Nov 1990;117(5):782-785; ⁶Endo A, et al. *J Pediatr.* Jun 2001;138(6):926-928].

The current recommendations for use of IG for PEP follow [MMWR 1998;47(RR-8):1-57]:

“Administration of IGIM to susceptible household contacts who are not vaccinated within 72 hours of initial exposure is recommended.

IGIM is indicated for susceptible household contacts of measles patients, particularly those for whom the risk for complications is increased (i.e., infants aged ≤ 12 months, pregnant women, or immunocompromised persons).

The usual recommended dose of IGIM is 0.25 mL/kg (0.11 mL/lb) of body weight (maximum dose = 15 mL).

Infants <6 months of age are usually immune because of passively acquired maternal antibodies. However, if measles is diagnosed in a mother, unvaccinated children of all ages in the household who lack other evidence of measles immunity should receive IG.”

Severely immunocompromised patients and other symptomatic HIV-infected patients who are exposed to measles should receive IG prophylaxis regardless of vaccination status because they may not be protected by the vaccine.

For patients receiving IGIV therapy, a standard dose of 100-400 mg/kg should be sufficient to prevent measles infection after exposures occurring within 3 weeks after administration of IGIV; for patients exposed to measles >3 weeks after receiving a standard IGIV dose, an additional dose should be considered.”

Because of the success of the US measles immunization program, measles has not been endemic in the US for over a decade. However, this success has epidemiologic and serologic implications for the use of passive measles antibodies to protect the few remaining people who are not immune and are exposed to measles. The working group considered a number of issues pertaining to the use of IG for measles PEP. First, recommendations regarding the type of exposure for which IG PEP is indicated may need to be clarified. Second, measles antibody concentrations may be lower in IG products due to the change in donor demographics; therefore, doses / volumes recommended for PEP may need to be revised. Third, susceptibility to measles among infants born in the US has increased; thus, recommendations for PEP in early infancy may need to be revised. Fourth, multiple IG preparations are licensed in the US. Therefore, the role of each product in measles prevention needs to be defined.

In the US, the FDA requires that all IG products must contain a measles antibody level of adequate potency¹. There are lower measles antibody concentrations from donor populations with predominately vaccine-induced immunity², while much higher volumes can be given with IGIV and IGSC compared to IGIM [¹DHHS, FDA. Additional Standards for Human Blood and Blood Products (21 CFR Part 640 Subpart J-Immune Globulin (Human). Code of Federal Regulations, Title 21, Volume 7, Revised April 1, 2005. Online at: [FDA Website Code of Federal Regulations Standards for Human Blood and Blood Products](#); ²Audet S, et al. *J Infect Dis.* 2006 Sep 15;194(6):781-9].

For IGIM, 0.25 ml/kg is the currently recommended dose. The measles antibody dose would be 6.3 IU/kg, which is very close to the Japanese study dose that was shown not to be protective. Another difficulty is that these estimates are only for people up to a threshold of 15 ml/kg. A 70 kg person would still be receiving 15 ml/kg and the antibody dose would be 5.4 IU/kg. Much higher quantities of measles antibody can be given with IGIV. Using the calculated serum measles antibody concentration, the expected titer a person would receive based on the recommended doses was assessed. For persons weighing 30 kg, the estimated protective level of measles antibody concentration is 120 or greater mIU/mL. At a current recommended dose of 0.25 ml/kg, the expected equilibrium titer at 4 to 5 days after administration of IGIM would be 63 mIU/mL, decreasing to 32 mIU/mL within 30 days. The higher recommended dose for immunocompromised persons of 0.50 ml/kg gives a titer of 126 mIU/mL at 4 to 5 days, just over the defined protective titer, and decreasing to 63 mIU/mL within 30 days. The recommended IGIV dose of 400 mg/kg offers a sustained high titer for the 30 days following administration. In terms of the effective IGIM administration dose of 0.5 mL/kg with a 15 mL maximum dose, once the 30 kg cut-off is reached for a 0.5 mL/kg dose, the titers are progressively lower for people who weigh more.

With regard to the evidence for increasing susceptibility to measles among infants in the US, the epidemiologic data from 2001-2008 and 2011 indicate that there is high measles incidence among US infants less than 12 months of age, with 14% of cases occurring among infants¹. This is a fairly high percentage of US cases, even though the numbers are still small. Infants aged 6 to 11 months had incidence between 3.5 and 5.6 per million, while incidence was lower for infants aged 0 through 5 months. Infants of vaccinated mothers are more likely to be susceptible at younger ages. A study among infants of vaccinated mothers in Belgium conducted between 2006-2009 found that at birth, 30% of infants had measles antibody titers below 300 mIU/mL, increasing to 97% by age 6 months². In 2004, a small US study showed that 48% (14/29) of 6-month-old infants had undetectable transplacentally derived measles neutralizing antibodies³. It is important to point out that most women giving birth in the US were born after 1963, the year measles vaccination began in the US. These women would be expected not to have been exposed to measles, and to have either vaccine-induced antibodies or no antibodies [¹Parker Fiebelkorn A, et al. *J Infect Dis.* Nov 15 2010;202(10):1520-1528. ²Leuridan E, et al. *BMJ.* 2010 May 18;340:c1626. ³Gans HA, et al. *J Infect Dis.* 2004 Jul 1;190(1):83-90].

Based on the presented information, the changes the working group proposed to measles post-exposure prophylaxis with IG were to remove wording that limits use to household exposure settings, increase the recommended dose of IGIM, include the use of IGIV, and expand the recommendation for use of IGIM to infants aged 0 through 5 months.

The proposed recommendations for the use of IG for post-exposure prophylaxis follow:

“The following patient groups are at risk for severe disease and complications from measles and should receive IG:

- Infants aged <12 months,
- Pregnant women without evidence of measles immunity, and
- Immunocompromised persons.

IGIM can be given to other persons who do not have evidence of measles immunity, but priority should be given to persons exposed in settings with intense, prolonged, close contact (e.g., household, daycare, classroom, etc.).”

The proposed recommendation for a dose of IG for post-exposure prophylaxis follows:

“The recommended dose of IG given intramuscularly (IGIM) is 0.5 mL/kg of body weight (maximum dose = 15 mL) and the recommended dose of IG given intravenously (IGIV) is 400 mg/kg.”

The proposed recommendations for the use of IG for post-exposure prophylaxis in infants aged <12 months follow:

“Because infants are at higher risk for severe measles and complications and infants are susceptible to measles if their mother is nonimmune or their maternal antibodies to measles has waned, IGIM should be given to infants aged <12 months who have been exposed to measles.

For infants aged 6 through 11 months, MMR vaccine can be given in place of IGIM, if administered within 72 hours of initial exposure.”

The proposed recommendation for the use of IG for post-exposure prophylaxis for pregnant women without evidence of immunity follows:

“Because pregnant women might be at risk for severe measles complications, IGIV should be given to pregnant women without evidence of measles immunity who have been exposed to measles.”

The proposed recommendations for the use of IG for post-exposure prophylaxis for severely immunocompromised persons follow:

“Severely immunocompromised patients [including HIV-infected persons with CD4 percentages <15% (all ages) or CD4 <200 cells/mm³ (age >5 years) and those who have not received MMR vaccine since receiving effective ART; some experts would include all HIV-infected persons, regardless of immunologic status or MMR vaccine status] who are exposed to measles should receive IGIV prophylaxis regardless of immunologic or vaccination status because they may not be protected by the vaccine.”

“For persons already receiving IGIV therapy, administration of at least 400 mg/kg within 3 weeks before measles exposure should be sufficient to prevent measles infection. For patients receiving subcutaneous immune globulin (IGSC) therapy, administration of at least 200 mg/kg body weight for two consecutive weeks before measles exposure should be sufficient.”

Vaccination of Persons with HIV Infection

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Dr. McLean noted that information regarding vaccination of persons with HIV infection was previously presented during the October 2011 ACIP meeting by Dr. George Siberry from NIH.

As a reminder, the current recommendations for persons with HIV infection follow [MMWR. 1998;47(RR-8):1-57]:

“Recommended for all asymptomatic HIV-infected persons who do not have evidence of severe immunosuppression (CD4% <15%)

- HIV-infected infants without severe immunosuppression should routinely receive MMR vaccine *as soon as possible upon reaching the first birthday*
- Consideration should be given to administering the second dose of MMR vaccine *as soon as 28 days after the first dose*

Consider for all symptomatic HIV-infected persons who do not have evidence of severe immunosuppression (CD4% <15%)

Not recommended for persons with severe immunosuppression.”

Since the availability of effective antiretroviral therapy (ART) has improved the immune status of patients, the working group reviewed the current recommendations and considered the following issues:

- Revaccination of persons vaccinated prior to receiving effective ART
- Recommendations based on symptomatic staging
- Recommended timing of vaccine doses

In terms of safety, there have been very few SAEs reported following vaccination with measles vaccine in HIV-infected persons. One well-known case was reported in 1996 in a 21-year old who received a second dose of MMR vaccine as part of college entrance requirements, and was not known at the time to have HIV. Ten months after vaccination, the patient developed giant cell pneumonitis and subsequently died. Since that time, no SAEs have been reported after small studies of administering MMR vaccine to children on ART with a past history of immunosuppression¹⁻⁴. No additional SAEs have been reported in the US, or worldwide despite immunization of millions of HIV-infected children [¹Melvin AJ, Mohan KM.. *Pediatrics*. Jun 2003;111(6 Pt 1):e641-644. ²Aurpibul L, et al. *HIV Med*. 2006;7(7):467-470. ³Farquar C. et al. *Pediatr Infect Dis J*. 2009;28(4):295-299. ⁴Abzug MJ, et al. *J Infect Dis*. 2012].

Regarding immunogenicity, the Moss paper from 2003 offered a nice overall summary [Moss WJ, et al.. *Bull World Health Organ*. 2003;81(1):61-70]. In the pre-ART era, response from measles vaccination was suboptimal. In those who did respond, there were lower antibody titer responses (Nair JID 2009) and faster antibody decay (Moss JID 2007). Factors associated with poorer response to immunization included low CD4 counts, high viral loads, and HIV stage. However, these factors varied by study and were not consistent across studies. There was also concern about the quality and duration of the antibody response to vaccination of infants not

receiving ART. This raised the question as to whether administration of effective ART would result in reappearance of immunity. Most perinatally HIV-infected youth in the US are now adolescents. A typical sequence for these adolescents was as follows: They received routine immunizations in infancy and early childhood with no ART since it was not available to them at the time. They may have experienced primary failure or loss of immunity, and then developed a variable degree of immunosuppression. When effective ART was initiated, they experienced recovery from immunosuppression. This raised the question: Does measles-specific immunity “recover” with ART-related reversal of immunosuppression? [Slide courtesy of Dr. George Siberry, NIH].

Two studies from the US and two international studies offer evidence that effective ART does not likely restore measles immunity. In all of these studies, the children received measles-containing vaccine as infants or prior to ART. Some had substantial past severe immunosuppression. After 6 months or more, the percent with detectable measles antibodies varied from 6% to 82%; however, in the two studies that assessed antibody levels, 42% (Kenya, Farquhar) and 52% (US, Abzug) had levels considered protective based on the definition in the studies [¹Melvin AJ, Mohan KM. *Pediatrics*. Jun 2003;111(6 Pt 1):e641-644; ²Aurpibul L, et al. *HIV Med*. Oct 2006;7(7):467-470; ³Farquhar C, et al. *Pediatr Infect Dis J*. Apr 2009;28(4):295-299; ⁴Abzug MJ, et al. *J Infect Dis*. Jun 12 2012]. A multi-center pediatric HIV cohort study showed that measles and rubella protection and mumps seropositivity were significantly lower from perinatal HIV-infected youth compared to HIV-exposed but uninfected youth [Siberry G, et al. Presented at the 4th International Workshop on HIV Pediatrics, July 2012].

Upon revaccination, most children do seroconvert after effective ART. In a small US study of children aged 3 to 14 years, in which all but one child were seronegative prior to revaccination, 83% became seropositive with a single repeated MMR after ART¹. Similarly, in seronegative children aged 5 years and older, 90% had protective measles antibodies, 100% had protective rubella antibodies, and 78% had protective mumps antibodies four weeks after vaccination². In the US cohort, 52% were considered seroprotected prior to revaccination and 89% had measles seroprotection following vaccination [¹Melvin AJ, Mohan KM. *Pediatrics*. Jun 2003;111(6 Pt 1):e641-644. ²Aurpibul L, et al. *Clin Infect Dis*. Sep 1 2007;45(5):637-642. ³Abzug MJ, et al. *J Infect Dis*. Jun 12 2012].

In terms of response rates by doses from the multi-center pediatric HIV/AIDS cohort study, once on ART, there was a nice dose-response effect as the post-ART MMR doses increased. For those with zero doses, there was a low rate of protection/seropositivity ranging from 45% to 53% for measles, mumps, and rubella. Response rates increased with one dose, and were higher following the second dose, ranging from 77% to 85% [Siberry G, et al. Presented at the 4th International Workshop on HIV Pediatrics, July 2012].

The majority of HIV-infected individuals in the US are adolescents and young adults who have received one or both doses of MMR vaccine prior to effective ART. The concern at this point is that they lack protection against measles due to a combination of primary vaccine failure, failure to establish memory response, and / or waning of response over time. Even if they responded well to ART, they are unlikely to have high levels of immunity if not revaccinated. There is increasing evidence to support MMR revaccination once stable, effective ART is in place to achieve the highest rate of protection in this group [Sutcliffe Lancet ID 2010;10: 630–42].

Regarding timing of doses for persons with HIV infection, there are very few newly diagnosed infants in the US, and they are routinely started on ART right away. ART will restore or maintain immunologic function of these infants, and it is expected that these infants and toddlers will have a response to MMR vaccine similar to that of HIV-uninfected children [Lima M, et al. *Pediatr Infect Dis J.* Jul 2004;23(7):604-607; Pensiero S, et al. *Proc Natl Acad Sci U S A.* May 12 2009;106(19):7939-7944]. Thus, the same reasons for recommending a second dose of MMR vaccine at age 4 through 6 years in uninfected children apply to these newly HIV-infected children.

The proposed changes regarding vaccination of persons with HIV infection included recommendation for revaccination of persons with perinatal HIV infection who were vaccinated prior to effective ART, removal of the distinction between asymptomatic and symptomatic HIV infection because the current CD4 values are a better predictor of who is too immunocompromised to be vaccinated, and the change in timing of the two routine doses to those aged 12 through 15 months and 4 through 6 years.

The proposed recommendation for revaccination of persons with perinatal HIV infection who do not have current evidence of severe immunosuppression follows:

“Persons with perinatal HIV infection who were vaccinated with measles-, rubella-, or mumps-containing vaccine prior to establishment of effective ART should receive two appropriately spaced doses of MMR vaccine once effective ART has been established [≥6 months with CD4 percentages ≥15% (all ages) and CD4 ≥200 cells/mm³ (age >5 years)] unless they have other acceptable current evidence of measles, rubella, and mumps immunity.

The proposed recommendation for vaccination of persons with HIV infection who do not have current evidence of severe immunosuppression follows:

Two doses of MMR vaccine are recommended for all persons aged ≥12 months with HIV infection who do not have evidence of current severe immunosuppression [i.e., must have CD4 percentages ≥15% (all ages) and CD4 ≥200 cells/mm³ (age >5 years) for ≥6 months] or other current evidence of measles, rubella, and mumps immunity.

The proposed recommendation for the timing of doses for persons with HIV infection follows:

The first dose of MMR vaccine should be administered at age 12 through 15 months and the second dose at age 4 through 6 years, or as early as 28 days after the first dose.

Discussion Points

Dr. Temte noted that while they would like a single vote to incorporate these recommendations all together, it would be appropriate to break the discussion into various topics. One issue not on the table for a recommendation was the third dose, given that there was insufficient information for or against any recommendation. Similar to any other issue, any guidance would be placed into the CDC surveillance document for guidance for health departments, but it would not come under the purview of ACIP.

Regarding the third dose, Dr. Plotkin did not see seroprevalence data in adolescent populations. There is a published study that shows that B-cell memory after mumps vaccine, in contrast to active measles and rubella vaccine, is not very good. Therefore, it may not be surprising that antibody disappears after vaccination. However, it would be beneficial to know what the seroprevalence is after two doses, particularly in the college entry aged population. While Dr. McLean mentioned that there was an anamnestic response, he was not convinced that it was anamnestic. While it was assumed to be anamnestic, it could be a primary response based on the evidence seen. As a result of this, there remained a question regarding whether certain populations, perhaps at college entry, should have a third dose routinely, similar to meningococcal vaccine. While he did not believe they were ready to discuss the possibility of a new mumps vaccine, there is that consideration, at least for a booster dose since there are plenty of other mumps strains besides the Jeryl Lynn strain. He emphasized to the committee that data are needed before decisions can be made about a third dose.

Dr. McLean replied that the working group is aware that more data need to be collected concerning mumps. Regarding seropositivity in adolescents, there are no data on those who received two doses. However, CDC is assessing the National Health and Nutrition Examination Survey (NHANES) data from 2009 through 2010 for the overall population and in the age groups. It appears to be comparable to previous years. Regarding the anamnestic response in the one study, she believed it was IgG response.

Dr. Keitel thought that in the briefing materials there was some discussion about determination of acceptable evidence of immunity among healthcare providers born before 1957. She noted that the presentation did not address this issue, and said she thought it was suggested that for healthcare workers the bar should be set higher. Even if they were born before 1957, their serologic status should be determined.

Dr. McLean responded that she did not include this in the presentation because it was not something the working group discussed. That recommendation was voted on previously, and the language was more permissive using the terminology "consider" because this would allow ACIP and Hospital Infection Control Practices Advisory Committee (HICPAC) support for health facilities already checking serologic status.

Dr. Elward (HICPAC) requested that Dr. Seward comment on the issue of healthcare personnel immunity, because that recommendation arose out of some outbreaks in Arizona and evidence of infection within healthcare personnel who would have been presumed to be immune based on those criteria.

Dr. Seward responded that in Arizona, it was a healthcare worker who was born after 1957 who was not vaccinated in accordance with current recommendations. There were some measles cases in 2011 in healthcare workers who had serologic evidence of immunity. The evidence of immunity guidance just offers a very good chance that someone will be immune, but nothing is 100%. Receiving two doses of vaccine results in only a 90% chance of immunity in a close exposure setting. Laboratory tests can be wrong, and for mumps there is not an exact correlate of immunity. This is the best that can be done for guidance in a practice setting for decisions. Studies of healthcare workers born before 1957 show that 2% to 5% lack evidence of immunity. The guidance states that in an outbreak setting, healthcare workers need to be tested for evidence of immunity. If they do not have serologic evidence, which is the only other evidence there is for healthcare workers, then they need to be vaccinated.

Regarding PEP with IGIV in high risk people, Dr. Harriman inquired as to whether a definition of “exposure” would be provided since there are many levels of intensity of exposure. For example, the pregnant woman sitting in a waiting room for perhaps a half an hour after a measles patient left.

Dr. McLean replied that the working group and CDC discussed levels of exposure, but there are so many possible situations that it would be difficult to include them all, so a general recommendation was proposed. If anything is included about level of exposure, it will be in the vaccine-preventable diseases chapter.

Dr. Temte noted that the recommendation considers people who are exposed, for example, the pregnant woman for whom there is no evidence of immunity. That takes a low likelihood event and makes it a much lower likelihood.

Dr. Harriman indicated that her practice always tests first and never presumes, and certainly does not want to administer PEP to someone who is IgG positive.

Referring to the recommendations for use of IG for PEP in pregnant women and immunocompromised persons, Dr. Keitel, wondered whether the language “without evidence of measles immunity” could be added for immunocompromised persons as well.

Dr. McLean responded that for immunocompromised persons it was somewhat tricky because it is being recommended for those with severe immune suppression regardless of immunologic evidence or MMR vaccination status. There was discussion about including a footnote with the definition of “severely immunocompromised.”

Dr. Wallace (SME) clarified that “severely immunocompromised” will be defined in the statement. It is unclear in these individuals whether a positive IgG really does constitute protection, given that the quality of their immune response may still be compromised. This is not a change from previous recommendations to prophylax at a very low threshold if an immunocompromised person is exposed.

Dr. Sawyer inquired as to whether there was a precise dose of IVIG. The current recommendation states 100 mg/kg to 400 mg/kg.

Dr. McLean confirmed that the recommendation currently stated 100 mg/kg to 400 mg/kg, while the proposed recommendation stated 400 mg/kg.

If infants under 6 months of age were to be included due to the presumption that their transplacental antibody had waned or they did not receive any transplacental antibody, Dr. Rubin wondered whether any consideration would be given to lowering the age for administration of MMR for PEP.

Dr. Temte recalled that this issue was raised as part of the discussion, but he did not think there was any evidence for use of MMR in PEP at that age. Vaccine response at a younger age is lower to the point at which one would not want to rely on that for immunity.

Dr. Wallace (SME) added that the younger an individual is, the lower their response may be to the measles vaccine. Some of that has to do with competition with maternally derived antibodies, as well as maturity of the immune system. In countries with endemic disease, the recommendation for the first dose can go down to 6 months, and the US will do this in an

outbreak setting. However, there are concerns that there are no data to administer MMR to those under 6 months of age, and some information suggests that there will not be a robust immune response and they may not respond well later.

Regarding the use of IGIV in pregnant women, Dr. Temte's impression was that this would almost always result in a referral to a hospital situation. He requested that Dr. Ault comment on the obstetrical experience. He also inquired as to whether there was any hesitancy on the part of obstetricians to provide an IV product versus an IM product to a pregnant woman.

Dr. Ault (ACOG) replied that 90% of women were likely to be seropositive, which would leave 10% of women in an exposure situation. Every labor and delivery facility is going to have an infusion. Starting an IV is basic care for pregnant women. Thus, he did not think this would be too great a burden. Giving the product would likely pose the greatest burden. He was at the University of Iowa during the large exposure from an international traveling student who managed to go to every healthcare facility in Iowa City during the week he was undiagnosed. He thought he remembered giving IM to several pregnant women he was around, so he did not think it would be that great of a burden. In terms of IV versus IM products, there are some conditions under which it has been proposed to give IGIV to pregnant women for various reasons. Most obstetricians would have been exposed to that sometime during their career, so he did not think there would be any hesitancy. It would be an unusual circumstance and infection control would be involved, but he did not think there would be any major barriers.

Regarding IGIM for infants less than 12 months of age, Dr. Harriman requested clarity regarding whether the proposed recommendation meant that all infants would be presumed to be susceptible regardless of their mother's IgG status. She wondered whether there would be any place for IgG testing in infants less than 6 months of age, or even 3 months of age.

Dr. McLean responded that the working group discussed IgG testing, but was concerned about the delay in giving IGIM and waiting for the results.

Dr. Wallace (SME) added that while they would not say testing could not be done, there is concern that the greater the delay the greater the potential for decreasing the efficacy.

Dr. Poland (ACP) noted that the Health Protection Agency (HPA) published a white paper a couple of years ago with a pretty extensive algorithm based on the age of the mother, age of the infant, which IG product to use, whether to use it with or without vaccine, et cetera. He wondered whether that was reviewed and whether that algorithm would be useful to consider. It seemed very practical and useful, and could probably handle many of the questions that were arising.

Dr. Salisbury (DOH, UK) responded that the algorithm was produced by the Health Protection Agency, and the standard guidance that goes out to all health professionals is linked to it. However, he did not readily know how much IGIM had been used as a consequence. The algorithm was designed to be straightforward and easy to follow so that health professionals could walk their way through it.

Dr. McLean added that the working group reviewed that document, but given the level of measles in the US, they thought it would be easier to have something simpler with the recommendation.

Ms. Stinchfield (NAPNAP) indicated that when Minnesota had a number of cases in 2011 and hundreds of exposures, they developed a chart because there were teams of people following up. It was based on age, vaccine status, type of exposure, whether they were immunocompromised, et cetera. She said she would be happy to share that chart.

Dr. McLean thought that everyone would go through an algorithm when there is an exposure, but they did not want to include numerous stipulations in the recommendation.

Dr. Wallace (SME) added that they are working with Minnesota Health Department and other health departments to assess their experiences, acquire further information, and determine whether this can be regimented more.

Dr. Temte thought the challenges involved the change in the environment in terms of moving from disease-originated immunity to vaccine-originated immunity, change in the products that are available for passive immunity, and the constraints placed upon practitioners by the volume for IM. To be clear, the only people for whom sufficient levels of IG can be provided are those who weigh less than 30 kg. Unfortunately, that eliminates almost all adults in the US and certainly does not address any pregnant patients. Therefore, the committee must weigh the scant evidence there is against what will reliably provide at least the best chance of immunity versus the cost and ease of application.

Regarding mumps serology, Dr. Seward reported that a laboratory study was conducted during the 2006 mumps outbreaks. In a college that was not affected by mumps, 400 serum specimens were collected. The immunity level then was 94% for mumps. Consideration was given to avidity testing, but an avidity test was not up and running then. The laboratory is still working on that now.

Regarding the recommendation for vaccination of persons with HIV infection who do not have current evidence of severe immunosuppression, Dr. Sawyer noted that there was an example of a CD4 cell count cutoff for age >5 years. However, the vaccine recommendation is for those ≥ 12 months. He wondered what recommendation would be provided for those between 12 months and 5 years of age. He assumed it would be a higher CD4 count graduated by age, and if that was the case, he was concerned about having this in the actual recommendation. If people do not read the remainder of the document, they may inadvertently immunize a young child who is below the threshold.

Dr. McLean clarified that for any age, a person would have to have a CD4 percentage of $\geq 15\%$ or higher. Those over 5 years of age would have to have both a CD4 percentage of $\geq 15\%$ and a CD4 count of ≥ 200 cells/mm³ for more than 6 months. This could be worded more clearly.

Vote: Recommendation for MMR Vaccine

Dr. Coyne-Beasley made a motion that the proposed recommendations from the MMR Vaccine Working Group be approved. Dr. Keitel seconded the motion with the proviso that the language be clarified regarding $\geq 15\%$ and ≥ 200 for persons with HIV infection. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Dr. Temte noted that a VFC resolution vote was not required, given that this did not represent a change to the vaccine recommendations per se.

Child / Adolescent Immunization Schedule 2013**Introduction****Dr. Renée Jenkins, Chair
ACIP Harmonized Schedule Working Group**

Dr. Jenkins indicated that the reason this topic was being presented to ACIP was so that ACIP could approve the proposed schedules necessary prior to publication in the *MMWR* in February 2013. AAP and AAFP also approve the proposed schedules prior to February 2013 publications. Annual schedules reflect recommendations already approved by ACIP. New policy is not established by the schedules. In terms of the general approach to the 0 through 18 year 2013 schedules, edits made to the 2012 schedule made by *MMWR* were incorporated into the first draft of the 2013 schedules. Numerous wording changes were also made to improve clarity and readability.

Review of Changes**Dr. Iyabode (Yabo) Beysolow, CDC Lead
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention**

Due to the increasing lack of space on the immunization schedules, the increasing complexity of the schedules, and the need to include newer vaccines on the harmonized childhood / adolescent schedule, the working group felt that a format change would be necessary. Based on a survey of the working group early in 2012, proposed changes included a 0 through 18 schedule to replace the existing 0 through 6 and 7 through 18 schedules. No changes were suggested to the existing catch-up table. In order to provide more room, the working group decided to combine footnotes from all 3 existing schedules into 1 footnote document. Footnotes have been redundant at times between the 3 existing schedules. The working group also

considered a high-risk indication table to serve as a resource for providers on ACIP recommendations for patients with certain conditions. With the current 2012 format, due to a lack of space, providers were frequently referred to the respective ACIP documents for further information on high-risk conditions. The working group hoped that this new table would serve as this source of information. During this session, Dr. Beysolow presented the field testing of the proposed schedule format changes developed by the working group, specifically with regard to the methodology and results of field testing, the recommendations from the group contracted to perform the testing, and recommendations from the working group to ACIP regarding format changes and specific footnote changes.

There were two components to the field study. The first was a pilot study conducted with 31 providers who had been referred by their respective working group member associations (e.g., AAP, AAFP, AAPA) and a convenience sampling of public health nurses from throughout the nation. This study was conducted by telephone using a live meeting format between August and September 2012. The second phase of the study was formative research conducted by Oak Ridge Institute for Science and Education (ORISE). This study was conducted in September 2012. The bulk of the presentation during this session focused on the findings from the formative research. The pilot study findings did not differ significantly from those of the formative research. The objectives of the formative research were to assess the 2013 draft schedules for ease of use, evaluate how comprehensible they were, and determine how providers would likely use the schedules. It was also the intent of this study to obtain feedback from providers about how to improve these drafts.

In depth interviews lasting 45 minutes were held with physicians (including 19 pediatricians, 9 family practitioners, and 1 internist who saw older children and adolescents in a family practice setting). Respondents were recruited from 4 cities across the US. In addition in each city, two mini focus groups were held with physician assistants and nurse practitioners together in one group, and nurses and medical assistants together in another group. All respondents spent at least 50% of their time in direct patient contact, and all respondents administered vaccines to at least 5 pediatric or adolescent patients per week. Physician respondents represented diverse practices that saw both VFC and commercially insured patients, and practiced in private practice settings and local health departments and clinics. Nurse practitioners and physician assistants were also from pediatric and family practice settings, both private practice and public health clinic settings, and similarly saw both VFC and commercially insured patients. The demographic distributions for nurses and medical assistants were similar.

Respondents initially were asked about the current 2012 schedules. They were shown the various schedule formats and asked first how they obtained the schedules they used in their settings, and secondly how frequently if any they used the schedules. Respondents were then shown the draft 2013 schedules and were asked whether they felt these were improvements over the 2012 schedules, or if there were any challenges they could see with the new format. They were shown the proposed combined 0 through 18 schedule and asked to compare to the current 0 through 6 and 7 through 18 schedule formats. Four versions of this schedule were introduced during the study based on feedback obtained from respondents early on. They also were shown the proposed combined footnotes document where footnotes from the current 0 through 6, 7 through 18, and catch-up schedules were all combined. Respondents were also shown the proposed high-risk table. An updated version of this table was shown to respondents as the study progressed, based on feedback from earlier respondents.

In terms of the responses to questions regarding the current 2012 schedule, many respondents reported that they knew the recommended schedule well. In particular, pediatricians and nurse practitioners, regardless of practice setting, were more likely to state that they knew the 0 through 6 and 7 through 18 schedules by memory. Some of the direct quotes from respondents included the following:

“Standard immunizations we know so well we don’t have to look.”

“That’s ingrained, you can do it in your sleep.”

“I like to show the parents.”

This feeling however was not as frequently expressed by nurses and medical assistants. When asked when and why they used the routine schedules, respondents stated various reasons including, training new clinicians and educating parents. Most respondents stated that they consulted the catch-up schedules most frequently out of the current 3 schedules, mainly for children with missed vaccines, incomplete vaccine history, or recent immigrants. Varying responses were received with regard to the question about where respondents got their schedules. Of the versions that respondents noted receiving, all appeared to be based on the CDC version, but not necessarily the actual CDC publication. Journals, notifications, and publications from professional organizations such as the AAP and AAFP were frequently noted as sources. The Red Book was also commonly cited. Respondents noted that hard copies of the schedules are frequently posted somewhere in the office for both clinician use and sometimes to show to parents.

Interestingly, many providers noted that in their setting, they customized a schedule specifically for their practice within CDC recommendations. Reasons for this included the need for physicians within a practice to do the same thing, and that they would then be less likely to miss a vaccine. Providers who were not aware of the parent-friendly version offered by CDC instead used the provider schedule to show parents and to validate recommendations to parents. Because many providers stated that they often did not refer to the routine schedule because they knew it by memory, they were probed further to determine how they were made aware of changes to the schedule. This was concerning, so this question was posed. Various sources were cited including online updates to The Red Book, email notification from various organizations, colleagues, and the local health department.

In terms of the reactions to the proposed 2013 schedule format changes, respondents were first shown the proposed 0 through 18 schedule format. This combination of the 0 through 6 and 7 through 18 schedules was well-received by all providers. They liked the larger size of the figure, and the continuity of age span. The first version of the figure shown to respondents had check marks which the working group originally intended to denote 1 dose of vaccine. This concept however was not easily understood by most respondents, or was at times misconstrued by most respondents to mean the vaccine dose had to be given at that time within the bar. There was also mixed response to the idea of including both catch-up and high-risk on this figure. Some respondents liked the idea of having this all on one page. Others felt that it made the table too busy, and that there were already separate tables addressing catch-up and high risk in the proposed 2013 format. This was particularly noted by nurses and medical assistants, notably the same group more likely to report using the routine schedule.

Based on feedback from respondents, 3 other versions were introduced as the study progressed. While Option 2 had the wording “1 dose” replace each check mark; Option 3 had no wording in the bars; and Option 4 had 1st dose, 2nd dose, 3rd dose et cetera in each bar. Option 4 was preferred by respondents and was perceived as more helpful than the other

versions. Another concern expressed by respondents was the “hatch” marking in the Hep A bar for children over 2 years of age. This “hatch” bar was introduced for the first time on the current 2012 schedule in an attempt to illustrate that the vaccine may be given to anyone previously unvaccinated who desired immunity against Hep A, and also to show that the vaccine should be given to persons at high risk for Hep A infection. However, the “hatch” marks were reported as confusing by respondents in this study, and also were interpreted by some as meaning that the vaccine should not be given during this time—almost like a hazard sign.

The next document that respondents were asked to give comments on was the combined footnotes. Respondents were questioned as to whether the footnotes appearing in a separate document, rather than under the figures, was a concern. Overall, the majority of field test respondents felt that having the footnotes separated was not an issue, and that if providers needed the information they would seek it out. Many also noted that footnote pages could easily be posted next to the figures on the wall in a clinic setting. The benefits of having larger font size of the footnotes by separating the footnotes from the figures was expressed by providers as outweighing any concerns of not having the footnotes under the figures.

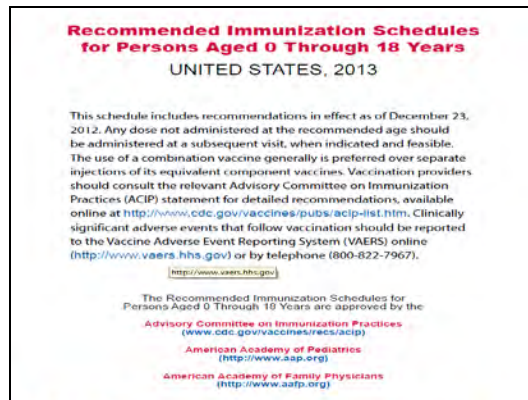
The next document that was shown to providers was the new proposed high risk table delineating vaccine recommendations for children with high-risk medical conditions. Overall, the concept of the high-risk table was well-received by respondents. Respondents felt that this was important information to convey. However, the format was not well-received and respondents found it difficult to maneuver through the table. Version 1 was reported as being very busy. A second version was shown to respondents later in the course of the testing based on feedback from earlier respondents. This format was noted as somewhat easier to understand. The formative research study revealed that primary care physicians typically consult the specialist when deciding to vaccinate children with high-risk medical conditions, but ultimately felt that it was the responsibility of the primary care provider to make sure the child was vaccinated. Specialists were consulted mainly for decision-making regarding the timing of live virus vaccines.

Based on the study findings, ORISE recommended using the version of the 0 through 18 schedule 1st dose, 2nd dose, 3rd dose, et cetera; and removing the catch-up and high risk bars from this schedule. For the High Risk Table, ORISE recommended using Version 2 because the format was better received; removing the footnotes from under this figure to a separate page; and giving examples under the column headings of specific diseases that would fall under that heading, for example sickle cell disease for asplenia. ORISE also recommended that hyperlinks be provided for all vaccine names on the figures to the respective footnotes; and for the benefit of those providers who are not using an electronic version of the schedule that the footnotes be as detailed as possible.

The working group convened to discuss the findings and recommendations based on those findings from the field study. Working group members agreed to move forward with proposing the 0 through 18 schedule to ACIP to replace the current 0 through 6 and 7 through 18 schedules. The working group agreed to use the version with 1st dose, 2nd dose, 3rd dose, et cetera labeling. Based on feedback from respondents, the working group agreed to highlight the headings of the 4 through 6 and 11 through 12 year old columns to show the importance of the school entry vaccine period, as well as the adolescent platform at these respective ages. The working group also agreed that it was important to hyperlink the vaccine names on the figures to their respective footnotes. The hatch bar was also replaced on the HepA vaccine row. The working group deliberated on the issue of including the green and purple bars on the routine 0 through 18 schedule. Despite some objection by providers to having these on the

routine schedule, the working group felt that the green catch-up bars would actually help to foster the notion that children not fully vaccinated may be caught up throughout childhood and adolescence. The green catch-up bars have been present on the 7 through 18 schedule for several years now, but not on the 0 through 6 schedule. The white space on the 0 through 6 schedule has been mentioned in the past by some providers as being confusing, and providers were not sure how to interpret that in terms of whether vaccine was not recommended during that timeframe or if catch-up was actually allowable. The working group hoped that keeping the green and purple bars on the routine schedule would help to allay some of those concerns.

The working group agreed to move forward with proposing the combined footnotes as two separate pages and not to keep them under the figures. This would allow for easier readability. The working group did not propose a recommendation at this time for changes to the catch-up table. After much deliberation, the working group felt that in order to have more time to work on the format of the high-risk indication table, as well as time to revisit specific content, they would defer proposing this additional table for 2013, but would consider it a work in progress that could hopefully be revisited for a vote for the 2014 schedule. Based on the working group recommendations, the proposed 2013 schedule format would be a 5-page booklet as follows:



Persons aged 0 through 6 years

Persons aged 7 through 18 years

Abbreviations

DTaP-IPV Diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine

MMr Measles, mumps, and rubella vaccine

MMrV Measles, mumps, rubella, and varicella vaccine

MMrV-IPV Measles, mumps, rubella, and varicella vaccine with inactivated poliovirus vaccine

MMrV-IPV/DTaP-IPV Measles, mumps, rubella, and varicella vaccine with inactivated poliovirus vaccine and diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine

MMrV-IPV/DTaP-IPV/Polio Measles, mumps, rubella, and varicella vaccine with inactivated poliovirus vaccine, diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine, and poliovirus vaccine

MMrV-IPV/DTaP-IPV/Polio/DTaP-IPV Measles, mumps, rubella, and varicella vaccine with inactivated poliovirus vaccine, diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine, and poliovirus vaccine and diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine

MMrV-IPV/DTaP-IPV/Polio/DTaP-IPV/Polio Measles, mumps, rubella, and varicella vaccine with inactivated poliovirus vaccine, diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine, and poliovirus vaccine and diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine and poliovirus vaccine

MMrV-IPV/DTaP-IPV/Polio/DTaP-IPV/Polio/DTaP-IPV Measles, mumps, rubella, and varicella vaccine with inactivated poliovirus vaccine, diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine, and poliovirus vaccine and diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine and poliovirus vaccine and diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine

MMrV-IPV/DTaP-IPV/Polio/DTaP-IPV/Polio/DTaP-IPV/Polio Measles, mumps, rubella, and varicella vaccine with inactivated poliovirus vaccine, diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine, and poliovirus vaccine and diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine and poliovirus vaccine and diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine and poliovirus vaccine

MMrV-IPV/DTaP-IPV/Polio/DTaP-IPV/Polio/DTaP-IPV/Polio/DTaP-IPV Measles, mumps, rubella, and varicella vaccine with inactivated poliovirus vaccine, diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine, and poliovirus vaccine and diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine and poliovirus vaccine and diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine and poliovirus vaccine and diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine

MMrV-IPV/DTaP-IPV/Polio/DTaP-IPV/Polio/DTaP-IPV/Polio/DTaP-IPV/Polio Measles, mumps, rubella, and varicella vaccine with inactivated poliovirus vaccine, diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine, and poliovirus vaccine and diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine and poliovirus vaccine and diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine and poliovirus vaccine and diphtheria, tetanus, acellular pertussis, and inactivated poliovirus vaccine and poliovirus vaccine

With regard to specific footnote changes, in general, because the footnotes were removed from beneath the figures in the proposed format for 2013 and combined into one document, subheadings were placed under each vaccine footnote to delineate routine vaccination, catch-up vaccination, and vaccination of persons with high-risk conditions. Under routine vaccination, general administration guidance is provided for each vaccine. Where appropriate, vaccine recommendations are broken down by age since the 0 through 6 and 7 through 18 footnotes are now combined. Pneumococcal conjugate vaccine and pneumococcal polysaccharide vaccine footnotes were separated for clarity. An additional footnote outlining the conditions for which PPSV23 and PCV13 for certain children are indicated was added. For influenza vaccines, because the schedule will span 2 influenza seasons, providers are referred to the respective ACIP vaccine recommendations for that season for guidance on dosing for children 6 months through 8 years of age. For MMR footnotes, clarity was provided regarding use of the vaccine in persons traveling internationally. For Hepatitis A, clarity was provided with regard to timing of doses. For meningococcal vaccine footnotes, a draft of the proposed wording based on the ACIP vote during this meeting for use of HibMenCY was shown for persons with high-risk medical conditions. For Tdap in pregnancy, language will be adopted as per the VFC vote.

In terms of next steps, the working group will make revisions as necessary based on feedback from ACIP and CDC internal clearance. The document will be submitted to *MMWR* for editing. The final edited copy will be sent to partner organizations for preparation of publication in their journals or their on-line publications by January 1, 2013. CDC is now offering a service called Content Syndication, given that despite the best efforts, there will be errors caught or updates to the schedules once published. By using Content Syndication, when the schedules are updated, immediately the schedules on partner sites will be updated. This will lessen the time-consuming process of checking CDC's site to determine whether any updates have been made. Further information regarding Content Syndication can be acquired from CDC's webpage at [CDC Website Content Syndication Tool](#).

Discussion Points

On the influenza bar, Dr. Keitel recommended changing to IIV for inactivated influenza vaccine in anticipation of quadrivalent vaccines.

Dr. Sawyer inquired as to whether there was discussion among the working group members or in the focus groups regarding the 2-dose influenza recommendation for children under 9 years of age, and whether to refer people specifically to the footnotes as is done for a third dose of rotavirus vaccine. As it stands, if one just looked at the table, they might not think about the second dose of influenza vaccine in children under 8 years of age.

Dr. Beysolow replied that the working group could discuss this to determine whether a possible change can be made within the bar.

Dr. Whitley-Williams (NMA) pointed out that since there remain so many questions regarding a child who is receiving a first dose of influenza vaccine and whether that child should receive two doses in the second season, perhaps a sentence could be added in the footnote about this. Otherwise, practitioners will have to go to the *MMWR*. While this is very clearly explained in the *MMWR*, practitioners administering the vaccine will have the schedule and footnotes up on the wall.

Dr. Beysolow responded that while they tried, they would basically have to include the whole algorithm because there are so many nuances. The concern was that this will be published in February and influenza season will be over a few months later, and that the next season it could potentially change. She did agree to take this back to the working group to determine whether some simpler language versus the algorithm could be included.

Dr. Middleman (SAHM) suggested orienting the schedule and the catch-up schedule in the same way, so that the open flyer can be hung in a landscape format.

Paul Etkind (NACCHO) inquired as to whether there was anything in the footnote to guide people about where to check whether an area to which they plan to travel is a high risk area for measles.

Dr. Beysolow replied that this is not included in the footnote. People would have to refer to the actual recommendations. In general, subject matter experts say that anywhere outside the continental US is considered to be international travel.

Dr. Pickering added that any infant traveling internationally, not just to a high risk area, is recommended to be immunized according to the measles recommendations. For children 12 months and older traveling internationally, a second dose should be given if it has not been. Exposures occur not only internationally, but also in airports during travel.

Kathleen Coelingh (MedImmune) noted that the live attenuated influenza vaccine (LAIV) of FluMist[®] formulation is switching in 2013-2014, so there will again be an issue of spanning. It was unclear whether the schedule dealt with this issue.

Dr. Beysolow responded that they planned to use the abbreviations that would incorporate IIV for the inactivated influenza vaccine and LAIV, although she was not sure whether consensus on the actual nomenclature had been reached yet. They would then refer to the respective year's ACIP recommendations for guidance on the use of a particular vaccine, with a hyperlink.

Dr. Temte inquired as to whether there would be applications for handheld devices such as the iPhone, and whether there were any private vendors who create immunization schedules that are not CDC's.

Dr. Beysolow responded that she did not think CDC was in a position yet to provide that. The version is available that can be done on the desktop.

Dr. Brewer (ANA) said she saw an app from the National Public Health Information Coalition (NPHIC) exhibited at the National Immunization Conference. It is not interactive, so it will not indicate which vaccination is needed based on a specific patient, but it will bring up the most current schedule.

Dr. Grogg (AOA) indicated that SHOTS is provided by the Society of Teaching Family Medicine (STFM), and the ACP also has an app.

Dr. Poland (ACP) pointed out that a URL was distributed that could be scanned to get to the ACP immunization app, which uses the ACIP schedule.

Dr. Pickering noted that there are child, adolescent, and adult interactive immunization schedules on the CDC / NCIRD website that were developed by CDC and Georgia Tech. This allows an individual's birth date and list of immunizations the person has had to be entered, and it then lists what the person needs immediately and in the future. He will send this to Dr. Beysolow.

Dan Hopfensperger (State of Wisconsin) advocated for immunization registries. Immunization systems usually have the ACIP immunization schedule built into them, and many have the childhood, adolescent, and adult schedules.

Vote: Child / Adolescent Immunization Schedule 2013

Dr. Bocchini made a motion that the proposed Child / Adolescent Immunization Schedule 2013 be approved. Dr. Rubin seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Adult Immunization Schedule 2013

Introduction

Dr. Tamera Coyne-Beasley, ACIP Lead Adult Immunization Working Group

Dr. Coyne-Beasley reminded everyone that each year, ACIP updates the adult immunization schedule to reflect and summarize existing ACIP policy. No new policies will be added to the schedule, unless they are actually verified or made during the October 2012 ACIP meeting, and verified or published before CDC publishes the adult schedule in February 2013. Monthly meetings were convened with the working group, and consultations were engaged in with various vaccine subject matter experts. The 2012 adult schedule also had to be approved by ACP, AAFP, ACOG, and American College of Nurse Midwives (ACNM).

Review of Changes

Carolyn B. Bridges, CDC Lead National Center for Immunization and Respiratory Diseases Centers for Disease Control and Prevention

Dr. Bridges reported that the proposed changes to the adult schedule for the 2012 charts included incorporation of the changes in the Tdap recommendations. Tdap recommendations are recommended for all adults, now including those 65 years and older. Therefore, the hashed bar was removed for 65 and older. A bar was added for PCV13 vaccine. The purple bar was removed for MMR for persons born before 1957, which is now consistent with the footnote.

to persons with a history of genital warts, abnormal Papanicolaou test, or positive HPV DNA test.”

For PPSV23 there is still some confusion about who should receive one, versus two, versus three doses. Some wording changes were made to the PPSV footnote to try to clarify that all adults 65 and older are recommended for PPSV, and to clarify the timing of doses for those possibly vaccinated earlier and all adults age 65 years and older without a history of PPSV vaccination. Language was also added to indicate that vaccine should be administered if vaccination status is unknown, and to specify that chronic renal failure and nephrotic syndrome were included among high risk / immunocompromising conditions. Language was inserted on the timing of vaccination with PPSV23 versus PCV13, and to refer to the PCV13 footnote. In terms of PPSV revaccination, clarification was made that persons <65 may have received 1 or 2 prior doses, but still were recommended to receive a dose of PPSV23 at age 65 or later if at least 5 years had passed since prior PPSV23 dose. For PCV 13, a footnote was added to the schedule based on provisional recommendations published in the *MMWR*. Minor verbiage changes were made to the Hepatitis A and B footnotes to use the exact wording from the full ACIP recommendations. Changes were made for Hepatitis A vaccine to indicate that people who use non-injection illicit drugs are among those groups recommended for vaccination, and for Hepatitis B vaccine to indicate that household contacts and sex partners of hepatitis B surface antigen positive persons are indicated for vaccination. Information was also added on the three-dose schedule for the Recombivax HB. No changes were made to the Zoster, MMR, meningococcal or Hib vaccines footnotes. However, the Adult Immunization Working Group will need to confer with the MMR Working Group based on the discussions earlier in the day.

Last year was the first year that a contraindications table accompanied the schedule. The information was updated for influenza vaccine to indicate that, “Persons who experience only hives with exposure to eggs should receive IIV.” For LAIV, clarification was made regarding which contraindications are based on package insert and which are based on ACIP recommendations, “Conditions for which ACIP recommends against use, but which are not contraindications in vaccine package: immune suppression, certain chronic medical conditions such as asthma, diabetes, heart or kidney disease, and pregnancy.” Minor changes were made to the contraindications table for Tdap, which now refers to prior neurologic reactions to pertussis-containing vaccines, not just to Tdap. The language was clarified for zoster and varicella vaccines about the use of antivirals in precautions, and the language is now consistent with LAIV and antivirals language, “Receipt of specific antivirals (i.e., acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination; if possible, avoid use of these antiviral drugs for 14 days after vaccination.” PCV13 was added to the table. For hepatitis A vaccine, pregnancy was deleted as a precaution, which makes this consistent with the hepatitis B vaccine recommendation. ACIP recommends HAV use during pregnancy when the benefits outweigh potential risk. Pregnancy is not listed as a contraindication or precaution for package insert. For example, the Havrix[®] package insert reads, “Animal reproduction studies have not been conducted with Havrix[®]. It is also not known whether Havrix[®] can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Havrix[®] should be given to a pregnant woman only if clearly needed.”

The next steps are to revise the adult schedule based on this ACIP meeting and further discussions with the SMEs and working group members. The schedule must be submitted to *MMWR* in early December for publication. Simultaneously, the schedule will be submitted to other interested organizations. The current organizations that formally approve the adult immunization schedule include AAFP, ACP, ACOG, and ACNM. Publication in the *MMWR* is anticipated in early February 2013 along with publication of 2011 National Health Interview Survey (NHIS) estimates of non-influenza vaccine coverage in adults. The *Annals of Internal Medicine* will publish the schedule the same week as *MMWR* publishes it.

Discussion Points

Dr. Temte asked whether a definition was included for “renal disease.” His practice is trying to characterize patients by the stage of chronic kidney disease based on estimated glomerular filtration rate (GFR). He wondered whether there was any guidance regarding how bad the kidneys needed to be to qualify for vaccination.

Dr. Bridges said she would have to review the specific wording, but as she recalled the 23-valent recommendation did not include specific GFR. It might vary by the separate ACIP recommendations.

Dr. Poland (ACP) added that the risk was only 2-fold, one if failure is severe enough to be on dialysis and the second if there is a chronic protein-losing nephropathy.

Referring to the diabetes / renal column, Dr. Schaffner (NFID) noted that the way the table was set up, it suggested that people with diabetes should be immunized with both pneumococcal vaccines.

Dr. Bridges reiterated that this was why instead of footnoting this, diabetes and renal should be divided into two separate columns.

Dr. Brewer (ANA) suggested printing the schedule in landscape format as was suggested for the childhood schedule so that they would be back-to-back.

Dr. Bridges indicated that several versions of the adult and pediatric schedules are created. The much larger version can be printed in landscape.

Dr. Sawyer noted that in the abbreviation “PPSV” was not included either the age-based or risk-based colored diagrams; whereas, it is included in the footnotes and contraindication table. He thought the era was such that providers who care for adults to make the distinction between polysaccharide and conjugate vaccine since they are both now indicated for certain groups. He suggested including PPSV in the diagrams as a point of education and a standard abbreviation.

Dr. Loehr (AAFP) pointed out that the zoster bar was entirely yellow, but in the bottom left the schedule stated, “For all persons in this category who meet the age requirements and lack documentation of vaccination or have no evidence of previous infection.” But zoster vaccine can be given if someone has had previous infection. Also, the white box under HPV during pregnancy stood out, but it was unclear whether the footnotes would state what to do for pregnancy and HPV. This is a common question.

Dr. Bridges replied that the HPV SMEs indicated that there is not an existing recommendation for pregnancy.

For PPSV, Dr. Bresnitz (Merck) suggested adding the number 23 to reflect the valence and to be consistent with the terminology for the pneumococcal vaccine. Both products have the numbers in their brand names as well, so it would be appropriate to have consistency from that perspective.

Dr. Middleman (SAHM) mentioned that the HPV footnote for males should also include those with HIV.

Dr. Bridges clarified that this does remain in the full footnote.

Regarding HPV and pregnancy, Dr. Jenkins noted that the CDC website states that there is a problem about the recommendation in terms of the evidence. The bottom line is that a pregnant woman should not receive any dose of HPV vaccine until her pregnancy is completed. She wondered whether that was sufficient enough to state as a contraindication not to give it.

Dr. Brooks responded that she would have to review the package insert to see if it was listed as a contraindication. That has generally been how the contraindications table has been approached, except for the example of influenza vaccination and the ACIP contraindications.

Dr. Middleman (SAHM) thought they should be cautious about including this as a contraindication, which has to be a condition that someone has that actually places them at risk of harm. For females, this is the only Category B. Most vaccines are pregnancy Category C.

Dr. Brooks thought the other difficulty was balancing the fact that the package inserts are sometimes not changed as rapidly as the science, or may differ from ACIP recommendations.

Dr. Friedland (GSK) indicated that the pregnancy category for Cervarix[®] is Category B. Pregnancy is not a contraindication in the product insert for Cervarix[®].

Dr. Bocchini noted that the current HPV recommendation does not require that the recipient be tested for pregnancy to receive the vaccine. However, it does state that if someone is pregnant, subsequent doses should be suspended until the pregnancy has ended.

Dr. Jenkins suggested that if the footnote did not include this information, it should at least state that HPV should not be given during pregnancy even though it is not contraindicated.

Dr. Brooks replied that the footnote did not currently include information about pregnancy, but that this information could be included.

Dr. Kinsinger (DVA) pointed out that the zoster footnotes stated that “persons with chronic medical conditions may be vaccinated unless their condition constitutes a contraindication,” but included nothing about age. If the age requirement applies to persons with chronic medical conditions, the footnote should state that clearly. Since the vaccine is recommended for essentially all people over 65, it was unclear to her why the second bullet was needed, because it implied that there was something different about those people.

Dr. Brooks replied that the second bullet was trying to address the issue of concerns about who should not be vaccinated. The age group could be added to the second bullet if that would offer clarity.

Barbara Kuter (Merck) indicated that Gardisil® is also a Category B and pregnancy is not contraindicated.

Vote: Adult Immunization Schedule 2013

Dr. Sawyer made a motion that the proposed Adult Immunization Schedule 2013 be approved with the proviso that the suggestions made be included. Dr. Jenkins seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Day 1: Public Comment

Hit Me With Your Best Shots: Taking Action to Improve Adult Immunization

**Dr. Sandra Fryhofer
Alternate ACIP Liaison and
Member of the Adult Immunization Advisory Committee
American College of Physicians**

Dr. Fryhofer reported that the ACP has a new remedy for increasing adult immunization rates designed to “get you in the mood” to vaccinate. She introduced the ACP Adult Immunization Advisor, a handy tool for the busy healthcare professional, a handy tool for the busy healthcare professional or student. Immunization recommendations can be searched by patient age, medical conditions, or special circumstances. This vaccine library provides easy access to vaccine indications, contraindications, administration, possible side effects, storage and handling, and coding. It also has vaccine-specific guides about use in pregnancy and nursing, and whether a booster is needed. It is free and is available for iPhone® and iPad®. But there is a disclaimer. It’s for adults only. The app is easily accessible. It can be downloaded directly from iTunes or from ACP’s immunization portal. The 4th Edition of the *ACP Guide to Adult Immunizations* is also available on the immunization portal for download. It contains information on 10 vaccines for adults, along with practical advice, practice improvement topics, and immunization guidelines for special populations. The Adult Immunization Advisory app was launched nationally on July 2, 2012. But a statewide launch was done in Georgia in September at the Immunize Georgia Meeting of Public Health Immunizers, and also at the Georgia ACP Chapter meeting. The title of the presentation was “Hit me With Your Best Shots.” The ACP is the nation’s largest medical specialty society, representing over 133,000 Doctors of Internal Medicine and medical students throughout the country. This is just another way in which the ACP is helping to increase adult immunization rates, and helping shape national vaccine policy. With that, Dr. Fryhofer marched off of the stage with a large syringe to “Hit Me with Your Best Shot” [written by Canadian singer / songwriter Eddie Schwartz, and recorded by American

singer Pat Benatar in 1979]. Dr. Temte thanked Dr. Fryhofer for setting a new standard for presentations at ACIP, and Dr. Pickering commented that it was good to see internists acting like pediatricians.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Wharton reported that Dr. Schuchat, the Director of NCIRD, was currently serving as Acting Director of CDC's Center for Global Health (CGH) where she was anticipated to remain for the next several months during the search for a permanent director of that important CDC office. In honor of World Polio Day on October 24th, Dr. Wharton acknowledged CDC's involvement in global polio eradication. Dr. Frieden activated CDC's Emergency Operations Center (EOC) last December in order to enhance CDC's response to the Global Polio Eradication Initiative by making the emergency operations response resources available to the polio eradication effort. Since that time, 425 personnel have worked in the EOC and in the field to support CDC's polio eradication efforts, and 121 employees have completed 228 field deployments in Angola, Chad, Nigeria, Côte d'Ivoire, and other areas. The most recent data released by the Global Polio Eradication Initiative on October 16th revealed that year-to-date, 171 cases of polio were reported from 4 countries. Of those, 66 were from 3 of the remaining polio-endemic countries (i.e., Nigeria, Pakistan, and Afghanistan). This is in comparison to 467 cases at this point last year. Although it continues to be a challenging situation, progress is being made. On February 25, 2012, WHO removed India from the list of countries that were considered never to have had interrupted polio transmission. There has not been a case of polio there since January 13, 2011, and no recent environmental samples have detected wild polio virus. On the domestic side, Dr. Wharton highlighted that NCIRD's Immunization Services Division's Assessment Team has been busy over the last several months with publication of immunization coverage data for kindergarten age children for the 2011-2012 school year, the NIS adolescent data for 2011, the NIS child data for 2011, and influenza vaccine coverage data for healthcare workers and pregnant women for the 2011-2012 season. This year's NIS child data represents the first time the dual-frame method has incorporated cell phones into the sampling frame. The survey data published included both landline and cell phone coverage. This has not resulted in much difference at the national level, but there are some differences at individual state levels. The areas where the population uses cell phones only are considerably different from the landline population. This represents a good advance in methodology.

Centers for Medicare and Medicaid Services (CMS)

Dr. Hance offered an update on CMS's influenza campaign, indicating that an immunization guide was posted on the CMS website that includes many resources. There are fact sheets, PSAs, and a mini-poster, all of which are in both Spanish and English. CMS also is working with its provider communications group to encourage more use of the immunization benefits through provider groups. CMS began providing an influenza message in all provider messages that reach approximately 68,000 providers. In terms of Medicaid, CMS is extremely close to having a final rule that increases primary care payments for two years in accordance with the ACA provision that includes immunizations. Attached to that is an update to the fee schedule for the VFC, which had not been updated since 1994. The proposed rule was published in May. CMS has worked through the comments, and the final rule will be published very soon. The effective date for the primary care payment increase is January 1, 2013.

Department of Defense (DoD)

Dr. Geibe offered a DoD services influenza compliance update. "Services" include the active duty and reserve components of the Army, Air Force, Marines, Navy, and Coast Guard. Given that compliance is not optional, uptake is high. As of October 23, 2012, the compliance rate for active duty was 71%, while the reserve component was somewhat lower at 52%. The current goal is to reach 90% by December 17, 2012, which the DoD should be able to do.

Department of Veteran's Affairs (DVA)

Dr. Kinsinger reported that the DVA's influenza seasonal campaign was in full swing. DVA ordered just over 2 million doses for the 2012-2013 influenza season, two-thirds of which have been shipped to medical centers. The remaining third were expected the week following this ACIP meeting, so DVA's supply is good. Every year, one of DVA's offices produces an influenza manual that provides staff with information about on-going influenza campaigns. There are posters, fliers, and other informational items. There has been significant discussion over the last year and a half within DVA with regard to the employee influenza vaccination program. A major summit was convened last June, the recommendation from which was to continue to make influenza vaccine voluntary rather than mandatory, and to strongly encourage employees to be vaccinated and to observe hand hygiene, hand washing, respiratory precautions, staying at home when sick, et cetera to try to control exposure to influenza.

Food and Drug Administration (FDA)

Dr. Sun reminded everyone that the next VRBPAC meeting would be convened November 14-15, 2012. At that time, VRBPAC will consider the safety and efficacy of two new vaccines with two new adjuvants. One of the vaccines is a pandemic H5N1 with an ASO3 adjuvant manufactured by GSK, and the other is a new Hepatitis B vaccine with an immunostimulatory sequence adjuvant manufactured by Dynavax. In June 2012, Congress passed the FDA Safety and Innovation Act, which has fairly wide-ranging implications for FDA. The act provides various new authorities to FDA with regard to the supply chain for globalization supplies and incentives to develop new antibiotics and enhancing surveillance post-marketing, for example. As it relates to vaccines, the act requires FDA to have closer interactions with manufacturers at various time points during the review of new vaccines, and a greater focus on earlier interactions with the manufacturers on pediatric development plans. The act also expands the federal government's capability for post-marketing safety surveillance, which would include vaccines.

Health Resources and Services Administration (HRSA)

Dr. Caserta reported that Dr. Evans recently retired, and noted that he admirably served on ACIP for two decades. HRSA is actively searching for his replacement, and will soon post the job announcement. Dr. Temte offered congratulations to Dr. Evans on his retirement, and noted that ACIP would miss him.

Indian Health Services (IHS)

Amy Groom offered an update on IHS influenza activities, reporting that IHS had begun monthly influenza calls and its influenza surveillance system. Weekly reports are posted on the IHS website that focus on influenza-like illness and tracks vaccine coverage in IHS's patient population. At the time of this report, approximately 11% of IHS's patient population had been vaccinated. Adult immunization is a high priority for the agency this year, with a number of policies having been put in place. One gap pertained to missing data, so IHS began to collect quarterly coverage data on its adult population. The first report was received on October 24, 2012, which showed that Tdap coverage among those 19 years of age and older was 62%. Dr. Groom thought this coverage level spoke to the power of an electronic reminder. IHS added a reminder for its clinicians in the IHS electronic health record as soon as ACIP made the recommendation for a dose for everyone, and she thought that was what was reflected in this high coverage rate.

National Vaccine Advisory Committee (NVAC)

Reporting for Dr. Orenstein during this ACIP meeting was Dr. Tan, given that Dr. Orenstein was attending WHO's Strategic Advisory Group of Experts (SAGE) meeting in Geneva, Switzerland. Dr. Tan delivered a summary of the NVAC meeting that was held September 11-12, 2012. During that meeting, several speakers addressed National Vaccine Plan (NVP) topics, including NVP implementation and stakeholder engagement. Progress updates were offered on the vaccine financing recommendations made by NVAC in 2009. The status of reaching the Healthy People 2020 immunizations goals and updates were presented from CDC on various immunization issues, specifically on pertussis resurgence. Speakers also offered input to help guide the future of topics to be addressed by NVAC, which included perspectives on health information technology, optimizing immunization delivery and tracking, and meaningful use objectives regarding the use of electronic health records to facilitate entry of critical vaccination information. Also discussed were the use of electronic immunization records at the VA and state and community-based immunization registries, and how bar coding of vaccines would fit in to that. A very productive session was convened on vaccine hesitancy, which addressed vaccine refusal and on-going efforts to address refusal, global perspectives on vaccine hesitancy, and a case study from Washington State where hesitancy has been a particular problem. As a result of that session, NVAC is undertaking a white paper to address vaccine hesitancy. Spearheading that white paper is NVAC member Dr. Vish Viswanath who is a communications expert from Harvard.

Other accomplishments of NVAC include an upcoming publication in *Public Health Reports* on the *Recommendations on Strategies to Achieve the Healthy People 2020 Annual Goal of 90% Influenza Vaccine Coverage for Health Care Personnel*, which were the recommendations adopted by NVAC during its February 2012 meeting. NVAC has three active working groups. The Immunization Infrastructure Working Group's recommendations in the report titled, *Protecting the Public's Health: Critical Functions of the 317 Program*, were unanimously adopted by NVAC members during its September 2012 meeting. That report will be submitted for publication in *Public Health Reports*. The Global Immunization Working Group will present final recommendations to NVAC during its February 2013 meeting, and a final draft report will be presented for a vote during the June 2013 meeting. A critical component of the *Global Immunization Report* will be to show that investments in global immunization not only provide humanitarian benefits, but also enhance domestic health and security. Regarding the Maternal Immunization Working Group, which is relevant considering some of ACIP's discussions regarding pertussis the previous day, Dr. Ritchard H. Beigi—who is now the co-Chair of that

working group—and Dr. Catherine Torres will present a draft report to NVAC in Spring 2013, with a final draft for vote in September 2013. The report will address vaccines currently recommended for pregnant women (e.g., influenza and pertussis), patient and provider barriers, federal opportunities to overcome these barriers, implementation of current recommendations for pregnant women, and vaccines currently under development that are targeted to pregnant women.

The next NVAC meeting is February 5-6, 2013. NVAC recently welcomed five new members, including the following:

Ritchard H. Beigi, MD, MS
University of Pittsburgh
Pittsburgh, Pennsylvania

Sarah Despress, JD
Pew Charitable Trust
Washington, DC

Ruth Lynfield, MD
Minnesota Department of Health
St. Paul, Minnesota

Yvonne Maldonado, MD
Stanford University
Stanford, California

Mitchel C. Rothholz, RPh, MBA
American Pharmacists Association
Alexandria, Virginia

National Vaccine Program Office (NVPO)

Dr. Gellin reported that NVAC advises NVPO, which presents topics to them on which NVPO would like advice. The NVP strategic plan was released in 2010 and was followed by the implementation plan, which is how measurement will be done over time, with annual reviews by NVAC. NVAC will provide the link to ACIP members for the implementation plan. Germaine to the discussions the previous day regarding pertussis uptake, the Maternal Immunization Working Group will produce its findings and present these to NVAC in June. In the meantime, one of the projects this group has undertaken is to assess the barriers to immunizing pregnant women against influenza, which NVPO has done in partnership with ACOG as a supplement to their journal from July 2012, which includes a series of related topics. NVAC will supply ACIP members with a link to that supplement. NVPO is supporting IOM's work titled *Ranking Vaccines: A Prioritization Framework*, the second phase of which begins with a public meeting via webcast on November 2, 2012. He encouraged ACIP members to review this report and offer feedback. With regard to the influenza season, there is an organized effort by the Assistant Secretary for Health on influenza. NVPO hopes to expand the Flu Vaccine Finder into an adult finder to support interest in adult immunizations more broadly.

National Institutes of Health (NIH)

Dr. Gorman reported that Dr. Fauci continues to emphasize that the Division of Acquired Immunodeficiency Syndrome (DAIDS) networks will expand their scope and reach to include diseases that are co-infections, particularly HCV and tuberculosis. Multiple announcements have recently closed, and NIH will soon begin its review process. The National Institute of Allergy and Infectious Diseases (NIAID) is undergoing a major information technology upgrade, which should improve video conferencing and support for the increased use of telework as the US Government tries to shrink its real estate footprint in Washington, DC. In terms of maternal and pregnancy studies, a group led by Mirjana Nesin has developed a report over the last year pertaining to the design of trials for vaccines and therapeutics in pregnant women, including toxicity tables. NIH hopes that this report will soon be widely available. The Division of Microbiology and Infectious Diseases (DMID) is currently conducting a Phase 4 rotavirus study. This is a mix-and-match study assessing various combinations that could be possible if a state changes its provider of rotavirus vaccine during the course of someone's vaccine. This study will soon enroll its 1000th patient in just over one year, and is currently at about 70% completion with enrollment. DMID is also conducting a study of an HCV vaccine, which is being performed in an intravenous drug using population at high risk. This study is about to achieve its designed initial assessment of safety and efficacy.

Japanese Encephalitis Working Group Update

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

Dr. Bocchini indicated that the Japanese Encephalitis Vaccine Working Group had been reactivated based on the development of data for the use of this vaccine in children. In 2009, an inactivated Vero cell culture-derived JE vaccine (JE-VC) was licensed for use in persons ≥ 17 years of age. ACIP recommendations for use of JE-VC in adults were approved in 2009 and were published in 2010. Currently, JE-VC is the only licensed JE vaccine available in the US. Therefore, there is no vaccine for children for prevention of this disease. Intercell Biomedical, the manufacturer of JE-VC, recently submitted a BLA for use of JE-VC in children 12 months through 16 years of age. Thus, the Japanese Encephalitis Working Group was reactivated, with meetings planned every 2 to 4 weeks beginning November 1, 2012. The working group will review the safety and immunogenicity data for JE-VC in children < 17 years of age and will develop recommendations for use of JE-VC in children. An ACIP vote is expected during the February or June 2013, depending upon when the decision is made by the FDA concerning licensure for this vaccine in children 12 months through 16 years of age. The working group includes members who are travel medicine experts, as well as pediatric and adult experts who are familiar with this vaccine.

Hepatitis B Vaccine

Introduction

Dr. Mark Sawyer, Chair Hepatitis Working Group

Dr. Sawyer reported that the term of reference for the Hepatitis Vaccine Working Group was to ensure hepatitis B protection for healthcare personnel (HCP), including trainees, who have written documentation of Hepatitis B (HepB) vaccination in the past without post-vaccination serologic testing. The working group was specifically requested by ACIP to engage in discussion pertaining to this issue to eventually provide guidance to institutions throughout the country regarding what to do given this increasing problem.

With regard to background, in 1982 ACIP recommended HepB vaccination for healthcare personnel¹. In the past, most healthcare personnel, including trainees, were unvaccinated until matriculation or hire. In 1997, ACIP recommended post-vaccination serologic testing 1 to 2 months post-vaccination for healthcare personnel at on-going risk for percutaneous injury² to determine the need for revaccination and to guide post-exposure management [¹MMWR 1982, ²MMWR 1997].

Different currently is that an increasing proportion of healthcare personnel entering training and the workforce have received HepB vaccination as infants or at least in the distant past. The birth dose continues to be recommended because it prevents chronic infection when the risk is greatest. However, post-vaccination serologic testing for antibody to hepatitis B surface antigen (anti-HBs) has not been recommended routinely following the infant HepB vaccination. As a result, people are entering the healthcare workforce not having had the benefit of post-vaccination testing immediately following vaccination. It is known that anti-HBs after vaccination wanes over time, although protection is believed to persist despite the waning antibody. In the changing context for occupationally-acquired Hepatitis B, healthcare schools and institutions are seeking guidance regarding how to identify and ensure protection for initial ≥ 3 dose non-responders.

Topics assessed by the working group have included the following:

- Changing epidemiology of hepatitis B
- Healthcare personnel risk of blood and body fluid (BBF) exposure, predominantly since 2002
- Healthcare personnel rates of reporting BBF exposures, predominantly since 2002 (it is important to recognize that a significant number of exposures are not being reported)
- Probability of hepatitis B surface antigen (HBsAg)-positive source patient, predominantly since 2002
- Efficacy of hepatitis B immune globulin (HBIG) for post-exposure prophylaxis
- Healthcare personnel HepB vaccine coverage levels
- Evidence of serologic and clinical protection after vaccination with HepB primary series
- Evidence of serologic protection after a "challenge" dose of HepB vaccine
- Long-term HepB vaccine protection
- Acute hepatitis B among healthcare personnel
- Survey among healthcare institutions in California to assess current practices

Hepatitis Working Group activities have included 19 working group teleconferences, a presentation to HICPAC in June 2012, and presentations during the ACIP meetings in February 2012 and June 2012. Considerations for guidance for trainees and non-trainees were presented to ACIP during the June 2012 meeting with regard to pre-exposure evaluation for protection and post-exposure management with evaluation for continuing protection. These two approaches, both of which have advantages and disadvantages, can be considered in terms of potential guidance.

During this session, information was presented with regard to Hepatitis B among healthcare personnel in terms of continuing risk for hepatitis B virus exposure, Hepatitis B vaccine coverage, and national surveillance; updates to cost-effectiveness analyses; long-term protection; current practices; and proposed guidance.

Risk of Hepatitis B Virus Infection among HCP

Sarah Schillie, MD, MPH, MBA

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

During this session, Dr. Schillie discussed the changing epidemiology of hepatitis B; hepatitis B (HepB) vaccine coverage among healthcare personnel; risk and reporting of occupational blood and body fluid exposures; and acute hepatitis B among healthcare personnel.

The number of acute hepatitis B cases in the US has declined. In 2010, there were 3350 cases reported to the NNDSS. When accounting for asymptomatic and unreported cases, an estimated 35,000 new cases of hepatitis B occurred in 2010. Although the number of cases of acute hepatitis B has declined, data from the NHANES survey indicate that the prevalence of chronic hepatitis B¹ has remained stable [Chronic Hepatitis B defined as the presence of both hepatitis B surface antigen (HBsAg) and antibody to hepatitis B core antigen (anti-HBc), prepared by H. Roberts]. Persons with chronic hepatitis B serve as the main reservoir for continued transmission. There are an estimated 800,000 to 1.4 million persons with chronic hepatitis B in the US.

The prevalence of chronic hepatitis B overall and among selected populations (e.g., Alaska Natives¹, inmates, injection drug users, immigrants, HIV-positive persons, and Asian and Pacific Islanders living in New York City), ranges from 0.3% to 24% [Brian McMahon and Brenna Simons, Alaska Native Tribal Health Consortium]. Prevalence also varies across healthcare settings. For the cost-effectiveness analysis, the prevalence of HBsAg-positivity was assumed to be 0.9%² among source patients [Representing 7,170 exposures from three healthcare institutions].

There has been a decline in hepatitis B infections among healthcare personnel from approximately 17,000 in 1983¹ to 263 in 2010². This decline has been attributed to hepatitis B vaccination and improvements in infection control [Beltrami 2000; ²Surveillance data, considering that occupational history was assessed for 43.6% of cases and using a correction factor of 10.5 to account for underreporting and asymptomatic infection].

According to the NHIS survey, 81% of healthcare personnel with direct patient contact received at least one dose of hepatitis B vaccine and 74% received 3 or more doses. The proportions were smaller for healthcare personnel without direct patient contact at 51% for those receiving at least one dose and 46% receiving 3 or more doses.

In terms of risk and reporting of occupational blood and body fluid exposures, 18% of healthcare personnel trainees sustain a percutaneous injury (e.g., needlestick, cut, or bite) each year and 22% sustain a mucosal exposure (e.g., blood or body fluid contact with mucous membranes or non-intact skin). The risk is lower for non-trainees. Of the percutaneous injuries sustained, 54% are reported to occupational health, while 17% of mucosal exposures are reported.

The Occupational Safety and Health Administration's (OSHA) Bloodborne Pathogens Standard states what employers must do to protect workers who are occupationally exposed to blood or other potentially infectious materials. OSHA mandates that employers offer HepB vaccine at no-cost to workers with potential exposure. Unpaid trainees and volunteers are not covered. The Bloodborne Pathogens Standard became effective in 1992 [http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=INTERPRETATIONS&p_id=21010]. The Needlestick Safety and Prevention Act directed OSHA to revise the Occupational Exposure to Bloodborne Pathogens Standard, and established in greater detail requirements that employers identify and use effective and safer medical devices. This became effective in 2001 [<http://www.osha.gov/SLTC/bloodbornepathogens/standards.html>].

Regarding rates of percutaneous injuries and mucosal exposures based on data from the Exposure Prevention Information Network (EPINet) from 1997-2009, percutaneous injuries have decreased from 30 to 40 injuries per 100 occupied bed prior to the Needlestick Safety and Prevention Act to about 20 injuries per 100 occupied beds in 2009. Mucosal exposures have decreased from approximately 10 exposures per 100 occupied beds in 1997 to approximately 7 exposures per 100 occupied beds in 2009 [<http://www.healthsystem.virginia.edu/pub/epinet/rates.html>].

In order to ascertain the number of healthcare personnel with acute hepatitis B, surveillance data from 2005-2010 were reviewed. Among the subset of cases for whom occupation was assessed (e.g., 46.0% and 43.6% of cases for 2009 and 2010, respectively), 203 cases of acute hepatitis B among healthcare personnel were reported to CDC. The question, "Has this patient ever received the 3-dose series of hepatitis B vaccine?" is routinely asked for surveillance cases. The response was "yes" for 19%, "unknown" for 24%, and "no" for 57%.

Additional information on vaccination history and response status was obtained for 76% of cases with "yes" and "unknown" responses. Among the 203 cases, the mean age was 41.7 years; 40% were males; 17% sustained an accidental stick with a needle or sharp object¹; 60% had other hepatitis B risk factors²; 41% were hospitalized; 38% developed chronic infection, although information on chronic infection was present for only 16 cases; there were no deaths; and 19% were vaccinated with 3 or more doses of hepatitis B vaccine [¹During 6 weeks – 6 months prior to illness; information on post-exposure prophylaxis not available; ²Other risk factors consist of: contact with hepatitis case, receipt of dialysis, blood transfusion, men who have sex with men, injection drug use, multiple sexual partners, surgery, acupuncture, or tattoo].

Among the 203 healthcare personnel with acute hepatitis B, 35 had received 3 or more hepatitis B vaccine doses. Of these 35, 7 had complete documentation of vaccination, including month, date, and year for all doses and 4 of 8 with information developed chronic infection. Among the vaccinated cases, there was one vaccine responder and 4 non-responders. Post-vaccination serologic results were unknown for the majority.

In summary, acute hepatitis B occurs among healthcare personnel who are unvaccinated or vaccine non-responders. Chronic hepatitis B occurs in some healthcare personnel. Hepatitis B vaccine coverage among healthcare personnel is not optimal; therefore, efforts are needed to improve coverage.

Cost-Effectiveness Updates and Hepatitis B Vaccine Long-Term Protection Studies

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During this session, Dr. Murphy updated the results of cost-effectiveness analyses shown to ACIP in June 2012. The cost-effectiveness analyses examined various approaches for identifying vaccine non-responders; that is, healthcare personnel with primary vaccine failure who, when identified, may receive revaccination or post-exposure prophylaxis. She also summarized the results of long-term protection studies for hepatitis B vaccination starting in infancy. The results of these studies informed the working group of continuing vaccine-induced protection over time.

As previously noted, an increasing proportion of healthcare personnel will be vaccinated in infancy and adolescence in the coming decade. Post-vaccination testing for protection is not recommended after routine vaccination; however, post-vaccination testing has been recommended since 1987 for healthcare personnel who are at on-going risk for percutaneous injury and serves as a guide to revaccination and post-exposure prophylaxis [MMWR 1997].

Seroprotection results are a useful surrogate of hepatitis B protection or efficacy after vaccination. HepB vaccine-induced antibody to anti-HBsAg of ≥ 10 mIU/mL correlates with priming for immune memory when anti-HBs is measured soon after completion of vaccination series. An anti-HBs < 10 mIU/mL generally suggests poor or non-response to vaccination [West DJ. Vaccine 1996;14:1019-27].

An important limitation of post-vaccination testing for identifying protective HepB vaccine response is waning of the anti-HBs titers over months or years. Levels of anti-HBs < 10 mIU/mL at time distant from vaccination does not distinguish^{1,2} vaccine responders who are protected and account for greater than 90% of healthy vaccinees, or vaccine non-responders who remain susceptible to hepatitis B infection and account for less than 10% of vaccinees. In the coming years, a substantial proportion of new healthcare personnel are expected to have anti-HBs < 10 mIU/mL upon matriculation and hire [¹MMWR 2005; ²Or have chronic HBV infection].

The Hepatitis Working Group considered multiple approaches for ensuring hepatitis B protection among previously vaccinated healthcare personnel. The two approaches most favored by the working group included pre-exposure evaluation for protection, and post-exposure management with evaluation at that time for continuing protection. The working group also favored applying the approach to both trainees and non-trainees for simplicity of implementation.

With the pre-exposure evaluation for protection, anti-HBs is measured upon matriculation or hire. Healthcare personnel with surface antigen ≥ 10 mIU/mL require no post-exposure prophylaxis for hepatitis B. Although prophylaxis may be indicated for other bloodborne pathogens. Healthcare personnel with anti-HBs < 10 mIU/mL are given a dose of HepB vaccine as a challenge to elicit a memory response, followed by re-measured anti-HBs. Persons whose

anti-HBs remains <10 mIU/mL after the challenge dose are given 2 more doses of HepB vaccine to complete revaccination. Those whose anti-HBs remains <10 mIU/mL after revaccination are counseled to seek management for exposure to blood and body fluids.

The post-exposure management and evaluation approach for continuing protection involves no management prior to blood and body fluid exposure. When an exposure occurs, evaluation consists of simultaneous testing of the healthcare personnel for anti-HBs, and testing of the source patient for hepatitis B surface antigen (HBsAg), which is a marker of infection. Healthcare personnel with anti-HBs <10 mIU/mL are revaccinated and non-responders may receive hepatitis B immune globulin (HBIG).

Pre and post-exposure approaches were considered in cost-effectiveness analyses. The cost-effectiveness model and inputs were described during the June 2012 ACIP meeting. Some inputs differ for trainees and non-trainees; thus, incremental cost-effectiveness ratios are reported separately for trainees and non-trainees. As a reminder, the working group provisionally defined "healthcare trainees" as "persons entering school and/or obtaining new job skills that involve contact with patients or with blood or other body fluids (BBF) from patients in a healthcare, laboratory, or public-safety setting [Adapted from MMWR. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. June 29, 2001/50(RR11);1-67].

The major differences in the inputs for trainees relative to non-trainees are that trainees are assumed to be younger by 10 years than non-trainees and, therefore, have higher total medical costs and QALY losses from hepatitis B infection. Trainees have a higher probability of blood and body fluid exposure than non-trainees and, therefore, have a greater risk of infection. Trainees are more likely to receive HepB vaccination at less than 1 year of age. It is estimated that by 2013, more than 80% of persons 18 to 20 years of age would have been vaccinated at less than 1 year of age. Data suggest that vaccination during infancy results in more rapid waning of post-vaccination antibody. In some studies, fewer persons vaccinated at 1 year or less have a memory response to a challenge dose of HepB vaccine relative to non-trainees. These observations leave open different interpretations of protection.

The original cost-effectiveness model assumed protection when anti-HBs was ≥ 10 mIU/mL in persons with documented HepB vaccine series. In this model, seroprotection is established by an anti-HBs ≥ 10 mIU/mL at any time; that is, with an initial test, after a challenge dose, or after revaccination. Healthcare personnel are considered unprotected until seroprotection is established with an anti-HBs result of ≥ 10 mIU/mL.

The incremental cost-effectiveness ratios (ICER) were determined for pre-exposure and post-exposure approaches relative to no intervention, and separately for trainees and non-trainees using the original model assumption of protection (i.e., anti-HBs result of ≥ 10 mIU/mL). The first-year and 10-year ICERs assess the investment in ensuring protection over one and 10-year periods of the healthcare personnel career. Regardless of approach, ICERs are highest in the first year and lower if considered over a 10-year period. Pre-exposure costs are higher than post-exposure costs in the first year, but are lower than post-exposure costs over 10 years. The rate of expected incidence infections is higher for the post-exposure approach than for the pre-exposure approach. This is because exposures result in infections among vaccine non-responders who have not previously been identified or who do not recognize or report their exposure.

Before considering the results of the cost-effectiveness analyses using a revised assumption of protection, it is first necessary to consider the seroprotection proportions achieved in clinical trials of recombinant HepB vaccine by age at vaccination. The results of many trials show that about 95% of healthy term infants achieve seroprotection after a hepatitis B vaccine series starting at birth¹. Premature infants respond less well, but have results similar to term infants when vaccinated starting at one month of age. In a large clinical trial among healthcare personnel, more than 90% of persons less than 40 years of age² and about 85% of personnel 40 years and older³ achieved seroprotection after a hepatitis B vaccine series. Chronic illness, smoking, obesity, and age resulted in lower proportions of healthcare personnel who are seroprotected [¹MMWR 2005; ²Averhoff F et al. *Am J Prev Med* 1998].

In June 2012, the Hepatitis Working Group was asked to report cost-effectiveness results using a 95% assumption of protection based on the proportion of infants seroprotected in clinical vaccine trials. This assumption did not require knowledge of the anti-HBs test results; however, the model retained costs of testing for anti-HBs and the cost of revaccination as prescribed in pre- and post-exposure approaches. The rationale for this model was to show the high incremental cost-effectiveness ratios of evaluation if 95% of healthcare personnel are protected through vaccination in the absence of measurable anti-HBs. The results of the revised ICERs are shown relative to no intervention when applying the 95% assumption of protection. The ICERs in the revised model were considerably higher in all categories than in the original model. However, the same patterns of decline were present in the revised model for the first year ICERs to the 10-year period ICERs for both pre- and post-exposure approaches. The same patterns of hepatitis B infection resulted, but the incidence of infection was considerably lower than in the original model because most healthcare workers are assumed to have vaccine-induced protection regardless of anti-HBs level. In summary, ICERs were highly sensitive to assumptions of vaccine-induced protection. First year ICERs were substantially higher than the 10-year ICERs regardless of assumption of protection. Generally, the pre-exposure approach is more cost-effective in the long-term and the post-exposure approach is more cost-effective in the short-term.

With respect to long-term HepB vaccine protection against acute subclinical and chronic hepatitis B virus infection, recall that ensuring hepatitis B protection for remotely vaccinated healthcare personnel relies on continuing vaccine-induced protection during the healthcare career. The approximate age of matriculation for many healthcare personnel trainees and new healthcare personnel hires is 18 to 20 years. Evidence for long-term protection after infant vaccination is available for approximately 20 years from populations with increased prevalence of chronic hepatitis B virus infection. Recall that the purpose of hepatitis B vaccination starting at birth is to prevent perinatal and early childhood hepatitis B infection. These early infections result in the highest age-specific rates of chronic hepatitis B infection; that is, about 90% of infants are infected at birth and about 30% of children under 5 years of age are infected in contrast to about 6% of persons infected later in life. Chronic hepatitis B virus infection in infancy and childhood results in an approximately 25% lifetime risk of premature death from cirrhosis, liver failure, and hepatocellular carcinoma (HCC). When routine vaccination has been introduced in populations with elevated prevalence of chronic hepatitis B, major reductions have been recognized in the childhood prevalence of chronic hepatitis B infection, with about a 70% reduction in hepatocellular carcinoma before age 20 years [McMahon BJ. *Hepatology* 2011;54:801-7; Chang M-H et al. *JNCI* 2009;101:1348-55; Wichajarn K et al. *Asian Pacific J Cancer Prev* 2008;9:507-10; Sun Z et al. *Cancer Detect Prev* 1991;15:313-8; Zun Z et al. *Vaccine* 2011;29:7835-41].

As vaccinated infants have aged into adults, there has been increasing interest in the durability of protection after hepatitis B vaccination starting in infancy. Dr. Murphy summarized the findings of 6 studies describing the long-term outcomes of persons who received hepatitis B vaccination in the first year of life. Studies were conducted in Alaska^{1,2}; Thailand³; Qidong, China⁴; Taipei, Taiwan⁵; Taoyuan, Taiwan⁶; and Northern Taiwan⁷ [¹McMahon BJ et al. *Ann Intern Med* 2005;142:333-41; ²McMahon BJ et al. *J Infect Dis* 2009;200:1390-6; ³Poovorawan Y et al. *J Viral Hepat* 2011;18:369-375; ⁴Zhu C-L, et al. *Vaccine* 2011;29:7835-41; ⁵Ni Y-H et al. *J Hepatology* 2012;57:730-5; ⁶Lai M-W et al. *Gastroenterology* 2012: on-line; and ⁷Su F-H, et al. *Vaccine* 2007;25:8085.

When vaccination was introduced in the 1980s, most of these populations had a high prevalence of chronic hepatitis B infection; that is more than 8% prevalence of chronic hepatitis B. Infant vaccination consisted of 3 or 4 doses of plasma-derived hepatitis B vaccine, except in Thailand where infants received 4 doses of recombinant vaccine. Three of the studies followed cohorts. In Alaska, an attempt was made to vaccinate all susceptible Alaska Natives. Subjects in 15 villages were selected for long-term follow-up. Thailand and Qidong infants were enrolled in vaccine clinical trials. Three other studies were seroprevalence surveys (Taipei, Taoyuan, Northern Taiwan). Two of the surveys examined convenience samples of children (Taipei, Taoyuan), and one examined new students enrolling in a college (Northern Taiwan). The initial number of subjects varied from almost 1600 in Alaska to less than 250 in the Thailand cohort. Subjects in Alaska were vaccinated starting at 6 months of age through 50 years of age. Infants in the other studies received the first dose of vaccine at birth. Blood samples were obtained from the cohorts annually or at other regular intervals; whereas, the seroprevalence surveys conducted one-time testing.

In the cohort studies, between 100 and 500 subjects (or approximately 24% and 50% of the original cohorts) agreed to participate in the last follow-up. Vaccination was verified in medical records or study records. In the seroprevalence surveys, the number of vaccine recipients ranged from 35 to more than 800. The method of verifying vaccination in the Taipei and Northern Taiwan surveys was with a personnel vaccine record or the national database, and was not stated in the Taoyuan survey.

Exclusion criteria varied. In the cohort studies, persons were excluded if they received booster vaccination, had perinatal infection, or were vaccine non-responders. Thus, the results of the cohort studies reflect long-term protection among vaccine responders. The exception was the Thailand study cohort which retained 63% of the original subjects who had received a booster dose of recombinant vaccine at age 5 years, and the Qidong cohort, which excluded 105 children with new hepatitis infection before age 5 years. In the seroprevalence surveys, information about vaccine boosters, perinatal infection, and primary vaccine non-response might have been unknown but was not reported. However, the Northern Taiwan college students were excluded if they had received a booster dose of hepatitis B vaccine.

Although most subjects who received vaccine booster doses were excluded, natural boosting might be expected because of the high prevalence of hepatitis B in these populations. Natural boosting was defined as "an increase in antibody to hepatitis B anti-HBs without anti-HBc or other marker of hepatitis B infection." Natural boosting was observed in roughly 10% of subjects in each decade of follow-up. In the Alaska Native population, the relative risk of natural boosting was two times higher among children and adolescents less than 19 years of age compared with older adults. Qidong reported the highest rates of natural boosting at 23% in the second decade of life.

The Alaska Native and Thailand cohorts examined for acute hepatitis B infection by history or other indicators. No acute hepatitis B infection was identified.

Subclinical infection was defined by persistently positive anti-HBc, which is not elicited by vaccination. Subclinical infections were detected in 1% to 12.8% (corrected) of subjects, although the rates in most studies were less than 7% of subjects. Transient hepatitis B surface antigen or hepatitis B virus DNA was detected in 2 of 24 Thailand subjects with subclinical infection. No chronic infection developed in the Alaska Native or Thailand subjects. In the Qidong cohort, 1.0% (corrected) of subjects developed chronic infection. In the seroprevalence surveys, most chronic infections were attributed to perinatal hepatitis B transmission, with a range of 1% to 6% of subjects. The Taoyuan seroprevalence survey examined for mutant hepatitis B virus and identified an additional chronic hepatitis B infection in the vaccinated group. It was not clear whether this infection and other reported chronic infections with mutant virus were acquired through perinatal transmission.

Although infants with weak or non-response to vaccination were excluded from the long-term follow-up cohorts in Alaska and Qidong infants, some information is available about their outcomes. The rates of chronic hepatitis B infection among Alaska Native vaccine non-responders was reported to be seven times higher than among vaccine responders at the 15-year follow-up, with a relative risk of 4.22 versus 0.61 infections per 1000 person years. In Qidong, 1.1% of children who no longer had measurable vaccine-induced antibody, but remained uninfected at age 5 years, developed chronic hepatitis B infection by the 20-year follow-up.

In summary, hepatitis B vaccination started in infancy or at birth protects responders from acute and chronic hepatitis B infection for at least 20 years in populations with a high prevalence of chronic hepatitis B virus infection. Subclinical hepatitis B infection occurs, but is generally uncommon and is of uncertain long-term significance. Vaccine non-responders remain susceptible to acute and chronic hepatitis B infection based on the US national surveillance data, which Dr. Schillie presented. Mutant hepatitis B virus infection appears to be rare, but can be associated with chronic infection. Current surveillance practice is not designed to detect infection with mutant hepatitis B virus; however, monitoring may be of interest in the future.

There are limitations to the long-term protection studies as they translate into predictions about protection among healthcare personnel. Although cohorts have been followed for 20 years, the number of studies is small and the number of subjects is declining. Most healthcare personnel start their training for healthcare careers at about 18 to 20 years of age. The results involve primarily infants who received plasma-derived vaccine. However, major differences in results are not expected in persons vaccinated with recombinant vaccine. The follow-up schedules, exclusion criteria, and definitions vary by study. Few studies have consistently performed hepatitis B DNA testing for mutant hepatitis B virus infection among subjects with subclinical infection.

The Hepatitis Working Group discussed possible studies to inform future decisions, and to provide guidance for healthcare personnel who continue to be at risk of exposure to hepatitis B in healthcare settings. Some studies to inform future decisions include the following:

- Correlates of protection in the absence of antibody to hepatitis B surface antigen (anti-HBs)
- Active monitoring for hepatitis B protection among vaccine recipients
- Comprehensive evaluation of vaccinated healthcare personnel responders and non-responders, and unvaccinated healthcare personnel exposed to blood and body fluid from hepatitis B surface antigen positive patients
- Additional long-term studies of protection (e.g., infants vaccinated with recombinant vaccine)
- Trials to examine higher dosage, or more immunogenic vaccines to induce protection among 3-dose vaccine non-responders
- Evaluation of antiviral therapy for post-exposure prophylaxis

Current Practices and Considerations for Guidance

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Dr. Schillie indicated that the working group had considered multiple approaches to ensure hepatitis B protection among previously vaccinated healthcare personnel for trainees and non-trainees. As noted earlier, the two approaches most favored by the working group were a pre-exposure evaluation for protection and a post-exposure management approach with evaluation for continuing protection.

In order to assess whether a pre-exposure or post-exposure approach is more common in current practice, a survey was administered electronically to 580 infection control and employee health staff listserv subscribers in California healthcare institutions. There were 153 responses representing a response rate of 39.3% response rate, considering that the denominator (389) as the number of acute care hospitals. Most respondents classified their institution as a non-government, not-for-profit community hospital, followed by investor-owned for-profit community hospital. Other institution types included state and local government community hospital, federal government hospital, non-federal long-term care hospital, hospital unit of an institution, or other.

The number of licensed beds ranged from 8 to 1801, with a median of 202. Nearly all institutions had adult beds (151 or 98.7%), and half had pediatric beds (78 or 51.0%). The proportion which were teaching hospitals was 24.2%. The number of healthcare personnel with reasonably anticipated risk for blood or body fluid exposure ranged from 35 to 15,421 with a median of 1000.

Respondents were asked, "How does your institution currently manage new healthcare personnel who have documentation of a complete hepatitis B vaccine series, but no documentation of post-vaccination serologic testing?" The majority of respondents (72%) reported that their institution uses a pre-exposure evaluation approach (includes institutions that do not revaccinate HCP if anti-HBs <10 mIU/mL and source patient is HBsAg-negative), while 16% reported a post-exposure management approach and 24% reported other approaches. Other approaches consisted of administering a challenge dose of vaccine, or giving healthcare personnel their choice. The total adds to more than 100% because institutions could select more than one response.

Respondents were asked, “For what proportion of healthcare personnel does your institution have a record of documented post-vaccination hepatitis B surface antibody level?”¹ [Includes anti-HBs obtained at any time in the past, including anti-HBs performed at other institutions] Response categories were in increments of 20%. Of the institutions, 9% had anti-HBs for less than 20% for healthcare personnel. Slightly more than half of institutions had anti-HBs for 80% or more of healthcare personnel. Based on these results, approximately 69% of healthcare personnel have a record of anti-HBs results.

In terms of the key features of the two approaches, the pre-exposure evaluation approach offers protection against unrecognized and unreported exposures, while the post-exposure management approach does not. The pre-exposure evaluation approach results in fewer infections and is also associated with more work now and less work on exposure, while the post-exposure management approach is associated with less work now and more work on exposure. As a result, the pre-exposure evaluation approach has lower 10-year incremental cost-effectiveness ratios, while the post-exposure management approach has lower initial incremental cost-effectiveness ratios.

Institutional characteristics may favor either a pre-exposure evaluation approach, or a post-exposure management approach. Institutions where healthcare personnel sustain frequent exposures and source patients have a high prevalence of anti-HBs positivity may prefer a pre-exposure approach. A pre-exposure approach may also be more desirable in settings where post-exposure prophylaxis is not readily available. Institutions such as long-term care facilities that have high staff turnover may prefer a post-exposure approach.

Discussion Points

Dr. Temte clarified that ACIP was not being asked to vote, but was instead being asked to provide guidance to the working group in terms of decision-making in terms of these two approaches. He inquired as to whether there was any estimate of turnover rates in long-term care facilities or within hospital settings, and how transferrable pre-exposure evaluation information might be from one institution to another and across state lines.

Dr. Schillie indicated that members of the working group have reported that turnover rates are very high in long-term care facilities, and this would make a pre-exposure approach much more difficult. In terms of how transferrable pre-exposure evaluation information is, healthcare personnel are encouraged to keep records so that when they transfer from one institution to another, the new institution does not have to redraw titers. The working group assessed the issue of registries and whether they would be appropriate in these circumstances, but there were concerns such as issues across states. For example, a trainee may be a resident of one state but may be training in another state. The working group decided that registry information might not be overly useful in these circumstances.

Among the 203 cases of acute hepatitis B that were reported to CDC, Dr. Keitel asked if it was known how many of those had direct patient contact. She also noted that it was her understanding that the plasma-derived vaccine was thought to be more immunogenic, and she wondered whether there were any long-term studies of antibody persistence comparing plasma-derived and recombinant vaccine.

Dr. Schillie replied that it was not known how many had direct patient contact. The surveillance questions ask about the frequency of blood and body fluid exposure. It is a dichotomous question based on number of times per week. That does not necessarily correlate with direct patient contact. For example, someone working in the laboratory might have more frequent exposure but no direct patient contact.

Dr. Murphy confirmed that the plasma-derived vaccine is said to have perhaps had higher efficacy. There were not very many efficacy studies using the recombinant vaccine among infants that assessed infection rather than seroprotection. The only long-term study is the one she presented from Thailand.

Since the recommendation was to potentially select a strategy based on whether an institution has a high frequency of bloodborne pathogen exposures, Dr. Duchin wondered if it would be feasible to target a class of healthcare workers within institutions and only stratify by institution, because they would have a spectrum of different types of healthcare workers at different risk.

Dr. Schillie responded that this would be an option. A recurrent theme that arose during working group discussions regarded the issue of trainees. All trainees are, by definition, high risk. Therefore, even if someone is ultimately going to be in a low risk specialty, when they are rotating through medical school they spend two months on surgery.

Regarding the revised model for cost-effectiveness, Dr. Duchin thought the costs seemed extremely high. He wondered whether the numbers were comparable to the type of cost-effectiveness figures ACIP has seen for other interventions, or if they were somehow not comparable because of the method used.

Dr. Murphy was not sure she could answer Dr. Duchin's first question, because that would mean comparing the methods people have used for other studies. However, she was told that cost-effectiveness analyses were done with the original recommendations for healthcare workers, and it was not cost-effective at that time. However, those numbers were not published. She agreed that the costs were very high.

In terms of education or to inform policy efforts, Dr. Poland (ACP) found it somewhat surprising that only 19% of the sample evaluated had been vaccinated. He wondered whether it was known why the other 80% were not vaccinated. In terms of a potential recommendation, he suggested considering an algorithm approach. He receives questions on this topic every week in terms of what to do with these individuals. In some studies (e.g., the Alaskan studies, Asian studies, and some studies in men who have sex with men) there were instances in which, despite having been immunized and HIV-negative, there were 1% to 7% rates of infection. This might be important in the sub-segment of healthcare workers who either have concomitant liver disease, or are taking medications that have liver consequences. He has observed in his institution that, broadly speaking, healthcare workers, particularly nursing aids and others, are increasingly older, fatter, and foreign-borne with unknown vaccine status. That may be critical to dose of vaccine, number of doses, and method of administration. He viewed all of those as confounding factors. An algorithm was published in the *American Journal of Preventive Medicine* in 1998 on this topic.

Dr. Schillie replied that they do not have information on why the other 80% were not vaccinated.

Ms. Rosenbaum wondered whether Dr. Schillie could elaborate on what is known about the degree to which state licensure laws or Medicare / Medicaid conditions of participation require either a pre- or post-exposure protocol.

Dr. Schillie replied that there is no requirement for either one or the other approach. OSHA is the most important regulatory body in this arena. OSHA does mandate that employers offer vaccination to healthcare personnel. The OSHA language is somewhat vague on whether pre-exposure surface antibody testing would be covered, or would be required for hospitals to perform at no cost to the worker. The OSHA language does state that healthcare institutions need to follow US Public Health Service guidelines. CDC has been in communication with OSHA, and the OSHA representative informed CDC that it is certainly OSHA's intent that these activities be covered.

Given the guidelines, Ms. Rosenbaum requested clarity regarding whether the assumption was that healthcare institutions were taking one of the two approaches.

Dr. Schillie responded that most healthcare institutions are taking either the pre-exposure evaluation approach, or a post-exposure management approach. About 7% of institutions are giving a challenge dose of vaccine first, and then testing titers subsequently to that.

Dr. Kelly Moore (AIM) emphasized that the idea of registries was a good option, because states vary tremendously. Some states do not have lifelong registries, but others like Tennessee do. Registries already capture history of chicken pox disease and other useful items, so depending upon the state, there may be a great option to solve the problem of documentation for post-vaccination serologic testing in their registries. Even though the information is not in a national registry, that information is shared between states all of the time and it becomes a permanent repository for a person. Although there is not an ideal national solution, states are getting increasingly better. For many states, this will be a great solution to tap into for this thorny issue.

Dr. Temte emphasized that registries are incredibly useful, and that he uses the Wisconsin Immunization Registry on a daily basis that is tied into his practice's EMR. Consequently, he is reaching saturation on vaccination of his adult patients because the information is available and usable. State registries must be considered as part of a whole. When someone works over a boarder or someone moves to a different jurisdiction, that information should be available. The technology is available, but it is a matter of states cooperating and having the impetus to do so.

Dr. Schaffner (NFID) said he inferred more from the tone of the conversation that the working group intended to have ACIP select or express a preference for one approach or the other. He wondered whether that was necessary, given that both approaches seemed to be applicable to different institutions, and institutions should choose one or the other and ought to do one or the other or a variation of them.

Dr. Schillie responded that a recent decision was made that a vote would not be requested during this meeting. Depending upon the individual characteristics of institutions, one approach or the other might be more appropriate.

Dr. Wharton clarified that CDC agreed with that assessment of the working group that multiple approaches may be appropriate for various institutions, so the agency did not plan to have ACIP select one approach over the other. Instead, CDC plans to develop guidance that will identify different options that institutions can undertake in order to address this issue.

Dr. Sawyer added that the working group was evenly split between the two options, and was unable to clearly select one option over another.

In terms of a pre-exposure technique, Dr. Warshawsky (NACI) wondered whether some caveats would be included for immunocompromised healthcare workers who might need periodic monitoring because they had a titer at one point, but it might wane over time.

Dr. Schillie replied that immunocompromised healthcare workers are covered under other recommendations. These recommendations focus on immunocompetent healthcare personnel.

Dr. Elward (HICPAC) confirmed that healthcare personnel turnover rates among healthcare facilities are high, especially among long-term care facilities. During the HICPAC meeting in June, there was a lot of discussion about the ability to distinguish between waning immunity versus an initial non-vaccine responder, and whether serology 20 years or more post-vaccination is really the best measure of long-term durable immunity. During the most recent HICPAC meeting, input from subject matter experts, including HICPAC's liaison from the American College of Occupational and Environmental Medicine (ACOEM). Of course, ACOEM will be somewhat biased because that represents larger academic tertiary care centers and larger healthcare centers. Many systems are testing post-vaccine serology at admission because people do not remember whether they were vaccinated, and are interpreting the current guidance to document evidence of post-vaccine serologic response to actually have antibody measurement done.

Dr. Bennett commented that in developing the guidance and giving an option to institutions, it would be critical to be very clear about what characteristics would lend an institution to choose one or the other option.

Dr. Keitel requested clarification regarding whether, among the 203 cases that were reported, only 19% had been vaccinated, under what circumstances hepatitis B vaccination would be required or not required, and whether the answer to this would be requiring healthcare providers to receive hepatitis B vaccine.

Dr. Schillie reiterated that for healthcare workers, OSHA requires that institutions offer the vaccine at no cost to the employee, but employees can sign a declination statement refusing the vaccine. She also noted that some of the surveillance cases did have one or two doses of vaccine, but not a complete series.

Dr. Sawyer pointed out that another important part of the guidance would be to try to do something about under-reporting. He was quite struck with the fact that more or less half of exposures are not being reported. Institutions that choose to follow a post-exposure strategy will not be able to assist people in preventing infections. If a post-exposure strategy is going to be offered as an option, it needs to be coupled with an effort to improve reporting.

Ms. Rosenbaum noted that this is part of a much broader set of issues pertaining to the immunization status of healthcare workers generally. Institutions offer immunizations, but collective bargaining rules and other issues apply. It remains an unsettled area of the law, which was why she was particularly interested in the exposure question. Since immunizations are not simply a condition of licensure for participation at healthcare institutions, home health programs, clinics, et cetera, this is a major challenge.

Dr. Brady (AAP) inquired as to whether there were any data regarding potential cost-effectiveness related to children's hospitals, considering that the vast majority of patients in those hospitals will have received the infant vaccine.

Dr. Schillie responded that the ICERs increase or the cost-effectiveness decreases as the rate of surface antigen positivity among source patients decreases. If the assumption is made that children's hospitals have a low rate of surface antigen positivity, the approaches become less cost-effective. For the sensitivity analysis for the cost-effectiveness analysis, an expert opinion was used and 0.3% was selected as the lower-bound, which was a third of the 0.9% that was used for the main analysis.

Dr. Loehr (AAFP) commented that his 200-bed community hospital is located in a college town where there is a fairly mobile turnover rate for employees of about 8% to 10% per year. He also requested clarity regarding whether the cost-effectiveness numbers were to prevent 1 case of chronic hepatitis B.

Dr. Schillie replied that the numerator was the cost and denominator was per QALY saved, so it was to save 1 QALY rather than to prevent 1 case.

Dr. Susan Even (ACHA) reported that college health centers are commonly the site of assuring that healthcare students' immunizations are current. A significant percentage of colleges and universities have strict requirements, so ACHA is implementing requirements. The post-exposure requirement would be more manageable. The students entering training programs have been required to have the 3-dose immunizations, and many of them are now entering having already received their vaccinations as infants. That perspective in terms of the workload and cost for trainees to continue to receive serology titers just to prove their immunity would pose a significant burden.

Dr. Schillie responded that those comments had been heard throughout the working group discussions. In the California survey, institutions were asked what option they felt would be the least work for the occupational or employee health staff, and 50% indicated that a pre-exposure approach would be the least amount of work. However, those were different institutions from colleges and universities.

Dr. Temte said he thought Dr. Even was addressing colleges with health training programs, and he wondered whether she had information about community and technical colleges that offer the vast amount of training for medical assistants, nurse assistants, laboratory technicians, and a cohort of other medical personnel who are very mobile and experience a lot of turnover.

Susan Even (ACHA) replied that ACHA does not have data about those groups, and does not have connections with them.

Regarding the long-term protection data cited by Dr. Murphy, Dr. Plotkin was somewhat troubled that most of the exposures later in life would have been mucosal exposures versus parenteral exposure. Therefore, he was not clear that the information could be totally applied, although he does believe in immune memory. He wondered whether some information from intravenous drug abusers in the US would be useful in terms of whether cases are occurring in those individuals despite immunization at birth.

Dr. Murphy responded that the possibility had been explored of following up with intravenous drug users. The challenge thus far had been to find a group for whom there are accurate vaccination records, especially for young childhood or infancy.

Human Papillomavirus (HPV) Vaccines

Letter from Texas Pediatric Society

Dr. Jonathan Temte
ACIP Chair

Dr. Temte read a letter dated July 27, 2012 from the Texas Pediatric Society (TPS) into the record:

“Dear Dr. Temte:

On behalf of the 2800 members of the Texas Pediatric Society, the Texas Chapter of the American Academy of Pediatrics, I’m writing to ask that the Advisory Committee on Immunization Practices consider supporting the administration of the human papillomavirus vaccine to children and adolescents presenting for sexual abuse and assault evaluations if they have not already been vaccinated. Current HPV vaccine recommendations, as you undoubtedly are aware, cover three doses in 11 to 12 year old males and females and those age 13 to 21 years of age who have not completed the series. The recommendation is permissive, of course, for children 9 to 10 years of age.

We recommend that patients 9 years of age and older should receive the vaccine if they have been victims of sexual abuse or assault. Sexual abuse and assault victims often have unmet medical needs, including lack of immunizations. In a random sample conducted by representatives of the Texas Pediatric Society Child Abuse and Neglect Committee, which combined data from four children’s hospitals, 56% of children 9 and older who presented for sexual abuse or assault had received no HPV vaccine, 30% had received 1 or 2 doses, and only 13.5% had received all 3 doses. Sexual abuse and assault victims are 2 to 3 times more likely to engage in unsafe or unprotected sexual intercourse, and at an earlier age than non-abused children and adolescents. Follow-up examinations for victims of sexual abuse and assault at the Center for Miracles at CHRISTUS Santa Rosa Children’s Hospital in San Antonio, Texas showed that of 727 adolescents and children, 47 had a new sexually transmitted infection approximately 4 weeks (mean interval time 33.6 days) after they had been sexually assaulted, 34 of which were HPV in 1 male and 33 females; 40% of these adolescents were sexually active. While the HPV vaccine may not prevent HPV infection transmitted during sexual abuse or assault, providing the HPV vaccine expeditiously to a patient population with considerable risk for future sexually transmitted infections, including high risk HPV, has significant potential for reducing some of the health harms and costs these victims face.

We understand that education of this vulnerable population is key, but we contend that vaccination is as well. Providing this level of protection as a standard of care will help protect children and adolescents who have been victims of sexual abuse and assault and live healthier lives. Protocols may be established by clinics to treat victims of sexual abuse and assault to ensure that all 3 doses are administered. There is built-in potential for administering the second dose in a follow-up exam conducted 4 to 8 weeks after the initial visit, and some clinics continue relationships with these patients well beyond that.

We thank you for the consideration for this recommendation. Moving forward, we plan to collaborate with our partners at the national and state levels on this important work, and are more than happy to answer any questions that you may have.

*Sincerely,
Stephen Whitney, MD
President, Texas Pediatric Society*

Dr. Temte indicated that copies of this letter were sent to Dr. Brady of the Committee of Infectious Disease (COID) and a number of other parties.

Introduction

Joseph A. Bocchini, Jr, MD Chair, ACIP HPV Vaccine Working Group

Dr. Bocchini indicated that Dr. Temte forwarded the letter from TPS to the working group, who reviewed it and made comments and recommendations that would be presented during this session.

Regarding the evolution of HPV vaccine recommendations in the US, the first recommendation was made in June 2006 for quadrivalent vaccine for routine use in females 11 or 12 years of age, and females 13 through 26 years of age if not previously vaccinated. In October 2009, bivalent vaccine was licensed and the recommendation was changed to include routine use of either quadrivalent or bivalent vaccine for females 11 or 12 years of age and 13 to 26 years of age if not previously vaccinated, and a permissive recommendation for quadrivalent vaccine for males 9 through 26 years of age. From the beginning, the recommendation has included that the vaccine could be given as early as 9 years of age depending upon the recommendation of the provider. In October 2011, the recommendation was changed to routine for males 11 or 12 years of age and males up to 13 to 21 years of age not previously vaccinated, with a condition that it may be given to males 22 through 26 years of age. For men who have sex with men (MSM) and immunocompromised males, quadrivalent vaccine is recommended through age 26. There was no change in the recommendation for use of quadrivalent or bivalent vaccine in females in October 2011.

To address the letter from the Texas Pediatric Society, as noted, vaccination is recommended as early as 9 years of age at the discretion of the provider. Therefore, it can be used for sexually abused children as young as 9 years of age. In discussion with the working group, it was felt that no further ACIP recommendation was needed at this time, but this additional information about use of the vaccine in sexually abused or victimized adolescents will be included under "Special Circumstances" when the statement is next updated. The working group also felt that it was important to address this issue in the primary resources that

physicians and other providers use when they care for children who may be sexually abused. Three major sources of information were identified, and the working group has had contact with specific individuals. Dr. Brady, Chair of COID, was also made aware of this letter. COID is responsible for the Red Book, which has a chapter on the management of sexually abused children for the identification and prevention of sexually transmitted diseases in that population of children. In addition, the AAP Committee on Adolescents has a clinical report that includes recommendations for children who are victimized. The latest edition of that report was in 2008, and it indicates use of Hepatitis B vaccine and discusses HPV vaccine. That policy was under revision at the time of this ACIP meeting. COID plans to review that policy, specifically as it relates to inclusion of HPV vaccine for children who are sexually abused. CDC's STD Treatment Guidelines, which will be revised in the spring of 2013, include a section on management and prevention of sexually transmitted diseases in sexually victimized children and will be updated as well. The working group believes that the primary resources will include specific guidance and that the ACIP statement will include that information as well in the next revision.

At the time of this ACIP meeting, no major new policy issues were being considered by the working group. Working group calls have included review of data from a Costa Rica bivalent vaccine trial related to oral HPV infection, and end of study data from the GSK bivalent HPV vaccine trial. At this ACIP meeting, data were presented on: 1) efficacy against oral HPV infection from the Costa Rica vaccine trial, 2) progress in vaccine uptake and reasons for non-vaccination based on NIS-Teen data from 2007-2011, and 3) future working group plans and CDC activities.

Oral HPV 16/18 Vaccine Efficacy among Females: Data from the Costa Rica Vaccine Trial (CVT)

**Dr. Aimée R Kreimer
Infections & Immunoepidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute, National Institutes of Health**

Dr. Kreimer began by disclosing that the Costa Rica Vaccine Trial (CVT) was sponsored and funded by the National Cancer Institute of the United States, with funding support from the National Institutes of Health, Office of Research on Women's Health, and conducted with support from the Ministry of Health of Costa Rica. The vaccine used in the CVT was provided by GSK Biologicals, under a Clinical Trials Agreement with the National Cancer Institute. GSK also provides support for aspects of the trial associated with regulatory submission needs of the company under grant FDA-IND7920. NCI and Costa Rica investigators were responsible for study design, data collection, and interpretation of data and had final editorial decisions on this presentation.

She then presented data regarding HPV 16 and 18 infections in the oral region, emphasizing that the reason this was important was because it is now known that HPV causes a subset of head and neck cancers specifically in the oropharynx. HPV16 causes some oropharyngeal (OP) cancers, more commonly among men than women. In the US, the incidence of OP cancer in men is increasing and may surpass the number of cervical cancers by 2020. The increase in the rate of cancer is due to disease attributable to HPV infection [Chaturvedi AK *et al* J Clin Oncol 2011; 29:4294].

Oral HPV natural history is largely unknown. In the US, oral HPV16 prevalence is 1%. Age-specific prevalence peaks among individuals aged 30 to 34 years and 60 to 64 years, and is associated with male gender and sexual behavior [Gillison ML *et al* JAMA 2012; 307:693]. This is quite different from what is observed in the cervix, where the HPV attack rate is highest among women in their late teens and early twenties, which is shortly after sexual debut for many women, and where the bolus of HPV cervical infections is seen. For oral HPV infection, the peak in prevalence appears to occur later. Oral HPV 16 prevalence is associated with male gender, as well as sexual behavior.

It is known that HPV infection causes cancer at multiple anatomic sites; thus, there have been vaccine efficacy studies at many of these sites as well. For the cervix, it is understood that HPV is a necessary cause of the cancer and there is an HPV-induced pre-malignant lesion that is referred to as cervical intraepithelial neoplasia (CIN). There is also screening for cervical cancer. The vaccines have shown efficacy for both persistent HPV 16 and 18 infections, as these associated pre-malignant lesions. Vaccine efficacy is quite high at more than 90%. Anal cancer also has a very high attributable proportion of HPV infection at 90%. Again, there is an HPV-induced pre-malignant lesion. The vaccine studies have shown that the efficacy is quite high against both persistent HPV 16 and 18 infection at the anus, and the associated pre-malignant lesion. There is more etiologic heterogeneity for cancers at the penis, vagina, and vulva, with about 40% of these cancers being due to HPV infection. For each of these sites, there are data to show that the vaccine works to protect against infections and in some cases, the pre-malignant lesions at these sites. It is interesting to note that for the oropharynx specifically, there is a broad range in the proportion of oropharynx cancers due to HPV infection. In developed countries such as the US and parts of Europe, it has been observed that HPV infection accounts for about 65% of contemporaneous oropharynx cancers. The proportion of oropharynx cancers attributed to HPV infection is less in developing countries where smoking is still playing a bigger role. It is also important to note that for oropharynx cancer, there is no opportunity for screening for these cancers unlike some of the HPV-induced cancers at other anatomic sites. To date, there have been no data on whether the vaccine protects against HPV infections at the oral region. It is also important to note that an HPV-induced pre-malignant lesion has not been identified for oropharynx cancer, so it would not be possible to direct HPV vaccine trials against this endpoint, leaving just a viral endpoint as a potential study outcome [Kreimer AR and Chaturvedi AK; Cancer Prevention Research 2011; 4: 1346].

Because of the lack of vaccine efficacy data against oral HPV, the following research questions were asked in the Costa Rica vaccine trial:

1. Will the HPV vaccine protect against oral HPV16/18 among healthy young women in Costa Rica?
2. If so, how does oral vaccine efficacy compare to cervical vaccine efficacy?

The Costa Rica Vaccine Trial was a community-based randomized trial in that a census was conducted in two regions in Costa Rica; 7466 women were enrolled from this census. They were randomized to receive in a blinded fashion either a control vaccine (Hepatitis A) or the bivalent HPV 16/18 vaccine. Women were intended to receive 3 doses of vaccine over a 6-month period, and were then followed annually for 4 years, although more often if clinically indicated.

Clinicians collected all specimens in the CVT. Cervical specimens were collected by a cervix brush at every study visit throughout the 4 years, because the study was specifically designed to evaluate the vaccine efficacy against cervical HPV and related lesions. As the importance of HPV for cancers at other anatomic sites was increasingly understood, specimen collection was introduced at these other sites at the 4-year study visit. This was still a randomized blinded visit 4-years post-vaccination, and there was only a 1-time specimen collection. In the oral region, an oral rinse / gargle was conducted, which can be considered the gold standard in the field for measuring oral HPV infection. HPV testing was done by DDL Diagnostic Laboratory, in order to harmonize CVT data with other trials of the bivalent HPV vaccine (GSK).

The analytic cohort of interest was all women who had oral and cervical HPV test results at the 4-year study visit and received 1 or more doses of vaccine. The endpoint was prevalent HPV16 or 18 infection detected one time 4-years post-vaccination. For the analysis, vaccine efficacy was evaluated against HPV16/18 infections at each of the anatomic sites, and a p was calculated for interaction by anatomical site using GEE. As noted, 7466 women were randomized to either the HPV group or the control group. The number of women who attended the final randomized blinded study visit was slightly more than 3000 per arm, with very high rates of retention. In the analysis, women were excluded if they did not have an oral specimen collection or did not have oral HPV test results. There were just under 3000 women per arm for this analysis. It is important to note that 92.5% of eligible women did accept oral specimen collection.

The Balance Table confirmed that randomization did in fact work, in that no differences were observed between the HPV and control arms on key variables, for example, age at enrollment and the cervical HPV 16/18 DNA status at enrollment. Some variables were assessed at the 4-year visit corresponding to when the oral specimen was collected. As an example, at the final randomized blinded visit, about 2/3 of the women reported ever having oral sex, which was the same by arm.

In terms of the results, based on the data for vaccine efficacy against HPV 16/18 infections in the oral region, it was observed that there were 15 HPV 16 infections in the oral region in the control arm compared to 1 in the vaccine arm for a vaccine efficacy of 93%. It is interesting to note that this low prevalence of HPV16 infection in the control arm has been repeatedly observed in the literature. Oral HPV infection is rare, especially among younger women.

It is known that about 90% of HPV-associated oropharynx cancers are due to HPV16 infections. It is the most important type for these cancers. The vaccine efficacy against oral HPV16 infections was 92% (52% to 100%), with 13 total HPV16 infections. Vaccine efficacy against oral HPV18 infections was 100% (-12% to 100%), but there were only 4 infections, so statistical significance was lacking.

In the comparison of oral HPV16/18 efficacy to that observed at the cervix among the same women at the same time point, it was observed that the cervix vaccine efficacy among this analytic cohort was lower than it was at the oral region. This finding was statistically significant.

It is important to note the limitations of this work. Most importantly, there was only a one-time oral specimen collection, which had two effects. First, there was no pre-vaccine oral HPV status, so an according-to-protocol like-analytic population could not be created. Thus, women who might have had prevalent oral HPV infection at the time of vaccination could not be removed from the analysis. In addition, while there is no pre-clinical state for HPV-associated cancer, it still would have been beneficial to be able to assess an endpoint such as oral HPV

persistence, which would have required oral specimen collection at at least two study visits. Though there was a large denominator of women of nearly 6000, because of the low prevalence of oral HPV infection, it was not possible to do stratified analyses.

In conclusion, the bivalent HPV vaccine strongly protects against oral HPV16/18 infections in women. Protection was higher than that observed at the cervix. The investigators believe that this reflects that most of the oral infections were incident at the 4-year study visits and thus could receive the full benefit of vaccination.

Women who receive prophylactic HPV vaccination for cervical cancer prevention will have the added benefit of less oral HPV infection. It is important to note that it is not known for sure whether this will translate into a reduction in HPV-associated head and neck cancers, but the investigators are optimistic that the deficit of infection noted in the vaccine arm may translate to a reduction of oropharyngeal cancer among vaccination populations in the future.

Discussion Points

Regarding some of the limitations mentioned, Dr. Vazquez inquired as to what is known about the natural progression of HPV infections in the throat and oropharynx. If she understood correctly, what is known about cervical infections is that the majority of the infections are transient, the body clears on its own, and those do not progress to premalignant and malignant infections. She wondered whether the same presumably occurred with oral infections such that transient infections were being detected. That would have a major impact on the conclusions.

Dr. Kreimer responded that the natural history and epidemiology of oral HPV infections have not been elucidated in the same detail as cervical HPV natural history. Having said that, the analysis still shows proof of principle that if the bivalent vaccine is administered to women, they will have less oral HPV 16/18 infections. At this point, it is unknown which of those infections would be transient and would resolve on their own compared to which would progress to cancer. The vaccine nonetheless protects against almost all of them.

Dr. Karron asked whether Dr. Kreimer thought there was an ascertainment issue in terms of the fact that protection was greater in the oropharynx than in the cervix, because multiple samples were collected over 4 years from the cervix; whereas, there was only a single sample from the oropharynx. It was not clear whether it was fair to make that comparison.

Dr. Kreimer clarified that for the analysis she showed for the cervix data, the endpoint was not accumulating. It was simply a cross-sectional prevalent cervical HPV infection endpoint. She thought what they were observing was that the oral infections were occurring later, post-vaccination. There is actually a phenomenon in Costa Rica in which women debut vaginal sex and then several years later will debut oral sex, so it is possible that the diminished cervical VE was resultant from cervical infections being present at the time of vaccination and thus attenuating vaccine efficacy. If oral HPV infections occur post-vaccination, they would be more likely to be protected by the vaccine, and that is why the higher vaccine efficacy is observed.

Dr. Tan (AMA) inquired as to whether prior HPV infection was screened for.

Dr. Kreimer responded that no screening was done on the cohort in terms of cervical, oral, or anal HPV infection. The study accepted all-comers. One of the strong conclusions at this point is that the vaccine protects against HPV infections at all anatomic sites where HPV infection causes cancer. The investigators were not claiming that people should be vaccinated only to protection against oral HPV infections based on these data, but that there will likely be an added benefit given these data.

Dr. Tan (AMA) said this suggested to him that because there is lower apparent efficacy in the cervix, there is something different mechanistically about the oral versus the cervical infection. Clearly, they began with a cohort that was not naïve, which was how he interpreted the lower efficacy for the cervical outcome.

Dr. Kreimer responded that they were beginning to understand that across anatomic sites, the infection does behave quite differently. The oral HPV epidemiology seems to peak later in age and is higher in men, while with the cervix it peaks earlier in age. If the penis and anus are brought in, it does not peak at all. It is just a flat bar across all ages. The attack rate of HPV infection depends on the anatomic site.

Dr. Pickering noted that while Dr. Kreimer stated that based on Dr. Gillison's data oral HPV16 prevalence is 1%, he thought it was 7% in that article. He wondered whether that was a difference in the serotypes.

Dr. Kreimer indicated that she had selected out specifically oral HPV16 infection, which was the 1%. The 7% statistic was across all HPV types, and when Dr. Gillison stratified by male / female and by age, there were differing amounts. If the data in Dr. Gillison's paper was subset to women in the age range from CVT, the observed oral HPV prevalence would be roughly similar to what the CVT study observed.

Dr. Pickering inquired as to whether HPV18 made up a large part of the 7% percent.

Dr. Kreimer replied that it did not. HPV18 is not found in either oropharynx cancer or in healthy people in the oral region. It is not as predominant as it is in the cervix.

Referring to the balance table, Dr. Keitel inquired as to whether the 8% of women in the HPV arm and the 9% of women in the control arm for cervical HPV16 and/or 18 DNA were excluded from the analysis in Year 4.

Dr. Kreimer responded that they were not. Oral and cervical vaccine efficacy was computed among all women. Those women will attenuate the vaccine efficacy. This was among all women who attended the 4-year study visit and had an oral specimen collection. Given that there were so few oral infections, the investigators did not want to limit the population further. The investigators did compute what Dr. Keitel was suggesting in an analysis restricted to women who did not have the infections at the cervix at the time of vaccination. The observed cervical vaccine efficacy of 72% increased to about 84%, evidence of the attenuation of including all women in the analysis.

Dr. Keitel said the numbers did not add up, because 239 were positive in the HPV arm at entry and the total listed was 219. She wondered whether this meant that women who were positive at baseline were excluded from the analysis.

Dr. Kreimer replied that all women were retained and none were excluded from the analysis. It was likely that at some point throughout the 4 years, these women were lost to follow-up for some reason (e.g., pregnancy, drop out, et cetera).

In the oral samples, Dr. Vazquez inquired as to whether the investigators looked for any other types of HPV not in the vaccine.

Dr. Kreimer responded that they did and that it was one of the study planned to evaluate (prior to unblinding the data). All samples were tested using the DDL primers that test for 25 known carcinogenic and non-carcinogenic HPV types. One of the secondary aims was to evaluate cross-protection, which has been observed in the trials against the cervix. One of the endpoints was a plan to evaluate a composite endpoint against HPV 31, 33, and 45 because cross-protection has been observed at the cervix and the anus. There were 8 total 31 infections and no 33 or 45 infections, which resulted in an oral vaccine efficacy against HPV 31 of 40%, which aligns with what has been observed at the cervix and the anus. However, because of the small number of events, the confidence interval includes zero.

Dr. Vazquez explained that this was not what she was thinking about. Regarding how bias could be affecting this, the definition of "infection" may or may not be the correct one for the oral infections. She wondered whether a different outcome could be selected that was not known to have cross-protection and was not expected to be affected by vaccination to assess difference in infection between those who received vaccine and those who did not. If a difference was not found in this assessment, the investigators could state that they found a statistically significant difference with respect to the vaccine types. While this does not prove it, it may help to show that chance was not the reason for the results.

Dr. Kreimer responded that they had conducted such an analysis, and vaccine efficacy was observed to be zero for all types considered. Or it moved around for individual HPV types where no VE was expected, but was never a meaningful vaccine efficacy. No vaccine efficacy was observed grouping the other 11 types considered to be non-carcinogenic beyond 16/18. There was no signal observed against 6 and 11, which are known to be associated with laryngeal papillomatosis. The investigators worked with the bivalent vaccine, so that would not be expected. From what has been observed, the investigators believe that these data are valid based on their analyses.

Progress in Vaccine Uptake and Reasons for Non-Vaccination

Christina Dorell, MD, MPH
Medical Epidemiologist
Immunization Services Division
National Center for Immunizations and Respiratory Diseases
Centers for Disease Control and Prevention

In this presentation, Dr. Dorell briefly discussed national and state vaccination estimates for adolescents ages 13 through 17 years in the US. Vaccination rates by select socio-demographic characteristics, including age, race, and income were presented. Intent and reasons for non-intent to receive the vaccine were also covered. Data for this presentation came from the National Immunization Survey-Teen (NIS-Teen). The NIS-Teen has been conducted annually since 2006. NIS-Teen is a random-digit-dialing household survey of parents of adolescents ages 13 through 17 years of age. Beginning in 2011, a cellular telephone sampling frame was included in the survey to improve representation of non-landline

households. After obtaining parental consent, all vaccination providers named by parents are mailed a questionnaire to obtain the adolescents' vaccination histories. All analyses are limited to adolescents with provider-verified immunization histories.

HPV vaccination rates are reported separately among girls and boys. Among girls, the HPV initiation rate was 53% in 2011, and the receipt of at least 3 doses was approximately 34%. The series completion rate refers to the percent of girls who received 3 doses among those who initiated the series and had at least 6 months between the first dose and the NIS-Teen interview date. This allows for the determination of completion rates among those who had sufficient time to complete the 3 dose series. Approximately 71% of girls completed the 3-dose series. 2011 HPV coverage among boys reflects coverage before the routine recommendation for HPV vaccination of males. Among boys, 8% received at least 1 HPV dose and 1% received 3 doses. Of those who initiated the series at least 6 months before the interview date and had enough time to complete the series, 28% completed the series.

With regard to the trend in vaccination coverage by survey year, between 2007 and 2008, HPV initiation among girls increased by 12.1 percentage points. From 2008 and 2009, the increase was about 7.1 percentage points. The increase was approximately 4 percentage points from 2009-2010 and also from 2010 to 2011. There was a similar trend with receipt of 3 doses among girls [Note: From 2007 to 2008, the increase was 8.8 percentage points; from 2008-2009, 5.3 percentage points; and from 2010-2011, 2.8 percentage points]. Trend lines for coverage with tetanus-diphtheria-acellular pertussis (Tdap) and the meningococcal conjugate vaccine demonstrated higher coverage and higher annual percentage point increases compared to HPV vaccination rates among girls. There were only two data points for male HPV vaccination coverage because of the relatively recent recommendations for male HPV vaccination. HPV initiation rates among boys increased by 6.9 percentage points from 2010 to 2011. Again, coverage with 3 HPV doses among boys in 2011 was only 1.3%.

In terms of HPV vaccination estimates by age at interview among girls, compared to girls 13 years of age, coverage with at least 1 HPV dose was significantly higher among girls 15 through 17 years of age, and coverage with at least 3 HPV doses was significantly higher among girls 14 through 17 years.

With respect to the percent of girls who received at least 1 HPV dose by age 13 in order to see how many girls are being vaccinated during the recommended ages, the birth cohorts from 2009, 2010, and 2011 had the opportunity to be vaccinated by age 13. Initiation rates for each of the last three birth cohorts has plateaued, with approximately 35% initiating the series by the recommended age of 11 or 12 years. The data showed that there has been little progress in increasing vaccination rates during the recommended age over the past three years.

In 2011, coverage with at least 1 HPV dose among girls ranged from 31% in Mississippi to 76% in Rhode Island. Coverage with at least 3 HPV doses among girls ranged from 15% in Arkansas to 56% in Rhode Island. Vaccination coverage with the first dose of the series differed significantly by race / ethnicity, with higher coverage among black and Hispanic girls than white girls. Hispanic girls also had significantly higher coverage with three doses than white girls. Similar to girls, black and Hispanic boys had significantly higher coverage with at least 1 HPV dose compared to white boys. Compared to white boys, Hispanic boys also had significantly higher 3-dose coverage. The estimate for 3-dose coverage among black boys did not meet reporting criteria and was not shown. Regarding national HPV vaccination rates by poverty status, among girls and boys, there was higher HPV initiation and receipt of 3 HPV doses among those living below poverty compared to those living at or above poverty.

In regard to parental intent for HPV vaccination among unvaccinated adolescents, rates were similar among parents of girls and boys. A little over 50% of parents of girls and boys reported that they were not too likely, or not likely at all to have their teen receive HPV vaccination within the next 12 months. Each year, the proportion of vaccinated girls has increased, subsequently decreasing the proportion who report that they are somewhat or very likely to have their teen receive the vaccine. The proportion of parents who report that they are not likely to receive the vaccine within the next 12 months has remained consistently around 25%. The proportion of those who are unsure has decreased slightly over time. Based on data collected before the routine recommendation for boys from 2010 and 2011, as mentioned before, the proportion vaccinated increased in 2011. Additionally, the proportion that was somewhat or very likely to have their teen receive the vaccine also increased, while the proportion unlikely to receive the vaccine decreased.

With respect to the top five parental reasons for intending not to vaccinate a teen, some reasons differed by gender. Among girls, the top five reasons included the following in this order: not needed, not sexually active, safety concerns, lack of knowledge about the vaccine, and not recommended by a health provider. Among boys, the top five reasons included the following in this order: not needed, not recommended by a health provider, lack of knowledge, not sexually active, and child is male. Among girls, the report of safety concerns by parents of daughters without intentions to receive the HPV vaccine has increased from 5.4% in 2008 to 19.3% in 2011. It is important to remember that as the pool of unvaccinated girls decreases, it becomes more concentrated with those who are more resistant against vaccination, which includes those with safety concerns.

To summarize HPV vaccination coverage among girls, HPV vaccination rates for 1 and 3 doses among girls increased each year since 2007; however, the size of the annual increase seems to be reaching a plateau over the past couple of years. Many girls are not receiving HPV vaccination at the recommended age of 11 or 12 years. Initiation rates are significantly higher among black and Hispanic girls compared to white girls. Hispanic girls were more likely than white girls to receive all 3 doses. Girls living below poverty were more likely to initiate and receive all 3 HPV doses than those living at or above the poverty line.

To summarize vaccination coverage among boys, the HPV initiation rate among boys increased by approximately 7 percentage points between 2010 and 2011 and reflects receipt of vaccination as a result of the 2009 ACIP guidance stating that HPV vaccination could be administered to males 9 through 26 years old. Similar to girls, black and Hispanic boys had significantly higher HPV initiation rates than white boys. Also, Hispanic boys had significantly higher rates of receiving 3 doses. Boys living below poverty had higher 1 and 3 dose HPV vaccination rates compared to those living at or above poverty.

To summarize intent to vaccinate and reasons for non-vaccination, among girls, the percent vaccinated or likely to get vaccinated combined has not changed much since 2008 and is currently approximately 70%. Less data are available for boys, but it has been observed that the proportion of parents of boys who were somewhat or very likely to have their sons receive the vaccine was 31% in 2011, reflecting intentions before the routine recommendation. Reasons for not intending to vaccinate a teen differed slightly by gender. However, for girls, the most common reasons for not vaccinating included not needed, not sexually active, and safety concerns.

In conclusion, some recommendations include the following:

- Encourage strong provider recommendations for HPV vaccination among girls and boys at the recommended age of 11 or 12 years;
- Increase parental awareness of HPV disease risk and HPV vaccine benefits for both girls and boys, including starting the series, completing it, and the safety of the vaccine;
- Enhance efforts to increase HPV initiation and series completion among racial/ethnic groups and income levels as needed; and
- Implement standing vaccination orders and reminder-recall systems to decrease missed vaccination opportunities.

Discussion Points

Dr. Harrison was curious as to whether there were any data available about what is occurring at the provider level in terms of whether providers are recommending according to the ACIP recommendations, but patients are refusing, or if there is not a concerted effort to advocate for the vaccine.

Dr. Markowitz replied that a provider survey was conducted, which showed that even though almost all providers were recommending the vaccine, they were mainly recommending it strongly to older adolescents 16 to 18 years of age. About half were recommending it strongly to the target age groups.

Dr. Sawyer noted that at the time the HPV vaccination program was begun, there was a great deal of concern about the cost of the vaccine and how that would affect uptake. It was striking from the survey that children living in poverty were more likely to be immunized than others. He assumed that was a testimony to the VFC program. On the other hand, cost and lack of insurance coverage were not listed as reasons for non-vaccination. He wondered whether there were any conclusions from the surveys or other sources about whether cost is a barrier at all.

Dr. Dorell responded that she showed the top 5 reasons. There were multiple other reasons, one of which was cost. However, it was very low at about 5%. People were able to state multiple reasons, so it was not mutually exclusive.

Regarding the 19% of the non-vaccinators who cited vaccine safety concerns, Dr. Sawyer inquired as to whether the survey allowed for any specificity about what those concerns were.

Dr. Dorell responded that in 2010, there was a separate module that asked what specific safety concerns parents had (e.g., lasting health problems, more acute health problems); however, those data have not yet been analyzed but will be.

Dr. Karron wondered whether the survey contained any data about sites of vaccine administration, and whether more vaccine was administered at public health clinics than in private practice.

Dr. Dorell responded that the way the data were programmed, responders were asked, "Where did you receive your vaccine?" The responses included: all private facilities, all public facilities, school clinics, et cetera. The majority of girls and boys are receiving the vaccine at all private facilities. A previous analysis of 2008-2009 data showed that those receiving all of their vaccines in public facilities were receiving less HPV vaccines compared to those receiving their vaccines in private facilities.

Dr. Bennett noted that generally when these surveys are conducted, it is observed that vaccines are not recommended by providers and that is why people do not get them. The rates shown by Dr. Dorell were relatively low for the "not recommended" responders. However, 23% thought that it was not needed. She inquired as to whether there were any data to show why people perceive this vaccine is not needed, and how that determination is made by parents.

Dr. Dorell replied that this cannot be determined from the NIS-Teen data. More information about this would likely be acquired from qualitative interviews, surveys, et cetera.

Among healthcare providers who may not be enthusiastic about recommending the vaccine, Dr. Duchin wondered whether there were any data to show any regional differences across the country. His perception was that there tended to be slower uptake on the West Coast, though it was not clear to him why that occurred. He also wondered whether any racial/ethnic disparities were observed among just children eligible for the VFC program.

Dr. Dorell responded that provider recommendations and differences by region were not assessed, but do plan to do so in the future. Though children eligible for the VFC program have not been assessed with regard to racial/ethnic disparities, this analysis can be done in the future.

Ms. Rosenbaum wondered if anything was known about whether providers were not recommending the vaccine due to cost, or because they believe that children not thought to be sexually active should not receive the vaccine.

Dr. Dorell replied that based on her literature review, it seems to be a combination of reasons. Reasons may differ by the type of provider as well in terms of pediatric versus family practices. Cost and reimbursement, sexual activity, and discomfort discussing the vaccine and sexual activity have been mentioned as reasons. NIS-Teen does not interview providers, but there are other provider surveys underway to better understand those issues.

Amy Groom (IHS) indicated that a survey was conducted of Indian Health Service providers to determine the barriers. It was found that similar to what is observed with the general population, providers are more comfortable recommending the vaccine for 13 year olds than they are for 11 to 12 year olds. However, IHS still has very high coverage rates, which she believes is related to the electronic health reminder. Even if there are providers who many not recommend it as strongly, it is nonetheless showing up at 11 years of age. Someone gets the prompt, and the nurse or provider has the opportunity to talk about it. This speaks to the role of registries, reminders, and electronic health records. The recommendations stated by Dr. Dorell addressed standing orders and reminder recall, which are typically associated with reminding the patient to return. Very important is for the reminder for the provider to offer the recommend vaccine.

Dr. Jenkins noted that one of the issues parents have in terms of safety is the fact that it is a new vaccine. She wondered how far out safety data are available.

Dr. Markowitz responded that the Immunization Safety Office has made several presentations to ACIP since vaccine was first recommended in 2006. There is a fairly substantial amount of data now from VAERS, VSD, and CISA. Some of those data were summarized during the June 2012 ACIP meeting. Those data systems are not following people prospectively. Six years of data have been accumulated. The reason the post-licensure data are so powerful is because there is a very large number of vaccinees in those evaluations. Some subjects are also being followed who were enrolled in the clinical trials. She thought that some data from the trials were to be presented during an international meeting in November.

Dr. Warshawsky (NACI) noted that Canada has similar challenges with uptake and variability between provinces and jurisdictions. In general, Canada's rates are approximately 50% to 80%. One of the mechanisms in most jurisdictions for distributing vaccinations is through school-based clinics. Consent forms are sent home to parents and students, and public health nurses deliver vaccines in many schools. That seems to be successful in increasing coverage rates.

Dr. Markowitz acknowledged that countries such as the UK and Canada have achieved higher coverage rates because they can vaccinate the target population all at once at schools. Those types of vaccine delivery systems have been able to achieve higher coverage in a shorter period of time.

Dr. Salisbury (DOH, UK) reported that the UK's coverage of 12 year old girls continues to increase. First dose coverage is currently just under 90%, while third dose coverage for 12 year old girls is about 86%. Because they are vaccinated in schools, when a teen enters the next year, it is possible to identify any girls who were not vaccinated in the 12 year old group. In subsequent years, it is found that vaccination of that 12 year old cohort is ever increasing. The UK is very committed to school-based immunization programs, given that they achieve very high coverage on time, with all girls being vaccinated. Scotland will be the first part of the UK to be able to assess impact data, because they screen at a younger age than England. The school-based program has been so successful in achieving high coverage in girls, for the UK it remains non-cost-effective to recommend vaccination of males. The data from the oral HPV study will be extremely important for everyone, but it is clearly important to know about cancer not just about infection. The UK comes under pressure about vaccinating males because of oropharyngeal cancer.

Dr. Campos-Outcalt noted that one of the issues for this vaccine for adolescents is that it requires 3 doses over a period of time. He wondered how much that was a subconscious reason for some of the more stated reasons, and whether consideration was being given to whether fewer doses could be used as an effective regimen.

Dr. Dorell replied that she had not seen the requirement for 3 doses listed among the responses given by parents.

Dr. Markowitz added that data were presented from the Costa Rica study during the June 2012 ACIP meeting that assessed the efficacy of 1, 2, and 3 doses with the bivalent vaccine against 16/18 infection. She also showed some data from immunogenicity studies that are assessing this issue, and there is a lot of interest in this question. This is also an issue for lower income countries that are seeking to introduce this vaccine. There will also be data from post-licensure effectiveness studies when countries begin assessing data at the population level pertaining to 2 versus 3 doses. She anticipates that there will be more data on this issue in the future.

Dr. Doskey (AHIP) noted that in 2012, HPV vaccine rates for females would become a Healthcare Effectiveness Data and Information Set (HEDIS) measure. Eventually that will affect providers' reimbursement with respect to contracting and quality measures. He wondered whether there was something similar in the Medicaid or VFC programs that contributed to their higher levels of immunization, or if it was completely separate and process-driven. On the positive side, as healthcare reform progresses, the number of grandfathered plans is decreasing faster than was originally predicted. So, the number of plans with universal coverage for immunization at a zero cost level to the patient or the member is rising rapidly.

Dr. Wharton responded that immunization coverage among the VFC eligible population is followed through the NIS, and there are targets for immunization coverage. However, there is not the same time of measure as there is for HEDIS. Her guess was that the lack of concern about reimbursement for vaccine purchase contributes to the higher rates of coverage among those below the poverty level.

Dr. Middleman (SAHM) said she had heard from a number of providers that the issue in terms of delaying until a patient turns 15 was not necessarily about having a discussion about sex, but regarded concerns about duration of protection. With recent experience, it is understandable that there would be some concern about duration of protection with vaccine. However, this speaks more to the job of professional organizations to make sure to remind providers that duration of protection is not a concern at this point for HPV vaccine.

Dr. Tan (AMA) noted that the 70% completion rate was much better than the rate has been in the past, which is very promising. He wondered whether there was any way to determine why the remaining 30% did not complete the series.

Dr. Dorell clarified that the 70% was among those who initiated in sufficient time to complete the series. Over the past couple of years, the range has been approximately 67% to 70%. For the 30% who did not complete, an analysis was done with 2008-2009 data and found that those more likely to complete were those who had private insurance or a higher income. It was the opposite of what was observed with initiation.

In terms of implementation programming, Dr. Tan (AMA) pointed out that it was important to focus on initiation with providers. In terms of completion, implementation programs should involve physicians and other complementary providers as well.

Dr. Gorman (NIH) wondered about availability of this vaccine in primary care physicians' offices, and whether any difference had been observed in ordering among VFC providers between MMR and HPV, for example. He also inquired as to whether there was a plan for a catch-up program for HPV vaccine that would include other delivery sites, as there has been for many other vaccinations.

Shannon Stokley (CDC) reported that among the physicians surveys conducted nationally, 98% of pediatricians and family physicians responded that they have HPV vaccine in their office and they are administering it. Availability of the vaccine within primary care practices does not seem to be an issue. Regarding catch-up programming, hospital emergency departments do not view HPV vaccination as part of their mission. It is known that some pharmacists, depending upon the laws within their state, may provide HPV vaccine. So that may be a place to access the second and third doses. Surveys conducted with retail-based clinics, which are separate from pharmacists, showed that they were uncomfortable initiating the HPV series. They really felt that initiation should be done by a primary care physician to have the conversation that might be

needed. They were certainly willing to provide the second and third doses. There has really not been a concerted effort to advocate for completing the series other than through the primary care setting, but it may be possible in other settings.

Ms. Rosenbaum pointed out that another possibility is the high involvement of publicly funded family planning clinics and community health centers with large family planning programs in all aspects of family planning for both boys and girls. These venues routinely report that they are doing a lot of immunizing. It would be helpful to know whether VFC is contributing, and whether it is the nature of who the providers are for lower income children and whether they have a different connection to sexuality discussions and immunizations.

Daniel Hopfensperger (Wisconsin Immunization Program; Association of Immunization Managers) indicated that Wisconsin has had fairly high rates. He wondered whether CDC could evaluate states that have mature registries that are using the recommended schedule. Wisconsin has had fairly high meningococcal rates, and thinks it is because they have a Tdap requirement and a varicella requirement for children entering 6th and 12th grades. AIM is developing a working group to assess whether such requirements are having an impact on HPV vaccine rates. He thought this could be done nationwide.

Marcella Bobinsky (State of New Hampshire; Association of Immunization Managers) reminded everyone that the adolescent platform is relatively new to everyone, especially in terms of being able to finance the HPV vaccine. Even though it was recommended by ACIP in 2006, it took some time for those vaccines to move out into the states. There are many elements in toolkits to promote a new vaccine and a new platform, such as requirements for school and provider education. There is a challenge with the HPV vaccine because few states are willing to make this a school requirement, and because the vaccine is not a favorite of providers in terms of an absolute recommend. It is very difficult to consider administering vaccines in emergency departments and other areas, because many states do not allow this by law and insurance systems are not ready to back-up that particular method of paying for vaccines distributed outside the medical home, especially in schools.

As an internist, Dr. Bennett said she was tremendously worried about young women between 18 and 26 years of age. The younger cohort is quickly aging into this group, but there are still people in that group who may or may not have access to this vaccine. She wondered if anyone could offer an idea of the rates in that age group.

Dr. Dorell replied that she did not have the rates on that age group. Dr. Markowitz added that data are collected on that age group, although from a different survey. They are not collected in the same way as NIS, which are provider-verified records. Instead, they are from self-report of vaccination. These data can certainly be presented to ACIP in the future.

Dr. Sawyer wondered whether they would be able to see any change in those rates coincident with the law allowing people up to age 26 to be covered under their parents' insurance.

Dr. Pickering wondered whether the fact that antibody levels are higher when the vaccine is given at an earlier age to adolescents and pre-adolescents equated to longer term higher levels against HPV strains.

Dr. Markowitz replied that the data available show that the antibody titers achieved soon after vaccination predicts longer term antibody titers. Studies in adolescents are on-going out to 14 years. She invited the pharmaceutical companies to comment on that.

Carlos Sattler (Merck) responded that Merck is assessing long-term follow-up of adolescents who received vaccination between the ages of 9 through 15. They anticipate being able to share some updated data on long-term follow-up at the upcoming International Papillomavirus Meeting at the end of November 2012 in Puerto Rico.

Dr. Friedland (GSK) reported that GSK continues to follow adolescents in its clinical trials for long-term antibody, persistence, and long-term efficacy. As the data are available, they will be published, presented, and shared with ACIP.

Dr. Wharton indicated that the data on coverage among 19 through 26 year olds are included in the National Health Interview Survey. The 2010 data that were published in February 2012 show that approximately 21% of females 19 through 26 years of age and 1% of males 19 through 21 years of age had received at least one dose.

Dr. Jenkins inquired as to whether conducting provider focus groups had been considered as a strategy.

Dr. Markowitz clarified that a large provider survey was conducted following licensure. A lot of work is currently being done with providers, and further information is being collected from them.

Shannon Stokley (CDC) indicated that CDC's communications group recently completed several in-depth interviews with providers and parents. They have heard from parents that their providers have told them they can wait. Mothers' gynecologists are also telling them that they can wait to have their daughters or sons vaccinated. What they hear from providers is that they are not willing to "go to the mat" for this vaccine. Even if a parent just asks a question about the vaccine, physicians are not willing to be more forceful about the recommendations.

Amy Groom (IHS) reported that while funding has not been an issue for the IHS adolescent population and they have about 80% coverage among this group for the first dose, funding has been a major issue for the 19 through 26 year old population. The most recent data indicate that about 40% of females 19 through 26 years of age and about 5% of males 19 through 21 years of age have received the vaccine.

Dr. Schaffner (NFID) noted that providers appeared to be the problem. He wondered if there were any data on whether there was a gender difference among providers and the strength of the recommendation.

Dr. Markowitz indicated that this was assessed in the surveys, but she did not have these data with her. She invited anyone who remembered the numbers to respond.

Shannon Stokley (CDC) said that while she would have to look it up to confirm, she did not remember any striking results related to gender differences.

Dr. Campos-Outcalt commented that he has spoken with a number of providers and some academics who take the position that because Pap smears are perceived as being a second tier of defense against cervical cancer, the vaccine is not really needed. Availability of the oral, anal, and other cancer location data should help to combat that.

Ms. Stinchfield (NAPNAP) wondered whether this was a reflection of provider fatigue with vaccine hesitancy conversations that seem to be getting increasingly longer and more difficult during visits. Perhaps everyone needs to focus on the simple message of this being an anti-cancer vaccine.

Dr. Temte put in a plea for adolescent medicine and family physicians to take forward the recommendations for sexually abused children.

Rotavirus Vaccines

Update on Rotavirus Vaccine Impact in the US

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Dr. Payne indicated that this would be an informational session during which he would bring everyone up to date on several recent and some unpublished reports regarding the epidemiological and laboratory sides of rotavirus. This included information on vaccine effectiveness studies for both licensed rotavirus vaccines in the US. These are the first vaccine effectiveness studies assessing rotavirus vaccines in concurrent use in the US childhood population. Overall, this is vaccine effectiveness against rotavirus-associated hospitalizations and emergency department visits. In addition, Dr. Payne shared data from rotavirus strain surveillance, including vaccine-derived strains.

There are current two licensed rotavirus vaccines in the US. The first, RotaTeq™, is produced by Merck. This is a bovine-human pentavalent vaccine with the strain components G1, G2, G3, G4, and P[8]. In February 2006, ACIP approved this vaccine for 3 doses given at 2, 4, and 6 months of age. The second vaccine, Rotarix®, is produced by GlaxoSmithKline. This is a human monovalent vaccine with the strain components G1 and P[8]. In June 2008, ACIP approved this vaccine for 2 doses given at 2 and 4 months of age. Both products are live attenuated oral vaccines. In clinical trials, heterotypic immunity was observed against other strains. As noted, both vaccines are ACIP-recommended for childhood vaccination in the US, with no preference.

With regard to the two surveillance platforms, both completed at approximately the same time and are cleared, but with unpublished results. The New Vaccine Surveillance Network (NVSN) is a 7-site network of hospitals and medical institutions throughout the US (e.g., Seattle, Oakland, Kansas City, Cincinnati, Nashville, Houston, and Rochester), with great geographic and demographic diversity. Overall, this network is conducting active surveillance for acute gastroenteritis. This is done because rotavirus is not a notifiable disease. In routine clinical practice, it is rarely tested for. Studies such as this require laboratory confirmation of rotavirus status. Very time-consuming and personnel-consuming surveillance is conducted, in which parental interviews, provider-verified vaccination status of the children, medical record information, and stool specimens are collected. The second platform is from the Emerging Infections Program (EIP). Typically 10 states participate in EIP and cover a wide range of active surveillance for different pathogens; however, a rotavirus specific study is being conducted in two of those sites (e.g., Connecticut and Atlanta).

During the post-licensure period, independent surveillance systems consistently have reported continued steep declines in rotavirus incidence and hospitalizations and emergency department visits, and the emergence of a biennial peak in rotavirus activity. Based on NVSN, during the pre-licensure period or just at licensure, 51% of those children presenting to the hospital with acute gastroenteritis symptoms were tested to have rotavirus. In the second year following licensure, that decreased precipitously to 6% in this surveillance system, and then has bounced back. This is believed to be the result of the accumulation of immunologic susceptible who have not been vaccinated who then are consumed upon exposure, typically at about a year following what would have been expected following the pre-licensure period. Based on 2012 data, there is approximately a 90% reduction of what was observed in hospitalizations for rotavirus in the pre-licensure period.

The objective of the NVSN effectiveness study was to assess the effectiveness of the pentavalent and monovalent rotavirus vaccines in concurrent use among US children under 5 years of age during 2009 through 2011 against rotavirus acute gastroenteritis inpatient and emergency department visits. All sites were included in the RotaTeq™-specific analyses Dr. Payne shared; however, vaccination coverage with Rotarix® that was under 5% seemed to be an efficiency drag upon the analyses, so three sites were not included in those Rotarix®-specific analyses (Seattle, Houston, Nashville). These were case-control logistic regression models adjusted for month / year of births, month / year of symptom onset, and surveillance site. Rotavirus cases were confirmed by enzyme immunoassay and genotyped, and vaccination records were confirmed. During this session, rotavirus-negative control results were presented.

With regard to full course vaccine effectiveness and 95% confidence interval for RotaTeq™ and Rotarix®, there was 84% vaccine effectiveness against hospitalizations and emergency department visits from RotaTeq™ and a 70% point estimate for Rotarix®. The confidence intervals clearly overlap. These are not statistically significant differences, despite the differences in the point estimate. One reason for the wider confidence intervals for the Rotarix®-specific analyses in this study is that there were far fewer cases in the Rotarix® analyses, and vaccine coverage for Rotarix® in the general network was lower than that for RotaTeq™. The RotaTeq™ sample size was 359 with a 1:3 case-control ratio, while the sample size for Rotarix® was only 60 cases with a 1:3 case-control ratio.

In terms of full course vaccine effectiveness and 95% confidence interval by rotavirus genotype for RotaTeq™ and Rotarix®, clearly confidence intervals overlapped across the board and were not statistically significant. The predominant genotypes were G1P[8], G2P[4], G3P[8], and G12P[8]. Notably, G12P[8] used to be considered an emerging genotype, but is now being observed with increasing predominance, and was one of the predominant strains observed during this time period. For G12P[8], RotaTeq™ had 83% effectiveness against rotavirus-associated hospitalizations and emergency department visits, so there is a very strong showing even against G12P[8].

With respect to age-specific analyses and the question regarding whether there is immunologic waning over time with these vaccines, in the RotaTeq™-specific analyses that goes through the fourth year of life, there is no clear evidence of waning, even through the fourth year of life. These are very strong showings. For the Rotarix®-specific analyses, the first-year assessment is not statistically significant. The confidence intervals are very wide, and only represent a handful of subjects. However, the second year of life is a very good 86% vaccine effectiveness, which was the limit of the study power for that analyses [Payne, et al. Preliminary Data – 2012].

Shifting to the EIP platform, there were 3 hospital sites in Georgia and 2 in Connecticut. There were slight differences in methodology overall, but there are a few. Children age-eligible to have received Rotarix®, who were hospitalized or visiting the emergency department with diarrhea were enrolled through active surveillance. Rotavirus cases were confirmed by enzyme immunoassay and genotyped, and vaccination records confirmed. Case-control logistic regression methods were employed, and rotavirus-negative control results were presented during this session. With regard to full course vaccine effectiveness and a 95% confidence interval among children aged ≥ 8 months, there was 91% vaccine effectiveness for RotaTeq™ and 88% vaccine effectiveness for Rotarix®, with very similar confidence interval bounds. The sample size for RotaTeq™ in this study was 87 cases, with about a 1:1 case-control ratio, and for Rotarix® the sample size was 94 or 94 cases, with about a 1:1.5 case-control ratio [Cortese, et al. Preliminary Data – 2012].

Putting this together with previously conducted and published studies, Dr. Boom's 3-dose RotaTeq™ vaccine effectiveness was 89% (70%, 96%) [Boom JA, et al. *Pediatrics* 2010]; Dr. Staat's finding was 87% (71%, 94%) [Staat MA, et al. *Pediatrics* 2011], and Dr. Cortese's finding was 89% (81%, 94%) [Cortese MM, et al. *Pediatrics* 2011]. Thus, Dr. Payne's finding of 84% (78%, 88%) [Payne DC, et al. PRELIMINARY]; and Dr. Cortese's finding of 91% (73%, 97%) [Cortese MM, et al. PRELIMINARY] are very consistent. The two studies that have been presented for post-licensure vaccine effectiveness for Rotarix® were NVSN for 2 doses, with vaccine effectiveness of 70% (39%, 86%) [Payne DC, et al. PRELIMINARY] and EIP with vaccine effectiveness of 88% (74%, 94%) [Cortese MM, et al. PRELIMINARY].

While internally each of these studies had very well, very closely matched cases to controls on numerous characteristics (e.g., race, ethnicity, socioeconomic status, insurance status, et cetera), there is a possibility that there are different distributions between the two platforms and most likely there are some differences. In addition, vaccine coverage within these communities is very different as well. For instance, about a 40% vaccine coverage estimate is expected for the sites used for the Rotarix® analysis as opposed to about double that in the EIP study. In addition, there are very small samples sizes in both studies.

Notably, one higher income assessment evaluated concurrent vaccine effectiveness for Rotarix® and RotaTeq™. This study was conducted in Navarre, Spain by Jesús Castilla. This followed very similar methods as the NVSN study, and found very similar results as well, with vaccine effectiveness for RotaTeq™ of 81% (95% CI=68–89%) and for Rotarix® of 75% (95% CI=60–85%).

In summary, high effectiveness has been observed for both rotavirus vaccines. Rotarix® vaccine effectiveness requires further monitoring, and plans are underway to study this more intensely in the coming year. No evidence of waning immunity at the limits of observed study power was detected for either vaccine, and no difference was observed in vaccine effectiveness by predominant genotype.

Detection of Vaccine-Derived Rotavirus Strains

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Dr. Payne reported that based on the very intensive strain monitoring that has been done over the last 15 years, in the pre-licensure period a G1P[8] distribution predominated the samples that were tested. Vaccine was implemented in 2006, and there have been some shifts in the distribution. In most surveillance systems, G3 has been the predominant strain and G12 has emerged to become more predominant [Longitudinal Variation of Rotavirus G Types in the United States, 1996-20; Courtesy of Parashar, Gentsch and Bowen]. There is no evidence to suggest that these changes are the result of any vaccine selective pressure. While still not completely understood, it is entirely possible that this is the result of secular variation. In the post-licensure analyses conducted, there does not appear to be any reason to believe that there is selective vaccine pressure upon the genotypes in predominant circulation [Payne, et al. Preliminary Data – 2012].

Vaccine-derived strains come in two fashions (e.g., shedding and reassortment). Shedding of a live, attenuated vaccine virus is the product of the intended in vivo replication of the vaccine in the intestines. Shed rotavirus vaccine virus has been observed in numerous studies and clinical trials in approximately 9% to 21% of infants receiving RotaTeq™ and 35% to 80% of infants receiving Rotarix® within approximately 2 weeks of vaccination. In 2009, ACIP made the following statement in the *MMWR*:

“ . . . the protection of the immunocompromised household member afforded by vaccinating the infant in the household and preventing wild-type rotavirus disease outweighs the small risk for transmitting vaccine virus to the immunocompromised household member and any subsequent theoretic risk for vaccine virus-associated disease.”

Regarding the recent reports that have been made by various countries regarding reassortment (e.g., Australia, Finland, and the US), this is not a new finding. This was observed during the development phase of the quadrivalent pre-RotaTeq™ vaccine, as well as during some of the clinical trials that were reported to FDA. RotaTeq™ is a pentavalent vaccine consisting of 5 different reassortants between a bovine parent strain designated WC3 whose serotype designation is P[5]G6 and human strains bearing either a G1, G2, G3, G4 or P[8] specificity. The resultant reassortants in most cases contain a single human serotype gene and 10 genes of bovine WC3. Two strains also contain a human rotavirus VP3 gene. In thorough laboratory analyses, it has been observed that G1 ad P[8] vaccine strain components reassort in vivo and produce a vaccine-derived G1P[8] reassortant strain. There is not a lot of research on this, and a number of questions remain. In laboratory analyses and some epidemiological assessments of this reassortant in even unvaccinated children, it does appear that transmission of the reassortant is, indeed, possible from human-to-human. In some cases that have been reported, it is possible that acute gastroenteritis symptoms are produced. These occurrences are exceedingly rare and do not pose a serious concern. For example, a single reassortant was detected in the 2008-2009 season among a catchment population of over 141,000 children under the age of 5 [Payne et al., *Pediatrics* 2009]. In the 2009-2010 season, a single Rotarix® strain was observed in a child who was unvaccinated and residing in an area with nearly zero

percent Rotarix® vaccine coverage. Upon further follow-up, this child had not traveled to Mexico.

In summary of the rotavirus strain reports, G3P[8] is now observed as the predominant strain in the post-licensure era. G12P[8] is no longer considered an emerging strain. The vaccine effectiveness observed in post-licensure studies is high is high against this strain. RotaTeq™ reassortants have been observed at low frequencies in several vaccinated populations. Human-to-human transmission of the RotaTeq™ reassortant appears to be possible. Despite testing these specimens for the breadth of possible AGE pathogens, there continue to be some cases in which no other pathogen has been found. It may be postulated that there may be some causality of acute gastroenteritis symptoms, although that is still open to active debate. Evidence regarding Rotarix® vaccine strain is limited, but some transmission to unvaccinated subjects may occur. Further monitoring of circulating serotypes with corresponding epidemiological and clinical data is very much needed, and active research is being conducted in this area.

Discussion Points

Given that in some states like Connecticut there was a change from one vaccine product to another, Dr. Vazquez wondered whether it was possible to assess vaccine effectiveness of mixed products in the NVSN data and / or effectiveness after partial doses.

Dr. Payne responded that for NVSN data, both issues have been assessed. For children who received both RotaTeq™ and Rotarix® doses, under recommendations, 5% had some sort of combination. That was not a sufficient sample size to conduct a vaccine analysis; however, a continued effort will be made to assess this even by compiling and aggregating data as this work continues. Analyses have been conducted for the NVSN of rotavirus vaccine dose-specific vaccine effectiveness. For the NVSN RotaTeq™ analysis, all three doses were independently statistically significant, with 70% vaccine effectiveness for 1 dose, 78% for 2 doses, and 84% for the full course. For the NVSN Rotarix® analysis, there was not ample study power to make an assessment for the single dose, so the full course was presented.

Dr. Sawyer requested assistance interpreting the evidence that suggested that there was not significant waning in the context of less severe disease in older children, parents of older children being less likely to take them for care, and doctors being less likely to test older children.

Dr. Payne replied that the issue of waning in the NVSN analysis centered around severe rotavirus-associated hospitalizations and emergency department visits. If an older child is able to rehydrate on their own without issue, perhaps at a lower level that would not be an issue. That is not captured by the NVSN data in terms of the waning analysis. That is an important distinction, but severe hospitalizations and emergency department visits resulting from rotavirus are considered to be valid.

Dr. Harrison wondered what the implications were for the increase in G3 cases in terms of ACIP.

Dr. Payne responded that the rise in predominance of the G3P[8] genotype that has been observed in many surveillance systems does not appear to have any implication on policy. There is no clear evidence that this is from some kind of selective adaptation of a genotype in the presence of a vaccine. The G3P[8] appears to have very good vaccine effectiveness with the analyses presented.

Dr. Vazquez asked Dr. Payne to comment on the ability to detect vaccine strain in terms of whether some of the cases were actually Rotarix®.

Dr. Payne indicated that in general, all subjects enrolled were tested by enzyme immunoassay (EIA). Those who were positive by EIA were all genotyped, and then elaborate sequencing protocols were used on those to detect whether there were similarities with the rotavirus vaccine strains themselves.

Dr. Duchin said he was fascinated by the publication showing the indirect effects on the older age groups, and he requested an update on that if possible. He also wondered about groups too old to be vaccinated and young adults.

Dr. Payne responded that even during the pre-licensure period in modeling exercises, it was observed that at a very good vaccine coverage level there would be a biennial peak of rotavirus, and this was also demonstrated empirically. Even in years with very steep declines of 90%, there are indirect effects, and the next year serves as a catch-up. Anyone who remains to be immunologically acceptable is exposed, and they meet that exposure with infection and perhaps do not have to seek medical care. Apparently some sort of indirect protection occurs cyclically. There has been a lot of research on those too old to be vaccinated, as well as young adults. Based on some of the studies now published, it appears that having a rotavirus-vaccinated child in the household may provide indirect benefits to others in the household, even older adults at the childbearing age and perhaps even older than that.

Dr. Pickering has received several calls about micro-preemies pointing out that by the time these very small infants are old enough or stable enough to receive rotavirus vaccine, they are past the first dose as which ACIP recommends it be given. They leave the hospital and are highly susceptible to rotavirus disease. He wondered whether the working group was considering liberalizing the current recommendations for administration of rotavirus vaccines for the first, second, and third doses.

Dr. Payne indicated that a recent publication found that by relaxing the age restrictions overall in lower and moderate income countries, there appears to be great benefit to children who have missed vaccinations. He deferred to others with regard specifically to micro-preemies.

Dr. Parashar (SME) responded that the concern with giving vaccine to micro-preemies while they were still within the nursery setting regarded the potential for transmission of the vaccine strain, and exposing other premature babies to the vaccine virus. However, by not administering the vaccine to these children until after they are discharged, some of these children become age-ineligible if not discharged by the upper limit for the first dose. An evaluation with the NVSN sites will assess the issue of transmission within nurseries to better understand how common this is, and whether it poses a risk.

Dr. Pickering noted that there is a difference between the two vaccines in terms of the amount of live virus in stools.

Dr. Parashar (SME) replied that the shedding data shows more antigen shedding and more live virus shedding with the monovalent vaccine than the pentavalent vaccine. Whether that translates into a difference in risk of disease and transmission is unclear. GSK conducted a study in the Dominican Republic with twin pairs in which one twin and not the other was immunized. There was about a 17% to 18% seroresponse rate in the unimmunized twin, so there is likely some potential for transmission of the vaccine virus strain.

Dr. Sawyer inquired as to whether the working group planned to revisit the age restrictions.

Dr. Bocchini inquired as to what percent of infants do not finish the course because they have aged out of the timeframe for the second or third dose of vaccine.

Dr. Parashar (SME) indicated that there are two restrictions on the vaccine. The first dose must be administered by 15 weeks, and the full series by 8 months of age. Both potentially could impact overall coverage. There are no specific data regarding how many children have been excluded from vaccination due to these restrictions. When this was assessed in terms of the timing of DTaP coverage, it was estimated that about 5% of children present for their first DTaP dose after 15 weeks of age. They are still trying to obtain specific data for how that impacts the rotavirus vaccine first-dose coverage. The third dose is also potentially an issue of about the same magnitude, in that there are children who complete their series after 8 months.

Vaccine Supply

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

Dr. Santoli presented a brief update on vaccine supply for adult hepatitis A vaccine, MMR-V vaccine, HPV vaccine, Pentacel[®], and DTaP.

Merck's adult hepatitis A vaccine is currently available for order as pre-filled syringes. Vials are expected to be available in the first quarter of 2013. With regard to MMR-V vaccine, ProQuad[®] is currently available for order.

The prefilled syringe presentation of Merck's HPV vaccine is on temporary backorder, with return to normal shipping times expected by early November 2012. The product is currently available to order. The 10-pack and single-pack vial presentations, which make up greater than 90% of doses distributed in the US, are not impacted. The overall supply of Merck's HPV vaccine is not impacted.

Availability of sanofi pasteur's Pentacel[®] and DAPTACEL[®] vaccines is currently reduced. Supply issues are anticipated to last through March 2013. Pentacel[®] availability has decreased significantly from the start of the shortage in late April 2012. However, sanofi pasteur's single antigen inactivated polio and Hib vaccines continue to be available in sufficient supply to address historic usage of Pentacel[®], as well as the single antigen vaccines. Regarding DTaP-containing vaccines in general, production and supply of GSK's single antigen and combination vaccines is currently sufficient to address any anticipated supply gaps for DTaP-containing vaccines.

CDC's Vaccine Supply / Shortage Webpage is available at the following:
<http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm>

Influenza

Introduction

Wendy Keitel, MD
Chair, Influenza Working Group

Dr. Keitel reported that over the last several months, the Influenza Working Group's activities have included finalization of the publication of the 2012-2013 ACIP Influenza Vaccine Statement [MMWR 2012; 61(32):613-618]; discussions regarding quadrivalent influenza vaccines, cell-based influenza vaccine, influenza surveillance, and 2011-2012 influenza vaccine coverage; and a review of the evidence base for TIV and LAIV in healthy children using GRADE.

Influenza Activity

Lyn Finelli, DrPH, MS
Lead, Influenza Surveillance and Outbreak Response Team
Epidemiology and Prevention Branch, Influenza Division
National Center for Immunizations and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Finelli began with an overview of surveillance, noting that at Week 42, the season had only just begun. Traditionally, the season begins at Week 40. With regard to influenza positive tests reported to CDC by the US WHO / National Respiratory and Enteric Virus Surveillance System (NREVSS) Collaborating Laboratories, there had been a mixed season so far with two weeks of reported data. At this point, the season was predominated by influenza B, which meant nothing so far. Influenza B, H3, and 2009 H1N1 have been reported. Last year was a very mild season. In a busy season, thousands of isolates are reported to CDC. With 140 isolates reported at the time of this meeting, it was the usual start to an influenza season. Also at this time, influenza-like illness (ILI) reported by the US Outpatient Influenza-like Illness Surveillance Network (ILINet) was approximately 1%. According to the influenza activity estimates reported by state and territorial epidemiologists, either no or sporadic activity was reported as of the week ending October 13, 2012. At this time, only one state was reporting local activity. Pneumonia and influenza mortality for the 122 US Cities for the week ending October 13, 2012 was within the epidemic baseline and threshold. In terms of pediatric mortality, there were only 34 deaths during the 2011-2012 season, which was a very mild season. During the 2010-2011 season, there were 122 deaths.

Over the last 5 or 7 years since surveillance has been conducted for variant influenza cases (e.g., swine origin influenza cases), there was a preponderance in the early years of influenza A swine origin H1N1 with some H1N2. From 2008 through 2009, there was a preponderance of H3N2. Something unusual occurred in 2011, which was the appearance of an H3N2 variant infection. That H3N2 variant had the M, or Matrix, gene from the 2009 H1N1 virus. There was also an H1N2 and an H1N1 that year. What was unusual about 2011 was that there were 12 cases, so it was a record or banner year for swine origin influenza virus infections in humans.

Of these 12 cases, 6 were human-to-human transmissions. This was alarming in that there was concern that the number of infections could increase. Thus, CDC engaged in significant epidemiological work in order to understand as much as possible about these infections. There was a large outbreak during the summer of 306 infections in 10 states. The outbreak began on July 9th and ended with the last reported confirmed case on September 7th. Indiana had the most confirmed cases (n=138) of H3N2v. Ohio was next with 106 confirmed cases, but they had over 100 rapid test positive cases, which were counted as probable rather than confirmed. Thus, Ohio probably actually had the most cases during this outbreak. The other 8 states had a scattered number of cases, ranging from about 5 to about 20 cases. The number of confirmed cases hospitalized was 16, the number of fatal confirmed cases was 1, and the number of confirmed cases with presumed human-to-human transmission was 15. The death occurred in a person in her late 50s with a number of underlying conditions. A very broad definition was used for human-to-human transmission, which extended to people with swine contact but whose incubation period was considered somewhat too long to have been infected by swine.

In terms of the epidemiologic parameters, the mean age of these cases was 8 years, with a range of 4 months to 74 years of age. The incubation period was 2 to 3 days, which is typical of seasonal influenza. The secondary attack rate was low. Symptoms were influenza-like, and the duration of illness was 3 to 4 days just like seasonal influenza. With regard to the distribution of cases and the proportion of cases H3N2v HI antibody titer greater than 40, there was very little to no immunity in very young children. The proportion of the population with cross reactive immunity increased beginning in the teenage age groups (10 to 17 years), peaked in the middle age groups (18 to 49), and fell slightly in those 50 years of age and older. The highest proportion of cases was in age groups without cross reactive immunity. This makes biologic sense, but also has to do with the fact that children in these age groups are more likely to have exposure because they are more likely to be exhibitors and to attend state and local fairs, and to have very concentrated contact with swine.

Regarding what is known about exposure, CDC has detailed exposure data for 203 of 260 cases. Of the 203 cases, 198 (98%) had either direct swine contact, indirect swine contact, or attended a fair. Over 50% had multiple days of exposure, and many were swine exhibitors or their families and friends. To put this into context, approximately 200,000 children and adolescents exhibit swine at state and county fairs each year in the US, primarily as part of 4H or Future Farmers of America projects. The risk to fairgoers is unknown, but is assumed to be low. The International Association of Fairs and Expositions (IAFE) data indicate that through October 2011, over 80 million persons attended state or county fairs. A 2011 Pennsylvania prospective fair survey showed that approximately 33% of fair visitors visit the swine barn [Wong K, et al. Outbreak of Novel Influenza A (H3N2) Variant Virus Infection Among Attendees of an Agricultural Fair, Pennsylvania, 2011. *Emerg Infect Dis.* 2012 [Article Outbreak of Novel Influenza A \(H3N2\) Variant Virus Infection Among Attendees of an Agricultural Fair, Pennsylvania, 2011](#)]. Thus, many swine barn visitors are potentially exposed briefly and indirectly. At least some of these exposures this year would have been to infected pigs since swine infection was widespread. However, few cases have reported brief, transient exposure.

In conclusion, fairs are places that pigs come together and if one are more pigs are infected, there is transmission among pigs and sometimes to people. People with direct and prolonged exposure have been those at risk of H3N2v infection to date. Risk of H3N2v infection is low in exhibitors, and is very low in casual visitors to fairs. No H3N2v cases have arisen from the general population without exposure to pigs or to sick people. There has been no significant person-to-person transmission, and there has been no community transmission to date. In most people, illness is short and self-limited and few people have been hospitalized. There has been

one death, and there could be more, so CDC will continue this surveillance over the next few months.

Influenza Vaccine Coverage

Dr. James A. Singleton National Center for Immunizations and Respiratory Diseases Centers for Disease Control and Prevention

Dr. Singleton presented an overview on influenza vaccine coverage for the 2011-2012 season, which was the second post-pandemic season and the second season with universal influenza vaccination recommendations. The vaccine strains remained the same as the previous season, and it was a relatively mild and late influenza season.

The data Dr. Singleton presented updated interim estimates previously posted online in March and November of 2011. These were final estimates for the general population using telephone interview surveys from September 2011 through June 2012. For children 6 months through 17 years of age, the data were from the National Immunization Survey (n=96,254). For adults 18 years of age and older, the data were from the Behavioral Risk Factor Surveillance System (BRFSS) (n=367,500). These are parental and self-reported vaccinations. The online report is available at: [CDC Website Vaccine Coverage Information](#). For healthcare personnel (n=2,348)¹ and pregnant women (n=1,660)², internet panel surveys were conducted in April 2012 [¹MMWR September 28, 2012 / Vol. 61 / No. 38 / Pg. 753 – 757; ²MMWR September 28, 2012 / Vol. 61 / No. 38 / Pg. 758 – 763].

During the 2011-2012 influenza season, 132 million doses of influenza doses were distributed in the US. The distribution was earlier than in other seasons, with more doses available earlier. As of October 12, 2012 115 million doses were distributed, which is expected to increase to 135 million by the end of the season. For children, coverage has reached approximately 50%, which is about the same last year as for this year. For adults, coverage is approximately 40%. For children 2011-2012 season, cumulative vaccination coverage by month was close to the 2010-2011 season with higher uptake earlier but converging at about the same rate. For adults, there was a slight decrease. For the 2011-2012 season, coverage with at least one dose for children 6 months through 17 years of age was 51.5%, which was essentially the same as the 2010-2011 season coverage (51.0%). Influenza vaccination for children decreased as age increased, with 74.6% coverage for children 6 through 23 months of age, 63.3% for children 2 through 4 years of age, 54.2% for children 5 through 12 years of age, and 33.7% for children 13 through 17 years of age. In terms of comparison to the prior season, there was a significant increase of 6.4% for children 6 through 23 months of age.

To evaluate full vaccination coverage with up to 2 doses as recommended by ACIP among children less than 9 years of age, data were examined from the eight Immunization Information System (IIS) sites Sentinel Site Project areas. For the 2011-2012 season, a child less than 9 years of age would need two doses unless they had received at least one dose of the 2010-2011 season influenza vaccination. Approximately 73% of 6 through 23 month olds, 61% of 24 through 59 month olds, and 73% of 5 through 8 years old would have needed to receive 2 valid doses of influenza vaccine according to the ACIP recommendations for the 2011-2012 season. As with the survey estimates, vaccination coverage decreased for older age groups. The ratio of full to 1+ vaccination coverage was 73% for children 6 through 23 month of age, 72% for children 24 through 59 months of age, and 65% for children 5 through 8 years of age. These ratios are higher than seen from the IIS Sentinel Sites in the prior season of 62%, 60%, and

55% respectively. The higher ratio or completion rate in 2011-2012 may be due to a lower proportion of children less than 9 years being recommended for two doses for the 2011-2012 season. In recent past seasons, 85% to 90% of children were recommended for two doses compared to 61% to 73% in the 2011-2012 season.

Coverage for adults 18 years of age and older was 38.8% for the 2011-2012 season, which was 1.7% lower than coverage estimates for the 2010-11 season. Vaccine coverage was lowest in those 18 through 49 years of age at 28.6% and highest in adults 65 years of age and older at 64.9%, which was consistent across both of the seasons. There was a consistent drop in coverage of up to 2% in adults. The change in adult coverage may be caused by the significant changes that were made to the BRFSS methodology, given that households with only cell phones were added to the sample and weighting methods were improved. An assessment is being made of the NIS data to determine whether the same trend is observed.

As observed in prior seasons, there is substantial variation by state in child and adult influenza vaccine coverage, with coverage for children ranging from 39% to 74% and adults from 28% to 49%. Vaccine coverage has also been assessed by race / ethnicity. Coverage among children 6 months through 17 years of age was highest among Hispanic children (59.5%) and non-Hispanic Asian children (58.2%). Coverage estimates for Hispanics (59.5%), non-Hispanic Asians (58.2%), and non-Hispanic blacks (53.7%) were higher than among non-Hispanic white children (47.6%). Coverage among adults 18 years of age and older was higher for non-Hispanic whites (41.9%) compared to other racial / ethnic groups except American Indians / Alaska Natives (AI / AN) (42.6%). From the 1996-1997 season to the 2003-2004 season, there was a gradual increase in coverage among healthcare workers. The vaccine shortage of 2005 created a decrease in coverage, and then there was a steeper acceleration in coverage to 63% with the preliminary estimate for the 2011-2012 season. The panel surveys showed somewhat higher coverage at that time of 67%. These data tend to run somewhat higher than the NIS, but they offer important data on variation of coverage by occupation and work setting. Physicians reached 86% coverage, nurses 78%, and clinical support staff 54%. Of healthcare workers in hospitals, 77% reported vaccination, while 68% in physician offices and 52% in long-term care facilities reported vaccination. Coverage among women who were pregnant during the influenza season was 47% for the 2011-2012 influenza season, consistent with 49% coverage estimates for the 2010-2011 season.

The most common place of vaccination among both adults (32.5%) and children (65.4%) was a doctor's office. These results are similar to results from the 2010-2011 season when 31.6% of adults and 60.2% of children were vaccinated in doctor's offices. Other common places of influenza vaccination reported for adults during the 2011-2012 season included medically related places besides doctor's offices (24.7%), pharmacies or stores (19.7%), and workplaces (13.8%). The second most common places of influenza vaccination for children were medically related places other than doctor's offices (22.7%).

In summary, coverage for children for the 2011-2012 season was similar to the 2010-2011 season coverage. Coverage for adults for the 2011-2012 season was 1.7% lower than for the 2010-2011 season. Changes in adult coverage may be due to changes made to the BRFSS methodology. Coverage among children was highest among Hispanic and non-Hispanic Asian children, and racial / ethnic disparities among adults persist. There is wide variation in coverage among states. Last season's increases for pregnant women and healthcare personnel were maintained. The most common places for vaccination among both adults and children were medical locations, while retail settings and work places were other important venues for adults.

There are a number of limitations. Tracking trends by season is complicated by multiple data sources with different timeliness and methods. In 2011, BRFSS added households with only cellular telephone service to the sampling frame and made changes to weighting methods. Data from before 2011 may not be directly comparable. Self-reported vaccination is not validated by medical records. Survey estimates may not be representative, and telephone survey response rates were low. Representativeness of internet panel survey estimates needs further evaluation.

Recommendations from the *Guide to Community Preventive Services* are to increase influenza vaccination coverage among all groups; reduce disparities in coverage among adults; implement proven interventions to increase coverage; enhance access to vaccination services; increasing community demand for vaccinations; implement provider- or system-based interventions; and implement community-based interventions in combination.

Most of the data provided during this session are available on FluVaxView, CDC's source for influenza vaccination coverage data located at: <http://www.cdc.gov/flu/fluview/index.htm>. The site also includes state level interactive maps by age group.

Discussion Points

Dr. Keitel inquired as to whether there was a precedent for this number of variant infections occurring within a single season without sustained human-to-human transmission. She also wondered about the average age of the swine exhibitors.

Dr. Finelli responded that this number of swine-to-human transmissions has never been observed among other than during the pandemic. Exhibitors are primarily older school-aged children and younger adolescents, so that average age of an exhibitor is between 8 and 12 years of age.

In terms of place of vaccination by age group, Ms. Stinchfield (NAPNAP) noted that doctors office was separated out from clinic or health center. She wondered whether that was private versus public, or how they differed.

Dr. Singleton replied that when people are asked where they got their influenza vaccination, their responses are coded into the categories that the interviewers see. It depends on what the coders perceives the location to be. He would call Kaiser a clinic or health center because that is how he views it, but someone else might call it a doctor's office.

Regarding H3N2v, Dr. Sun (FDA) wondered whether there was a similar epizootic in pigs which could account for the increase. He also inquired as to whether any interventions were instituted that caused the sharp decrease in the cases since the peak.

Dr. Finelli responded that there is no direct evidence of an epizootic. There is only anecdotal evidence. Swine veterinarians and those who work at state and local fairs say that they observed much more transmission and much more swine illness this year than last year. There is some swine surveillance in the community, but CDC does not have the denominator to quantitate it at this point. As swine surveillance gains momentum in the future, CDC hopes to have that kind of denominator. Though it remains unclear whether it was causal, Indiana did a stellar job controlling swine-to-human transmission. Their initial outbreaks occurred at a number of small, local fairs. Of the 138 cases, two fairs contributed about 90 cases. They were very concerned that there would be massive transmission during their large state fair because so

many swine were shown during that fair. They put in a number of stop-gap measures. For example, the pigs' temperatures were taken before unloading them the trucks, many veterinarians were on site, the pigs were observed 5 times per day, pigs were removed from the site if they looked ill, and the children who were showing the pigs were empowered to look at other people's pigs and tell someone if they thought swine were ill. There was no transmission there. After the Indiana outbreak, others heard of this. USDA and other animal health colleagues helped state and local governments intervene, and disseminated a lot of materials to help people. Transmission slows significant, though it remains unclear whether this was causal. From the epi-curve, it appears that transmission slowed considerably. By no means in August when transmission slowed considerably were state and local fairs over. They were only about half to two-thirds over.

Dr. Whitley-Williams (NMA) requested further information about racial / ethnic disparities among adults with regard to pneumonia- and influenza-related mortality during the past season given the coverage rates.

Dr. Finelli replied that for the past year, there were 34 influenza-related pediatric deaths. The patterns by race / ethnicity were similar to all past years. There is a racial / ethnic disparity, with African Americans and Hispanic children having slightly more influenza-associated mortality than their proportion in the US population. That is consistent over that past few years. That is pediatric mortality, as CDC does not track adult mortality. For the past year, CDC does not have specific race / ethnic data on deaths. Those data will not be available for a couple of years when the national NHIS data are available.

Dr. Gellin (NVPO) inquired as to whether location of vaccination is tracked over time, and whether there was any insight into where schools are.

Dr. Singleton responded that for adults, CDC has data that goes back sporadically to the late 1990s. However, monitoring just began for children during the 2009-2010 season. There was a lot more school-located vaccination during the H1N1 pandemic than subsequent seasons. They are assessing this by state, but he was not able to comment on what those data show at this point. The 2011-2012 data have not yet been assessed in detail by state. Hawaii has been active in advocating school-located vaccination.

Influenza Vaccines for Healthy Children

Dr. Lisa Grohskopf

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

Dr. Grohskopf indicated that in addition to presenting this information on behalf of the ACIP Influenza Working Group, she was also presenting on behalf of the team members at the Mayo Knowledge and Encounter Research Unit led by Dr. Hassan Murad. Dr. Murad conducted the analysis and review, with input from the ACIP Influenza Working Group.

The first national US recommendation for influenza vaccination was issued by the Surgeon General in 1960 a few years before the ACIP was formed. Among the groups recommended for routine annual vaccination were persons of all ages who suffered from chronic debilitating disease (e.g., rheumatic heart disease, other cardiovascular diseases, chronic bronchopulmonary diseases such as asthma or bronchitis, and diabetes) [Burney LE. Public Health Rep. 1960 Oct;75(10):944]. Over the course of time, particularly within the last decade,

this was somewhat expanded. In 2003, expansion of the recommendation for annual influenza vaccination of the general pediatric population began with the recommendation for annual vaccination of all children 6 through 23 months of age. In 2006, the recommendation was expanded to all children 6 through 59 months of age. The recommendation was further expanded in 2008 to all children 6 months through 18 years of age.

For the last several years, influenza vaccine providers have had a choice between two vaccines for the majority of pediatric patients. The first, inactivated influenza vaccine (IIV), is administered to children by intramuscular injection. IIV was first approved in the US in 1945. Various preparations currently are available from several manufacturers. While the age indications for the specific preparations differ, there are IIV vaccines for children as young as 6 months of age. The more recently available LAIV vaccine is administered intranasally. LAIV was approved in the US in 2003, and is recommended for healthy non-pregnant persons ages 2 through 49 years. It is not currently recommended for persons at high risk of influenza-related complications. Canada and the UK currently express, in one form or another, a preference for LAIV over trivalent inactivated influenza vaccines (TIV) for children 2 through 17 years of age who have no contraindications. In the US, ACIP / CDC currently express no preference for LAIV or TIV within this age group.

Within the past decade, several studies have noted greater relative effectiveness of LAIV as compared with IIV in children, particularly among younger children. ACIP is currently examining the evidence related to LAIV and IIV among children, and the question regarding whether the evidence supports consideration of a preferential recommendation of LAIV among children as the first potential influenza recommendation to be evaluated using GRADE methodology. Consideration of a preferential recommendation requires consideration of a variety of factors, including relative effectiveness, safety, supply, cost, and programmatic feasibility.

This presentation concentrated on the relative effectiveness of these two vaccines in healthy children. The question framed by the Influenza Working Group to be discussed during this session was, "What is the evidence for the relative effectiveness of LAIV versus IIV for healthy children?" Because it was known that some studies have not noticed a greater effectiveness for LAIV versus IIV among older persons, it was understood that a potential recommendation might differ for younger versus older children or adults versus children. Therefore, the question was initially formulated for children with two different age groups in mind: 2 through 8 years of age, and 9 through 18 years of age. The lower limit of 2 years for the younger children in this age group was selected because this is the lowest age at which LAIV currently indicated in the US. The upper limit of 8 years for children was chosen in part for simplicity. It is not known at approximately what age the relative effectiveness of one vaccine versus another would change; however, 8 years is already the age to be considered in another important pediatric recommendation, which is the upper limit age at which consideration has to be given to whether a child needs one or two doses. At least for this round of working analyses, in the absence of compelling evidence for a different specific age cutoff, 8 years was selected.

After framing the question, the working group discussed the inclusion and exclusion criteria for the various studies to be considered. Included trials would be randomized trials of IIV and LAIV conducted among healthy children. Data containing bivalent vaccines were considered acceptable. However, in these cases, only appropriate outcomes would be considered. For example, in a study of bivalent LAIV using only influenza A antigens (H1N1 and H3N2), only influenza A outcomes would be evaluated. Studies specifically designed to evaluate children with chronic medical conditions such as asthma will be assessed separately in the GRADE process. Data pertaining to adjuvanted, whole-virus, and virosomal vaccines; live-attenuated

vaccines derived from different master strains from those used for US products; and vaccines with antigen quantified by means other than mcg hemagglutinin (HA) were excluded. Also excluded were studies enrolling only children under 2 years of age. The working group then generated and evaluated a list of effectiveness outcomes. The outcomes judged by the majority of the group to be critical included laboratory-confirmed influenza, mortality, hospitalization, and medically-attended acute respiratory illness. The outcomes judged to be important but not critical for decision making included influenza-like illness and otitis media. This presentation concentrated on the most specific of these outcomes, laboratory-confirmed influenza. Next a review of the literature was conducted to identify randomized trials evaluating LAIV and IIV. Studies were identified through existing systematic reviews, review of previous ACIP influenza statements, and a literature search. Two reviewers independently evaluated study eligibility and extracted descriptive, methodological, and efficacy data. Members of the working group were consulted about the studies to be included in this process. Comparisons among studies were conducted using a random effects model, and the quality of evidence was assessed following the GRADE approach.

With regard to the trials analyzed, 22 randomized trials were identified that assessed LAIV, IIV, or both. Of these, 6 included LAIV and IIV. Of these 6, 3 directly compared LAIV and IIV; and 3 had LAIV, IIV, and placebo arms. From these 6, excluded trials included 1 of children with asthma; 1 of bivalent LAIV (influenza A only) which reported only influenza B infections; and 1 of bivalent LAIV (influenza A only) which used placebo or inactivated B controls, for which influenza A data were not extractable. This left 3 trials that were included in the analyses, 2 directly comparing LAIV and IIV; and 1 with LAIV, IIV, and placebo arms. The three studies included Ashkenazi (2006), Belshe (2007), and Clover (1991). The Ashkenazi study was conducted in several nations in Europe as well as Israel for the 2002-2003 season, with trivalent LAIV and trivalent IIV arms in 2187 children 6 through 59 months of age. Belshe was conducted in the US, Europe, the Middle East, and Asia for the 2004-2005 season, with trivalent LAIV and trivalent IIV arms in 8352 children ages 6 through 71 months of age. Clover was conducted in the US (Houston) for the 1986 through 87 season, with bivalent LAIV containing A(H1N1) and A(H3N2) antigens, trivalent IIV, and placebo arms in 192 children 3 through 19 years of age.

In terms of the evidence profile for 2 through 8 year olds with the outcome of laboratory-confirmed influenza, all three studies were included in this analysis. Overall, no serious concerns were noted with regard to inconsistency, indirectness, or imprecision across the three studies. Overall, however, risk of bias was judged to be serious across the three studies. Ashkenazi was an open label study; and Clover did not report sufficient details regarding randomization, allocation concealment, blinding, or loss to follow-up. This resulted in the overall downgrading of the quality of evidence from 1 to 2. The estimated pooled weighted relative risk across the studies for use of LAIV versus IIV was 0.50 with a 95% confidence interval of 0.37-0.67 and an absolute risk estimate of 20 fewer cases (13 fewer to 25 fewer). This is statistically significant.

Regarding the age inclusion criteria, some children fell outside of the 2 year minimum, but the decision was made to include ages that overlapped with the analysis criteria. Not all studies stratified by age. The Ashkenazi results were not age-stratified, so the data included was without regard to age match. Belshe included age stratifications, so these data includes 24 months through 59 months. Clover included results for 3 through 9 years, and that was age-stratified. In addition, when age was stratified, the specific outcomes with regard to well-matched strains of influenza versus not well-matched strains of influenza were not always stratified. For Ashkenazi, data were included for influenza infections without regard to match

with the vaccine strain. Data for well-matched strains were included in the age stratified analysis for Belshe. Clove specifically evaluated an H1N1 strain that differed from the strain included in the vaccine.

In terms of the evidence profile for 9 through 18 year olds, only the Clover paper was suitable. For this study, there were no serious issues with regard to consistency or indirectness. However, there were serious concerns with regard to risk of bias and imprecision due to the lack of information offered about randomization, allocation concealment, blinding, and loss to follow-up. Because of the relatively small number of children and relatively small number infections in this age stratum, there is some imprecision. There is a very wide confidence interval for this estimate, with an estimated pooled relative risk of 10 with a confidence interval of 0.60-165. Given the issues with risk of bias and imprecision, the overall quality of evidence for this study was downgraded from 1 to 3.

In summary, in this analysis, LAIV was noted to provide greater relative protection than IIV against culture-confirmed influenza among healthy younger children ages 6 months through 9 years as assessed across 3 randomized studies. Less data were available from randomized studies of older children. There was only one study, which showed that LAIV was not significantly more effective. There were some limitations. Only a small number of studies were identified, particularly for older children. Some children under 2 years of age were included in this analysis because of lack of age stratification of the data. The studies were conducted during different seasons in geographically diverse regions, which meant that some subtleties that may have differed from season to season or place to place may not have been captured or controlled for in this particular approach, such as whether the circulating strains matched the vaccine strain. The working group was not proposing a vote for LAIV versus TIV at this time, given that this was the first session to address this topic and that additional issues need to be considered. For example, in terms of safety assessment, quadrivalent LAIV is expected to replace the current trivalent LAIV for the 2013-2014 season. One issue has been raised with regard to safety evaluation is that because this is a new vaccine, post-marketing safety experience with Q-LAIV will not be available for a while. Also yet to be reviewed are issues related to vaccine supply and the relative cost of the two vaccines. With that in mind, the next steps are to continue with plans for assessment and on-going safety evaluation of the quadrivalent LAIV, review of supply and economic data, and collection of additional information requested by ACIP for presentation in future meetings.

Discussion Points

Dr. Warshawky (NACI) requested clarification regarding whether LAIV is contraindicated in people with medical conditions.

Dr. Grohskopf replied that in the US, the package insert does not specifically list chronic medical conditions as a contraindication. However, ACIP has recommended against use in that population due to lack of data.

Dr. Ambrose (MedImmune) noted that an additional limitation of the Clover study was that serologic endpoints were used in addition to viral confirmation to assess the incidence of influenza. The literature has shown that to be a particular biased endpoint in terms of inactivated vaccine. That study itself described that because people's post-vaccination titers are so high following an inactivated vaccine, subsequent infection cannot be detected by serology. The only data that are culture-confirmed that do not have the serology bias can be pulled out of the Clover study. There were fewer cases of culture-confirmed influenza in that

study in the LAIV group. A large study in over 2000 children 6 through 17 years of age with asthma showed fewer cases of culture-confirmed influenza among the LAIV group.

Dr. Grohskopf responded that within Clover, some further criteria were applied to illnesses that were associated with serologic evidence, but not culture. Also considered in this study was whether the illness had occurred within a certain number of days of another illness within the household.

Dr. Karron pointed out that some studies suggest that LAIV performs better in terms of antigenic mismatch. She wondered whether it was possible in the studies considered for this analysis to specifically assess the issue of antigenic mismatch, or to highlight that as something that should be assessed prospectively in the quadrivalent studies.

Dr. Grohskopf responded that the Belshe stratified based on match, no match, or without regard to match. However, those data were not age stratified so for this particular analysis the age stratification data were favored. Assessing it the other way, it does not look substantially different. The issue of match is obviously important. Consideration was given to assessing surveillance data to determine whether there were ways to adjust for match based on season and geographic location. For the US, depending how far back, surveillance data could be helpful. However, this was not practical for large multi-national studies.

Dr. Gorman (NIH) noted that with any live attenuated vaccine there is the double-edged sword of potential herd immunity and potential herd infection. He wondered whether there was any consideration in the review by the working group of the halo effect of the live attenuated vaccine.

Dr. Grohskopf replied that the working group did not evaluate that question for these trials.

Dr. Keitel added that the herd immunity effect has been documented for live attenuated and inactivated vaccines. A cluster randomized trial in the Hutterite communities in the Northern US and Canada demonstrated that immunization of school children with an inactivated vaccine conferred protection among older people in the community. When widely used among school children who are considered to be transmitters of influenza, both live and inactivated vaccines can confer substantial benefit to people who are either unimmunized or are less likely to respond to immunization.

Dr. Sawyer noted that part of the safety concern with live attenuated vaccine is reassortment of the vaccine strains with natural strains, such as in people who go to state fairs. He requested a reminder of the body of evidence to date about reassortment with a live attenuated vaccine and naturally circulating strains.

Dr. Keitel responded that to her knowledge, there was limited evidence of reassortment with wild type viruses.

Dr. Coelingh (MedImmune) added that MedImmune has approached this in a couple of ways. Reassortants have never been observed between wild type strains and vaccine strains serendipitously in the field. However, MedImmune has directly approached this by actually making reassortants containing one or more genes from the virulent wild type strain. Universally, these all are attenuated when the reassortment occurs because the genes for reassortment are carried on the master donor virus. Generally, they will be more attenuated than the wild type strain.

Potential Public Health Impact of Quadrivalent Influenza Vaccines

Dr. Carrie Reed

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

Dr. Reed reported that influenza B viruses circulate globally every year. They are subdivided into two lineages that currently co-circulate annually: B/Yamagata and B/Victoria. Severe complications and deaths caused by influenza B viruses occur in all age groups. The current trivalent vaccine includes one lineage of influenza B virus lineage each year. Protection after vaccination with one lineage against the other lineage not in the vaccine is unclear, although it is thought to be low. Co-circulation of both lineages means some degree of mismatch between vaccine and circulating strains is possible in some years. That can reduce the overall trivalent vaccine effectiveness, and can also reduce public confidence in the value of influenza vaccines.

The question raised several years ago was, "Compared to TIV, what would be the additional public health impact from QIV on influenza disease outcomes in the US?" The approach was to take a historical perspective; frame the question as, "What if QIV had been used instead of TIV over the last 10 years?"; and calculate the marginal impact on estimates of influenza-associated cases, hospitalizations, and death. The method was to include data from the last 10 influenza seasons from literature reviews and from surveillance data in order to capture the natural variability that exists between seasons. The population average of all ages was used in the data included, which may not capture the variability by age group, but there was a limit to the data available across all 10 seasons for all of the age groups. The analysis was set up in a spreadsheet-based tool that was also published online with the publication of the manuscript so that users could change the inputs (e.g., assumptions, age-specific data, update to future influenza seasons).

The tool calculates the expected burden of influenza during each season, assuming that there was the same vaccine coverage and vaccine efficacy each year, but now with efficacy against both B lineages. Outcomes included rates of illness, hospitalization, and death. The expected rates were then compared with QIV to the rates observed with TIV, and calculated what the additional averted outcomes would be in each of the seasons. A lot of data were needed to feed into these calculations, including information on rates of influenza-associated health outcomes; and information on illness, hospitalization, and death. In order to do this, information was needed by type, subtype, and lineage over the past 10 seasons. Data were also needed on vaccine effectiveness ideally by type, subtype, and lineage over 10 seasons. Also needed was virologic surveillance to determine the annual distribution of type, subtype, and lineage. Data on vaccine coverage over the same time period were also needed.

To briefly summarize the results of the analysis, in terms of cases averted under a QIV scenario compared to TIV in the US population over the 10 seasons combined, a total of 2.7 million illnesses were averted along with 21,000 additional hospitalizations and 1300 additional deaths. There was a lot of variability by season, which was largely influenced by the distribution of viruses each year. One B lineage was strongly predominant over the other in some seasons, while other seasons the two lineages were fairly mixed. Considering the strain that was included in the vaccine during each of those years, there was a match in 5 years and no match in 5 years.

As an example for one season, 2007–2008 was the biggest season in the analysis during which additional outcomes averted with QIV included 1.1 million fewer cases, 7500 fewer hospitalizations, and 300 fewer deaths. In this season, the virologic surveillance indicated that 29% of the viruses circulating were type B, and 98% of those were in the lineage not included in the vaccine. The TIV supply greatly exceeded the demand, so there would not have been an impact of potentially fewer doses of QIV. That is, taking a historical perspective, the use of resources to grow four viruses instead of three may have meant that fewer doses would have been available during those years. That might only have been a concern if the doses available would not have met the demand during those same years. If so, decreased coverage may have result in a net increase in cases of influenza in some years.

Therefore, the additional variable of vaccine production was added to the analysis for those same 10 years. The first question was, “Over the past 10 seasons, how many doses of QIV could have been produced?” The spreadsheet tool includes a sheet that optimizes the number of doses of QIV that may be produced with same production capacity as TIV. The second question was, “How does this relate to the number of doses administered that year compared to the number of QIV doses available to TIV doses administered?” In the early seasons, the doses administered exceeded QIV produced. However, in the most recent seasons the amount administered remained below the QIV produced.

As another example of this analysis, in the 2004–2005 season virologic surveillance showed that about 25% of circulating strains were influenza B viruses, and that 26% of those were the lineage not in the vaccine. Problems with production led to decreased supply and administration of vaccine. If that had been divided across four viruses instead of three, it was estimated that an additional loss in coverage if fewer doses of QIV available resulted in 15% fewer persons vaccinated would be a net increase of 151,000 cases with QIV versus what would have been observed with higher coverage against three viruses.

There were some limitations to the analyses. Several assumptions were made from the limited data that were available for those 10 seasons. Data were entered as a population average, but may vary by age; health impact (cases, hospitalizations, deaths); and strain / lineage circulating during each of those years. A major reason that the spreadsheet model was included was so that people could download and adjust the inputs as data were available to do so. Additional considerations that were not included directly in the analyses were economic costs associated with the two different vaccines; potential differences in adverse events; and alternative strategies for reducing influenza impact (e.g., efforts to increase TIV coverage or improve immunogenicity).

In conclusion, during the early years when TIV vaccine supply was similar to demand (e.g., 2002-2005), the calculations indicated that fewer doses of QIV might potentially have been produced than doses of vaccine administered. That ranged from 2% to 15% lower. Fewer persons vaccinated with QIV could have led to modest increases in morbidity or mortality during some seasons. When TIV supply exceeds demand (e.g., 2005-2009), vaccine-induced protection against both B lineages using QIV could have led to a modest reduction in morbidity and mortality. Absolute impact varies by season depending upon the amount and distribution of influenza B viruses.

Quadrivalent Live Attenuated Influenza Vaccine (Q/LAIV)

Raburn Mallory, MD
Senior Director Clinical Development
MedImmune

During this session, Dr. Mallory presented the clinical data that supported approval of MedImmune's quadrivalent live attenuated influenza vaccine. MedImmune is transitioning from its current trivalent formulation of live attenuated influenza vaccine to a quadrivalent formulation. The quadrivalent formulation was approved for use in the US on February 29, 2012 under the brand name FluMist® Quadrivalent. FluMist® will be available in the US for the 2013-2014 influenza season. The quadrivalent formulation was developed to address the fact that B strains from 2 lineages have been co-circulating recently. The B strain selected for inclusion in the vaccine has not matched the predominant strain in a number of past years. MedImmune's quadrivalent vaccine is identical to its trivalent formulation with exception of the fact that it contains an additional B strain. As a result, the indication granted for the quadrivalent vaccine is the same as the one for the trivalent vaccine.

To switch to a quadrivalent vaccine is not expected to impact the WHO / Vaccine and Related Biologic Products Advisory Committee (VRBPAC) vaccine strain selection and reagent production, given that the WHO has picked an additional second B strain in their recommendations for the past two years. MedImmune has the manufacturing capacity to produce a quadrivalent vaccine every year. The manufacturing process is not expected to delay the early availability of the quadrivalent live attenuated vaccine.

MedImmune conducted two primary studies for the quadrivalent vaccine. The first study enrolled about 1800 adults and was initiated in 2009. This was followed in 2010 by a pediatric study that enrolled 2312 subjects. In both of these studies, the vaccine was administered using the AccuSpray™ device currently used for MedImmune's approved influenza vaccine FluMist®. An additional study was conducted in adults to assess different delivery devices. Approval was not sought for this device because an unacceptable number of the devices failed to open in the study. However, the safety data from this study were included in MedImmune's review.

With regard to the study design for the adult study and the pediatric study of subjects 9 through 17 years of age, subjects were vaccinated on Day 0 and then had their blood drawn for immunogenicity 28 days later. They were followed from Day 0 to Day 14 for solicited symptoms, and from Day 0 to Day 28 for adverse events. Serious adverse events and new onset chronic diseases were assessed for 180 days after vaccination. The study design for children 2 through 8 years of age was somewhat different. In order to gather additional safety data, these children received 2 doses of vaccine on Day 0 and again on Day 28. Their blood was drawn for immunogenicity after either the first dose of vaccine if they had not been vaccinated against influenza in previous years, or after the second dose of vaccine if they had received a previous influenza vaccination. The safety follow-up is similar to the adult study, with solicited symptoms and adverse events being followed after each of the two doses.

In terms of immunogenicity, the same endpoints were used for adult and pediatric studies. The endpoints were agreed upon with the FDA. Antibody responses to hemagglutinin (HA), a protein found on the vaccine virus surface, were assessed. The ratio of these antibody responses were calculated by dividing the value of the trivalent arm by the value of the quadrivalent arm. A ratio of 1 indicated identical immunogenicity between the two arms. In order for the quadrivalent vaccine to be determined non-inferior in terms of immunogenicity to

the trivalent vaccine, the upper bound of the 95% confidence interval for this ratio had to be ≤ 1.5 for all 4 strains. Secondary immunogenicity endpoints included seroconversion and proportion of subjects who achieved antibody titers of ≥ 32 , though this information was not presented during this session in the interest of time.

With respect to the results of the primary endpoints for the adult study, all of the GMT ratios were close to 1 and none of the upper bounds of the 95% confidence intervals exceeded 1.5. The adult study met its primary endpoint, demonstrating non-inferior immunogenicity of the quadrivalent vaccine compared to the trivalent vaccine. There were similar results for the pediatric study. The GMT ratios in the pediatric study were close to 1, and the 95% confidence intervals did not exceed 1.5. The pediatric study also met its primary endpoint in terms of immunogenicity.

The immunological benefit of the quadrivalent vaccine compared to the trivalent vaccine was also assessed. In this analysis, the responses to the B strains in the quadrivalent vaccine were compared to trivalent comparators that either contained the same B strain or a B strain from the other lineage. In seronegative subjects who received the quadrivalent vaccine, the seroconversion rate was 83% for the B-Yamagata strain. The seroconversion rate for this strain in subjects who received the trivalent vaccine that contained it was similar at 85%. Not surprisingly, a much lower seroconversion rate was observed in subjects who received the trivalent vaccine that contained the B-Victoria strain and did not contain the B-Yamagata strain. In adults and children, the quadrivalent vaccine induced statistically higher immune responses for the B strains that were not contained in the trivalent comparators.

Regarding the safety data, solicited symptoms were recorded by adults from Day 0 through Day 14 following vaccination. The solicited symptoms were comparable in quadrivalent and trivalent vaccine recipients. The highest rate difference was for runny / stuffy nose, which was 4.1% higher in quadrivalent vaccine recipients. However, none of these differences was statistically significant. In all children following Dose 1, the proportion of subjects who experienced solicited symptoms was similar for quadrivalent and trivalent vaccine recipients, with no statistically significant differences. In terms of the data for children 2 through 8 years of age who received 2 doses of vaccine, the only solicited symptom that was statistically elevated following Dose 1 in the quadrivalent vaccine recipients was fever greater than 38 degrees. This occurred at a rate of 6.6% in the quadrivalent vaccine recipients compared to 4.2% in the trivalent vaccine recipients. However, it is important to note that the median duration of fever in the study was one day and there were no febrile seizures during the study. Following Dose 2, solicited symptoms were generally reported at lower rates, and there were no statistically significant differences between the two arms.

The adverse events across the two adult studies and the pediatric study occurred at similar rates. The pediatric study was specifically assessed to determine whether there was evidence for wheezing, particularly in the youngest subset of children. No evidence was observed for a wheezing signal. The rates of wheezing in the quadrivalent and trivalent vaccine arms were low and similar in the pediatric study. Two serious adverse events were considered to be possibly or probably related to dosing. The first was a spontaneous abortion in a quadrivalent vaccine recipient who had a false negative pregnancy test at screening. The second was a hypersensitivity case in a trivalent vaccine recipient that occurred 26 hours after dosing. It is known that hypersensitivity events have been associated with the trivalent live vaccine, as well as inactivated influenza vaccines. No related new onsets of chronic diseases were observed, and there were no deaths in the quadrivalent pivotal adult or pediatric studies.

In summary, MedImmune is transitioning its current trivalent vaccine to a quadrivalent formulation to address the co-circulation of the B strains. The studies demonstrated that the quadrivalent vaccine was non-inferior in terms of immunogenicity to the trivalent vaccine. The quadrivalent vaccine also demonstrated higher immune responses to B strains that were not contained in the trivalent comparators. The quadrivalent vaccine has a favorable safety profile, comparable to the trivalent formulation, and is expected to have an efficacy / effectiveness profile similar to that of the trivalent vaccine but with broader coverage of B strains.

Fluzone® Quadrivalent Influenza Virus Vaccine in Individuals 6 Months and Older

David P. Greenberg, MD
sanofi pasteur

During this session, Dr. Greenberg presented the clinical data from sanofi pasteur's Fluzone® quadrivalent clinical development program. He reiterated that in 6 of the last 12 seasons, the B-lineage selected by VRBPAC did not match the circulating B lineage. Therefore, VRBPAC and others asked manufacturers to develop quadrivalent vaccines. Notably, in 2011-2012, even if the B Yamagata lineage had been chosen for that year's vaccine, there still would have been nearly a 50% mismatch because of the even distribution between the two lineages.

Responses against the heterologous B virus are significantly reduced in all age groups and do not reach seroprotective levels in human volunteers^{1,2}. Limited protection would be expected with TIV or LAIV when the vaccine and circulating strains are from different influenza B lineages^{3,4}. For example, in 2006-2007 when the vaccine strain was mismatched in Canada, vaccine effectiveness against Type B was 19% (95% CI; -112% to 69%)⁵ [¹Rota PA, et al. *Virology* 1990; 175:59-68; ²Camilloni, B, et al. *Vaccine* 27:31(2009):4099-103; ³Belshe RB et al. *Vaccine* 2009;28:2149-56; ⁴Belshe, R. *Vaccine* 28S (2010) D45-D53; and ⁵Skowronski. *JID* 2009; Jan 15, 199(2):168-79].

The influenza B lineage strains¹⁻³ represents approximately 25% of circulating strains each year. Epidemics are observed every few years. In general what has been reported in the literature is that the burden of influenza B is associated with morbidity and mortality that is lower than that for A/H3N2, but higher than for A/H1N1. Overall, influenza B is a significant cause of absenteeism, clinic visits, hospitalizations and deaths across all ages [¹<http://gamapserver.who.int/GlobalAtlas/home.asp>; ²Couch R, VRBPAC Presentation, February 2007. [FDA Website Influenza B Strain Information](#); and ³Simonsen, et al., *JID* 2000;181:831].

Case studies have demonstrated that influenza B can be a particular problem, especially in children. Influenza B can be a substantial burden in children and young adults¹⁻³. Myositis, myalgia, and leukopenia appear to be more common in children infected with influenza type B than in children with type A strains⁴⁻⁶. Additional type B-associated illnesses and complications include encephalitis, encephalopathy, myelitis, pneumonia, bronchitis, bronchiolitis, croup, pharyngitis, otitis media, and sinusitis⁷. Hospitalization may be more common in children with influenza type B than in children with type A strains⁴ [¹Belshe RB. *Vaccine*. 2010;28(suppl 4):D45-D53; ²Olson DR. *PLoS Med*. 2007;4(8):1349-1361; ³Glezen WP. *Am J Epidemiol*. 1980;111(1):13-22; ⁴Hite LK. *Int J Infect Dis*. 2007;11(1):40-47; ⁵Hu J-J. *J Microbiol Immunol Infect*. 2004;37(2):95-98; ⁶Peltola V. *Clin Infect Dis*. 2003;36(3):299-305; ⁷Couch R, VRBPAC Presentation, February 2007 [FDA Website Influenza B Strains](#)].

Sanofi pasteur had a successful pre-Biologics License Application (BLA) meeting with the FDA's Center for Biologics Evaluation and Research (CBER) in July 2012, and the license application was filed in August 2012. The FDA was reviewing the file at the time of this ACIP meeting. The FDA Action Date for expected licensure is in June 2013.

Fluzone[®] quadrivalent vaccine is manufactured the same as sanofi pasteur's trivalent vaccine^{1,2}. It has the same characteristics, and the only difference is that it contains the two B strains for a total of four strains instead of three. Of note, the anticipated age indication for the quadrivalent vaccine is the same as the current vaccine starting at ≥ 6 months of age and older. Single dose syringes and vials will be available for the launch in 2013, and multi-dose vials will be available in 2014 [¹Sanofi Pasteur Inc. Data on file, February 2011. MKT22284; ²Sanofi Pasteur Inc. Data on file July 2011. MKT23902].

Sanofi pasteur has studied the quadrivalent Fluzone[®] vaccine in a Phase 2 study in adults and in Phase 3 studies in the elderly and children. A total of 3307 persons have received Fluzone[®] QIV in these three studies. The adult study was an open label study, and the elderly and pediatric studies were conducted in a blinded fashion. In all three studies, subjects were randomized to one of three groups with an allocation ratio of 1:1:1 (adult, elderly) or ~4:1:1 (pediatric). The study groups were QIV (both B lineages; N=3307 subjects), Licensed TIV (Victoria lineage; N=1149 subjects), and Alternate B TIV (Yamagata lineage; N=1136 subjects) [Numbers represent total subjects in the safety analysis set for the 3 studies combined].

In each study, all vaccines contained the same A/H1N1 and A/H3N2 strains¹, but differed with respect to their B strains. Each study vaccine was formulated to contain 15 mcg hemagglutinin per strain per 0.5 mL dose (7.5 mcg HA per strain per 0.25 mL dose for children age 6 mo to < 36 months). Adult and elderly subjects were administered 1 dose. Children were administered 1 dose or 2 doses 4 weeks apart as per ACIP² recommendations for the 2010-2011 influenza season of either 0.25 mL dose for children age 6 months to < 36 months or 0.5 mL dose for children 3 years to < 9 years of age [¹Adult study: A/Brisbane/59/2007(H1N1) and A/Uruguay/716/2007(H3N2); Elderly and pediatric studies: A/California/07/2009 (H1N1) and A/Victoria/210/2009 (H3N2); ²Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention].

Given the limited time for this presentation, Dr. Greenberg focused on sanofi pasteur's pediatric study, although he provided summary data for all three studies. In the pediatric study, solicited injection site and systemic reactions were collected for 7 days post-vaccination, unsolicited adverse events for 28 days, and serious adverse events for 6 months. With regard to the solicited systemic reaction rates among children 6 months through 23 months of age, reaction rates were comparable across vaccines for each systemic event (e.g., irritability, crying, drowsiness, and fever). Importantly, fever was not elevated among the quadrivalent recipients compared to the trivalent recipients in this young population. For children 2 through 8 years of age, comparable rates were observed across the three study vaccines and there was no excess of fever among the quadrivalent versus the trivalent recipients. For all children in each age group, rates of solicited injection site reactions were comparable across the vaccine groups. In the adult and elderly studies, no serious adverse events were attributable to the quadrivalent vaccine. In the pediatric study, one serious adverse event was judged as possibly related to quadrivalent vaccination, which was a case of croup occurring 3 days post-vaccination. An episode of febrile seizure was thought to be related to licensed trivalent vaccine in one child, and in another child to alternate B trivalent vaccine.

In summary of the safety data, the safety profile of quadrivalent vaccine was comparable to that of each control trivalent vaccine in all three studies, as assessed by rates of solicited injection-site and systemic reactions, unsolicited adverse events, and serious adverse events. The most common injection site reactions were pain or tenderness. The most common systemic reactions varied by age and included myalgia, headache, and malaise (irritability, crying, and drowsiness in young children). Most solicited reactions were judged to be grade 1 or 2 in intensity and resolved within three days. There were no unusual patterns of unsolicited adverse events or reactions.

In terms of the post-vaccination GMTs in children 6 through 8 years of age, antibody responses to quadrivalent vaccine were comparable to the control trivalent recipients for each strain. For B/Brisbane and B/Florida, the response to each trivalent vaccine not containing the respective B strain was only about a quarter of the response to the same strain in the quadrivalent recipients. This finding supports the need for quadrivalent vaccine, especially in children who have little experience with influenza and minimal cross protective antibodies.

The immunogenicity profile of quadrivalent vaccine was comparable to those of the control trivalent vaccine recipients as evaluated by GMTs, seroconversion rates, and seroprotection rates. Quadrivalent vaccine induced seroconversion rates were comparable to each control trivalent vaccine containing the same strains. Seroconversion to the B strains not contained in each trivalent vaccine recipient was only about a quarter of the response in quadrivalent vaccine recipients. In summary, the immunogenicity profile of the quadrivalent vaccine was comparable to those of the control trivalent vaccines by all immunologic parameters in all three age groups. Quadrivalent vaccine induced statistically non-inferior GMTs and seroconversion rates to each A strain (H1N1 and H3N2) and each B-lineage strain (Brisbane and Florida) compared with each control trivalent vaccine containing the respective strains in 35 of 36 analyses in adults, elderly, and children. Among subjects ≥ 65 years of age, the seroconversion rate for A/H1N1 was 4% lower in the quadrivalent vaccine group than in the control trivalent vaccine group. This was marginal and should have no clinical ramifications, given that non-inferiority of the GMT was achieved and that the seroprotection rate against this strain was 91%. Further, quadrivalent vaccine induced statistically superior GMTs and seroconversion rates to each B-lineage strain compared with each control trivalent vaccine not containing the respective strain in 15 of 16 analyses in elderly and children. Among subjects > 65 years, the GMT for B/Brisbane was 74 in the quadrivalent group and only 42 in the comparative group. This should have no clinical consequences, given that the immunological endpoints were non-inferior and superiority was achieved for seroconversion rates of that strain.

In conclusion, sanofi pasteur developed Fluzone[®] QIV to address the co-circulation of the two B lineages, the history of frequent mismatches, and the limited protection afforded by trivalent vaccine against the mismatched B strain as expressed by VRBPAC and others. Fluzone[®] QIV has the same safety and immunogenicity profiles as the currently licensed Fluzone[®] TIV, plus the additional protection for the second B strain. Also, Fluzone[®] QIV may be particularly helpful for children because of their lack of exposure to influenza viruses and limited ability to mount cross reactive antibody responses to the alternate B lineage. Therefore, it makes sense to transition to quadrivalent vaccine over the next few years. sanofi pasteur distributes over 40% of all influenza vaccines used in the US. A limited supply of Fluzone[®] QIV will be distributed during the 2013-2014 season as a result of the timing of anticipated licensure. Licensure is not expected until mid-year 2013, long after pre-orders for Fluzone[®] TIV will have already been placed. Sales representatives cannot speak to healthcare practitioners about Fluzone[®] QIV until after it is licensed. Consequently, many of these discussions will take place after they

begin receiving their trivalent vaccine. Coverage for Fluzone[®] QIV may not be in place with all private payers at the beginning of the 2013 influenza vaccination season, given the timing.

Clinical Development of GSK's Fluarix[®] Quadrivalent Influenza Vaccine

Varsha Jain, MD, MPH
Director, Seasonal Influenza
Vaccine Discovery Development
GSK Vaccines

Dr. Jain emphasized that influenza B disease can be serious and is only partially addressed by trivalent vaccine; therefore, GSK is developing a quadrivalent vaccine containing two B strains. On average, approximately 25% of the time influenza B circulates ranging from 1% to 46%¹. Influenza B mortality is second to A/H3N2, especially in those ≥ 65 years of age². In 2010-2011, 38% (44/115) of all influenza associated pediatric deaths were due to influenza B³. In 6 out of the past 11 seasons, the B strain contained in the vaccine was not the predominant circulating strain¹. Quadrivalent vaccine seems to be the logical next step to improve seasonal influenza vaccines [¹Data derived from surveillance reports in the MMWR, 2000-01 to 2010-11 ([CDC Quadrivalent Influenza Vaccine Information](#)); ²Thompson WW et al JAMA 2003; 289(2): 179-186; ³MMWR 2011; 60(36)].

GSK developed two quadrivalent vaccine candidates, and has two licensed trivalent vaccines (Fluarix[®] and FluLaval[®]). GSK has submitted license applications for both quadrivalent formulations. D-QIV (Fluarix[®] Quadrivalent) was submitted early in 2012. The only difference is that an extra B strain is added of the alternate lineage. D-QIV is manufactured in Dresden, Germany. The second QIV candidate is Q-QIV (FluLaval[®] Quadrivalent), which is manufactured in Quebec, Canada. The target indication for QIV is active immunization for the prevention of disease caused by the 2 influenza A virus subtypes and the 2 influenza B virus types contained in the vaccine in adults and children from 3 years of age.

The two pivotal studies D-QIV had similar objectives. The pediatric study (D-QIV-003) was conducted in children 3 through 17 years of age, and the adult study (D-QIV-008) was conducted in subjects 18 years of age and above. Immunogenic superiority was confirmed for the QIV for the added B strain versus two TIV formulations that contained different B strains in subjects 3 through 17 years of age and adults 18 years of age and older. Immunogenic non-inferiority of QIV was also confirmed for the 3 common strains shared with each of the two TIVs in subjects 3 through 17 years of age and adults 18 years of age and older. In addition, reactogenicity, safety, and immunogenicity parameters were also described. In the adult study, consistency of pre-production of QIV lots was demonstrated. In the interest of time, Dr. Jain described only the endpoints of superiority, reactogenicity, and safety for both studies.

The study designs were similar for the pediatric and adult studies. Both were randomized controlled blinded trials. The pediatric study was conducted in 3 through 17 year olds, and was age stratified further in 3 through 8 and 9 through 17 year olds 2:1, with a greater number of younger than older children. Over 3000 children were enrolled in the pediatric study, and more than 4000 subjects in the adult study. The adult study was also stratified by those 18 to 64 years of age and those 64 years of age and older. In both studies, QIV was compared to two formulations of TIV. Again, the QIV just contained an extra B strain from an alternate lineage so both B/Yamagata and B/Victoria were included in the QIV. The same two A strains were in both QIVs, but each of the TIVs contained either a B/Victoria strain and the A strains, or a B/Yamagata and the A strains. The pediatric study was conducted in 5 countries, including the

US. The adult study was conducted in 6 countries. The US contributed the maximum number of subjects in both studies. In the pediatric study, the primed subjects received 1 dose and unprimed subjects received 2 doses. The priming definition was used from the ACIP definition, and it was by previous influenza vaccine priming. Subjects who received 2 or more doses of influenza vaccine in the past, they were considered primed. In the adult study, each individual received only one dose. Blood samples were collected pre- and post-vaccination, and reactogenicity and safety assessment was done initially for 7 days for local and general symptoms, and then for 28 and up to 6 months of extended safety follow-up.

In terms of the results for the antibody responses in the pediatric study, for all 4 strains for H1N1 and H3N2, similar responses were observed at about 400 and 200 respectively. For B/Victoria and B/Yamagata, the QIV and the TIV containing the corresponding B strain showed similar responses. Regarding the response compared to a TIV-containing alternate B lineage (e.g., the B strain is contained in the QIV but not in the TIV), superior response is observed in the quadrivalent vaccine but not in the trivalent vaccine. For adults, non-inferiority was observed for all 4 strains to the corresponding TIV. The pre-defined criteria for superiority were also met. A 2.5-fold GMT increase was observed in the pediatric study, and a 1.5-fold GMT increase was observed in the adult study for the B/Yamagata strain. Similarly for B/Victoria, which was contained in the QIV but not in the TIV Yamagata, there was a 2.9-fold increase in the GMT ratio in the pediatric study and a 1.6-fold increase in the adult study. A 30% to 40% increase was observed in the seroconversion rates in the pediatric study; whereas, a 10% to 16% increase was observed in the seroconversion rate differences for the adult trial.

For reactogenicity and safety, similar responses were observed for QIV versus both TIV vaccines. All symptoms and Grade 3 symptoms were similar for all vaccines. Serious adverse events were also reported in a similar percent of subjects. No serious adverse events were considered to be related to vaccination in the pediatric or adult study. Similar responses were observed in the adult study for reactogenicity and safety for QIV and TIV. No differences were observed for any symptoms, general symptoms, or local symptoms between QIV and TIV. No differences were observed for the long-term safety follow-up. No serious adverse events were reported to be related by the investigators.

In summary, for D-QIV all objectives in the pediatric and adult studies were met. A superior immune response to the additional B lineage was demonstrated. There was no compromise in the immune response for the three shared strains in the QIV. That is, by adding an extra B strain, the responses to the 3 strains common to the TIV were not reduced. In other words, non-inferiority was demonstrated. An acceptable reactogenicity and safety profile was observed for QIV similar to TIV. D-QIV is expected to improve protection against influenza B relative to TIV. D-QIV licensure is anticipated in December 2012, and Q-QIV licensure is anticipated in 2013. GSK can supply up to 15 million doses of QIV for the US for the 2013-2014 influenza season, and up to 75 million doses for the 2014-2015 influenza season. TIV will continue to be available for the 2013-2014 influenza season.

VFC Resolution Update: Influenza Vaccines

Dr. Jeanne M. Santoli
Immunization Services Division
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Dr. Santoli indicated that the purpose of this resolution was to update the resolution to include anticipated quadrivalent influenza vaccines. The resolution currently has two components: 1) An inactivated vaccine component, referred to as TIV; and 2) A live attenuated vaccine component, referred to as LAIV. The proposed change was to replace the abbreviation TIV with the abbreviation IIV. There were no other proposed changes to the VFC influenza resolution that was approved June 2012.

Vote: VFC Resolution Update for Influenza

Dr. Coyne-Beasley made a motion that the proposed recommendations for the VFC Resolution Update for Influenza be approved. Dr. Sawyer seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Discussion Points

Dr. Duchin requested information from the manufacturers regarding the difference in the frequency of adverse events between the QIV and comparative groups that the studies were powered to detect.

Dr. Greenberg replied that the Phase 3 studies, particularly the pediatric study with over 4000 subjects, typically evaluate for serious or unusual adverse events at a rate of 0.1%. It is not a comparison to a control group.

Dr. Duchin clarified that he was interested in knowing to what degree the study was powered to detect a difference in the various adverse events for which QIV and TIV were said to be similar.

Dr. Greenberg responded that for safety, all of the studies were descriptive for safety. The thousands of subjects that any of the manufacturers evaluated, there are generally descriptive data. The power calculations for sanofi pasteur's studies were based on immunogenicity and comparison for showing non-inferiority for the strains included in all of the vaccines, and superiority for the B strain not included in the control TIV. He suspected the same was true for the other manufacturers' studies as well.

Dr. Jain indicated that GSK's pediatric and adult studies were descriptive for safety. Usually with at least 300 subjects in the control and comparator arms, a 1% difference should be detectable. GSK have over 1000 subjects in each arm in each of the studies, so they should have been able to detect 1% or more of a difference. No such difference was observed, even for pain and temperature. Since there were 15 µg more of antigen, it was anticipated that there might be some difference in the local reactogenicity, but this was not observed.

Dr. Temte inquired as to whether there were any studies of co-administration, particularly with the pneumococcal vaccine.

Dr. Greenberg replied that for the pediatric study, the quadrivalent and trivalent vaccines were given alone not with pneumococcal polysaccharide conjugate vaccine.

Dr. Mallory indicated that the same was true for the MedImmune studies as well.

Dr. Jain indicated that in replied that in their pediatric study, co-administration of vaccines was allowed because they did not want to delay routine childhood vaccinations. However, a specific analysis was not conducted in terms of immune responses.

Dr. Karron wondered whether the manufacturers wanted to comment about their plans to replace TIV or LAIV with a quadrivalent formulation exclusively for the US market in the years to come, or whether they plan to have both products available.

Dr. Hosbach reminded everyone that sanofi pasteur represents about 40% of the distribution of influenza vaccination in the US, or probably slightly higher at this point. For the first year, the plan is to have a small introduction of the quadrivalent vaccine. For the season following, more quadrivalent vaccine will be introduced. The transition will probably occur over a few years. There are also 2 other products, an IV product and a high-dose product that will also be transitioned over time as they go through their clinical trials as required by FDA.

Given the broader coverage for the B vaccines, Dr. Mallory indicated that MedImmune intends to transition from the trivalent vaccine to the quadrivalent vaccine for the 2013-2014 season.

Dr. Thomas, GSK, indicated that similar to sanofi pasteur, GSK's approach is to provide some relatively small quantity of quadrivalent vaccine to the market consistent with what is believed to be demand in the upcoming season. The transition will be made over the next number of years, and TIV will be available during that time.

Dr. Harrison inquired as to what the anticipated price differential would be between the trivalent and quadrivalent vaccines.

Dr. Coelingh responded that it was early to anticipate pricing, because there is discussion about converting to the quadrivalent vaccine for the 2013-2014 season. However, MedImmune anticipates that the pricing will be comparable to its current trivalent FluMist® formulation.

Dr. Hosbach replied that sanofi pasteur typically does not discuss pricing, especially when competitors are in the room. However, GSK is happy to share that information when closer to launching these products. Inactivated influenza vaccine is substantially lower in price than the LAIV vaccine, and it could be expected that there would be somewhat of a premium for adding an additional strain.

Dr. Thomas indicated that GSK also does not discuss pricing with its competitors in the room. However, he did note that since GSK did not yet have an approved quadrivalent vaccine, a final price had not yet been established.

Dr. Vazquez requested further information about wheezing in terms of how it was assessed, which Dr. Mallory discussed during his presentation, given that it is an issue and it is a contraindication to give FluMist® to asthmatic children. She also asked whether asthmatics were excluded from the study.

Dr. Mallory replied that in the study conducted by Belshe, there was a signal for wheezing for the live vaccine in children under 2 years of age compared to the inactivated vaccine. This was not observed in children under the age of 2. Thus, the MedImmune study assessed children 2 through 17 years of age to determine whether there was a wheezing signal in older or younger children. The adverse event data recorded were assessed for the preferred terms “bronchospasm” or “asthma” for adverse events. In general, the rates in the trivalent and quadrivalent arms for FluMist® were low and there were no statistically significant differences. Asthmatics were excluded from the study. In accordance with MedImmune’s labeling, children with recurrent wheezing and children with asthma have not been studied adequately, so they were not included in the study.

Cell Culture Vaccine

David Pratt, MD, MPH

Novartis Vaccines & Diagnostics

Dr. Pratt presented the rationale for the Novartis cell culture inactivated influenza virus vaccine (ccIV) program. He also reviewed ccIV in terms of product characteristics; an overview of clinical trials; a summary of clinical data; and a brief review of Phase III data regarding immunogenicity, efficacy, and safety and tolerability. A cell-culture based influenza vaccine has been recognized as an unmet public health need¹. Cell-culture derived vaccine provides important redundancy to a current production method that relies on a vulnerable avian species. Cell culture offers an alternative growth medium for viruses that replicate poorly in egg systems [1Cell culture as a substrate for the production of influenza vaccines: memorandum from a WHO meeting. *Bull World Health Organ.* 1995;73(4):431-435].

The Novartis ccIV vaccine was under review at the FDA during the time of this ACIP meeting. An Action Date was expected within the next several weeks. This is a subunit vaccine that is grown on the Madin Darby Canine Kidney (MDCK 33016) cell line, which is Novartis’s proprietary cell line. It contains no preservatives or antibiotics, and is supplied as a single 0.5 ml dose in a pre-filled syringe. This vaccine is indicated for people ages 18 and older for the prevention of two types of A and a B strain of influenza. The administration route is intramuscular injection for adults, preferably in the region of the deltoid muscle of the upper arm.

More than 6700 doses of ccIV have been administered to adults. The immunogenicity of the ccIV vaccine showed that it exceeded the US CBER criteria against all tested strains. Responses were non-inferior to a conventional egg-derived TIV at 21 days. In terms of efficacy, vaccination with ccIV showed a reduced rate of community-acquired influenza compared to placebo. Rates of laboratory-confirmed influenza were reduced for both vaccine-like strains, as well as all circulating strains. ccIV was well-tolerated during the 21-day study period. Of the ccIV recipients, 13% reported an unsolicited adverse event. The frequency was similar in the comparator egg-derived group. Serious adverse events in adults age 18-64 were 1% for ccIV

and for a licensed US comparator. In those over 65 years of age, the rate was about 4% for cclIV and the comparator. None were adjudicated to be vaccine-related.

In a Phase 3 cclIV trial in adults 18 through 64 years of age showing HI immune responses at Day 21 post-vaccination for the 2004-2005 season, for seroconversion, seroprotection, and GMT titer ratios, the cclIV product was comparable to the egg-derived comparator. In a Phase 3 trial of those over age 65, with slightly smaller samples sizes, both products performed very well. The cclIV immune responses across age groups were non-inferior to an egg-derived TIV. In terms of efficacy against circulating strains, noting that this analysis pertained to absolute efficacy, cclIV performed nicely against vaccine strains at 83.8%. Against all circulating strains, cclIV performed at 69.5%. The cclIV and egg-based products did not perform as well against non-matched strains, a problem that has been a struggle for a long time.

Regarding adverse events in adults 18 through 64 years of age based on pooled data submitted to the FDA of solicited and unsolicited reactions up to 7 days post-vaccination, the solicited reactions were comparable between the cell-based and egg-based products. The unsolicited reactions were also quite comparable between the two products. The results were similar for those over 65 years of age, with slightly less reactogenicity, but comparable in both regards.

In summary, a cell-culture based influenza vaccine would offer an important manufacturing alternative to egg-based production. Novartis plans to produce cell-culture based influenza vaccines at its location in Holly Springs, North Carolina. The Novartis cell-culture based influenza vaccine BLA was under review at the time of this meeting for use in individuals 18 years of age and older. This will serve as a platform for other types of vaccines to be produced in the future. The immediate next step would be a submission for children 3 years of age and older.

Discussion Points

Dr. Keitel requested information about Novartis's plans with regard to development of a quadrivalent product.

Dr. Pratt replied that Novartis currently had a quadrivalent product in field trials, and that this was part of the development scheme. The exact date for introduction had not yet been fixed at the time of this meeting.

Dr. Kimberlin (AAP) inquired as to whether the studies for children 3 years of age and older had been conducted yet.

Dr. Pratt responded that some data had been collected in children. Some of the studies he showed included pediatric patients.

Dr. Gorman (NIH) inquired as to why the studies for the cell-culture based influenza vaccine did not go down to the ACIP recommended age of 6 months.

Dr. Pratt indicated that the clinical trials were designed as he presented them, and he was not aware of the reason the design did not include children 6 months of age.

Clement Lewin indicated that the reason these studies did not include children below the age of 3 was because Novartis had an adjuvanted vaccine in development for children 6 months through 6 years of age, which they believe offers superior efficacy in a population unprimed for the vaccine. Some data were published in the *NEJM* last year, so this was Novartis's strategy.

Lisa Dunkle (Protein Sciences Corporation) said she was happy to hear the presentations from all of the manufacturers of the current influenzas and the new cell-based vaccine from Novartis soon to be approved. She said she wanted to ACIP and other interested parties to be aware that Protein Sciences Corporation's novel recombinant purified protein vaccine would soon be approved for 18 through 49 year olds by FDA within the next couple of months, and that Protein Sciences Corporations looked forward to working with ACIP to develop recommendations for its use.



Day 2: Public Comment

No comments were offered during the open public comment session on the second day of the October 2012 ACIP meeting.



Certification

Upon reviewing the foregoing version of the October 24-25, 2012 ACIP meeting minutes, Dr. Jonathan Temte, ACIP Chair, certified that to the best of his knowledge, they are accurate and complete. His original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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