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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
February 23-24, 2011
Atlanta, Georgia

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Centers for Disease Control and Prevention
1600 Clifton Road, NE, Tom Harkin Global Communications Center (Building 19), Atlanta, Georgia
February 23-24, 2011

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
Wednesday, February 23, 2011			
8:00	**Welcome & Introductions**		Dr. Carol Baker (Chair, ACIP) Dr. Larry Pickering (Executive Secretary, ACIP; CDC)
8:30	**Pertussis**		
	· Introduction		Dr. Mark Sawyer (ACIP, WG Chair)
	· Brief update on pertussis surveillance 2010	Information	Dr. Jennifer Liang (CDC/NCIRD)
	· Proposed recommendations on use of Tdap in healthcare personnel	Vote	Dr. Jennifer Liang (CDC/NCIRD)
	· Proposed recommendation on use of post-exposure prophylaxis in healthcare personnel		Dr. Jennifer Liang (CDC/NCIRD)
	· Overview of Tdap use during pregnancy		
	· Historical perspective and published literature	Information & Discussion	Dr. Tejpratap Tiwari (CDC/NCIRD)
	· Unpublished and recent data		Dr. Jennifer Liang (CDC/NCIRD)
	· Considerations for use of Tdap in pregnant women		Dr. Jennifer Liang (CDC/NCIRD)
10:30	***Break***		
11:00	**Japanese Encephalitis Vaccine**		
	· Introduction	Information & Discussion	Dr. Paul Cieslak (ACIP, WG Chair); Dr. Marc Fischer (CDC/NCEZID)
	· Data supporting use of a booster dose		Dr. Katrin Dubischar-Kastner (Intercell)
	· Recommendations for use of a booster dose	Vote	Dr. Marc Fischer (CDC/NCEZID)
11:30	**Immunization of Healthcare Personnel (HCP)**		
	· Introduction	Information & Discussion	Ms. Kris Ehresmann (ACIP, WG Chair)
	· Immunization of HCP recommendations	Vote	Dr. Harry Keyserling (Emory University School of Medicine)
12:05	***Lunch***		
1:20	**Immunization Safety Office Update: Vaccines and Febrile Seizures**		
	· Introduction and background	Information	Dr. Frank Destefano (CDC/NCEZID)
	· Febrile seizures in the Vaccine Safety		Dr. Grace Lee (Harvard Medical School)

	Datalink (VSD)		
2:20	**Influenza**		
	· Introduction	Information & Discussion	Dr. Wendy Keitel (ACIP, WG Chair)
	· Epidemiology and surveillance update		Dr. Lisa Grohskopf (CDC/NCIRD)
	· Vaccine distribution/uptake		Dr. Cindy Weinbaum (CDC/NCIRD)
	· Antiviral guidance		Dr. Tim Uyeki (CDC/NCIRD)
	· Influenza vaccines and egg allergies		Dr. Lisa Grohskopf (CDC/NCIRD)
	· Proposed recommendations		Dr. Lisa Grohskopf (CDC/NCIRD)
3:20	***Break***		
3:40	**Herpes Zoster (HZ)**		
	· Introduction	Information & Discussion	Dr. Paul Cieslak (ACIP, WG Chair)
	· Background regarding HZ and HZ vaccine		Dr. Rafael Harpaz (CDC/NCIRD)
	· Field effectiveness of HZ vaccine in persons 60 years of age and older		Dr. Hung Fu Tseng (Southern California Kaiser Permanente)
	· Update: HZ vaccine safety: VAERS & VSD data		Dr. Zanie Leroy (CDC/NCEZID); Dr. Hung Fu Tseng (SCKP)
	· Results of phase 4 safety study of HZ vaccine		Dr. Janie Parrino (Merck)
	· Efficacy of HZ vaccine in persons 50-59 years of age		Dr. Janie Parrino (Merck)
	· Safety and immunogenicity of HZ vaccine in persons 50-59 years of age		Dr. Janie Parrino (Merck)
5:20	**Vaccine Supply**	Information	Dr. Jeanne Santoli (CDC/NCIRD)
5:30	**Public Comments**		
5:45	**Adjourn**		

Thursday, February 24, 2011

8:00	**Unfinished Business**		Dr. Carol Baker (Chair, ACIP)
8:15	**Evidence Based Recommendations**		
	· Update on EB recommendation implementation	Information	Dr. Jon Temte (ACIP, WG Chair)
8:20	**Immunization in the United Kingdom**		
	· Immunization coverage levels in the United Kingdom	Information	Dr. David Salisbury (Department of Health, United Kingdom)
8:50	**Human Papillomavirus Vaccines**		

	(HPV)		
	· Introduction and HPV epidemiology overview	Information & Discussion	Dr. Eileen Dunne (CDC/NCHHSTP)
	· Update on HPV-related cancers		Dr. Mona Saraiya (CDC/NCCDPHP)
	· Anal HPV infection and cancer		Dr. Joel Palefsky (UCSF)
	· Cost effectiveness updates and review		Dr. Harrell Chesson (CDC/NCHHSTP)
	· HPV Work Group plans		Dr. Lauri Markowitz (CDC/NCHHSTP)
10:00	***Break***		
10:30	**Hepatitis B Vaccine**		
	· Update: Work Group activities	Information & Discussion	Dr. Mark Sawyer (ACIP, WG Chair)
	· Update: diabetes mellitus statistics		Ms. Nilka Burrows (CDC/NCCDPHP)
	· Hepatitis B incidence and diabetes mellitus		Ms. Meredith Reilly (CDC/NCHHSTP)
	· Next steps		Dr. Trudy Murphy (CDC/NCHHSTP)
11:30	**13-valent Pneumococcal Conjugate Vaccine (PCV13)**		
	· Introduction	Information & Discussion	Dr. Mike Marcy (ACIP, WG Chair)
	· Safety and immunogenicity of PCV13 in adults		Dr. Peter Paradiso (Pfizer)
	· Cost-effectiveness of PCV13 vaccination of adults ≥50 years of age		Dr. Richard Zimmerman (University of Pittsburgh), Dr. Kenneth Smith (University of Pittsburgh)
	· Public health and economic impact of PCV13 in U.S. adults ≥50 years of age		Dr. David Strutton (Pfizer)
1:00	**Public comment**		
1:15	**Adjourn**		

Acronyms

AAAAI	American Academy of Allergy, Asthma, and Immunology
AAP	American Academy of Pediatrics
AAPA	American Academy of Physicians Assistants
ACHA	American College Health Association
ACNM	American College of Nurses and Midwives
ACP	American College of Physicians
ACIP	Advisory Committee on Immunization Practices
ADL	Activities of Daily Living
AEs	Adverse Events
AEMS	Adverse Event Monitoring Sub-Study, SPS
AI / AN	American Indian / Alaska Native
AIM	Association of Immunization Managers
AIN	Anal Intraepithelial Neoplasia
AMA	American Medical Association
ANA	American Nurses Association
ASTHO	Association of State and Territorial Health Officials
BLA	Biologics License Application
BMI	Body Mass Index
BRFSS	Behavioral Risk Factor Surveillance System
CAPiTA	Community Acquired Pneumonia Immunization Trial in Adults
CDC	Centers for Disease Control and Prevention
CEC	Clinical Evaluation Committee
CHS	Community Health Survey
CIN	Cervical Intraephithelial Neoplasia
CKD	Chronic Kidney Disease
CMI	Cell-Mediated Immunity
CMS	Centers for Medicare and Medicaid Services
COI	Conflict of Interest
COID	Committee on Infectious Disease (AAP)
CTSA	Clinical Translational Science Awards
CSTE	Council of State and Territorial Epidemiologists
DoD	Department of Defense
DSMB	Data Safety Monitoring Board
DTaP	Diphtheria, Tetanus, and Pertussis
DVA	Department of Veterans Affairs
EBGM	Empirical Bayesian Geometric Mean
EBRWG	Evidence-Based Recommendations Work Group
EIP	Emerging Infections Program
ESRD	End-Stage Renal Disease
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
GMTs	Geometric Mean Titers
GRADE	Grades of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HCP	Healthcare Personnel
HCUP	Healthcare Cost and Utilization Project
HICPAC	Healthcare Infection Control Practices Advisory Committee
HepA	Hepatitis A
HepB	Hepatitis B
HHS	Department of Health and Human Services

Hib	*Haemophilus influenzae B*
HPV	Human Papillomavirus
HZV	Herpes Zoster Vaccine
HRSA	Health Resources and Services Administration
ICD-9	International Classification of Diseases, Ninth Revision
IDSA	Infectious Disease Society of America
IDU	Injection Drug Use
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHS	Indian Health Services
ILI	Influenza-Like Illness
ILINet	Influenza-Like Illness Surveillance Network
IND	Investigational New Drug
IOM	Institute of Medicine
IPD	Invasive Pneumococcal Disease
ITT	Intent to Treat
IVRS	Interactive Voice Response System
JE	Japanese Encephalitis
JE-MB	Inactivated Mouse Brain-Derived JE Vaccine
LLOQ	Lower Limit of Quantification
LLR	Log Likelihood Ratio
maxSPRT	Maximized Sequential Probability Ratio Testing
MedDRA	Medical Dictionary for Regulatory Activities
MIIT	Modified Intent to Treat
MMR	Measles, Mumps, Rubella
MMWR	*Morbidity and Mortality Weekly Report*
MSM	Men Who Have Sex With Men
NACCHO	National Association of County and City Health Officials
NCATS	National Center for Advancing of Translational Science
NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
NFID	National Foundation for Infectious Diseases
NHIS	National Health Interview Survey
NIAAA	National Institute for Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIDA	National Institute for Drug Abuse
NIH	National Institutes of Health
NISAA	National Institute for Substance Abuse and Addiction
NMA	National Medical Association
NNDSS	National Notifiable Diseases Surveillance System
NPP	Non-bacteremic Pneumococcal Pneumonia
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
OBS	Observational Study
OD	Office of the Director (of CDC)
OPA	Opsonophagocytic
OSHA	Occupational Safety and Health Administration
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PEP	Post-Exposure Prophylaxis
PHN	Post-Herpetic Neuralgia

PPV	Positive Predictive Value
PPV23	23-Valent Polysaccharide Vaccine
PRAMS	Pregnancy Risk Assessment Monitoring System
PRNT	Plaque Reduction Neutralization Test
QALY	Quality-Adjusted Life Year
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RRP	Recurrent Respiratory Papillomatosis
RSV	Respiratory Syncytial Virus
SAEs	Serious Adverse Events
SAGE	Strategic Advisory Group of Experts, WHO
SAHM	Society for Adolescent Health and Medicine
sBLA	Supplemental Biologics License Application
SCCS	Self-Control Case Series
SCR	Seroconversion Rate
SES	Socioeconomic Status
SHAs	Strategic Health Authorities
SHEA	Society for Healthcare Epidemiology of America
SME	Subject Matter Expert
SPR	Seroprotection Rate
SPS	Shingles Prevention Studies
Tdap	Tetanus and Reduced Diphtheria Toxoids
TIV	Trivalent Inactivated Influenza Vaccines
UK	United Kingdom
US	United States
VAERS	Vaccine Adverse Event Reporting System
VFC	Vaccines for Children
VICP	Vaccine Injury Compensation Program
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VRC	Vaccination Report Card
VSD	Vaccine Safety Datalink
VZV	Varicella-Zoster Virus
WG	Work Group
WHO	World Health Organization
WPQ	Work Productivity Questionnaire
ZBPI	Zoster Brief Pain Inventory
ZEST	Zostavax® Efficacy and Safety Trial

February 23, 2011

Welcome and Introductions

Dr. Carol Baker
Chair, ACIP

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

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

Dr. Pickering welcomed everyone to the February 2011 Advisory Committee on Immunization Practices (ACIP) meeting. He said he was happy to announce that Dr. Thomas Frieden, Director of the Centers for Disease Control and Prevention (CDC), would provide opening remarks at 8:30 am.

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

Handouts of the presentations were distributed to the ACIP members and were made available for others on the tables outside of the auditorium. Slides presented at this meeting will be posted on the ACIP website approximately one week after the meeting concludes, the live webcast will be posted within three weeks following the meeting, and meeting minutes will be available on the website within 90 days of the termination of the meeting. Members of the press interested in conducting interviews with various ACIP members were instructed to contact Tom Skinner for assistance in arranging the interviews.

Dr. Pickering recognized the following visitors from the World Health Organization's (WHO's) Pan American Health Organization (PAHO), and from Ministries of Health of PAHO member countries:

- Dr. Andrea Vicari, PAHO Regional Advisor for HPV vaccine, PHAO Office, Washington, DC
- Dr. Cara Janusz, PAHO Technical Officer, PAHO Office
- Dr. Renato Valenzuela, President, Honduras National Immunization Advisory Committee, Honduras
- Dr. Karen Lewis-Bell, Director, Family Health Services, Ministry of Health, Jamaica
- Dr. Fulvia Guerra, Advisory Committee on Immunization Practices, Panama
- Dr. Noelia Speranza, National Advisory Committee on Vaccination, Uruguay

He also welcomed the following visitors from Japan:

- Dr. Nobuhiko Okabe, Director, Infectious Disease Surveillance Center, National Institute of Infectious Disease, Tokyo, Japan
- Dr. Kenji Okada, Director of Medical Division, Fukuoka National Hospital. Fukuoka, Japan (pertussis expert in Japan)

In addition, Dr. Pickering welcomed visitor Dr. Lu Li, Deputy Director of the Institute of Immunization and Infectious Disease Control, Beijing Municipal Centre for Disease Control and Prevention. Dr. Li is spending five months at CDC as a visiting scientist.

Also welcomed were a new *ex officio* member and new liaison organizations:

New *Ex Officio* Member

- Commander Jesse Geibe, MD, MPH, MBA, Medical Corps Defense Department Liaison Officer CDC. Commander Geibe is the new *ex officio* member representing the Department of Defense (DoD). He replaces Colonel Ted Cieslak.

New Liaison Organizations

- **American Academy of Physicians Assistants (AAPA)**: Marie-Michèle Leger, MOH, PA-C; Director, Clinical and International Affairs, AAPA, Alexandria, Virginia has been selected to represent AAPA as its liaison representative to ACIP.

- **Association of Immunization Managers (AIM)**: Kelly Moore, MD, MPH; Medical Director, State Immunization Program, Tennessee Department of Health has been selected to represent AIM as its liaison representative to ACIP.

- **Association of State and Territorial Health Officials (ASTHO)**: José Montero, MD, MPH; Director, Division of Public Health Services, New Hampshire Department of Health and Human Services has been selected to represent ASTHO as its liaison representative to ACIP.

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

***Ex Officio* Members**

- Dr. Norman Baylor, *ex officio* member representing the Food and Drug Administration (FDA) was unable to attend; Dr. Wellington Sun attended on his behalf.

- James Cheek, MD, MPH, liaison for Indian Health Services (IHS) was unable to attend; Amy Groom, MPH, Director, IHS National Immunization Program attended on his behalf.

Liaison Representatives

- Katie Brewer, MSN, RN from the American Nurses Association (ANA) was unable to attend; Carol E. Hayes, CNM, MN, NPH from the Georgia State University School of Nursing attended on her behalf.

- Dr. Greg Poland, MD, liaison for the American College of Physicians (ACP) was unable to attend; Dr. Sandra Fryhofer, Clinical Professor of Medicine, Emory University School of Medicine attended on his behalf.

To avoid disruptions during the meeting, those present were instructed to conduct all business not directly related to discussions of ACIP in the hall and to turn off all cell phones or place them in the vibrate mode. Given that the meeting could not begin unless a quorum of members was present, all appointed members were asked to return from breaks and lunch in a timely manner to participate in the meeting. Members were also reminded that a group photograph would be taken in the auditorium before lunch.

Topics presented during the ACIP meeting include open discussion with time reserved for public comment. During this meeting, a time for public comment was scheduled following the afternoon sessions during both meeting days. In certain circumstances, a formal comment period may be scheduled during the deliberations of a specific agenda item rather than at the end of the day in order to be considered before a vote is taken. Those who planned to make public comments were instructed to visit the registration desk in the rear of the room to have Stephanie Thomas record their name and provide information on the process. Those who registered to make public comments were instructed to state their name, organization if applicable, and any conflicts of interest (COIs) prior to making their comments.

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

ACIP currently has 13 work groups, 4 of which are permanent: Childhood Immunization Schedule, Adult Immunization Schedule, Influenza, and General Recommendations. The others are task-oriented and terminate when the task is complete. The ACIP Respiratory Syncytial Virus (RSV) Immunoprophylaxis Work Group was formed in 2009 to review safety, and efficacy and potentially to provide recommendations for use of the immunoprophylaxis product, motavizumab. The product was under review by the FDA for prophylaxis of serious RSV disease in high risk infants and children. In December 2010, AstraZeneca, the pharmaceutical company developing the product, withdrew their Biologics License Application (BLA). As a result, ACIP's RSV Immunoprophylaxis Work Group has been disbanded. CDC recognizes the burden of respiratory syncytial virus infections in young infants, especially infants with high risk conditions. CDC will continue to work with partners to review issues related to the burden of RSV disease in all populations, including infants with high risk conditions, and methods for prevention and will present relevant information to ACIP when appropriate.

Detailed instructions for submission of names of potential candidates to serve as ACIP members may be found on the ACIP website:

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

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

Applications for ACIP membership are due no later than November 18, 2011 for the term beginning July 1, 2012. Interested parties were encouraged to complete an application and submit it by the deadline.

The following information was shared pertaining to ACIP:

Next ACIP Meeting: June 22-23, 2011
Registration Deadlines: Non-U.S. Citizens June 3, 2011 / US Citizens June 10, 2011

Vaccine Safety: www.cdc.gov/vaccinesafety/

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

Childhood Vaccine Scheduler (interactive):
http://www.cdc.gov/vaccines/recs/scheduler/catchup.htm

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

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

Dr. Pickering noted that at every meeting, an update is provided on the status of ACIP recommendations. Since the October 2010 ACIP meeting, 7 ACIP recommendations have been published, including:

- 3 full statements, published in the *Morbidity and Mortality Weekly Report* (*MMWR)* recommendations and reports series
- 2 policy notes, published in *MMWR* weekly series
- 2 immunization schedules, one for children and adolescents and one for adults, published in the *MMWR* weekly series

All of these recommendations and schedules can be found on the ACIP web site, and are referenced in the following table:

	Publication		MWWR
Topic		**Date**	**Reference**
PCV13 and PPSV23 (infants and children)		12/10/2010	Vol 59(RR11):1-18
Policy Note: Tdap Vaccine		01/14/2011	Vol 60(01):13-15
Antiviral Agents – Influenza		01/21/2011	Vol 60(RR1):1-28
Policy Note: Meningococcal Conjugate Vaccines		01/28/2011	Vol 60(03):72-76
General Recommendations on Immunization		01/28/2011	Vol 60(RR2):1-61
2011 Adult Immunization Schedule (≥19 years)		02/04/2011	Vol 60(04):1-4
2011 Child/Adolescent Immunization Schedule (0 through 18 years)		02/11/2011	Vol 60(05):1-4

The following conflicts of interest were declared by ACIP members:

- ❑ Dr. Tamera Coyne-Beasley: Research support for clinical trials from Merck
- ❑ Dr. Janet Englund: Research support to her university from MedImmune, sanofi pasteur, Novartis, Admark, Adamas, and Chimerix
- ❑ Dr. Wendy Keitel: Research support to her institution from Novartis
- ❑ Dr. Cody Meissner: Payments made to Tufts University Medical Center by MedImmune and Pfizer for participation in multi-center clinical trials
- ❑ The remainder of the ACIP members declared no conflicts

Discussion Points

Dr. Kimberlin (AAP) requested clarification regarding whether withdrawal of the BLA for motavizumab for prophylaxis of serious RSV disease in high risk infants and children meant that there would be no further development of motavizumab, or merely no further development of motavizumab as a prophylaxis molecule.

Doris Makari (MedImmune) responded that in December, they made the decision following internal discussions and meetings with the FDA to withdraw the motavizumab prophylaxis BLA. At this point, other decisions must be made regarding other potential uses for motavizumab.

On behalf of the 15 ACIP members, 30 liaison organizations, 8 government *ex officio* organizations, international visitors from PAHO nations, China, and Japan, and the audience on-site and joining them via webcast, Dr. Pickering expressed gratitude for Dr. Frieden's presence to officially open the February 2011 ACIP meeting.

Thomas R. Frieden, MD, MPH
Director, Centers for Disease Control and Prevention
Administrator, Agency for Toxic Substances and Disease Registry

Vaccines, as all of us know, are one of the best buys in public health. They are a great example of innovation and of public good. With public goods come very important public responsibilities. The Vaccines for Children (VFC) program takes that public good to the next level, making sure that all children can benefit from vaccination. VFC has been a major success, virtually eliminating disparities in pediatric vaccine coverage in this country, permitting the vaccination of millions of vulnerable children each year, and protecting not only them, but also their communities from increasing numbers of diseases and conditions and subsequent disability and death. The VFC program now covers nearly half of all children in this country, and includes vaccines targeting 16 different diseases. CDC now spends more than $3.5 billion each year purchasing vaccines for the VFC program. Stewardship of this program is both a privilege and a serious responsibility.

CDC and the entire immunization enterprise view the VFC program as a true public / private partnership. We in the public sector partner with a number of entities in the private sector, including healthcare providers who deliver nearly 90% of the publically purchased vaccines. Think for a moment what the public brings to the table in this program. We provide through not only VFC, but also other vaccine legislation: substantial investments into vaccine safety research; communication and outreach to physicians; standard-setting and recommendations; vaccine distribution; protection against liability; and a large guaranteed market. We depend on private vaccine manufacturers to continue to produce these life-saving vaccines and to invest in the development of new and better vaccines. The development and availability of newer vaccines since VFC began 17 years ago has expanded the prevention impact of our programs, but most newer products and new formulations of old products have come at substantially higher prices. We have also seen prices rising after initial federal contracts were set, and prices failing to fall when vaccine schedules are compressed or a second vaccine manufacturer enters the market. These are not things that we would expect under normal economic conditions.

I know that many of you consider policy choices with the nation's budget concerns in the back of your minds. As you all know, there are significant pressures on governmental budgets at the state, federal, and local levels. At a time when budgets are under intense review, ACIP considerations and the public value and risk-benefit ratios of various vaccine recommendations are made even more difficult with the rising prices of vaccines. While the budget pressures I mentioned are not unique to CDC or to immunization, I know that ACIP members have been wrestling with complex policy decisions. Certainly, if vaccine prices were coming down instead of going up or were responding as we would expect them to under market conditions, there would be an easier set of decisions.

I appreciate the hard work of the committee and work groups to assure the best recommendations to protect our children and our adults in this society…A few years ago when I first met ACIP I said [jokingly], "So you're the folks who turned our children into pin cushions." They said, "Yes, and we're trying to turn the adults into pin cushions, too." This has been a tremendous public health success and a wonderful example of evidence-based policy leading to an entitlement that protects not only individuals, but also communities. ACIP recommendations have long been viewed as standard by most insurance companies and were formally recognized in the Patient Protection and Affordable Care Act (PPACA) as the basis for insurance coverage with no co-payments.

I don't have any perfect method for you to approach your important deliberations on cost-effectiveness, but I do know that a careful review of the evidence is essential. I do also know that, particularly in immunization policy, transparency and sunlight is a wonderful disinfectant. We're deeply committed to transparency in the decision-making process. We're deeply committed to transparency about adverse events following vaccination, even if they bear no causal relation to vaccination, so that all can see openly what the information is. We're deeply committed to making public vaccination rates in different parts of the country and of different groups, for example, healthcare workers' vaccination against influenza—critically important to protect themselves, their families, and their patients. I think that manufacturers need to think about transparency in some of their decision-making processes as well.

I want to thank you very much for taking on this hard work on behalf of CDC, but also more importantly, on behalf of all who benefit from vaccination and the progress of vaccinations in this country. Thank you very much.

Tribute to Dr. Samuel Katz

Dr. Carol Baker
Chair, ACIP

Today we say farewell to Dr. Samuel L. Katz as he departs as the IDSA liaison on March 1st. Dr. Katz has contributed enormously to the ACIP in a number of capacities. He served as a voting member of the ACIP from 1982 through 1993 (clearly they had different terms back in those days), including being Chair of the committee from 1985 through 1993. Dr. Temte has mentioned his huge contribution, the thing I love most about coming to the meeting, the gift of the bell. During his tenure, Dr. Katz saw *Haemophilus influenzae* type B vaccine decrease the disease burden by 99%, set the stage for a transition to acellular pertussis vaccines, and recognized the need for a second dose of MMR vaccine. Since 1998, Dr. Katz has represented the Infectious Disease Society of America as liaison representative to the ACIP. In this capacity, Dr. Katz has participated as a member of several ACIP work groups, where his years of experience in both vaccine research and implementation of immunization programs have proved invaluable.

First International Conference on Measles Immunization. **8 November 1961**, NIH, Bethesda Maryland.
Left to right : **Samuel Katz**, Ann Holloway, Kevin McCarthy, Anna Mitus, Milan Milovanovic, John Enders, Gisele Ruckle, Frederick Robbins, Ikuyu Nagata.

Many of you know Dr. Katz began his career in Boston where, after his initial training in pediatrics, he was a research fellow in virology and infectious disease working with Nobel Laureate John F. Enders for 12 years. Together they developed the live attenuated measles vaccine virus vaccine. After a series of clinical trials proved measles vaccine effective and safe, it was licensed in 1963. By 1968, the incidence of measles plummeted to historically low levels. Once the vaccine was proved effective domestically, Dr. Katz was eager to see its success taken globally, and now it is used worldwide.

Unlike many, Dr. Katz left the Charles River in Boston for greener pastures at Duke University where he was Chairman of the Department of Pediatrics, mentoring students and residence for over two decades. Among those influenced at Duke were ACIP members and Chairs John Modlin and Jeff Davis. During those years, Dr. Katz also received too many awards to mention, including election to the Institute of Medicine (IOM).

It was during his time at Duke that I first met Dr. Katz and was amazed as he seemed to remember every person he ever met, even me. He provided me with the encouragement in pursuit of my interest in vaccines which was pivotal to any success that I may have achieved. Most of all, I enjoyed his company and say from my heart, Sam, you are a gentleman, a scholar, and a true example of humility and good humor.

Dr. Katz and Dr. Besser February 2009

Dr. Katz has shared his personal and medical pursuits with his wife of many years, Dr. Catherine Wilfert, an infectious disease and pediatric HIV expert who preceded Dr. Katz as ACIP Chair. Drs. Katz and Wilfert also raised a total of eight sons and daughters and many grandchildren. Sam's life has extended beyond his family and expertise in pediatrics and vaccinology. He has many other interests, including being a percussion performance artist in a jazz band, obviously something he still enjoys.

Sam, you will be greatly missed, but you deserve a little respite. I know your Cathy will keep you busy and Kathy Neuzil will do her best to fill your "big shoes" as the new IDSA liaison.

On behalf of the ACIP members, liaisons, CDC staff, and everyone else here today, thank you so much for your service.

Discussion Points

Dr. Katz: I am moved to tears, but it has been a wonderful experience. The joys, and the privileges, and the responsibilities of working with ACIP are unmatched and I congratulate all of you who will continue to do so. I hope not to be a stranger; I will show up every once in a while. Thank you for a very unexpected tribute.

Dr. Baker: Sam, we do expect you to show up from time to time. This is just a temporary goodbye in your official capacity, so the best to you.

Pertussis

Introduction

Dr. Mark Sawyer, Chair
ACIP Pertussis Vaccine Work Group

Dr. Sawyer introduced the pertussis session, first acknowledging the Pertussis Vaccine Work Group members. He offered special thanks to Dr. Jennifer Liang, their CDC work group lead who has led them through multiple discussion, and gave particular recognition to Peter McIntyre from Australia who had been joining the work group at 6:00 am on Saturday mornings Australia time.

The terms of reference under which the Pertussis Vaccine WorkGroup was convened several years ago include the following:

1. 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.

2. Review new data on Tdap including
    - Effectiveness of current ACIP recommendations
    - Interval between Td booster and Tdap
    - Use of Tdap in adults ages 65 yrs and older
    - Pregnant and breastfeeding women
        - → Use of Tdap
        - → Cocooning strategies
    - Vaccinated healthcare personnel and need for post-exposure prophylaxis
    - Revaccination

3. Review updated epidemiology of tetanus and diphtheria

During this session, presentations included an update on pertussis epidemiology in the United States for 2010, use of Tdap in healthcare personnel (HCP), use of post-exposure prophylaxis in HCP, and use of Tdap in pregnant women.

Update on Pertussis in the United States, 2010

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

Dr. Liang reminded everyone that the work group previously presented the epidemiology of pertussis in the June 2010 ACIP meeting, and on the California outbreak at the October 2010 ACIP meeting. During this session, Dr. Liang highlighted the relevant epidemiology from 2010.

With respect to the reported pertussis cases form 1922-2009, there is a cyclical recurrence every 3 to 5 years. The number of pertussis cases has been increasing since the 1970s. There was a peak in 2004-2005 during which more than 25,000 cases were reported. Pertussis cases again are on the rise. After several years of reported cases declining, the provisional 2010 pertussis data has over 21,000 reported cases.

In terms of the reported pertussis incidence by age group from 1990 to 2009, infants have substantially higher rates of disease and the largest burden of death compared to other age groups. Many of these afflicted infants cannot be fully vaccinated until age 6 months and require other strategies for prevention of pertussis.

A breakdown in age groups of reported pertussis-related deaths over the past 30 years show that the majority of deaths occur in infants 0 through 1 month of age, before they are eligible to receive the first dose of DTaP. This does not include 2010 California outbreak in which 9 of 10 deaths occurred in infants less than 2 months of age.

Dr. Liang shared a map to illustrate the broad range of pertussis incidence in the United States (U.S.). The provisional 2010 data show that there were 21,291 reported cases of pertussis, with an overall U.S. incidence rate of 6.9 per 100,000. Because of delays in reporting, she clarified that the map did not accurately reflect the incidence for all states. California's incidence in 2010 was 23.4 per 100,000.

As of February 14, 2011, California data showed that 8,990 confirmed, probable and suspect cases of pertussis were reported in 2010. With regard to the epidemic curve of pertussis cases by week of onset, cases peaked in some parts of the state in summer of 2010, but numbers are anticipated to remain high in 2011. There have been 10 deaths to date. Only one of the 10 mothers had received Tdap [California Department of Public Health].

Pertussis remains cyclic and is generally increasing. Infant deaths continue to occur, with more than 90% of deaths in infants less than 4 months of age. Effective interventions are still needed.

Use of Tdap in Health Care Personnel

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

Dr. Liang presented an overview of what was discussed by the work group, and the proposed revisions to the current recommendations for use of Tap in health-care personnel.

There are 12 to 14 million healthcare personnel in the U.S. Protecting HCP from acquiring and transmitting infectious diseases is a public health goal. The incidence data for pertussis in healthcare personnel are lacking, and there are limited data on rate of infection. A 1992 study from Vanderbilt, a tertiary care university hospital, compared stored sera collected 1 to 3 years previously from 106 residents and 39 emergency department employees. Five subjects had serological evidence of pertussis infection. The annual incidence rates of pertussis based on serology were 1.3% among resident physicians and 3.6% among emergency department nurses and physicians.

The 2005 ACIP recommendations were based upon several conclusions made by ACIP after thorough review of literature and data, including the following: transmission of pertussis is well-documented in healthcare settings; the frequency and proximity of patient interaction puts healthcare personnel at increased risk for infection and potential to expose many persons; health-care associated outbreaks have been documented where infected healthcare personnel were identified as the source of infection for susceptible contacts; and investigation and control measures are both costly and disruptive.

The 2005 ACIP recommendations for use of Tdap in healthcare personnel currently recommend that healthcare personnel with direct patient contact should receive Tdap as soon as feasible, and that other healthcare personnel should receive Tdap when they are scheduled for the next Td. The recommendations also address interval since last dose of Td. In both cases, the work group felt the language should be simplified. The specific recommendations read as follows:

- HCP in hospitals or ambulatory care settings who have direct patient contact should receive a single dose of Tdap as soon as feasible if they have not previously received Tdap. Although Td booster doses are routinely recommended at an interval of 10 years, an interval as short as 2 years from the last dose of Td is recommended for the Tdap dose among these HCP. These HCP include but are not limited to physicians, other primary care providers, nurses, aides, respiratory therapists, radiology technicians, students (e.g., medical, nursing, and other), dentists, social workers, chaplains, volunteers, and dietary and clerical workers.

- Other HCP (i.e., not in hospitals or ambulatory care settings or without direct patient contact) should receive a single dose of Tdap to replace the next scheduled Td according to the routine recommendation at an interval no greater than 10 years since the last Td. They are encouraged to receive the Tdap dose at an interval as short as 2 years following the last Td.

Following are the additional recommendations for use of Tdap in healthcare personnel, which state that priority should be given to healthcare personnel in direct contact with infants less than 12 months of age; healthcare facilities should provide Tdap; and Tdap is not licensed for multiple administrations:

- Vaccinating HCP with Tdap will protect them against pertussis and is expected to reduce transmission to patients, other HCP, household members, and persons in the community. Priority should be given to vaccination of HCP who have direct contact with infants <12 months of age (see Prevention of Pertussis Among Infants Aged <12 Months by Vaccinating their Adult Contacts).

- Hospitals and ambulatory-care facilities should provide Tdap for HCP and use approaches that maximize vaccination rates (e.g., education about the benefits of vaccination, convenient access, and the provision of Tdap at no charge) (see Implementing a Hospital Tdap Program).

- Tdap is not licensed for multiple administrations. After receipt of Tdap, HCP should receive Td for booster immunization against tetanus and diphtheria according to previously published guidelines (33).

Two papers report that hospital-based coverage rates were 60%[1] and 72%[2], but these were part of vaccination campaigns which occurred after a pertussis outbreak. However, from the 2008 National Health Interview Survey, self-reported Tdap vaccination coverage among healthcare personnel was less than 16%[3] [[1]Leekha S, Thompson RL, Sampathkumar P. Epidemiology and Control of Pertussis Outbreaks in a Tertiary Care Center and the Resource Consumption Associated With These Outbreaks. Infect Control Hosp Epidemiol 2009; 30:467-473. [2]Fontanilla JM, Kirkland KB , Cotter JG, Talbot EA. Ability of Healthcare Workers to Recall Previous Receipt of Tetanus-Containing Vaccination. Infect Control Hosp Epidemiol 2010; 31(6):647-649. [3]CDC. Tetanus and Pertussis Vaccination Coverage Among Adults Aged ≥18 Years—United States, 1999 and 2008. MMWR. 59(40);1302-1306].

At the time of licensure in 2005, Tdap efficacy was based on serological bridging studies from infant efficacy studies. Immune response to Tdap was non-inferior to the immune response of infants receiving DTaP. From the adult pertussis trial, overall vaccine efficacy of an acellular pertussis vaccine was 92%. Recent post-licensure studies of Tdap show vaccine effectiveness ranging from 66% to 78%.

In reviewing the current language, the work group supports new direct language to remove barriers to facilitate the uptake of Tdap. The proposed language will also incorporate the recent changes made by ACIP at the October 2010 meeting for the removal of interval language and inclusion of HCP ages 65 years and older.

The work group unanimously supported the following proposed recommendation for the use of Tdap in healthcare personnel, keeping in mind that these recommendations will be included with the general Tdap recommendations. The proposed language is:

- Health-care personnel (HCP), regardless of age, should receive a single dose of Tdap as soon as feasible if they have not previously received Tdap and regardless of the time since last Td dose.

- Tdap is not currently licensed for multiple administrations. After receipt of Tdap, HCP should receive routine booster immunization against tetanus and diphtheria according to previously published guidelines.

- Hospitals[¶¶] and ambulatory-care facilities should provide Tdap for HCP and use approaches that maximize vaccination rates (e.g., education about the benefits of vaccination, convenient access, and the provision of Tdap at no charge).

[¶¶] Hospitals, as defined by the Joint Commission on Accreditation of Healthcare Organizations, do not include long-term–care facilities such as nursing homes, skilled-nursing facilities, or rehabilitation and convalescent care facilities. Ambulatory-care settings include all outpatient and walk-in facilities.

Discussion Points

Dr. Turner (ACHA) reported that many medical and nursing schools across the country are starting to require Tdap for admission to their programs. That has been an extremely effective way, at least to get young HCP immunized early.

Dr. Schaffner (NFID) thought that it was fine include this in the General Recommendations if it passed, and he expressed his hope that there would also be independent activities to clearly bring this to the attention of the hospital community.

Dr. Liang responded that this would be updated in the upcoming session on immunization practice recommendations for HCP.

Dr. Jenkins inquired as to whether there were any discussions pertaining to the burden on hospitals if they supply vaccine at no charge to their personnel.

Dr. Liang responded that the work group did not specifically review any of those data, but that was part of the consideration for 2005 recommendations.

Dr. Keyserling (SHEA) reported that the new recommendations for HCP immunizations include a cost analysis of no pertussis vaccination versus pertussis vaccination for HPC. He believed that this reflected a $2.30 benefit.

Dr. Fryhofer (ACP) asked whether the work group discussed how this would be implemented. For example, for staff privileges in hospital settings, documentation of antibody levels must be shown to hepatitis and other diseases. She wondered whether self-reporting would be satisfactory or if there is a requirement for blood testing.

Dr. Liang indicated that at this time, there are no serologic correlates of protection for pertussis. Receipt of Tdap is based upon vaccine history.

Dr. Baker added that their medical school, entrants are asked whether they have received Tdap. Because of when Tdap was first recommended and available, they have no recollection of receiving it, so it is administered to all entrants.

Dr. Temte wondered if there was any explanation for the wonderful response to vaccine with DTaP, but a new emergence.

Dr. Clark (SME) responded that in the future they would offer a more formal presentation on the epidemiology of pertussis and the program overall. There are numerous hypotheses about why there is resurgence in disease, including increased recognition and confirmation testing and reporting. There are also real increases in transmission, as documented in other countries by sero surveys. Strain changes are hypothesized by minorities in the pertussis community. The explanations do not necessarily correlate well with the changes observed in the U.S. epidemiology.

Motion: Proposed Tdap Recommendation for Healthcare Personnel

Dr. Chilton made a motion to accept the recommendation as presented. Dr. Keitel seconded the motion. The motion carried with 14 affirmative votes, 1 abstention, and 0 negative votes.

Use of Post-Exposure Prophylaxis in Health-Care Personnel

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

Dr. Liang presented information the work group used to discuss revising recommendation on use of post-exposure prophylaxis (PEP) in healthcare personnel. The language from the 2005 ACIP guidelines is consistent with ACIP recommendations and is found in the General Recommendations, but falls short of stating that ACIP recommends that health-care facilities should continue post-exposure prophylaxis for vaccinated healthcare personnel who have unprotected exposure to pertussis. The statement also provides an alternative strategy for managing exposed vaccinated healthcare personnel with daily monitoring. The 2005 guidelines read as follows:

- Until studies define the optimal management of exposed vaccinated HCP or a consensus of experts is developed, health-care facilities should continue postexposure prophylaxis for vaccinated HCP who have unprotected exposure to pertussis.

- Alternatively, each health-care facility can determine an appropriate strategy for managing exposed vaccinated HCP. Daily monitoring of pertussis-exposed HCP who received Tdap might be a reasonable strategy for postexposure management, because the incubation period of pertussis is up to 21 days and the minimal risk for transmission before the onset of signs and symptoms of pertussis. In considering this approach,

hospitals should maximize efforts to prevent transmission of *B. pertussis* to infants and other groups of vulnerable persons.

[CDC. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for use of Tdap among health-care personnel. MMWR 2006;55(No. RR-17)].

Based on the 2005 recommendations, one study tried to answer the question: Is symptom monitoring without post-exposure prophylaxis following pertussis exposure non-inferior to antibiotic post-exposure prophylaxis among Tdap-vaccinated healthcare personnel? During the study period, 116 exposures occurred among 94 different healthcare personnel. Pertussis infection did not occur in 90% of exposed healthcare personnel who did not receive PEP, and in 98% of exposed healthcare personnel who did receive post-exposure prophylaxis. Pre-defined non-inferiority criteria were not met, which suggests there may be a benefit to PEP in vaccinated HCP [Goins W, Edwards KM, Vnencak-Jones CL, Thayer, VS, Swift M, Schaffner W, Talbot T. A Comparison of Two Strategies to Prevent Pertussis in Vaccinated Healthcare Personnel Following Pertussis Exposure. Presented at SHEA 2010]. This study did not assess whether vaccinated HCP will transmit pertussis.

Work group interpretations of the data were: post-exposure prophylaxis may reduce infection; ability of vaccinated healthcare personnel to transmit was not assessed; and the low risk of pertussis in each group suggests that both strategies may be acceptable. The work group concluded that this study does not exclude PEP for vaccinated HCP. Work Group considerations for reducing risk of transmission of pertussis in healthcare facilities were that Tdap coverage in healthcare personnel is sub-optimal and the duration of protection afforded by Tdap is unknown. In addition, vaccinating HCP with Tdap is an adjunct to other pertussis prevention measures. The Vanderbilt study provides some data that both strategies are acceptable. Although data on the need for post-exposure prophylaxis in Tdap-vaccinated healthcare personnel was not definitive, the work group feels that vaccine status does not change the approach to evaluating the need for post-exposure prophylaxis. Among members of the work group, it was noted that different institutions have different approaches. Therefore, the group feels that the language needs to allow flexibility in implementation of the recommendation.

In terms of the components of comprehensive strategies for managing healthcare personnel who have been exposed to pertussis and have contact with persons at risk for severe disease or others, the only difference in strategies is the use of PEP in HCP in contact with others. Being at risk for severe disease is well-described in infants and less well-defined for others, but this will be defined elsewhere in the general statement. The work group felt that PEP is necessary for those in contact with persons at risk for severe disease.

The work group unanimously supported the following proposed language for the recommendation for post-exposure prophylaxis in healthcare personnel supported by the work group (the first two bullets provide the context for the recommendation, which is the third bullet, and supportive information and definitions will be provided in the background):

- Health-care facilities should maximize efforts to prevent transmission of *Bordetella pertussis*. Droplet precautions should be taken to prevent unprotected exposure to pertussis.

- Data on the need for postexposure antimicrobial prophylaxis in Tdap-vaccinated HCP are inconclusive. Some vaccinated HCP are still at risk for *B. pertussis*. Tdap may not preclude the need for postexposure prophylaxis.

- Postexposure antimicrobial prophylaxis is recommended for all HCP who have unprotected exposure to pertussis and are likely to expose a patient at risk for severe pertussis (e.g., hospitalized neonates and pregnant women). Other vaccinated HCP should either receive postexposure prophylaxis or be monitored daily for 21 days after pertussis exposure and treated at the onset of signs and symptoms of pertussis.

Discussion Points

Dr. Baker inquired as to whether, like the last recommendation, this would be included in the immunization of HCP document.

Dr. Liang replied that it would be included.

Dr. Cieslak asked for clarification of what was meant by "exposure."

Dr. Liang responded that for direct exposure, transmission has been documented through direct contact with aerosolized droplets, so for HCP this would mean direct contact with patients who have cough and have been diagnosed with pertussis.

If a patient with pertussis was coughing in an emergency department and exposed 20 people working there, Dr. Cieslak wondered whether they would all be considered exposed or if it would just be the HCP attending to that patient.

Dr. Elward (HICPAC) responded that exposure is generally defined as being within 6 feet of a patient who is coughing for more than 5 minutes, or conducting a procedure that would involve intimate contact with their secretions, like endotracheal intubation without wearing a mask.

Dr. Liang added that this information would be provided in the background section.

Dr. Judson thought this was an important practical consideration, because over the years his experience has been that diagnosis is often made well after the fact, and defining exposure at the time it occurs is really tough.

Dr. Duchin thought that criteria should be included in the guidelines as to what would be recommended to healthcare facilities as the threshold for removing and treating a healthcare worker. He requested more detail about what was meant in the proposed language by "unprotected exposure."

Dr. Elward responded that most people would interpret "unprotected exposure" as the absence of a mask.

Dr. Duchin suggested the inclusion of pregnant women in the example of hospitalized neonates as a high risk population for whom PEP should be administered.

Regarding unprotected exposure, Ms. Stinchfield (NAPNAP) thought that because this was in a vaccine statement, people may read that as Tdap or no Tdap. She suggested spelling out that "unprotected exposure" means having not worn a mask regardless of Tdap vaccine status.

Dr. Jenkins inquired as to how effective PEP is in terms of protection once there are signs and symptoms.

Knowing that there is variability in implementation in healthcare facilities regarding exposure definitions and some uncertainty regarding high risk definitions, Dr. Clark (SME) indicated that they tried to keep this information in the background section. "Treatment at earliest onset of signs and symptoms" means upper respiratory infection consistent with pertussis. The spirit is to assume that it is pertussis and treat it. Early treatment is more likely to be effective than waiting for cough onset. This recommendation is specifically for those who choose monitoring to treat at the onset of signs and symptoms. Vaccination is not part of that, although if someone is unvaccinated, there would be language to recommend taking the opportunity to vaccinate them. The vaccine is merely to catch them up if they are unvaccinated. The prevention strategy is PEP.

Dr. Campos-Outcalt suggested making clear that the PEP referred to in this recommendation is antibiotic therapy. He also indicated that there was a recent publication about how to collect specimens correctly for polymerase chain reaction (PCR). It took a great deal of care to describe how to protect the specimen from contamination, but it did not mention how to protect HCP from contamination when collecting specimens.

Dr. Baker noted that the early symptoms of pertussis are like the common cold. The PEP intervention is antibiotic therapy, but she did not know of any convincing data that early antibiotic treatment would modify the course of the disease, although it clearly will decrease transmission of the organisms from the person who might have pertussis.

Dr. Marcy agreed that the statement should include clarification about PEP. It seemed to him if monitoring for signs and symptoms, they would always be "closing the barn door after the horse was out." He did not think this made a lot of sense because they would not be able to separate a cold from pertussis, and would exposing children for a long time before actually treated.

Dr. Elward (HICPAC) thought that this issue could be solved by education of HCP. A good infection control program will counsel HCPs about what to look for, so that even if there is a subtle sign or symptom (e.g., cough or runny nose) that person will be be given PEP immediately, even before receiving test results.

Dr. Duchin wondered whether HCPs who were observed to have a runny nose and were treated should be excluded.

Dr. Sawyer said that the language presented to ACIP was based on the practical experience of many people on the work group who have such programs already in place, such that exposed HCP are monitored on a daily basis by occupational health. At the earliest sign of respiratory illness, they are given PEP and are excluded from work for 5 days, which is the exclusion period for people suspected of pertussis. This approach, although imperfect, has worked in many institutions.

Dr. Marcy thought the statement should include language indicating that HCPs thought to be exposed should be monitored on a daily basis.

If starting prophylaxis before test results are received on the putative source case, Dr. Cieslak wondered what the definition of "suspected pertussis" would be in terms of the threshold to trigger PEP if not waiting for test results.

Dr. Elward (HICPAC) responded that the threshold is very low because the initial stages of pertussis are highly non-specific. Any respiratory symptom would prompt initiation of antibiotics in someone who has had an exposure.

Dr. Sawyer thought that intent was for these guidelines to come into play when there was exposure to a documented case, not just a suspected case of pertussis. The source case is documented and exposed HCP are followed. HCP are suspect and are put on treatment and are excluded from work. They may or may not be tested.

Ms. Rosenbaum wondered whether there was a way to assure all other patients that a HCP was not infectious. It sounded as if there was so much uncertainty about the symptoms and the nature of the exposure, she was concerned that someone with an exposure to unconfirmed disease and could not start PEP would be safe around others. The deeper issue regards why there are so many unvaccinated HCP.

Dr. Judson thought overall the recommendations were problematic. Very few places have pertussis expertise and are monitoring the clinical situation. If ACIP members had this many questions about what constitutes exposure, PEP, efficacy, et cetera, it was not going to play well in most medical settings.

Ms. Hayes (ANA) inquired about what the dosing is for PEP and whether the recommendation includes the actual medications and dosages.

Dr. Sawyer responded that the recommendations would refer to existing documents pertaining to what constitutes a significant exposure and the guidelines for treatment and doses. No changes are proposed for PEP. The recommendation simply tries to clarify when PEP might be used or not used in previously immunized or unimmunized HCP. The intent is to provide flexibility for institutions to consider immunization as one of many criteria to assess the need for PEP.

Dr. Englund thought that this particular piece added critical information that would be easily available for healthcare centers that are dealing with pertussis on a regular basis. For pediatric hospitals, this is a daily issue. To have this guidance will be very helpful as long as the references are included to all of the other articles. She did not think they should include dosing in the recommendation because it might change and should be up to the facility.

Dr. Hahn (CSTE) pointed out that one controversy regarded whether all hospitals could do this realistically for 21 days. The agreement was that some facilities are not capable of that, and there was discussion about including that language. While that did not end up in the final language, perhaps it would offer comfort to the committee to include something to the effect of: "If it is feasible for a facility to conduct daily monitoring, this is an option. If not, PEP of all who are considered exposed is the better option."

Ms. Stinchfield (Children's Hospital Minnesota) agreed that this is a very common event in children's hospitals and public health. She thought they were making this much more difficult than it needed to be. Hospital infection control programs and employee health programs

understand precautions and types of antibiotics. The question regards whether to give antibiotics to vaccinated healthcare personnel.

Dr. Coyne-Beasley thought it would be beneficial if the language stated, "unprotected, documented exposure."

Dr. Marcy emphasized that these recommendations were not specifically directed to children's hospitals. Many hospitals are not as sophisticated in their understanding of this, so he did not believe they should set children's hospitals as the standard.

Dr. Schuchat thought this was a healthy and hearty discussion, but reminded ACIP members that the critical piece they were being asked to vote on was in the context of a Tdap-vaccinated HCP, i.e., whether the previous recommendations should be modified about PEP. Unlike a lot of issues about which ACIP has to deliberate, Vanderbilt conducted a nice randomized controlled trial (RCT) giving ACIP evidence to inform their decision-making.

Dr. Cieslak suggested inserting the word "antimicrobial" before each use of the word "prophylaxis" and that "lab-confirmed" be inserted before "pertussis."

Dr. Liang read the revision of the second bullet, "Data on the need for post-exposure antimicrobial prophylaxis Tdap-vaccinated healthcare personnel are inconclusive. Some vaccinated healthcare personnel are still at risk for *B. pertussis*. Tdap may not preclude the need for post-exposure prophylaxis. Postexposure antimicrobial prophylaxis is recommend for all HCP who have unprotected exposure to pertussis and are likely to expose a patient at risk for severe pertussis (e.g., hospitalized neonates and pregnant women). Other vaccinated HCP should either receive postexposure prophylaxis or be monitored daily for 21 days after pertussis exposure and treated at the onset of signs and symptoms of pertussis."

Dr. Baker felt that including "lab-confirmed" was a problem, given that testing in adults is not that good. In addition, not all hospitals even have PCR testing. The intent was not to indicate that those who tested negative should not receive PEP.

Dr. Sawyer thought Dr. Cieslak's point was related to the source case. Currently, the language reads "who have unprotected exposure to pertussis." He personally felt it should be left there. The definition of what pertussis is may vary and may fall short of lab-confirmation but if there is enough epidemiologic data (e.g., other family members with documented pertussis, a cough illness that is typical of pertussis), he thought the language "unprotected exposure to pertussis" was clear enough.

Dr. Baker noted that other CDC documents define pertussis very well, and lab-confirmed is just one component of the definition. She agreed with Dr. Sawyer.

Regarding the RCT, Dr. Elward (HICPAC) noted that the concern of the work group was that there were very small numbers in each arm (N=44) upon which to make a change in the recommendation that could have major implications. This is a well-done study and it is unlikely to be replicated. Facilities need to be provided with flexibility if they have the expertise to conduct daily monitoring. There must be some incentives to vaccinate HCP with Tdap.

On the third bullet referring to hospitalized neonates, Dr. Whitley-Williams (NMA) noted that the highest number of cases was in 2 to 3 month olds. When they refer to hospitalized neonates, technically they mean those babies in the nursery who are less than 1 month of age or 28 days of age and, in fact, are excluding the 2 to 3 month olds. Various hospitals are now cross-training and their HCPs are working all over the hospital. Granted there has to be a case-by-case basis interpretation of the recommendations by each hospital, sometimes being too specific may exclude infants at risk.

Dr. Baker thought Dr. Liang's first slide on cases showed that the first month of life had the highest number of cases.

Dr. Liang responded that with regard to the deaths, in 0 to 1 month olds 152 deaths were reported from 2000 to 2009 and 23 deaths were reported in 2 to 3 month olds.

Dr. Clark (SME) added that cases peaked a little later.

Regarding HCP not providing care to high risk patients, Dr. Campos-Outcalt wondered why consideration was not given to dividing HCP by vaccine status. That would emphasize the importance of being vaccinated.

Dr. Clark (SME) replied that this had to do with the flexibility of the language. Institutions may choose to do that, and this language allows for that. However, it cannot definitively be said that this is an equally effective strategy based on the available data.

Dr. Baker pointed out that adults typically do not know what vaccinations they have had. Until there are better adult registries, that cannot be practically considered for a recommendation.

Given that the duration of protection for Tdap in adults is not known, Dr. Brady (AAP) noted that if they were to say that vaccinated HCP did not need to receive PEP, there would have to be some kind of understanding about when they were vaccinated.

Dr. Pickering agreed that until adult registries become active, that is why CDC developed an adult immunization scheduler that should help adults keep track of all of the immunizations they receive.

Dr. Duchin requested clarification regarding whether the option to observe and give PEP if symptoms developed was only for vaccinated HCP, and if so, he suggested inserting the word "vaccinated" after "other" in the second sentence of the final bullet.

Dr. Judson thought one question this raised regarded where the purview of ACIP ended. In terms of antimicrobial PEP in a very complicated area, it is possible to refer people to other sources about what to do in a pertussis epidemic.

Dr. Baker responded that for many vaccine-preventable diseases, ACIP has included antimicrobial PEP as part of their statements (e.g., pertussis, meningococcal disease, *Haemophilus influenzae B*).

Motion: Proposed Recommendation for Post-Exposure Prophylaxis in Healthcare Personnel

Ms. Ehresmann made a motion to accept the recommendation with the revisions suggested throughout the discussion period. Dr. Duchin seconded the motion. The motion carried with 15 affirmative votes, 0 abstentions, and 0 negative votes.

Considerations for Use of Tdap in Pregnant Women

Tejpratap Tiwari, MD
ACIP Pertussis Vaccine Work Group
Advisory Committee for Immunization Practices

Dr. Tiwari indicated that the objective during this session was to seek ACIP guidance and direction regarding potential change(s) in current recommendations on the use of Tdap in pregnant women.

Approximately 4,000,000 births occur per year in the U.S., which translates to about 66.8 live births per 1,000 women ages 15 through 44 years[1]. Approximately 12% of women have interpregnancy interval of less than 6 months, 23.7% from 6 to less than18 months, and 61.3% of 18 months or more[2]. Vaccines currently recommended during pregnancy include influenza, Td, and Hepatitis B. According to data from the National Health Interview Survey (NHIS), 11.3% of women were vaccinated against seasonal influenza from 2008 to 2009[3], 50.7% were vaccinated against seasonal influenza from 2009 to 2010, and 46.6% were vaccinated against H1N1 in 2009 H1N1 according to the Pregnancy Risk Assessment Monitoring System (PRAMS)[3] [[1]CDC. National Vital Statistics Reports. 2010. Vol 58, No 25. http://www.cdc.gov/nchs/data/ nvsr/nvsr58/nvsr58_25.pdf; [2]CDC. Pregnancy Nutrition Surveillance System. 2009. http://www.cdc.gov/pednss/pnss_tables/pdf/national_table2.pdf; [3]CDC. Seasonal Influenza and 2009 H1N1 Influenza Vaccination Coverage Among Pregnant Women --- 10 States, 2009--10 Influenza Season. MMWR. 59(47);1541-1545]

Regarding considerations for maternal vaccination, maternal IgG antibodies are transferred primarily after week 32 of gestation. Maternal antibody levels in newborns rapidly decrease within the first 2 months for many infectious diseases. Serologic correlates of protection with antibody titers to PT, FHA, or any other pertussis antigens have not been established.

After a 5-dose series primary series of Tdap before 7 years of age, immunogenicity of Tdap (BOOSTRIX®, ADACEL®) against tetanus, diphtheria, and pertussis is supported by results from randomized controlled clinical trials (RCTs) among adults and adolescents. Safety is also supported by the results of RCTs among adolescents and adults. However, pregnant women were excluded from pre-licensure RCTs. Therefore, data are unavailable for safety, immunogenicity, and pregnancy outcomes.

The current status is that Tdap vaccines are not licensed for use during pregnancy. However, the American Academy of Pediatrics (AAP) has recommendation use in pregnant adolescents. ACIP recommends Tdap use during the post-partum period, and under certain circumstances during pregnancy if the benefits outweigh risks (e.g., outbreak settings). Manufacturers have set up registries to monitor safety and pregnancy outcomes in women who received Tdap, and two RCTs are in progress.

As noted, pregnancy is not a contraindication to Tdap or Td immunization in the AAP recommendation for Tdap use in pregnancy. The AAP recommends that pregnant adolescents be given the same considerations for immunization as non-pregnant adolescents. If Tdap or Td vaccine is indicated, administration in the second or third trimester (e.g., before 36 weeks of gestation) is preferred, when feasible, to minimize a perception of an association of immunization with adverse pregnancy outcomes, which are more common during the first trimester. No evidence exists of a risk of immunizing pregnant women with inactivated bacterial vaccines or toxoids, or inactivated viral vaccines [Source: America Academy of Pediatrics Committee on Infectious Diseases. Prevention of pertussis among adolescents: recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine. *Pediatrics*. 2006;117:965-78].

In terms of the ACIP recommendation for Tdap vaccination in the post-partum period, for women who have not received Tdap previously (including women who are breastfeeding), Tdap is recommended as soon as feasible in the immediate post-partum period to protect the women from pertussis and reduce the risk for exposing their infants to pertussis. The postpartum Tdap vaccination should be administered before discharge from the hospital or birthing center. If Tdap cannot be administered at or before discharge, the dose should be administered as soon as feasible thereafter. Elevated levels of pertussis antibodies in the mother are likely within 1 to 2 weeks after Tdap vaccination.

ACIP recommends administration of Td for booster protection against tetanus and diphtheria in pregnant women. However, healthcare providers may choose to administer Tdap instead of Td during pregnancy to add protection against pertussis in special situations. In these situations, the pregnant woman should be informed of the lack of data confirming the safety and immunogenicity of Tdap in pregnant women, the unknown potential for early protection of the infant against pertussis by transplacental maternal antibodies, and the possible adverse effect of maternal antibodies on the ability of the infant to mount an adequate immune response to antigens in pediatric DTaP or conjugate vaccines containing tetanus toxoid and diphtheria toxoid. Special situations in which Tdap might be used might include instances when a pregnant woman has insufficient tetanus or diphtheria protection until delivery, or is at increased risk for pertussis. This includes adolescents aged 11 through 18 years, healthcare personnel, and women employed in institutions in which a pertussis outbreak is occurring or living in a community in which a pertussis outbreak is occurring. Adverse pregnancy outcomes are most common in the first trimester. To minimize the perception of an association of vaccine with an adverse outcome, vaccinating with tetanus toxoid-containing vaccines during the second or third trimester is preferred.

Dr. Tiwari then reviewed data on use of pertussis vaccine during pregnancy as it pertained to the following questions:

- How safe is pertussis vaccine given to pregnant women?
- What is the effect on course and outcome of pregnancy?
- Is pertussis vaccine immunogenic in pregnant women?
- Is transplacental transfer of pertussis antibodies to the neonate protective?
- What is the effect on the immune response to primary DTP / DTaP series in infants born to women who received DTP / Tdap during pregnancy?

In terms of how safe pertussis vaccines are when given to pregnant women, Tdap is classified as an FDA pregnancy-use Category C agent, which is defined as follows: "Risk cannot be ruled out. Adequate, well-controlled human studies are lacking, and animal studies have shown a risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is administered during pregnancy, but the potential benefits may outweigh the potential risk."

The possibility of protecting young infants by immunizing their mothers during the third trimester of pregnancy has been investigated since the 1930s. Significant vaccine-related adverse events among pregnant women were not report in these studies following the use of DTP in pregnancy. These early studies from 1938 through 1951 are the only ones recorded [Lichty 1938; Cohen 1943 and 1946; Mishulow 1941 and 1942 (subset of Cohen 1943); Kendrick 1945; Adams 1947; and Cohen 1951]. Since these studies were conducted, no other clinical trial data have been published on the use of whole-cell vaccine or acellular pertussis vaccine in pregnant women. Prior to 2006, there was sparse, if any, data from manufacturer-based pregnancy Tdap registries or reports to Vaccine Adverse Event Reporting System (VAERS).

Regarding whether pertussis vaccine is immunogenic in pregnant women, a substantial rise in titers to *B. pertussis* antigens is observed in maternal post-vaccination sera compared with pre-vaccine titers. In terms of whether pertussis antibodies are transferred transplacentally after maternal immunization, pertussis antibody titers in infants range from 50% of maternal titers to approximately equal titers in mother-infant pairs [Cohen, 1943; Adams, 1947; Litchy, 1938; Kendrick 1945]. Babies born to DTP immunized mothers had approximately 2.9 times greater levels of antibodies to pertussis than did control babies [Kendrick 1945]. Maternal PT and filamentous hemagglutinin IgG antibodies had a half-life of approximately 5 weeks (36.3 and 40.3 days, respectively) and dropped to undetectable levels by 4 months of age in infants whose mothers were not immunized, or by 6 months of life in infants whose mothers were immunized [Adams 1947; Van Savage, 1990; Baraff, 1958].

In terms of studies in 1990 and 2003 pertaining to placental transfer of pertussis antibody, there were three groups. Group 1 was comprised of 34 sets of paired umbilical cord and maternal sera collected to investigate maternal-fetal antibody transfer. Group 2 included sera collected from 50 infants immunized with either conventional DTwP or DTaP. Group 3 consisted of serial serum samples collected throughout the first 6 months of life for 17 children who had never been immunized against pertussis. This investigation showed a natural decline of placentally-acquired pertussis antibodies. In Group 1, the geometric mean titer (GMT) of antibody to cord sera was about 14 ELISA units, which was about 2.9 times higher than that found in maternal sera, suggesting that antibody to PT was actively transported across the placenta. The GMT of FHA in all infants was about 27 ELISA units and did not differ significantly from that found in maternal sera. Similarly for agglutinin titers, there was no significant difference between maternal and infant sera. For Group 2, the GMTs for PT and FHA antibodies did not differ significantly between the two vaccine groups. The GMTs for PT and FHA antibody levels for the

17 infants in Group 3 declined progressively with age [Van Savage et al. 1990; Edwards et al. 2003].

As noted, the possibility of protecting young infants against pertussis by immunizing their mothers during the third trimester of pregnancy has been investigated since the 1930s. However, the role of transplacental maternal antibodies in infant protection against pertussis remains undefined. Pre-vaccine era observations concluded that infants have no "congenital immunity" and are susceptible to pertussis from the "day of birth," with the possible exception of an infant whose mother had pertussis during pregnancy. Transplacental maternal antibodies might explain the smaller proportion of infant pertussis deaths observed in the first month of life compared with the second and third months of life during the pre-vaccine era. An alternative explanation might be that parents avoid exposing newborn infants to ill contacts. However, this observation of pertussis deaths has become blunted in the post-vaccine era, particularly during the 1980s and 1990s.

Animal studies were able to demonstrate protection in mice that received sera from infants born to mothers immunized during pregnancy, and were challenged with virulent *B. pertussis*. Unfortunately, no large efficacy studies of maternal immunization on infant protection have been conducted to assess whether infant titers resulting from maternal immunization were protectve. Two retrospective surveys were conducted after early DTP vaccine trials in pregnant women to assess infant protection. In the first survey during the 1940s, a subset of 100 / 170 (59%) women who received 6 doses of whole-cell pertussis vaccine during the third trimester and 100 unvaccinated women were questioned regarding pertussis in their infants during the first year of life. During the first 6 months of life, 8 exposures (3 were "close exposures") and no cases of pertussis were reported among infants born to vaccinated mothers; 6 exposures and 3 cases of infant pertussis were reported among infants born to unvaccinated mothers, and from age 6 through 11 months, two cases of infant pertussis were reported in each group [Cohen P. J Pediatr 1946;29:609-619]. In the second survey, a subset of 66 / 106 (62%) women who received 3 doses of whole-cell pertussis vaccine in the third trimester reported 2 exposures and no pertussis among their infants before age 6 months. Survey results suggested that a high concentration of transplacental pertussis antibodies might provide protection against pertussis in the first 6 months of life [Cohen. P. J Pediatr 1951;38:696-704].

Regarding the effect on immune response to primary DTP / DTaP series in infants born to women who received DTP or Tdap during pregnancy, historic studies have demonstrated that the immune response to immunization with DTP vaccine 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 [van Savage 1990; Adams 1947; Sako 1945; *Baraff 1958; Burstyn 1983, Englund 1995*]. In contrast, immunization of infants with aP vaccine is not similarly inhibited by circulating maternal antibody [Van Savage 1990; Englund1995; Roduit 2002; Henninger 1994]. Substantially lower infant IgG anti-PT after 3 doses of pediatric DTP among infants with "high" pre-vaccination levels of maternal IgG anti-PT than among infants with "low" or no measurable pre-vaccination level of maternal IgG anti-PT were noted in some studies [Sako 1945; Provenzano 1965; Van Savage 1990; Baraff 1984; Burstyn 1983; Englund 1995].

In a more recent study, Englund and co-workers reported that transplacental IgG anti-PT might interfere less with infant responses after three doses of pediatric DTP. When the results from several DTP products in the study were combined, the percentage decreased in the post-dose three infant response for all antigens, with an increase in pre-immunization levels of twice to four times the minimum level of protection for transplacental maternal DTP. The decline was about 3% for anti-PT, 13% for anti-PRM, 17% for FIM,10% for AGG, and 8% for CHO. The

same study reported no consistent correlation between pre-immunization titers of pertussis antibodies and the frequency of adverse events following the first dose of DTP / DTaP in infants [Englund JA et al. Pediatrics 1995;96:580-4].

Evidence exists of T-cell priming for booster (anamnestic) responses in infants who have relatively poor humoral immune responses to active immunization with wP or aP vaccine in the presence of inhibitory concentrations of transplacental maternal antibody. Protection against pertussis in T-cell primed infants in the absence of specific humoral antibodies has not been established.

To summarize these historical data, regarding safety, adverse events rates for DTP-vaccinated pregnant women did not different significantly from non-pregnant women. Pregnancy outcomes in DTP-vaccinated women were similar to outcomes in unvaccinated women. DTP / Tdap is immunogenic in pregnant women, but there are no data from large clinical trials for DTP or Tdap. Protective efficacy against transplacental pertussis antibody may be protective in early infancy for DTP-vaccinated pregnant women, but this has not yet been studied for Tdap-vaccinated women. The immune response of infants to primary DTaP / DTP series has not been adequately evaluated in those born to women who have received Tdap during pregnancy.

Overview of Tdap Use During Pregnancy

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Dr. Liang reported that since the 2005 ACIP recommendations, additional data are now available and have been presented to the work group. Concerns regarding the use of Tdap in pregnant women include safety for pregnant women, safety for newborns, transplacental transfer of pertussis antibodies to neonates, adverse impact on primary DTaP response, and programmatic considerations.

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

From January 1, 2005 through June 30, 2010, of 10,350 reports after Tdap vaccines, 129 involved pregnant women who submitted a report to VAERS. Although there were reports of 20 spontaneous abortions, 2 stillbirths, and 2 congenital anomalies, VAERS is not designed to assess whether a vaccine caused an adverse event. A review of VAERS reports in pregnant women who received Tdap vaccines revealed no elevated frequency or unusual patterns.

Both GSK and sanofi pasteur maintain vaccination pregnancy registries to collect data on pregnancy outcomes and newborn health status outcomes following vaccination. Both were kind enough to allow Dr. Liang to present on their behalf. The work group reviewed their data in detail, and she provided the summary points. Boostrix® was licensed in 2005 for 10 through 18 year olds, and in 2008 for adults. GSK maintains a registry to collect data on pregnancy

outcomes and newborn health status outcomes following vaccination. From its U.S. market launch in 2005 through August 2, 2010, 33 pregnancies were prospectively registered. Of these pregnancies, 18 were lost to follow-up. Outcomes were reported for seven pregnancies, and consisted of six live infants born without birth defects and one spontaneous abortion at seven weeks gestation. The remaining eight pregnancies were on-going at the time of last contact. In addition to the prospective reports of pregnancy received to the pregnancy registry from the U.S., GSK has received 13 reports from other countries. Just over half of these reported normal outcomes. The rest are on-going or were lost to follow-up. There have been no birth defects after Boostrix® vaccination reported to GSK.

Adacel® was licensed in 2005 for 11-64 year olds. There were a total of 539 reports in this registry. Of 49 study reports, there were 34 (69%) with no AEs, 10 (20%) SAEs, 5 (10%) non-serious AEs, 47 (96%) with known pregnancy outcome, and 44 live births with 1 unrelated congenital anomaly that was diagnosed pre-vaccination. Of 490 spontaneous reports (480 from prospective reports and 10 from retrospective reports) there were 267 (54%) with no AEs, 29 (6%) with SAEs, 34 (7%) with non-serious AEs, and 158 (34%) with AE status not reported. Of the 480 prospective spontaneous reports, 119 (25%) had a known pregnancy outcome. There were 101 live births with no congenital anomalies. Of the 10 retrospective spontaneous reports, there were 10 (100%) with known pregnancy outcome. There were 8 live births with 1 congenital anomaly (multiple medications and vaccines). Conclusions by sanofi pasteur are that available data on Adacel® administration during pregnancy do not suggest concern for maternal or infant health. The data are consistent with those from other passive pregnancy registries for inactivated vaccines. This finding should provide assurance to women who have received Adacel® vaccine during pregnancy and to their healthcare providers. The work group agreed with the interpretation that the available data on Adacel® administration during pregnancy do not suggest concerns for maternal or infant health.

Several additional small studies further support the safety of vaccinating pregnant women with Tdap on maternal and infant outcomes. No adverse events, or few which were reported, were not judged to be caused by vaccines [Klein NP, et al. Post-marketing safety evaluation of a tetanus toxoid, reduced diphtheria toxoid and 3-component acellular pertussis vaccine administered to a cohort of adolescents in a United States health maintenance organization. Pediatr Infect Dis J. 2010 Jul;29(7):613-7; 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 Nov 23;28(50):8001-7; Shakib JH. Tetanus, diphtheria, acellular pertussis vaccine during pregnancy. Presented to ACIP Pertussis Vaccines WG, January 2011; 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; Halperin B, Halperin S. Protection of Young Infants against pertussis through immunization of pregnant women: a series of maternal immunization studies. Presented to ACIP Pertussis Vaccines WG, January 2011].

Based on a review of the accumulated evidence, the work group concluded that all data collected support the safety of Tdap in mothers and newborns; data are not sufficient to exclude occurrence of a rare adverse event; and other clinical trial data assessing safety are consistent with results. The work group also discussed that vaccinating to maximize maternal antibody transfer during late second and third trimesters limits the potential for birth defects which they felt to be a primary concern. Evidence that vaccinating pregnant women with Tdap is safe to both pregnant women and newborns supports maternal vaccination.

A study from the Netherlands on unvaccinated mothers measured the maternal antibodies for pertussis in 197 paired maternal delivery and cord blood samples. There were low levels of pertussis antibodies in unvaccinated mothers. There is active transport of transplacental antibodies, but overall low levels of pertussis 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 of healthy U.S. women who delivered healthy term infants at >37 weeks gestation, similar to the de Voer et al study, the major conclusion is that healthy unvaccinated women have low levels of antibodies and low levels are transferred to their newborns [Shakib JH, Ralston S, Raissy HH, Stoddard GJ, Edwards KM, Byington CL. Pertussis antibodies in postpartum women and their newborns. J Perinatol. 2010 Feb;30(2):93-7. Epub 2009 Oct 8]. Another study evaluated Tdap vaccinated pregnant women compared to women who did not receive Tdap. Newborns from mothers who received Tdap during pregnancy had significantly higher concentrations of antibodies to diphtheria, tetanus, and pertussis antigens when compared to newborns from mothers who did not receive Tdap during pregnancy [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]. A study from Belgium, which was somewhat confusing, compared titers of siblings whose mothers were vaccinated with Boostrix® between 2 consecutive pregnancies. Serum samples were taken from cord and infants at 1 month from both offspring. The mean interval between vaccination with Tdap and the next delivery was 12.7 months with a range from 8 to 18 months. The study showed that titers in 1 month infants born after maternal booster vaccination were significantly higher compared with siblings born before maternal booster [Leuridan E, et al. Effect of a prepregnancy pertussis booster dose on maternal antibody titers in young infants. Pediatr Infect Dis J. 2011 Jan 4. [Epub ahead of print]. While Tdap is currently licensed for a single lifetime dose, the work group discussed the potential need for additional doses in subsequent pregnancies. These are the only published data that address duration of Tdap benefits. The work group concluded that there is effective maternal-infant antibody transfer after Tdap, and that maternal antibodies are likely to provide infants protection against pertussis. Evidence of transplacental transfer of pertussis antibodies to neonates supports maternal vaccination. All of these data support historical data.

The adverse impact on primary DTaP response was the primary concern in 2006 around recommendations for maternal immunization with Tdap. There remains limited data available. During a suspected pertussis outbreak at Dartmouth-Hitchcock Medical Center in 2006, healthcare personnel were vaccinated with Adacel®. Among them were 16 pregnant women. A prospective cohort study evaluated these 16 women versus 54 pregnant women who did not receive Tdap and their infants. Although the sample size was limited, for infants from vaccinated mothers compared to the controls, antibody levels remained persistently higher up to the first DTaP. Following the third DTaP, pertussis antibody levels were slightly lower. Before and after the fourth DTaP, pertussis antibody levels were similar. Given the small numbers, these data are somewhat difficult to interpret. In addition, the absence of a correlate of protection to pertussis makes translation to clinical relevance difficult [Hardy-Fairbanks AJ et al. Immune response in infants following receipt of pertussis immunization by their mothers during pregnancy. 48th Annual Meeting of the Infectious Diseases Society of America. October 21-24, 2010. Bernstein HH. Immune response in infants following receipt of pertussis immunization by their mothers during pregnancy. Presented to ACIP Pertussis Vaccines WG, December 2010].

There are currently two studies in progress looking further at the important issue of interference. The first study, led by Dr. Carol Baker, is a double-blinded randomized control phase 1 trial using either Adacel® or saline. Anticipated completion of enrollment is late February 2011 and the final infant visit is to be March 2012. Serology results will not be available until after the study is completed. The second study, lead by Beth Halperin, is a double blinded randomized clinical trial using Tdap and Td vaccine. This is a large trial that plans to enroll 444 pregnant women in two stages. Enrollment for stage one is complete with 50 pregnant women. Anticipated completion of enrollment is March 2011 and the final infant visit to be April 2012. Serology results will not be available until the study is completed.

The work group conclusions on interference were that the 444 women in the Halperin study will detect a 10% difference in antibodies. Without a correlate of protection, it is difficult to power any interventional study sufficiently. Most work group members felt that transplacental antibodies may well blunt infant immune response to primary DTaP. Clinical importance of blunting is not clear because immune correlates of protection for pertussis are unknown. The work group expressed that the worst case scenario of maternal immunization would be shifting the risk period, reducing the risk of disease and deaths in <4 month olds, where 90% of pertussis-related deaths occur, and possibly increasing the risk in older infants. Some advocated that the benefit likely outweighs the risk. Whether there is an adverse impact of maternal vaccination on primary DTaP response remains unclear. The work group concluded that there remains a potential for blunting of primary DTaP response, but that the benefits may outweighs the risks.

In terms of programmatic considerations regarding maternal vaccination, other than maternal vaccination, there are other vaccination strategies to protect infants. One strategy would be infant birth dose, which is appealing because it directly protects the infant. However, there is no vaccine currently in the pipeline. The other two are current strategies. As previously discussed in June 2010, post-partum vaccination or cocooning is programmatically challenging and there are no published data on effectiveness. The work group felt that scale-up was a major challenge. This was clearly observed in California this past year when 10 young infants died of pertussis. Even with limited additional data, because of all of these challenges, the work group wanted to reconsider maternal vaccination. The work group acknowledges that vaccinating pregnant women is not without challenges. As seen from influenza coverage, achieving high coverage among pregnant women is challenging, but improving.

Regarding economic considerations, there were no cost-benefit or cost-effectiveness analyses of cocooning presented to ACIP in 2005. There is one recent study from the Netherlands which analyzed the cost-effectiveness of maternal vaccination, cocooning, and infant birth dose. Cocooning and maternal vaccination were cost-effective from a payer's perspective and cost-saving from a societal perspective. Favorable cost-effectiveness was generally robust. Both strategies were sensitive for changes in assumptions on underreporting of pertussis disease. However, even at lower levels of underreporting, cost-effectiveness remained favorable [Westra TA, de Vries R, Tamminga JJ, Sauboin CJ, Postma MJ. Cost-effectiveness analysis of various pertussis vaccination strategies primarily aimed at protecting infants in the Netherlands. Clin Ther. 2010 Aug;32(8):1479-95]. Evidence around programmatic considerations is supportive to maternal vaccination.

Based on the data they have reviewed thus far, the work group concluded that current strategies to prevent infant deaths were insufficient. All but one work group member felt that safety data were supportive of maternal vaccination for good maternal and neonatal outcomes. Acellular vaccine may lead to some interference for infant DTaP immunization, but clinical relevance of interference may never be clear. The majority of the work group members wanted to modify current recommendations now, but the work group is split on this issue since additional data will not be conclusive. The work group is looking toward ACIP for their guidance and thinking on these conclusions.

Discussion Points

Dr. Baker noted that cocooning as a strategy means cocooning a baby with all household contacts and close contacts during the first year of life, and certainly during the first few months of life. She wondered whether there were any data on that recommendation being implemented in the U.S. Clearly, California did not implement this strategy before their epidemic.

Dr. Liang responded that there are some small studies that have shown some success. There has been concern about the ability to sustain cocooning when trying to scale-up the program because of various challenges.

Dr. Baker inquired as to whether it was fair to say that the ACIP recommendation had not been generally followed by hospitals.

Dr. Liang responded that this was her understanding.

Dr. Baker noted that she made the comment in 2005, when this was first discussed, that cocooning is a very difficult immunization platform to implement. They are conducting a demonstration project in a hospital that delivers about 5,000 babies per year. This is costing about $1 million per year, including donated vaccine and funding from outside sources.

Dr. Temte wondered whether any thought had been given to implementation in terms of when during pregnancy administration of this vaccine would be routine. For example, one of the reasons that influenza vaccine uptake is not as good as it should be is that it can occur anytime during pregnancy. However, physicians are really good about checking rubella status, testing for gestational diabetes, and various other things routinely throughout the course of pregnancy because they are programmed in.

Dr. Gall (ACOG) responded that in 2005 when the cocooning tstrategy was proposed by ACIP, there were no field trials on effectivenesst. The lack of those field trials has proven to be prophetic because hospitals are not doing this. According to the literature, only a small percentage of mothers will be infected with pertussis if their baby acquires it. In 50% of cases, it is not the mother or grandparents who transmit the disease. It would be difficult to control for all of the friends and others who may be around a new baby. The cocooning strategy really does not work, and the epidemic in California drives home that this is going to occur repeatedly. Therefore, he thought post-partum vaccination was ineffective. In 2010, his program administered 975 doses of Tdap to pregnant women. They have extensive experience with this over the last several years, and it works exceptionally well. They recommend vaccine primarily during the second trimester. Some of the women in the study received the vaccine during a previous pregnancy and some received it during the first trimester.

Dr. Coyne-Beasley asked whether further information was available about the strategies used in the Netherlands where vaccination was shown to be cost-effective, particularly in terms of who was actually engaged in cocooning.

Dr. Clark (SME) responded that the Netherlands evaluation that was presented was just a cost-effectiveness model of maternal pregnancy immunization and vaccinating the mother. They are relatively comparable.

Dr. Baker indicated that her group had presented an abstract at IDSA assessing post-partum vaccination not household contacts, and found immunizing only the mother was ineffective in preventing infant pertussis cases.

With regard to the Netherlands study, Dr. Duchin inquired as to whether the incidence of disease was comparable to the U.S. incidence.

Dr. Clark (SME) replied that the baseline incidence used in the Netherlands study was about 125 cases per 100,000 infants, which is somewhat higher but relatively comparable to the U.S. at 60 to 80 per 100,000 infants in different cycles. While this changes it, it was still robust to substantial under-reporting. They also incorporated some data they have about prospective serosurveys.

Dr. Marcy thought it was important to keep in mind that a major concern is that there may be low levels of protective antibodies in infants after they receive their DTaP immunization. However, there are no serologic correlates of protection, it is unknown what levels are protective, and it is unknown what "low" means.

Dr. Baker indicated that currently, routine rubella screening is available and postpartum measles, mumps, rubella vaccine (MMR) vaccine is routinely given to seronegative women. That is part of the Medicaid bundle. Although recommended, Tdap is not currently part of the Medicaid bundle.

Ms. Hayes (ANA and ACNM) indicated that it had been extremely difficult for the American College of Nurse Midwives (ACNM) as a professional organization to convince nurse midwives that vaccinating pregnant women with influenza vaccine is a good idea. She thinks that as safe as it sounds to vaccinate with Tdap during pregnancy, the vagary of the potential insult to the fetus scares most pregnant women. The 10-year history of people thinking that vaccines can be dangerous in general to children is even scarier to most pregnant women. A better job must be done with public education. The hospitals in the area where she works and lives have had a very difficult time activating routine standing orders for all post-partum women to be vaccinated. This is not occurring in most of these hospitals.

Dr. Chilton indicated that both hospitals in which he currently works are fairly successfully implementing cocooning. Noting that Dr. Baker had been very much involved in determining what immunizations can and should be given during pregnancy, with respect to the two studies underway at her institution, about 500 women will be enrolled. He suspected that the upper limits of the confidence interval for a zero result on increase in birth defects or spontaneous abortion would still be fairly high. He wondered whether it would be low enough to make Dr. Baker clear that it is safe to immunize pregnant women.

Dr. Baker responded that she is already clear, but the study design of the 48-person study is a very narrow 30 to 32 weeks gestation. If any minor congenital anomaly occurred, it occurred

during the first trimester. Spontaneous abortions after that time are very uncommon. The numbers will be very small and they have not observed any problems. Even in the Dalhousie study, which is much larger, the primary issue has not been safety because there is so much historical data. Geneticists have been on conference calls with the investigators to discuss safety, and their experts have wondered why they were having this conversation about birth defects when immunization is being administered at weeks 30 to 32. The Dalhousie study begins somewhat earlier in gestation, but it is a very narrow window during a time when a woman would have time to respond and have high levels of antibody available for transfer. The decision to vaccinate pregnant women with influenza vaccine was based on a risk-benefit situation. While she agreed that there was a major education need, in her cocooning project, they have a fulltime nurse who educates women post-partum who is not paid by the hospital. This is a largely Hispanic population, for whom they have 96% Tdap uptake. Educating pregnant women about a disease that might affect them and their baby is important, but it is a major job because this has not even been done with influenza for which there is clearly a huge burden in the pregnant woman herself and a risk of losing a baby or having a very sick baby.

Dr. Schuchat added that CDC recognizes that education is expensive and intensive for hospitals and practitioners. The agency has been trying to improve and update the toolkit of materials available for providers and parents. The influenza pandemic changed attitudes in providers of obstetric care and in pregnant women, and greater use of influenza vaccine was observed in 2010 that seemed to be sustained in 2011. With the pertussis outbreak in California and the stories of families who suffered tragically during that outbreak, they are trying to more actively capture the voices and disseminate them. The updated toolkit includes stories from actual families who have gone through these diseases and make the situation clearer in terms of the risk-benefit, and will encompass some of the pregnancy issues that have arisen.

Dr. Baker asked whether these materials are available in Spanish and Asian languages.

Dr. Schuchat responded that if they are not, they will be. She was certain that the pertussis materials were already available in Spanish. California and CDC colleagues did a nice job of preparing excellent materials for that condition.

Dr. Keitel echoed Dr. Marcy's comment about the lack of a correlate of protection, which was going to continue to plague them. For all of the discussions they were having (e.g., immunization of healthcare providers, adults, et certa.) there is not a good sense of the duration of protection and whether a booster is needed, which might make sense in view of the fact that immunity for pertussis itself seemed to wane after 9 and 12 years. She wondered whether the proposed recommendation would be analyzed using evidence-based recommendations.

Dr. Sawyer replied that to date, the formal evidence-based guideline had not been used. They are awaiting guidance from CDC regarding whether the work group should become one of the pilot groups.

Dr. Pickering indicated that there would be an update on implementation of evidence-based guidelines. The plan for the future is for all recommendations to be evidence-based.

Ms. Rosenbaum said she was still trying to fully understand the hospital compliance issue. It was not clear to her whether it was a matter of the payment not being included in the labor and delivery payment to the hospital, a cultural issue in the hospital, et certa.

Dr. Baker responded that it is multi-factorial. Many obstetricians in her community are willing to give standing orders for postpartum immunization; however, it is not part of the package so the patient pays for it. Given the cost of having a baby, the cost is not high. However, for public hospitals this is a major cost.

Regarding the educational issue, Dr. Meissner pointed out that with influenza during pregnancy there is a clear increase in risk for the mother during infection. His understanding was that pertussis during gestation is not associated with more severe disease than in a woman who is not pregnant. The importance of being certain that the vaccine is safe for the fetus as well as not interfering with the infant's immune response after birth is particularly important.

Dr. Baker replied that in contrast to influenza for which there are wonderful laboratory diagnosis and surveillance, it is not clear that there is on-going surveillance in pregnant women for the diagnosis of pertussis. There are data on non-pregnant adults in terms of prolonged costs, loss of work, and complications from the severity of the cough (e.g., weight loss, insomnia, fractures). Adult physicians are not as good at thinking considering a pertussis diagnosis. Adults themselves do not have as high an inoculum of the bacteria, so the diagnostics are less perfect.

Dr. Liang indicated that no data are collected at the national level on whether pertussis cases are in pregnant women; however, some states may collect that data. CDC has three enhanced pertussis surveillance sites in which they will be asking for pregnancy status.

Regarding the issue of hospital compliance, Ms. Rosenbaum thought there had been some conversation regarding a possible discussion between Centers for Medicare and Medicaid Services (CMS) and CDC about the issuance of CMS guidelines under Medicare / Medicaid clarifying payment policies and hospitals' obligations under Medicare conditions of participation to at least offer the immunization. She was concerned that this institutional barrier was not being addressed. There is not a good explanation of why the vaccine is not being covered, why the hospitals are not being paid, and why in states where the vaccine is covered hospitals are still not complying. This is an issue under all three public insurance programs, and would be an issue under exchange plans by 2014. It seemed to her that they should be thinking about much more active involvement between CDC and CMS about what the standards should be to ensure that infants are as protected as possible, especially at this point with concerns about cost in the Medicaid program being what they are.

Dr. Baker reminded everyone that Dr. Rosenbaum posed the same question to CMS during the October 2010 ACIP meeting, and there was no answer providedr. The CMS representative was not present during the February 2011 meeting, but she requested that Dr. Schuchat respond.

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Dr. Schuchat replied that there is a significant amount of dialogue with CMS on a number of immunization issues. Insurance companies should be covering Tdap as a recommended vaccine for adults without co-pays. One of the issues for institutions that are caring for pregnant women and their newborns is that family members are not patients in the package of care. While some hospitals have programs for family members and caretakers of infants, they must determine who to bill for this. There are likely to be fixes, but they have not been worked out in every institution in every state. There are separate issues with CMS in terms of incentives for participation that include reporting coverage of influenza vaccine in healthcare workers. That is a different angle.

Ms. Rosenbaum said that her sympathy for hospitals was rather minor. There are incentives and obligatory issues. This is risk exposure on any number of fronts, including exposure under state law risk considerations as well. It would be nice to have some sort of ad hoc subgroup to meet with payers and hospital associations to work this through. This is not an issue that should be this insoluble.

Ms. Haynes (ANA and ACNM) reminded everyone that while the rate varies from community to community and state to state, roughly 50% of births in the U.S. are paid for by Medicaid.

Dr. Sawyer pointed out that all of the solutions they could dream up for coverage would not address the rest of the family. Dr. Gall made the point that it is very difficult to immunize the whole family. Amongst the multiple factors that preclude post-partum immunization as an ideal strategy is the chaos of the 24 to 36 hours that women are in the hospital when they deliver, as opposed to the 8 to 15 visits they have during pregnancy with their obstetrician. Dr. Sawyer thought both solutions must be considered in order to protect babies.

Dr. Baker added that there is no question that all of the epidemiology regarding pertussis disease suggests that the mother is the most important person. Some women have pertussis when they deliver, so immunizing them post-partum is not going to work. The data available and that will be available for the next couple of years suggest that pertussis immunization is safe for pregnant women. There are a number of issues regarding timing in pregnancy that suggest safety. It is not a live viral vaccine. One study showed the vaccine to be safe even with multiple doses. It seems safe to the newborn, and the antibodies are transferred. There could be interference, but it should be primarily with the first dose. That is the priming dose, which does not protect at all. She cannot believe that the newborn T-cells are going to be affected by B-cell derived antibody. *Haemophilus influenzae* b interference has been observed in infants where there is a protective antibody level defined by the FDA, but no biologic interference. This is a tremendous public health burden in terms of hospitalizations, deaths, and costs. It is difficult to have data when pregnant women are always going to be excluded from clinical trials. Political will is needed somewhere in the world to conduct large studies in pregnant women.

Presupposing that there would be a recommendation for Tdap use in pregnant women, Dr. Temte wondered whether any thought was given to Vaccine Safety Datalink (VSD) studies to assess individuals receiving Tdap and outcomes.

Dr. Sawyer made the anecdotal observation that in California, the state department of health has recommended immunization during pregnancy since July 2010. As a result, thousands of women are currently being immunized. Thus far, no significant problems have been reported. Hopefully the VSD can take advantage of that experience.

Dr. Duchin inquired as to whether there were any data on the number of expected deaths that would be prevented due to maternal immunization. The total number of deaths is not large, but there is hospitalization and other morbidity.

Dr. Clark (SME) responded that it sounded like the work group would like to hear more about the preventable burden.

Regarding the VSD data, Dr. Liang was told that there is a proposal to evaluate the data being collected, although there was not yet a timeline.

Dr. Plotkin (VaxConsult and sanofi pasteur) indicated that what was being proposed was an immunologic intervention. That is, mothers would be immunized so that infants would have transplacental antibodies. It was said a couple of times that there are no correlates of protection. The studies of acellular pertussis vaccines conducted in the 1990s repeatedly showed that purified antigens inducing antibodies protected against pertussis. Studies conducted in Sweden since then by Jim Cherry have shown this. The problem is not that there are no correlates. There are several correlates and there are relative correlates. That is to say that antibodies against PT, FHA, et cetera show protection at high titer. However, the protection is not absolute. The Swedes have proposed that 5 international units of antibody be considered as the correlate of protection. It is not like antibodies against *Haemophilus influenza* b, but the point is that immunization and antibodies do protect. Therefore, what is being proposed is very reasonable to protect infants during the first few months of life when maternal antibodies though decreasing will be much higher than they will be in the infant of a mother who has not been immunized.

Dr. Decker (sanofi pasteur) indicated that this is an enormously complex area. It is one of the few that ACIP deals with in which the regulatory, legal, and medical situations are complicated and unhelpful. The data are unhelpful, with the exception of the epidemiological data. Not only did he fully agree with what Dr. Plotkin said, but he pointed out that even before they get to the studies that assess regression analyses of the antibody data to develop the predictive efficacies, there are licensure criteria for the vaccines. It is a truism that there is not a correlate of protection for pertussis antibody, but like most truisms this is true only in the broadest generalities and is false in many specifics. Particularly for each of the U.S.-licensed acellular pertussis vaccines, there are specific FDA sanctioned correlates of immunity. There is no reason at all why the antibodies of the studies that the National Institutes of Health (NIH) and the Dalhousie group are conducting currently cannot be compared to those and reasonable inferences drawn, even before the results of the work by Cherry et al are applied to them 10.5 years ago that developed specific correlates for specific vaccines. There are correlates of immunity and these will be helpful in guiding decisions about whether the antibody levels produced by transplacental transfer are protective. From 2005 when Adacel® and Boostrix® were first licensed and their data were presented to ACIP, the committee was told that Adacel® would be Pregnancy Category B because that is what the company and the FDA then thought. However, literally days before that became official, the lawyers at FDA reviewed it and discovered that “one i had not been dotted,” and therefore the vaccine was Category C. At the beginning of this session, a slide was shown listing those categories, none of which are factually correct with respect to pertussis vaccine. Category C is explicitly false as a matter of science with respect to pertussis vaccines, but both pertussis vaccines are Category C because there is no other category that could be reasonably applied because the others are worse. In 2005, Dr. Baylor assured this group that FDA recognized how ludicrous these categories were, and that there would be prompt effort to revise them. With that in mind, he asked Dr. Sun where they stood on that progress.

Dr. Sun (FDA) responded that those efforts are still on-going. FDA recognizes this; however, he could not predict when these pregnancy categories would no longer be used. However, they will undergo a change in the near future and there will be guidances published to clarify what the future categories will be.

Dr. Decker (sanofi pasteur) noted that there are also legal impediments. As far as he knew, no court of appeals in the U.S. had yet ruled on a case in which the plaintiff’s attorney brought forth a claim on behalf of an infant who was in utero at the time when the mother received a vaccine seeking tort action compensation for the infant. As far as he knew, this remained an untested

area of the law. Those who appreciate the Vaccine Injury Compensation Program (VICP) and the reinforcement of it that the Supreme Court provided this February believe that it was intended to cover an infant after maternal immunization, but it has not been tested. That induces a level of anxiety that impedes progress.

Geoffrey Evans (HRSA) replied that the legal representatives tell him that the case law is missed. No case has been compensated because the act protects those who are vaccine recipients. It has not ever gotten to the merits of causation in terms of a case. Just three or four cases have gone through, none of which have been compensated so far. Different decisions have been reached on the eligibility under the act as far as vaccine recipient, but none of them got further in terms of the actual causation, so it is not clear that these cases are viable under the compensation program.

Paul Mendelman (LigoCyte Pharmaceuticals, Inc.) reported that he had about three decades of experience conducting vaccine clinical trials for industry. While he loves antibodies, he loves data more. He offered a word of caution. He just red Sinclair Lewis's "Aerosmith" and he suggested reading this to understand what medical care in the U.S. was like in the early 1900s. They are not that far off from they were then for pregnant women. To quote data from 1938 to 1951 really troubled him. There was whole-cell DTP vaccine which was known to be a lousy vaccine after the DTaP study efficacy trials were conducted because they were the comparator arm. It is very difficult for him to understand how data before DTaP was available could prove that DTaP is safe. He was present at the vaccine Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting for the acellular pertussis licensures by GSK and sanofi pasteur. The numbers in those trials were very small: 500, 1000, 11 to 64 years of age. Which decade of life did the vaccine work the best in or was it most safe in? These studies can be done in pregnant women. They should be data-driven, RCTs paid for by the U.S. government or by the manufacturers. This is not an 85,000 Prevnar-13 study for community-acquired pneumonia in the Netherlands. This is 1,000 pregnant women in both arms. They could obtain IRB, FDA, and consent form approval for second and third trimesters of life. There are altruistic mothers and fathers who will sign those consent forms and completely understand exactly what they were being asked to do. He said he was very worried about conventional wisdom, and did not think the answers to any of the questions posed (e.g., safe to pregnant women, safe to newborn, transplacental transfer, adverse impact on primary DTaP response) were "yes."

Japanese Encephalitis Vaccine

Introduction

Paul Cieslak, MD, Chair
ACIP Japanese Encephalitis Vaccines Work Group

Dr. Cieslak first acknowledged the contributions of the workgroup members. He reminded everyone that the new Japanese encephalitis (JE) vaccine was licensed in the U.S. in March 2009. Prior to that, there was only one JE vaccine (JE-VAX®), which was a mouse brain-derived product. The new vaccine (IXIARO®) is a cell culture-derived vaccine. In June 2009, a revised ACIP statement was approved to recommend the use of IXIARO® in adults, which is the only group for whom it is labeled. The remaining supplies of JE-VAX® were reserved for children, given that it was the only vaccine approved for use in children. At the time of the recommendation, the duration of immunity was unknown. Since that time, new data became available and the FDA approved an indication for a booster dose in September 2010. The purpose of this session was for ACIP to vote on whether to recommend a booster dose.

Data Supporting use of a Booster Dose

Marc Fischer, MD, MPH
Arboviral Diseases Branch
Centers for Disease Control and Prevention

Dr. Fischer reminded everyone that JE is a mosquito-borne disease, which is the leading cause of encephalitis in Asia. In endemic areas, most adults have protective immunity. JE occurs primarily among children in rural and agricultural areas. Among an estimated 50,000 to 65,000 cases annually, 20% to 30% of patients die and 30% to 50% of survivors have significant sequelae.

Given that most travelers from non-endemic countries are not immune, travel-associated JE can occur among persons of any age. Recommendations regarding the use of JE vaccine for travelers must weigh the risks of travel-associated JE with the benefits and potential risks of JE vaccine. The overall risk of JE disease among travelers to Asia is very low. Risk varies based on location, duration, season, and activities. When JE does occur, it is a severe disease with substantial morbidity and mortality and there is no specific treatment. Safe and effective vaccines are available; however, these vaccines are relatively expensive and the possibility of rare serious adverse events cannot be excluded. Because humans are not amplifying hosts, JE vaccine protects the person who receives it but does not prevent the spread of the disease. Given these considerations, in June 2009, ACIP approved the following recommendations for the prevention of JE among travelers [CDC. MMWR 2010;59(RR-1)]

1. Travelers to JE-endemic countries should be advised of risks of JE disease and the importance of measures to reduce mosquito bites

2. JE vaccine is recommended for travelers who plan to spend a month or longer in endemic areas during the JE virus transmission season

3. JE vaccine should also be considered for short-term travelers to endemic areas during the virus transmission season if they will travel outside of an urban area and their activities will increase the risk of JE virus exposure

4. JE vaccine is not recommended for short-term travelers whose visit will be restricted to urban areas or times outside of a well-defined JE virus transmission season

As Dr. Cieslak mentioned, two JE vaccines are currently licensed in the US. The first is the inactivated mouse brain-derived JE vaccine, JE-VAX®, which has been licensed in the US since 1992 and is recommended for use in adults and children ≥1 year of age. In March 2009, the FDA approved IXIARO®, an inactivated Vero cell culture-derived JE vaccine for use in adults ≥17 years of age. Inactivated Vero cell culture-derived JE vaccine (JE-VC) is manufactured by Intercell and is distributed in the US by Novartis. JE-VC was licensed based on its ability to induce JE virus neutralizing antibodies as a surrogate for protection. It is administered in a 2-dose primary series on days 0 and 28. When JE-VC was first licensed, the need for and timing of a booster dose was unknown. Since then, several studies have been published regarding duration of neutralizing antibodies and response to a booster dose. In September 2010, the FDA approved a label change for the use of a booster dose of JE-VC.

Data Supporting the Use of a Booster Dose of IXIARO® Japanese Encephalitis Vaccine, Inactivated, Adsorbed

Dr. Katrin Dubischar-Kastner
Intercell AG

Dr. Dubischar-Kastner indicated that as mentioned earlier, IXIARO® was licensed by the FDA in March 2009 for active immunization for the prevention of disease caused by Japanese encephalitis virus (JEV) in persons 17 years of age and older. Not surprisingly, at the time of licensure, limited data were available on persistence of immunity following primary vaccination with IXIARO®, and safety and immunogenicity of a booster dose with IXIARO®. Data have now been generated, reviewed by FDA, and revised prescribing information for IXIARO® was approved in September 2010 that now contains the relevant data.

Three clinical trials provided data on the persistence of antibodies after primary immunization with IXIARO®, and participants were followed up to 36 months after initiation of the primary series. Two clinical trials provided data on safety and immunogenicity of booster doses with IXIARO®:

- Main Booster Dose Trial: Study IC51-311 investigated the safety / immunogenicity of a booster dose given at 15 months after the first dose of the primary immunization, regardless of a person's individual serostatus at that point.

- Supportive Booster Dose Trial: Study IC51-305 investigated the safety / immunogenicity of booster doses given at 11 or 23 months after the first dose of the primary immunization in subjects who were seronegative prior to the booster

The licensure of IXIARO® was initially based on immunogenicity criteria. In all of Intercell's studies, JEV neutralizing antibodies after IXIARO® immunization were determined using a Plaque Reduction Neutralization Test (PRNT). A neutralizing antibody titer of $PRNT_{50}$ ≥1:10 is considered a protective titer by WHO. $PRNT_{50}$ ≥1:10 was used as the cut-off to determine the seroconversion rate (SCR) in naïve subjects or the seroprotection rate (SPR) in immune subjects in the booster studies.

In terms of the data generated on antibody persistence, in the first study, IC51-303, a cohort of 181 subjects from the pivitol safety and immunogenicity trials were followed up. Their response at Day 56 (primary immunization) was a GMT of 311 and a seroconversion rate was 99%. Following them over time, at Month 6 the SPR dropped to 95%. A further decline in SRP was observed at Month 12 when it dropped to 83%. Antibodies remained at approximately the same level (82%) at Month 24. The second study, IC51-311, assesssed the persistence of antibodies just before administration of the booster dose. The time point was at Month 15 following the primary dose, at which time there was a seroprotection rate of about 70%. The third study, IC51-305, followed up a cohort of 116 subjects whose initial response to the vaccine seemed to be comparable to the other studies with an SPR of 97% and a GMT of 219. However, a more rapid decline was observed in antibodies than in study 303, with a protection rate of 83% at Month 6, 58% at Month 12, and 48% at Month 24. The differences observed between studies IC51-303 and IC51-305 is most likely due to the different geographic locations where these studies were conducted. IC51-303 was conduted primarily in Central Europe in Austria and Southern Germany where the majority of people are vaccinated against tick-borne encephalitis virus, which is a related *Flavivirus*. In contrast, IC51-305 was carried out in the Northern part of Germany and in Ireland. In those populations, subjects were unlikely to have had previous exposure to tick-borne encephalitis vaccine.

The main booster trial conducted with IXIARO® was study IC51-311. In terms of the design of the study, the population included 198 subjects without major protocol violations in the preceding clinical trial in three sites in Germany and Austria. They received a single booster dose of IXIARO® 15 months post-first dose of the primary immunization. Serological testing was done before the booster and at 1, 6, and 12 months following administration of the booster. Before the booster dose, the GMT titer in the cohort was about 22.5 and about 70% of the subjects still had protective antibody levels. Within four weeks after the booster dose through Day 28, all of these subjects achieved protective antibody levels and the GMT in the group increased approximately 40-fold to 900. The seroprotection rates remained high throughout the study, with 98.5% at 6 months. At month 12 months after the booster dose, the GMT was approximately 360, which is still above the level observed after primary immunization.

In the supportive study, booster doses were administered to subjects who had become sero-negative before the booster. A booster dose was administered at 11 months after the primary dose. By definition, Day 0 would be the pre-booster time point. All subjects had zero antibodies and 16 subjects received the booster dose at that time. By 28 days after the booster dose, all of the subjects seroconverted. Basically, all of these subjects maintained protective titers out to Month 13 or one year following the booster. Boosters were also administered at Month 23 to 24 subjects who were sero-negative before receiving a booster. All of the subjects seroconvereted within four weeks following the booster.

Regarding IXIARO® local safety data from the main booster study, solicited local adverse events were collected up to 7 days after the booster dose. Approximately 30.8% of subjects experienced any local AE in the 7 days following the booster dose. The primary symptoms were tenderness in about 19% and pain in about 13% of the subjects. That aligns with what has been observed in the primary immunization series. The majority of the reactions were of either mild or moderate intensity. Regarding systemic data summarized from subject diaries for 7 days after the vaccination, about 23.2% of subjects experienced any AEs. The most prominent symptoms observed were headache (10.8%), fatigue (9.6%), influenza-like illness (7.2%), and myalgia (6.7%). These four AEs were the only ones observed in more than 5% of subjects overall.

In summary, in trials of persistence of immunity following primary vaccination, the rate of subjects that still had protective titers varied between 58% and 83% twelve months after the first dose. IXIARO® given as a booster dose at 15 months after the first primary dose resulted in 100% seroprotection rate and a 40-fold increased geometric mean titer of 900. A year after the booster dose, SPR was still high at 98.5%, with a GMT of 361. An IXIARO® booster dose in seronegative subjects (with a complete primary series) led to 200% seroconversion regardless of whether the booster was administered at 11 or 23 months after the first dose of the primary series. Local and systemic adverse events following IXIARO® booster dose were in-line with the good safety profile demonstrated for the primary series in clinical trials. A recommendation on subsequent booster doses cannot be given at this time. Given the robust immune responses, Intercell does not anticipate that subsequent annual booster doses will be needed.

The “Dosage and Administration” section of the FDA-approved Prescribing Information for IXIARO was updated in September 2010 for booster data as follows:

> “If the primary series was administered more than 1 year previously, a booster dose may be given prior to potential re-exposure. Data on the timing of, and the response to, a booster administered more than 2 years after receipt of the final dose of vaccine (primary series or booster) are not available.”

Discussion Points

Dr. Meissner inquired as to whether there was any information on the speed of the antibody response following the booster dose, thinking about the issue regarding whether waning immunity correlates to susceptibility of disease.

Dr. Dubischar-Kastner responded that they do not have these data for the booster dose. They have data from the primary series showing that the neutralizing antibody responses are fully developed by 7 days after the second dose. She would assume that it is no later in the case of a booster dose.

Dr. Baker asked whether there a population beyond 60 years of age in the adults defined as 17 years of age and older.

Dr. Dubischar-Kastner replied that there very few people beyond 60 years of age in the booster studies. There were a couple of individuals over 60 years of age in the primary immunization series. In the booster studies, only 1 or 2 subjects were carried over. In one study, the mean age was about 30 years and in another study the mean age was about 40 years.

Regarding the hypothesis that Northern Europeans were primed with tick-borne encephalitis vaccine, Dr. Keitel wondered whether that was tested by assessing antibody responses following the first dose of vaccine.

Dr. Dubischar-Kastner indicated that this was assessed in the pivotal immunogenicity study. They observed an enhanced GMT and enhanced sero-conversion rate to tick-borne encephalitis positive subjects when they received the first dose of vaccine. This did not reach 100%. It was approximately 70%.

Dr. Pickering asked whether there were plans to follow these individuals longer, and whether anything could be learned about the durability of the antibody by evaluating patients who have had the disease (e.g., JE survivors).

Dr. Dubischar-Kastner replied that longer follow-up is not currently being conducted with these subjects. In the pediatric booster studies, the cohort will be followed for at least two years after receiving their booster dose. To get idea on persistence of antibodies, they did modeling on antibody decline. The model suggests that majority of subjects (95%) would continue to have protective antibody levels at about 4 years after the booster dose. She was not aware of data on the persistence of antibodies, especially in survivors of JE. The paradigm was always that the infection in childhood would confer lifelong immunity and that was why the majority of disease cases were seen in children.

Dr. Baker wondered whether Dr. Okabe might have information on antibodies following JE survivors.

Dr. Okabe responded that they do not have such data on survivor cases.

Dr. Katz (IDSA) reported that the original vaccine, which has been discontinued, was a live attenuated virus. With that there were uncommon but serious reactions in some young children. The vaccine is now inactivated. He wondered why they were persisting with the 17 years of age cutoff, and whether any thought had been given to assessing this vaccine in younger children.

Dr. Dubischar-Kastner replied that pediatric studies are planned. Intercell is currently conducting 4 clinical trials in children and is assessing children down to two months of age.

Dr. Fischer clarified that the previous vaccine was inactivated, but it was a mouse brain-derived vaccine, while this is cell culture-derived vaccine. He noted that he planned to provide a brief update at the end of the session on the status of vaccine availability and development for children.

Recommendations for Use of a Booster Dose of JE-VC Vaccine

Marc Fischer, MD, MPH
Arboviral Diseases Branch
Centers for Disease Control and Prevention

In developing the proposed recommendations for a booster dose, the work group began with the FDA approved language, reviewed the available data, and considered what is known and the limitations of the data. It is known that JE virus neutralizing antibodies correlate with protection, and that in the available studies 17% to 42% of vaccines no longer had detectable neutralizing antibodies at 12 months after receiving the 2-dose primary series. In addition, of all subjects who responded (n=238) to a booster dose administered between 11 and 23 months after the primary series, over 98% were still protected at 12 months after the booster dose. What is not known is whether a person who responded to a JE vaccine primary series but then loses neutralizing antibodies is still protected through memory B-cell or cell-mediated response. Therefore, the true duration of protection for most people is unknown with and without a booster dose. In addition, response to a booster dose administered 2 years after the 2-dose primary series has not been studied, and there are no data on the need for and timing of subsequent booster doses.

Given these considerations, including the risk of the disease and the limitations of the data, the work group proposed the following recommendations, which are permissive, for a booster dose of JE-VC:

> "If the primary series of JE-VC was administered more than 1 year previously, a booster dose may be given prior to potential JE virus exposure (See Recommendations for the Use of JE vaccine). Data on the response to a booster dose administered more than 2 years after the primary series are not available. Data on the need for and timing of additional booster doses also are not available."

Discussion Points

Dr. Duchin asked for the rationale behind the selection of a permissive recommendation and not to recommend the booster dose.

Dr. Fischer responded that given the low risk of the disease and the data that are available regarding the range of the proportion of people who are still protected at a year and whether they are really still at risk of disease, it was felt that there were not enough data to suggest a stronger recommendation. Dr. Cieslak agreed that this reflected the deliberations of the work group.

Dr. Temte asked how many doses this would involve per year. His suspicion was that this would be a very small number. The financial aspects are born primarily by the individual not by any larger groups.

Dr. Fischer indicated that there are millions of travelers to Asia, but the proportion who would meet the recommendation guidelines is not known. As far as the previous vaccine, based on distribution numbers there were on the order of close to 100,000 doses administered in the U.S. each year. The vast majority of those doses were administered by DoD. Only about 30% on average was for civilian or private sector use.

Dr. Sawyer asked whether there was discussion in the work group about further guidance to practitioners regarding the circumstances under which they may administer a booster dose. Was it the intent of the work group that all travelers who meet the standard recommendations for a first dose would also get a booster?

Dr. Cieslak responded that the work group did not intend to say that everybody should receive a booster dose because it is unknown whether they are actually still at risk after their antibody titers have waged. The group for whom the booster should be considered is exactly the same group as the primary series.

Dr. Fischer added that the only additional guidance offered refers to the primary recommendations, which address three groups of travelers and laboratory workers.

Dr. Judson thought the suggested recommendation was appropriately cautious, and that the language "may be given a booster" was pretty bland.

Dr. Baker noted that most of those traveling to Asia who are aware of the disease are likely to go to a travel medicine specialist versus a general practitioner. With that in mind, she wondered whether there was adequate advice in the prior documents regarding the various groups of travelers to guide physicians.

Dr. Fischer said he thought that there was—within the limits of data. This is a fairly rare disease, so defining exactly who is at risk is not easy. Within the limitations, the recommendations lay out as best they can who is believed to be at higher risk and should be considered for vaccination.

Stephan Foster (APhA) noted that the data shown suggested that immunity wanes after one year. He wondered whether the recommendation was going to be for a booster at one year or 15 months as in the booster dose study.

Dr. Fischer clarified that the proposed recommendation would be for any time after a year. In the booster dose study, the booster was administered at 15 months. The studies that assessed the duration of the neutralizing antibodies ranged between 12 months and 24 months. Some studies show boosters given out to 23 months, so the group felt fairly confident that people would respond well out to 23 months and probably beyond, but there are no data. They felt that leaving the recommendation open to administering the booster dose any time after a year would be adequate.

Dr. Englund expressed concern that "may be given" might not be sufficient for travel medicine clinics. In Northern Germany, a major percentage of people (58%) are protected after one year. In that case, the word "may" is too weak. While she agreed that they should give practitioners options, travel clinics are used to following check boxes and this recommendation is weak. By two years the data show that 42% are unprotected, for which the recommendation should say "should." She was especially concerned for practitioners who are not fully vested in reading all of the available literature about JE vaccine that the statement does not offer enough advice.

Dr. Baker noted that many travel medicine clinics are actually run by nurses rather than physicians.

Dr. Temte reminded everyone that for the evidence-based guidelines adopted in October 2010 there are two levels of recommendations: universal and Category 2 for individual clinical decision-making. He felt that the proposed recommendation was very appropriate for the individual clinical decision-making category, for which the terminology would be "may be used" versus the terminology "should be" that is used in the universal language.

Dr. Meissner thought it was also important to keep in mind the number of cases of JEV infection in the past few years.

Dr. Fischer responded that they published a review recently that addressed published cases, which obviously is not all cases. In the last 18 years since the vaccine has been available in the U.S., there have been 5 travel-associated JE cases among U.S. citizen. Prior to 1973, there were many cases related to the Vietnam War and the Korean Conflict among soldiers. Over a period of the 37 years since 1973, there have been 56 total travel-associated cases, 16 of which were among U.S. citizens. Thus, reported cases are less than one case per year among U.S. travelers. While the exact number of U.S. travelers to Asia is unknown, it is in the millions.

Regarding evidence-based recommendations, Dr. Keitel asked whether the language would state "may" for the primary immunization.

Dr. Temte responded that Category 1 recommendations would be for all individuals either universally or within a well-defined category. Individuals who are defined as a person currently aged 18 or older traveling to an area with a high endemicity of JE during a specific time period could be classified as a Category 1. In the context of a clinic that has a travel medicine component, such decisions are made on the level of close communication with the clinician making the decision. Until the clinical decision process occurs, the information will be unknown (e.g., when the patient is traveling, et cetera). "May" in the right circumstance is done all of the time. At a rate of 20,000 immunizations per year, this is a very selected group versus a universal group.

Reflecting on the discussion ACIP had regarding the meningococcal booster, Dr. Duchin pointed out that just like children who are at high risk during the peak of meningococcal disease, travelers at high risk should be protected. Based on antibody data only, in the absence of any convincing evidence of increase in disease due to waning immunity, ACIP recommended that a booster dose of meningococcal vaccine "should" be given. He said he was trying to reconcile the two approaches. It seemed to him that if a patient was traveling to an area where they would be at risk, they should receive optimum protection, which is the booster dose.

Dr. Cieslak responded that the work group did not think they had enough evidence to state that these individuals "should" be vaccinated. The risk is very low for the vast majority of travelers, and it is unclear whether they are protected. It is known that the antibody at a $PRNT_{50}$ of at least 1:10 is protective based on prior vaccine studies and passive transfer of antibody in animal models. While this is known to be sufficient, it is not known whether it is necessary for immunity. It may well be that an individual will have a brisk memory response after exposure and will be protected on that basis, or that there are T-cell factors that come into play.

Dr. Duchin thought that was reasonable, but slightly different logic was used when making the meningococcal recommendation. The JE booster is not a major expense like the meningococcal booster, so he thought they should err on side of protecting travelers if it was believed that they may not be protected.

Dr. Cieslak replied that the JE vaccine is expensive, it is unknown how many cases will be prevented, the safety record is limited, and the risk is very low—all of which factored into the decision for use of the word "may."

Regarding the class of travelers and degree of risk, Dr. Baker pointed out that for yellow fever vaccine there is a precaution for those over 60 years of age. Many people over 60 years of age travel to yellow fever-endemic areas. For yellow fever, there is the same amount of data (or lack thereof) as there is for JE. As a travel medicine clinic director, she was fairly comfortable with the proposed language.

Dr. Meissner did not think the analogy with meningococcal vaccine was quite the same because it was clear that if antibodies fell below a protective level, the amount of time that was necessary to generate a response was insufficient to protect against meningococcal disease. That is not known for JE.

Dr. Judson thought the 5 to 15-day incubation period would allow time for response, which would be quite different from meningococcal disease. The real clinical judgment issue regarded trying to anticipate exposure. For most people, risk will be incredibly low. From a public health standpoint, anything that deals with mosquito-borne illness (e.g., dengue, yellow fever, malaria) the emphasis should be on avoiding mosquito bites regardless of location.

Dr. Pickering pointed out that the same criteria are used to give the primary series as are used to give the booster dose of JE. The risk of disease for both, although low, is the same. The recommendation for the primary series is that it "should" be given, while the booster dose "may" be given. The recommendations for the primary and booster series are discordant, but it seemed as though they should be similar.

Dr. Cieslak indicated that for the primary series, people were divided into three groups: 1) those who were definitely thought to be at high risk and should be vaccinated (e.g., people spending more than a month engaged in a lot of rural activities; 2) those who it was thought should not be given the vaccine (e.g., those traveling for a short time and staying in a hotel in an urban area); and 3) those for whom a conversation should occur with a travel medicine physician. The vast majority of people would not fall into the first group, but would fit in one of the other groups. The people in first group, for whom primary vaccine was recommended, may still be protected. The consensus of the work group was that the members felt apprehensive about saying "should" be given when data may prove that nobody ever needed another dose.

Dr. Fischer added that consideration was given to a stratified recommendation, but felt that it was complicated and unnecessary. Neutralizing antibodies were similar for JE-VAX® and IXIARO®.

Dr. Duchin asked whether additional data would be forthcoming to help them make a more precise recommendation.

Given the rarity of the disease, Dr. Cieslak doubted it.

With only 5 cases in 3 decades, Dr. Marcy noted that the N was really not large enough to make a decision. He wondered whether people who live in endemic areas contract JE in hotels.

Dr. Fischer responded that this varies from country to country, but most cases occur in rural agricultural countries. Occasional cases are reported from suburban or urban areas, but often there is rice production on the margins of such areas. There have been reports of cases from suburban Bangkok; however, the vast majority of cases occur in rural and agricultural areas.

Dr. Coyne-Beasley requested affirmation that because disease is not transmitted person to person, the presence of people did not matter.

Dr. Fischer confirmed that humans are dead-end hosts. Most people who become infected are asymptomatic. Less than 1% of humans become ill, but they do not have high enough levels or viremia or long enough durations to subsequently infect a mosquito. Humans receive infection from a mosquito and the cycle is maintained through mosquitoes primarily through birds and pigs.

Dr. Plotkin (VaxConsult and sanofi pasteur) clarified that most indigenous people are protected by live vaccine, so that really does not apply. Elderly Japanese people do still have antibodies to JE virus, which appears to be long-lasting after infection. WHO has said that a 1:10 neutralizing titer is the correlate of protection. This vaccine is given twice—at 0 and 28 days. Classically, for an inactivated vaccine, for long-lasting immunity a booster dose should be given about 6 months after the initial series. The likelihood that B-cells are still producing antibodies or that memory B-cells are going to come up rapidly is not obvious. If he had received the primary series and was going to live in a rural area in Thailand and his physician did not recommend a booster knowing that he had a 50 / 50 chance of still having antibodies, he would call that malpractice. His opinion was that a booster dose should be given to those at risk at 15 months or so.

Motion: Proposed Recommendation for JE-VC Vaccine

Dr. Sawyer made a motion to accept the recommendation as presented. Ms. Ehresmann seconded the motion. The motion carried with 11 affirmative votes, 2 abstentions, and 2 negative votes.

Update on Status of JE Vaccine for US Children

Marc Fischer, MD, MPH
Arboviral Diseases Branch
Centers for Disease Control and Prevention

Dr. Fischer reminded everyone that inactivated mouse brain-derived JE vaccine (JE-MB) is the only JE vaccine licensed for use in U.S., children less than 17 years of age. JE-MB is no longer being produced, and all doses remaining in the private sector will expire in March 2011.

The inactivated Vero cell culture-derived JE vaccine (JE-VC) is not licensed for use in children less than 17 years of age. To date, a pediatric dose-ranging study has been completed in approximately 60 children aged 1 through 3 years in India. There is an on-going safety and immunogenicity study in 1869 children aged 2 months to 17 years in the Philippines, and a safety and immunogenicity bridging study has been started in the US and other non-endemic countries (e.g., Europe, Australia) with a targeted enrollment of approximately 100 children. Despite these on-going studies, it will likely be 2 to 3 years before JE-VC is licensed in the US for use in children. Interim options for use of JE-VC are currently being discussed, including off-label use of JE-VC and making JE-VC available through a treatment investigational new drug (IND).

In the interim, the primary ACIP recommendations for the prevention of JE among children travelers remain in place and are as follows:

> "Travelers to JE-endemic countries should be advised of the risks of JE and the importance of personal protective measures to reduce the risk for mosquito bites."
>
> "All travelers should take precautions to avoid mosquito bites to reduce the risk for JE and other vector-borne infectious diseases. These precautions include using insect repellent, permethrin-impregnated clothing, and bed nets, and staying in accommodations with screened or air-conditioned rooms."

Discussion Points

Dr. Katz (IDSA) noted that in terms of behavior patterns, children are much less likely to follow the advice given about non-vaccine protection strategies. He suggested that stronger emphasis be placed on children.

Dr. Baker inquired as to how a 16-year old traveler who was clearly at risk would be handled in terms of this recommendation.

Dr. Fischer responded that there are no data at this point. The studies were performed in 18 year olds and older, and an extension was made down to 17 primarily because of use in military populations. That could certainly be applied to a lower age, but there are no data regarding studies in lower age ranges.

Dr. Coyne-Beasley inquired as to whether the remaining vaccine would be part of this recommendation, and how long the supply was expected to last.

Dr. Hosbach (sanofi pasteur) responded that sanofi pasteur has several hundred doses left. They sent notification to all previous customers to indicate that it is expiring on March 14, 2011. Therefore, after the first week of March, they could not sell anymore vaccine because it takes up to 14 days to immunize with the 3-dose series in an accelerated fashion.

Dr. Baker pointed out that once something was licensed and available, any physician could use it off-label. She asked whether there was any other choice for a physician who has a patient at risk under 18 years of age to acquire / administer vaccine.

Dr. Lewin (Novartis Vaccines and Diagnostics) responded that Novartis is committed to trying to make vaccine available since there is no other option. They are willing to work with the FDA on the potential of a treatment IND. That would obviously take time to put into place. Guidance from ACIP on the use of vaccine would be helpful, given that Novartis cannot recommend off-label use.

Regarding implications for liability protection, Dr. Campos-Outcalt (AAFP) noted that this vaccine is not covered by the Vaccines For Children (VFC) program vaccine. Therefore, he wondered what the implications for coverage would be if the vaccine was used in children.

Dr. Fischer indicated that the work group was not planning to bring recommendations for off-label use of the vaccine to ACIP. The plan was to work on a treatment IND if possible, and to make information known about use in children available so that physicians could make decisions.

Dr. Pickering wondered whether their travel medicine colleagues could provide guidance for use of the vaccine in children. He also inquired as to whether there were countries in which a booster dose of this vaccine was being used in children, and whether any safety data would be available from the Philippines that could be assessed before the final data are analyzed.

Dr. Fischer replied that there are interim results to be completed by end of this year. There are interim safety data in approximately 1900 children who were enrolled, which can be made available. He indicated that Dr. Dubischar-Kastner could present additional data from the Philippine trial if the members wished to review it. Because that was not the primary purpose of this session, those data were not included.

Dr. Okabe indicated that the experience in Japan is that JEV continues to exist. That is why they recommend that all children have 2 primary doses and a dose 1 year later. A total of 3 doses are required as the primary immunization. Booster doses will be given at about 10 years old. They are now introducing a new vaccine that is Vero cell-derived that is to be used as a routine immunization. Even though elderly people did not receive vaccine, their antibody levels are very high because of natural infection.

Dr. Baker thought that while they awaited additional data, guidance was still needed for travelers. She requested that additional data be presented during the next ACIP meeting.

Regarding the use of the vaccine in other countries, Dr. Dubischar-Kastner clarified that what was stated about the immunization program in Japan was not related to Intercell vaccine that is being used as a booster there.

Dr. Baker inquired as to whether a vote was necessary. Dr. Fischer replied that it was not, given that this language had already been approved.

Immunization of Healthcare Personnel

Kristen Ehresmann, RN, MPH
Minnesota Department of Health
Chair, ACIP Adult Immunization Work Group

Ms. Ehresmann acknowledged the members of the subset of the Adult Immunization Work Group who were involved in the issue of immunization of healthcare personnel. The term of reference for the group was to update the healthcare worker vaccination statement of 1997, which read as follows:

> Immunization of Health-Care Workers: Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC) CDC.
>
> *MMWR* 1997;46(No. RR-18):1-42.
> http://www.cdc.gov/mmwr/preview/mmwrhtml/00050577.htm

Much has occurred in the ensuing 14 years since the 1997 statement. Some of the overarching considerations were to change the standard terminology from healthcare worker (HCW) to healthcare personnel (HCP). Part of the rationale for that was to broaden the definition and to clarify that HCP refers to paid and unpaid individuals in that setting. Another major consideration was the decision to publish these guidelines as an ACIP statement, not a joint ACIP / HICPAC statement. However, review and input were obtained from HICPAC.

The purpose of this session was to present an overview of the updated report, which was provided to ACIP members in early February 2011, to address any discussion points raised, and to vote. Subsequent changes to the report will be made to reflect votes taken during this ACIP meeting. The report will then go through official CDC clearance and is expected to be published in an *MMWR* by the end of 2011.

Immunization of Healthcare Personnel

Harry Keyserling, MD
Emory University School of Medicine
ACIP Liaison, Society for Healthcare Epidemiology of America

Dr. Keyserling indicated that the following offers an overview of how the report is organized:

- Summary and Introduction
  - Definition of HCP and settings where applicable
  - Target audience
  - Documenting and tracking of vaccination records
  - Policy development
  - Disease specific outbreak control measures

- Recommendations presented by disease - two main categories:
  - Recommended based on risks to HCP in work settings
  - May be indicated in certain circumstances
- Other vaccines recommended for adults
  - PPSV, Td, HPV, Zoster, HepA
- Catch-up and travel vaccination
- Work restrictions

As mentioned, the definition of who needs to be immunized has changed. The target audience for the document is healthcare facility administrators, infection control personnel, and employee health clinicians. The document includes a strong recommendation that each healthcare facility maintain an electronic database to include vaccination history and serologic history, and that these results be given to healthcare personnel so that as they move from job to job, they will be able to document their serology and immunization status.

The definition of HCP was based on the March 2008 HHS definition of HCP, available at http://www.hhs.gov/ash/initiatives/vacctoolkit/definition.html, and is as follows:

> HCP refers to all paid and unpaid persons working in healthcare settings who have the potential for exposure to patients and/or to infectious materials, including body substances, contaminated medical supplies and equipment, contaminated environmental surfaces, or contaminated air. HCP might include (but are not limited to) physicians, nurses, nursing assistants, therapists, technicians, emergency medical service personnel, dental personnel, pharmacists, laboratory personnel, autopsy personnel, students and trainees, contractual staff not employed by the health-care facility, and persons (e.g., clerical, dietary, house-keeping, laundry, security, maintenance, billing, and volunteers) not directly involved in patient care but potentially exposed to infectious agents that can be transmitted to and from HCP and patients. These recommendations apply to HCP in acute care hospitals, nursing homes, skilled nursing facilities, physician's offices, urgent care centers, and outpatient clinics, and to persons who provide home healthcare and emergency medical services.

Recommendations are presented in two major categories: 1) Recommended for All HCP (Hepatitis B, Influenza, Measles, Mumps, Rubella, Pertussis, Varicella), and 2) Immunization May be Indicated (Meningococcal, Typhoid, Polio).

The following five tables are included in the report:

Table 1: Recommendations for immunization practices
(MMWR publications by subject area)

Table 2: Immunizing agents and immunization schedules
(All vaccines covered in report and VZIG, HBIG)

Table 3: Recommended postexposure prophylaxis for percutaneous or permucosal exposure to HepB virus

Table 4: Immunization of HCP with special conditions
(i.e., pregnancy, HIV, immunosuppression, asplenia, renal failure, diabetes, alcoholism)

Table 5: Work restrictions for HCP exposed to or infected with certain vaccine-preventable diseases

Highlights of main changes since the 1997 publication include the following:

Hepatitis B
- ❑ HCP and trainees at high risk for percutaneous or mucosal exposure to blood or body fluids should be tested after receipt of the complete HepB vaccine series to determine their response to vaccine and guide postexposure prophylaxis. *
- ❑ HCP and trainees in certain populations at high risk for chronic hepatitis B (e.g., those born in countries with high and intermediate endemnicity) should be tested for HBsAg and anti-HBc/anti-HBs to determine infection status.
- ❑ Chronic HepB infection is not grounds for exclusion from medical practice or training; these infected persons should seek counsel from a review panel.

* Note: Summary Table at end of document and Briefing Document originally noted incorrectly that all HCP require HepB postvaccination serologic testing. There have also been other minor edits to these summary changes.

Influenza
- ❑ All HCP should receive an annual influenza vaccination.
- ❑ Comprehensive programs to increase vaccine coverage among HCP are needed and might include variety of strategies (e.g., declinations, mandatory vaccination).

MMR
- ❑ History of disease no longer considered adequate presumptive evidence of measles or mumps immunity for HCP; laboratory confirmation of disease was added as acceptable presumptive evidence of immunity.
- ❑ The footnotes changed regarding the recommendations for personnel born before 1957 in routine and outbreak contexts.

Pertussis
- ❑ Since 2005, ACIP has recommended that all adults <65 years, including those who have or who anticipate having close contact with an infant aged <12 months (e.g., HCP), should receive a single dose of Tdap to reduce morbidity and mortality associated with transmission of pertussis. In 2010, the ACIP voted that HCP 65 of age and older who have close contact with an infant should also receive a single dose of Tdap.
- ❑ Currently, there are two licensed Tdap vaccines for persons aged 10 or 11-64 years in the United States.
- ❑ The minimum interval was removed, and Tdap can now be administered regardless of interval since last Td-containing vaccine.
- ❑ As a result of the discussions earlier in the morning, some of these recommendations will need to be modified

Meningococcal
- ❑ Since 2010, ACIP has recommended that HCP with anatomic or functional asplenia, or persistent complement component deficiencies receive a 2-dose primary series of meningococcal conjugate vaccine. HCP with HIV infection who are vaccinated should also receive a 2-dose series.
- ❑ Those HCP who remain in groups at high-risk are recommended to be revaccinated every 5 years.

In terms of incorporating new Tdap recommendations, Dr. Keyserling pointed out that the discussion earlier in the morning superseded the language of the changes made and that the final version of those discussions would be incorporated into the final document.

Another issue regarded clarification about who should have HepB postvaccination serologic testing. This is restricted to individuals in situations that would put them at high risk for exposure to blood or other body fluids. This is under the jurisdiction of Occupational Safety and Health Administration (OSHA) that has been able to mandate HepB vaccine in healthcare institutions:

> To determine the need for revaccination and to guide postexposure prophylaxis, postvaccination serologic testing should be performed for all HCP ~~and other workers~~ at high risk for occupational percutaneous or mucosal exposure to blood or body fluids. Postvaccination serologic testing is performed 1-2 months after administration of the last dose of the vaccine series using a method that allows detection of the protective concentration of anti-HBs (≥10 mIU/mL). Persons found to have anti-HBs concentrations of ≥10 mIU/mL after receipt of the primary vaccine series are considered immune and the result should be documented. Immunocompetent persons have long-term protection and do not need further periodic testing to assess anti-HBs levels. Postvaccination testing for persons at low risk for mucosal or percutaneous exposure to blood or body fluids (e.g., public safety workers and HCP without direct patient contact) likely is not cost effective (*36*); however, persons who do not undergo postvaccination testing should be counseled to seek immediate testing if exposed.

Regarding ACIP member comments on the document, as noted the draft was distributed to members in early February 2011. Comments were received from 12 of 15 ACIP members, all of which were reviewed by many of CDC's subject matter experts (SMEs) who were instrumental in crafting the document. No major concerns were noted by members; however, there were many comments. In terms of general comments, many people were concerned that the document needed to weigh in on mandating influenza vaccination as a condition of employment. OSHA mandates and ACIP recommends. There is discussion in the document that many professional organizations have endorsed the concept of mandatory immunization, and in 2007 the Joint Commission began requiring hospitals to report their immunization coverage. Therefore, progress is slowly being made toward increasing immunization uptake to the level it should be. There were also many comments regarding whether the document could be stronger in its statements and use the word "should" rather than "may want to consider" or "could." This is a recurring theme. For the document developers, the scope of their responsibility was not to create policy, so whatever verbiage is used is taken from prior ACIP recommendations without modification. The document reflects policy. Many people wanted to recommend new policy. One of the important by-products of having this work group is that during in their deliberations they identified many gaps. Many of these issues were referred to other work groups for consideration for modification of future recommendations for healthcare personnel. Specific comments from ACIP members are highlighted in the following table, all of which will be addressed before finalizing the document:

Comment	Response
(HepB) Should include data on giving double dose of Twinrix to non-responders	Available data not relevant to US based on variable number doses HepB by IM route – no change
(HepB) Unclear wording under HCP and Trainees at Additional Risk	Revised wording *
(HepB) Clarify when to give HBIG	Revised wording *
(HepB) Clarify how often to give HBIG to continually exposed non-responders	No specific data aware of but revisions made to text and Table 3 *
(Flu) Mention availability of LAIV FluMist for those persons with fear of needles	Sentence revised *
(Flu) Update regarding new egg allergy non-precautions for flu	Agree with point but valid as written; new language being discussed by workgroup
(Flu) Specify what facilities should do with flu coverage data after collected	Paragraph revised *
Comment	Response
(MMR) Delete vague wording (‘generally’) from recommendation for pre-vaccination testing before MMR	Revised sentence *
(MMR) Under presumptive evidence of immunity, does not agree with birth before 1957	ACIP voted in June 2009 to include birth before 1957 as presumptive evidence immunity – no change
(MMR) At least one study has shown encephalitis after MMR vaccine	Conflicting data; sentence revised *
(Measles) Doubt there is data to show patient wearing a mask 24/7 is effective in preventing measles	Wearing mask considered standard airborne precautions – no change
(Measles) Should note that measles spread before rash appears	Added paragraph *
(Measles) Under Vaccine Safety, does not agree with statement that there is no evidence of transmission of vaccine virus	Revised wording *
(Measles) Clarify mask use for outbreak control	Revised wording *
Comment	Response
(Mumps) Use better wording to describe mumps manifestations – “sialadenitis including classic parotitis”	Revised sentence *
(Mumps) Patient should be isolated for 5 days after salivary gland infection or sialadenitis also, not just parotitis	Current recommendation (based on literature) states parotitis – no change
(Rubella) Better specification regarding excluding HCP when exposed	Revised sentence *
(Rubella) Disagrees with statement that IG not recommended for PEP of rubella in early pregnancy	Revised wording to be more consistent with 1998 ACIP MMR recommendations *
Comment	Response
(VAR) Period of contagion is more than 1-2 days before rash	For consistency with CDC documents and weight of existing evidence –no change
(VAR) Birth before 1980 should be included as evidence of immunity	Birth before 1980 not evidence of immunity for HCP – no change
(VAR) No chance to provide laboratory evidence of immunity if commercial assays not sensitive	Language consistent with other ACIP guidance – no change

(VAR) Zostavax not addressed as substititute for VZV for older HCP	This would be new policy and thus no plan to change at this time *
(VAR) Clarify postexposure prophylaxis with vaccine or Ig, and time frame	Paragraph revised *
(VAR) VZIG no longer available as noted	Sentence revised *
(VAR) Incorrect statement in varicella section regarding time HCP without evidence immunity should be excluded from facility	Sentence revised *
Comment	Response
(Pertussis) Unclear description of cost model to vaccinate HCP	Sentence revised *
(Pertussis) Testing patient for pertussis after 7 days is extreme; clarify how to obtain specimens	Sentence revised *
(MCV) Polysaccharde meningococcal description missing from text	Will be added
(Typhoid) Typhoid VE information missing from text	Will be added
(Polio) Confusing statements regarding which persons should be vaccinated	Sentence revised *
Comment	Response
Incorrect indications noted for HPV vaccine (Cervarix), under 'Other Vaccines Recommended for Adults'	Sentence corrected to note correct indication (cervical cancer) *
Definition of furloughed employee should not include 'monetary issues', under 'Work Restrictions'	Sentence revised *
Mention cholera vaccine , under 'Catch-up and Travel Vaccination'	The two cholera vaccines are not licensed/ not available in US. Yellow Book does not recommend their use.
Incorrect route of injection for Typhoid and incorrect description of flu vaccines (Table 2)	Tables corrected *

In conclusion, Dr. Keyserling outlined some potential topics for discussion. The work group does want to document immunity to Hepatitis B for individuals who are exposed to blood and other body fluids. ACIP has not addressed this issue specifically, but healthcare facilities are now faced with making decisions. Twenty years ago, ACIP began recommending universal infant Hepatitis B vaccine and there was significant catch-up among young children. Currently, most people who are matriculating at professional schools have a childhood history of immunization but may not have documentation of their immunizations. Healthcare facilities and other settings seeking to document pre-exposure immunity may wish to evaluate HCP and trainees serologically to ensure they are protected against HepB. Options for managing these persons are presented on pages 10 and 11 of the document, with the following language:

> Increasing numbers of persons entering the healthcare workforce received hepatitis B vaccination as infants, children, or adolescents as a routine component of preventive care. Some of these persons will lack documentation of their vaccination and most will lack documentation of having responded to the vaccine. On entering healthcare training or the workforce, vaccine-induced anti-HBs might no longer be measurable because anti-HBs levels wane over time; however, most (≥90%) fully vaccinated children and adults are considered protected against hepatitis B regardless of when they were vaccinated or what their anti-HBs levels are.

Healthcare facilities and other settings (e.g., public safety and assisted living) seeking to document preexposure immunity status for newly hired HCP and trainees who have a history of vaccination but no documented serologic test result can manage these workers in one of the following ways, depending on time since initial vaccination and cost-related considerations.

Persons vaccinated more than 10 years previously are less likely to have measurable anti-HBs than those vaccinated more recently (*23,24*); determining seroprotection through prevaccination serologic testing is less likely to result in a positive anti-HBs test. These HCP and trainees can be vaccinated with a single booster dose of hepatitis B vaccine and tested for antibody status 1-2 months later. If a protective response is not achieved, the vaccination series should be completed with two more doses, and antibody response tested and documented.

Alternatively, persons vaccinated more than 10 years previously can be revaccinated with a 3-dose series of hepatitis B vaccine followed by serologic testing 1-2 months after administration of the last dose. Antibody response to the vaccine should be documented.

Persons vaccinated in the last 10 years can be tested for anti-HBs before receiving a booster dose or being revaccinated. Those found to have concentrations of ≥10 mIU/mL should be considered immune, and antibody response should be documented. HCP found to have anti-HBs <10mIU/mL can be managed like those who were vaccinated more than 5 years previously.

Another issue that the workgroup wants to bring up is that even though these recommendations will likely be updated at a shorter interval than 14 years, it will never be truly concurrent with recent ACIP recommendations. One possibility to address this would involve the creation of another immunization schedule. The infant, adolescent, and adult catch-up schedules are updated annually. The work group would like for ACIP to consider adding to this an annual HCP vaccination schedule modeled after the adult schedule.

Discussion Points

Dr. Baker indicated that the full document was distributed well in advance of this meeting to the full ACIP membership. With that in mind, she wondered if they could vote on the full document since much of what was included was previously approved.

Dr. Keyserling responded that the work group was seeking a vote on the entire document, not just the components pertaining to HepB.

It was not clear to Dr. Jenkins whether they were voting to approve the document with the corrections suggested, since there were many comments.

Dr. Baker clarified that the discussion earlier in the morning regarding pertussis had been voted on and approved, and that the document would be updated accordingly.

Dr. Chilton noted that the table of specific ACIP comments included an answer to question regarding the use of Zostavax® instead of varicella for HCP who do not have demonstrated immunity to varicella. It seemed to him it would be appropriate to allow Zostavax® to be given

instead of one of the two doses. Dr. Keyserling responded that the document states that Zostavax® is universally recommended for all adults over age 60, but they cannot make a specific recommendation for HCP without policy being generated. Dr. Jane Seward responded that for HCP, as stated in the varicella vaccine recommendation, those who lack evidence of immunity should receive two doses of varicella vaccine regardless of age. Zoster vaccine is recommended for prevention of herpes zoster in those aged 60 and above. Within those recommendations, the vaccines should not be interchanged, and wording is included to allow a dose of Zostavax® given in error to count as a dose. The CDC SMEs thought that it was appropriate to maintain the existing recommendations in terms of the HCP document.

Dr. Baker asked whether they were implying that the hospital should pay for Zostavax®. Dr. Seward replied that they were not. Zostavax® is not recommended for HCP based on their profession.

Dr. Coyne-Beasley expressed concern about the number of changes recommended. She just received the document that morning and did not have an opportunity to review the revisions, and wondered whether the vote should be postponed until the members had an opportunity to review the revisions. She felt that some of the changes were fairly substantial and personally would be more comfortable reviewing all of the changes before voting.

Dr. Baker clarified that the ACIP members received the document three to four weeks prior to the meeting, including a note from Dr. Smith instructing the members to review the document before the February 2011 ACIP meeting.

Dr. Coyne-Beasley replied that she did receive that version, but it did not include the latest revisions.

Dr. Shefer (SME) replied that there were no major issues. Most were simply word clarifications. Further changes will also be made once the document is submitted to *MMWR* due to the editing process.

Dr. Baker said that her understanding in reviewing the document was that there were word clarifications, but that there were no new recommendations that are not already part of ACIP statements. The exception was HepB serologic testing, which seemed to be new.

Dr. Shefer (SME) responded that there is no new policy. The only new component is that for those who were vaccinated many years ago, options are presented—not recommendations. She emphasized that these options could be removed if members were not comfortable with them, but questions do arise about this so it would be beneficial to include options. That is the only place in the document that information is introduced as options.

Dr. Coyne-Beasley maintained that there were some fairly significant changes in the document, some of which were content-related. For example, one change regarded whether the bivalent HPV vaccine protects against other anogenital cancers.

Dr. Shefer replied that this was a very minor edit.

Dr. Coyne-Beasley disagreed because initially the language implied that HPV vaccine covered multiple cancers when, in fact, it is licensed solely for one cancer. That is a fairly significant difference from the original document. It was an issue to her that some people may not have recognized that as a major change.

To address Dr. Coyne-Beasley's concerns, Dr. Pickering clarified that generally this document would contain nothing new that does not appear in current ACIP recommendations. If the HPV statement was wrong, it will be corrected. The document will have to agree with the current HPV statement. Often there are editorial changes. In the past, ACIP has indicated that if the editorial changes are straightforward and do not change the substance, ACIP allows the SMEs to make those changes. In addition, the hepatitis screening recommendations are guidelines. They are not part of the recommendations. If ACIP feels they should not be included, they can be removed. He requested that Dr. Elward comment on whether HICPAC would address any guidelines not included in the ACIP guidelines.

Regarding the options for managing HepB serologic testing in people with a remote history of immunization, Dr. Keitel pointed out that the option to do nothing was not included. This means that most people would now either need to receive a booster dose of vaccine and have their antibody tested or have a 3-dose series and have their antibody tested. That seemed like a major change.

Dr. Keyserling indicated that there had been numerous requests from CDC about how to handle this. The work group thought it probably needed to be fleshed out at a much higher level, assessing cost-effectiveness and other issues in the future. The problem is that people have to make decisions, which is why they equivocated in these options and used soft language.

Dr. Trudy Murphy clarified that this is not a recommendation. These are merely options. The most important issue for this discussion regarded pre-vaccine testing or at least documentation before administering additional dosage as a booster. It is fairly simple to do a cost-effectiveness analysis for this option. In the 2006 statement, a formula is included for determining this if screening people to determine their immunity before vaccinating them. Using that formula with the current cost of vaccine and testing, for those with a seroprevalence level in the 30% to 40% range or higher, it is cost-effective to screen before vaccinating. The facility would need to have some idea of the seroprevalence level in the population coming through. There are some preliminary data, but these have not been fleshed out enough to present. At least for those entering training currently, the levels are well above 75%. Therefore, it would be very cost-effective if the facility wished to pre-screen before vaccination. The way the document is worded, these are potential options for facilities seeking to have that information.

Dr. Elward (HICPAC) indicated that the HICPAC comments noted that this would be a practice change due to serologic screening for hepatitis B vaccination. HICPAC posed questions related to that and cost-effectiveness. There are no plans for HICPAC to include that at this time in the Healthcare Personnel Infection Control Guidelines. HICPAC instead deferred those issues to ACIP, given that the plan was for HICPAC not to address this at this time.

Dr. Murphy indicated that the Hepatitis Work Group could provide guidelines on this topic if they are not included in this statement.

Dr. Elward (HICPAC) added that this would be very helpful because questions do arise about this issue. It was a topic of discussion during last year's Society for Healthcare Epidemiology of

America meeting. As the cohort who was vaccinated at birth move into the workforce, people need to know how to handle them.

Dr. Turner (ACHA) expressed concern about the screening people who received the vaccine more than 10 years ago. At his school, the University of Virginia, all students entering nursing school and medical school were previously vaccinated, either as toddlers or in the 6th grade. Every fall, 400 new students arrive on his campus. Their hospital charges $116 for antibody testing and $71 per shot. The university would have to expend approximately $47,000 to screen all of these students. Given that greater than 90% of this population would be immune, he was troubled by inclusion of this option.

Dr. Baker reiterated that one option would be to remove the options from this document, and that Dr. Murphy assured them that guidance could be provided elsewhere.

Dr. Sawyer supported removing this option and addressing it elsewhere as an alternative. While it had been stated that this was not a recommendation, many will perceive it as such. In the context of the new evidence grading, this is yet a new category that ACIP has not yet discussed. He thought the Hepatitis Work Group would be the appropriate place to deliberate this.

Dr. Jenkins inquired as to whether there was a time-sensitive issue with regard to finalizing and publishing the document.

Dr. Shefer (SME) responded that it has been a while since the document was updated, and it would be nice to get it out. If presented again, minor issues would be covered that will likely be caught during the clearance and *MMWR* editing processes. However, there is no set schedule. Most of the feedback was positive, concordant, and involved minor revisions.

Dr. Baker emphasized that due to the nature of the document, it will go through an extensive clearance process and *MMWR* review.

Dr. Pickering stressed that while HICPAC was not going to be a co-author on the document, they have reviewed the document, offered input, and were comfortable with the revisions.

Dr. Elward (HICPAC) responded that this was correct, and that the only point of clarification pertained to the hepatitis B screening, serology, and cost-effectiveness options.

Dr. Temte said that part of the problem for him was that they began with the premise that increasing numbers of people will not have access to their old records. His facility has pretty good registry information, so he thought it was necessary to also consider people who do have good records in this age group and that provision of the 3-dose series is adequate.

Dr. Murphy replied that this document does not address people who do not have records. It addresses the issue of how to document the serologic response to vaccination. The work group took time to review past issues. Historically, because vaccination seroprotection rates were so high, people did not think it was necessary to conduct post-vaccination testing. However, they found the many healthcare professionals required repeated testing in the face of exposures. That is how the initial recommendations for post-vaccination testing arose. It simply became an

unmanageable problem to test people who were exposed. Post-vaccination testing is not a new recommendation.

Dr. Temte suggested removing the premise about people who are unable to find records, because that does not apply.

Dr. Murphy clarified that it is not a matter of records—it is documentation of serology response.

Dr. Turner (ACHA) suggested that one option to consider would be to recommend post-exposure testing on those who have been vaccinated in remote past. If they are negative, administer HepB vaccine, and then retest them after first vaccination. That is what SHEA currently recommends and is what his schools does.

Dr. Keyserling responded that this is included in the document in terms of post-exposure evaluation.

Motion: Updated Guidelines for Immunization of Healthcare Personnel

Dr. Sawyer made a motion to accept the document with the amendments as submitted and as further reviewed by the SMEs, with the removal of the hepatitis B post-vaccination and pre-revaccination screening options. Dr. Cieslak seconded the motion. The motion carried with 12 affirmative votes, 3 abstentions, and 0 negative votes.

Immunization Safety Office Update: Vaccines and Febrile Seizures

Introduction and Background

Frank DeStefano, MD, MPH
Immunization Safety Office
Division of Healthcare Quality Promotion,
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention (CDC)

Dr. DeStefano indicated that in January 2011, FDA posted on their website the finding a potential signal of an association between the 2010-2011 trivalent inactivated influenza vaccine (TIV) and febrile seizures observed in their data mining analyses for VAERS. The purpose of this session was to provide an update on the assessment of the signal for 2010-2011 TIV and febrile seizures reported from VAERS; and to share preliminary data on the possible contribution of other vaccines to a potential association between TIV and febrile seizures.

Febrile seizures are defined as seizures that occur in febrile children who do not have an intracranial infection, metabolic disturbance, or history of afebrile seizures[1,2]. They usually occur between the ages of 6 to 60 months, peak at age 14 to 18 months, and affect approximately 2% to 5% of young children in the United States[1]. The prognosis is generally excellent, with few sequelae[1,2], although about one-third of children who have a first febrile seizure will have recurrence[3]. Fever-reducing medications such as acetaminophen have not

been shown to prevent febrile seizures, but may decrease immune response to certain vaccines[1,4] [[1]AAP. Pediatrics. 2008;121:1281-6. [2]Johnston M. Nelson Textbook of Pediatrics. 2007. [3]Baulac et al. Lancet Neurol. 2004;3:421-30. [4]Prymula et al. Lancet. 2009;374:1339-50].

Fever following vaccination in young children is a common event. Fever is mentioned as a possible side-effect on most vaccine package inserts. For pneumococcal conjugate vaccines (PCV13/7)*, fever >100.4F following PCV13/7 is common in the first 7 days (up to 36% in some studies). High grade fevers of 104F or greater following PCV13 tend to be rare (<1%). For MMR/MMRV vaccines, fever tends to correlate with the high risk period for febrile seizures 5 to 12 days after dose 1*. The rate of medically attended fever following vaccination is low (6.4 per 1,000)† [*Information from product package inserts, ACIP recommendations and notices published in the MMWR, The Pink Book (11th Edition) † Lin et al. Vaccine. 2010;28:4169-74].

Fever following vaccination can potentially increase the risk for febrile seizures in children. The clinical presentation and prognosis of febrile seizures following vaccination are not different from febrile seizures from other causes. Whole-cell pertussis and measles-containing vaccines have been associated with an increased risk of febrile seizures.

The primary studies regarding the association between whole-cell pertussis vaccine and febrile seizures are those conducted by Farrington and Barlow. The Farrington case-only study was conducted in the U.K. and enrolled hospitalized children. The Barlow cohort study was conducted in four U.S. managed care organizations, with cases drawn predominantly from emergency department and hospital discharges. The Farrington study included 443 children less than one year of age with febrile seizures and the Barlow study included 679,942 children, of whom 340,386 received DTwP. The risk window for the Farrington study was 0 to 3 days / dose 3 and for the Barlow study was the day of vaccination and included all doses. Although the studies had different designs, the relative risk (95% CI) for the Farrington study was 3.0 (1.6-5.5) and for the Barlow study was 5.7 (2.0-16.4). The attributable risk for the Farrington study was 8/100,000 doses and for the Barlow study was 6-9/100,000 [Farrington et al. Lancet. 1995; 345:567-9; Barlow et al. N Engl J Med. 2001;345:656-61]. The attributable risk estimate is lower than for the combination measles-mumps-rubella vaccine (MMR) even though the relative risk is higher than for MMR. The explanation for that is that these are seizures occurring in children under one year of age when the underlying background incidence rate of febrile seizure is lower. When the relative risk is applied to the underlying lower risk, the attributable risk is lower.

DTaP was developed to have lower reactogenicity than the whole-cell pertussis vaccine and has been used in the U.S. since the mid 1990s. A study was conducted in the Vaccine Safety Datalink (VSD) by Huang et al that was published in 2010, which evaluated the risk of febrile seizures with the acellular pertussis vaccine. Two different designs were used to assess risk intervals of 0 to 3 days and the day of vaccination, with no increased risk found in either of those timeframes. The study also evaluated risk according to dose with similar results, including the fourth dose that is given in the second year of life.

The primary studies of febrile seizure and MMR were conducted by Farrington in 1995, Barlow in 2001, and Vestergaard in 2004. The source of data for the Farrington case-only study was children hospitalized in 5 districts in England. The study included 1,057 febrile seizure cases in children 12 to 24 months of age. The risk interval was 6 to 11 days, the relative risk was 3.0 (2.3-4.1), and the attributable risk was 38/100,000 doses. The source of data for the Barlow cohort study was 4 US managed care organizations. The population included 679,942 children of whom 137,457 received MMR. The risk interval was 8 to 14 days, the relative risk was 2.8

(1.4-5.6), and the attributable risk was 25-34/100,000. The source of data for the Vestergaard cohort study was Danish birth cohorts, with follow-up by linkage with national registries. The population was 537,171 children of whom 439,251 received MMR. The risk interval was 2 weeks, the relative risk was 2.8 (2.6-3.0), and the attributable risk was 156/100,000 [Farrington et al. Lancet. 1995; 345:567-9; Barlow et al. N Engl J Med. 2001;345:656-61; Vestergaard et al. JAMA. 2004;292:351-7].

Studies of MMR and varicella (V) vaccine and the combination measles-mumps-rubella-varicella (MMRV) vaccine have demonstrated that MMRV has a greater risk of febrile seizures compared to MMR+V administered simultaneously, but as separate injections. When MMR+V are given simultaneously, but as separate injections, the relative risk for the two primary studies has been approximately 2.0. MMRV has an attributable risk of approximately 40 additional febrile seizures per 100,000 doses administered compared to MMR+V administered separately. The two main studies of febrile seizures and MMRV vaccine were conducted by Jacobsen in 2009 and Klein in 2010. The source of data for the Jacobsen study was a large US managed care organization. This matched cohort population included 31,298 children who were given MMRV and 31,298 children who were given MMR+V. The risk interval was 5 to 12 days, the relative risk was 2.2 (1.04-4.6), and the attributable risk was 38/100,000 doses. The sources of data for the Klein study were 7 US managed care organizations. This cohort study included 83,107 children who received MMRV and 376,534 children who received MMR+V. The risk interval was 7 to 10 days, the relative risk was 2.0 (1.4-2.7), and the attributable risk was 43/100,000 [Jacobsen et al. Vaccine. 2009;27:4656-61; Klein et al. Pediatrics. 2010;126:e1-8].

Cases of febrile seizure have been reported following other recommended childhood vaccines, but an increased risk has not been established. Because febrile seizures are common, temporally-associated febrile seizures following vaccination would be expected. Prior to the 2010 Southern Hemisphere influenza vaccine manufactured by CSL used in Australia and New Zealand, increased risks of febrile seizure have not been established for recommended childhood vaccines other than whole-cell pertussis and measles-containing vaccines.

In April 2010, Australia suspended 2010 seasonal trivalent influenza vaccination for all children under the age of 5 years after reports of increased rates of febrile seizures following vaccination. Seizures were found to cluster on days 0 through 1 post-vaccination. A preliminary investigation was launched by the Australian Therapeutic Goods Administration in April 2010 [http://www.tga.gov.au/alerts/medicines/fluvaccine-report100702.htm]. Data suggested an increase in febrile seizures, primarily among children under 5 years of age in the 24-hour period after vaccination with 2010 Southern Hemisphere seasonal influenza vaccine made by CSL. Approximately 75% children who had febrile seizures received only CSL TIV, and they received no other vaccines in the same visit. No increased febrile seizure risk was documented with non-CSL influenza vaccine products. The Australians estimated that the rate was up to 9 per 1,000 for CSL in children under 5 years of age compared to an estimated less than 1 per 1,000 for Panvax, the CSL monovalent H1N1 influenza vaccine. They identified no biological, clinical, or epidemiological factors to explain these higher than expected rates of febrile seizures. Extensive testing of retention and field samples of vaccine has revealed no abnormalities. In the US, the CSL influenza vaccine (Afluria) is not recommended for children less than 9 years for the 2010-2011 influenza season due to these findings [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5931a4.htm]. No increased risk for febrile seizures was observed for 2009 H1N1 monovalent influenza vaccine.

Due to the Australian findings, enhanced monitoring was conducted for febrile seizures for 2010-2011 influenza vaccine in the VAERS database. This included periodic data mining of

VAERS data conducted by FDA. CDC searched the VAERS database broadly to identify possible cases of febrile seizure to increase sensitivity. Medical officers at CDC and FDA reviewed all seizure reports in children under 5 years of age who received influenza vaccine. Seizure monitoring was also incorporated into the VSD rapid cycle analysis (RCA) for influenza vaccine. VSD RCA was modified to include a more specific 0- to 1-day risk window based on 2010 Southern Hemisphere CSL findings. Previously, a 0- to 7-day risk window was used.

The FDA VAERS data mining signal was reported in January 2011. Data mining was conducted using a statistic called the Empirical Bayesian Geometric Mean (EBGM), which detects disproportional reporting in the VAERS database. In this case, this methodology intended to determine whether the proportion of febrile seizures reported after a TIV vaccine was greater than the proportion of febrile seizures following all other inactivated vaccines. A measure is used that is known as the lower limit of EB05. If that is greater than or equal to 2, the event-vaccine pair is considered to be a potential signal and is further evaluated. EBGMs do not demonstrate causality and VAERS generally cannot be used to establish a causal association. FDA VAERS data mining signaled for Fluzone® and febrile seizure in December 2010, with an EB05 >2, with no stratification of the database according to age. The signal strengthened in the 0-18 months age stratum, and persisted into January 2011.

A CDC / FDA clinical review was conducted of VAERS febrile seizure reports after 2010-2011 TIV. There were 53 VAERS reports of verified febrile seizure in children less than 5 years of after any influenza vaccine (reports received by 12/13/10). Of these, 42 were in children 6 through23 months of age following Fluzone® TIV and 10 (24%) were classified as serious (report coded as serious when the following outcomes occurred: death, hospitalization, prolongation of hospitalization, life-threatening illness, persistent or significant disability, congenital anomaly; other reports coded as non-serious). Most of the children were hospitalized overnight for observation. There were no deaths—all children recovered. The majority (86%) had onset in 0-1 day window, and 27 of 42 (64%) received concomitant vaccines. There were no patterns identified with lot numbers or geographic distribution of the cases.

FDA and CDC announcements on Fluzone® and febrile seizures were posted on the FDA website on January 20, 2011 and on the VAERS website the next day. The links are as follows:

- "FDA and CDC Update on Fluzone Influenza Vaccine and VAERS Reports of Febrile Seizures in Children"

  http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm240037.htm

- "UPDATE: Vaccine Adverse Event Reporting System (VAERS) Data on Febrile Seizures after Vaccination with Fluzone®, a 2010-2011 Trivalent Inactivated Vaccine, in Children"

  http://vaers.hhs.gov/resources/VAERSupdate_FebrileSeizures_Children.pdf

During this same period, VSD had also been monitoring for seizures following 2010-2011 vaccines using RCA. The preliminary VSD results were presented by Dr. Grace Lee.

Febrile Seizures in the Vaccine Safety Data Link

Grace Lee, MD, MPH on behalf of the Influenza and Pneumococcal Conjugate Vaccine RCA Working Groups, Harvard Pilgrim Health Care Institute, Southern California Kaiser Permanente, Centers for Disease Control and Prevention

Dr. Lee emphasized that all data in the current season are preliminary and are expected to change as additional data become available. She explained that the VSD is a collaboration between CDC and 10 managed care organizations (e.g., e.g., Group Health Cooperative, Harvard Pilgrim, Health Partners, Kaiser Permanente Colorado, Kaiser Permanente Georgia, Kaiser Permanente Hawaii, Marshfield Clinic, Northern California Kaiser Permanente, Northwest Kaiser Permanente, and Southern California Kaiser Permanente). There are currently data on approximately 9.2 million persons, 2.2 million children and 7 million adults, and representing approximately 3% of the U.S. population. VSD RCA conducts near real-time surveillance to monitor vaccine safety, particularly for newer vaccines.

Of the 10 VSD sites across the country, 8 are currently providing data for surveillance. Each VSD site updates person-level files on a weekly basis that include demographics; electronic vaccine records; and in-patient, out-patient, and emergency department visit dates and diagnosis codes. These are all linked on a weekly basis by site-specific study IDs. After the 8 participating VSD sites update their person-level files weekly on vaccine exposure and outcomes, CDC and the VSD Data Coordinating Center for each study submit programs to VSD sites weekly to provide aggregate counts of vaccines and outcomes without person-level identifiers. The person-level data remains at each of the VSD sites. In order to preserve patient confidentiality, the only information that crosses the firewall is aggregate counts. Sequential analyses are then conducted on these aggregated data by Harvard for influenza RCA and SCK for pneumococcal conjugate RCA.

For the febrile seizure investigation in VSD, Dr. Lee described prospective surveillance for febrile seizures in influenza RCA, the signal identified in the system, the signal evaluation in the influenza RCA study, prospective surveillance for febrile seizures in for the PCV13 RCA study, and results from the joint signal evaluation in influenza and pneumococcal RCA studies.

With regard to prospective surveillance for febrile seizures in influenza RCA during the 2010-2011 season, the lead site was Harvard Pilgrim Health Care Institute. The seizure definition in the influenza RCA focused on two age groups: 6 months through 4 years and 5 through 17 years. The ICD-9 codes used were those with the prefix 780.3 (convulsions and seizures, referred to as 780.3*), and only seizures in the in-patient or emergency department setting were included. A risk window of 0 to 1 days was used based on the findings from Australia, and a comparison window of 14 to 15 days after vaccination was used. Also required was that the seizures be the first diagnosed within a 6-month period in order to improve specificity and avoid including non-incident case.

Two study designs were used for the seizures outcome. The primary and preferred approach was a self-controlled design, in which the risk of febrile seizures in a 0- to 1-day window was compared to a subsequent comparison window in the same individuals at 14 to 15 days post-vaccination. Because this approach is self-controlled, fixed confounders such as co-morbidities are implicitly adjusted for. A current versus historical approach was also used to compare the risk of febrile seizures in the 0- to 1-day window among current vaccines to the risk of febrile seizures in a historical cohort of TIV vaccinees from the 2005-2006 through the 2009-2010 season. This alternative approach had greater power to signal, but also has its own limitation. For example, the characteristics of the vaccinees in the current cohort may be different from the characteristics of the vaccinees in the historical cohorts. Because of the increased scrutiny of

febrile seizures, both approaches were used in weekly sequential analyses, though the self-controlled design was the primary approach.

The weekly sequential analyses for influenza RCA uses Maximized Sequential Probability Ratio Testing (maxSPRT). This was developed by Martin Kulldorff, the biostatistician at Harvard Pilgrim [Kulldorff M et al. Available at: http://www.populationmedicine.org; Sequential Analysis, in press]. MaxSPRT uses a test statistic called the log likelihood ratio (LLR) and the null hypothesis is rejected if the LLR reaches the critical value. In the real-time surveillance, the investigators had to adjust for data lags in order to avoid biasing to the null. For the self-controlled analyses, cases observed in the risk window were not included until they were certain that greater than 95% of data were available in the subsequent comparison window. For the current versus historical analyses, expected counts were adjusted accordingly for site and setting-specific data lags for comparison in order to compare the observed counts in the risk window fairly to the expected counts.

In the near real-time surveillance, the investigators focused on first dose TIV only. The vast majority of vaccines were administered in October and November 2010 in the study population. In terms of the results of the current versus historical RCA for 6- through 59 months of age, the critical value threshold was exceeded during the week of November 14, 2010. The risk ratio settled at just above 2.0 at the end of January 2011. In terms of the results for the self-controlled RCA in ages 6 through 59 months, no signal was observed with this approach the week of November 14, 2010. However, as the season progressed there was a signal the week of December 26, 2010. The risk ratio using the self-controlled approach was just below 4.0 by the week of January 30, 2011.

When the current versus historical analysis signaled in November, a signal evaluation was initiated beginning with a chart review to confirm that the cases identified by ICD-9 codes were true cases. For cases identified in the automated data or electronic data through December 25, 2010, each site reviewed cases in the risk and comparison windows in the current season for 6 through 59 month old children. Of the 20 cases evaluated in total, 16 (80%) were chart-confirmed as febrile seizures. This chart confirmation rate was similar to that found in previous published VSD studies, including confirmation rates of 82% in a study of PCV-7 (Shui et al) and 94% in a study of MMRV (Klein et al). The positive predictive value of ICD-9 codes for seizures in the outpatient setting (Shui) has been shown to be much lower at 12%, thus confirming the choice of only including seizures in the in-patient or emergency department settings.

During the influenza RCA surveillance, a 14 to 15 comparison window was utilized. However, as part of the signal evaluation a longer comparison window of 14 to 20 days was used to increase the sample size and precision of background rates. Before this change was made, an evaluation of day-of-the-week effects for seizures was performed to ensure that if the risk window occurred on a particular day of the week, it could be compared to a window that included events for the entire week. This evaluation showed that the day of the week effects were minimal. Results using the self-controlled design showed the same relative risk of 3.8 for both the 14-15 day and 14-20 day comparison periods. Therefore the subsequent signal evaluation used a 14-20-day comparison window.

Since the febrile seizures signal following TIV in the current season was based on a 0- to 1-day risk window, which was a newly defined risk window due to the Australian seizure signal, the following question was raised: If this definition was applied to prior seasons, would we also have found an elevated risk for febrile seizures in a 0- to 1-day risk versus a 14- to 20-day comparison windows? In a self-controlled designed across multiple seasons for children 6

through 59 months of age, the relative risk of febrile seizures in the prior seasons (2005-2006 through 2009-2010) for the TIV vaccine varied from year-to-year, with a pooled relative risk over that time period of 1.5. However, the relative risk of febrile seizures in the 2010-2011 season is notably higher (RR 3.8) than in prior seasons for TIV or for H1N1 MIV in the 2009-2010 season (RR 0.8).

Consideration then had to be given to why the findings in the current season for TIV differed from prior seasons. To explore this further, seizure cases in the current season were examined more closely. In a self-controlled design stratified by age and gender using ICD9 data on data available through January 29, 2011 , the relative risk following TIV was higher for 6 through 23 month old children than for 24 through 59 month olds, and higher for males than females. Next, the febrile seizure case evaluation was focused on cases (N=20) in the 6 to 23 month old age group and considered what other vaccines were received at the same visit. Among febrile seizure cases in children 6 through 23 months, 17 of the 20 (85%) had received concomitant vaccines. The several unique combinations of vaccines received by the 20 cases are shown in the following table:

Concomitant Vaccines among Seizure Cases 6-23 months (N=20), 2010-11

Vaccines given on same day	N = 20
TIV + PCV13 + MMR + HepA + Hib + DTaP	1
TIV + PCV13 + Hib + Rota + DTaP-HepB-IPV	3
TIV + PCV13 + MMR + Var + DTaP	2
TIV + PCV13 + MMR + Var + HepA	1
TIV + PCV13 + HepA + Var + DTaP	2
TIV + PCV13 + MMR + Hib + DTaP	1
TIV + MMR + Var + HepA + DTaP	2
TIV + PCV13 + HepA + Hib + DTaP	1
TIV + PCV13 + Hib + DTaP-HepB-IPV	1
TIV + PCV13 + Hib	1
TIV + PCV 13	2
TIV only	3

For the 20 seizure cases, the majority concomitantly received either PCV13 (75%) and / or DTaP-containing vaccines (65%). Many received PCV13 and DTaP-containing vaccines simultaneously, and only 15% of seizure cases received TIV only (e.g., no concomitant vaccines given). In contrast, among all the 77,338 TIV vaccinees, fewer TIV vaccine recipients concomitantly received PCV13 (36%) and / or DTaP-containing vaccines (34%); whereas, 44% received TIV only (Table below). Of note, many children received PCV13 and DTaP simultaneously with TIV, but only PCV13 was new this season.

Concomitant Vaccines among Cases (N=20) and Vaccinees 6-23 months (N=77,338), 2010-11

Concomitant vaccines	Seizure Cases (N=20)	TIV Vaccinees (N=77,338)
PCV13*	15 (75%)	27,648 (36%)
DTaP* (4 cases received combo vaccines)	13 (65%)	26,420 (34%)
Hib	8 (40%)	23,607 (31%)
MMR	7 (35%)	11,470 (15%)
Varicella	7 (35%)	11,191 (15%)
Hep A	7 (35%)	15,612 (20%)
IPV (4 cases received combo vaccines)	4 (20%)	16,339 (21%)
Hep B (4 cases received combo vaccines)	4 (20%)	13,698 (18%)
Rotavirus	3 (15%)	10,975 (14%)
None (TIV only)	3 (15%)	33,973 (44%)

•11 seizure cases and 20,114 TIV vaccinees received PCV13 +DTaP;
•all concomitant vaccines were +/- others

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When the self-controlled design was stratified by receipt of concomitant PCV13 vaccine among children 6 to 23 months of age, it was observed that children who received influenza plus PCV13 (+/- other vaccines) had a greater increase in risk for febrile seizures compared to children who received influenza (+/- other vaccines) without concomitant PCV13. Next, the investigators asked their VSD colleagues leading the PCV13 RCA in Southern California Kaiser what they were finding in their on-going PCV13 RCA study in terms of whether PCV13 vaccinees had a higher risk of febrile seizures. Southern California Kaiser is prospectively conducting surveillance for febrile seizures following PCV13 vaccines in 1 to 23 month old children. In the PCV13 RCA study, the seizure definition uses a 0- to 7-day risk window with similar ICD-9 codes, and compares PCV13 vaccinees in the current season to PCV7 vaccinees in historical season. No signal was identified in this study.

A joint signal evaluation was then conducted by Harvard Pilgrim Health Care Institute, Southern California Kaiser, and CDC for influenza and PCV13 vaccines. The study rationale was to further evaluate the potential contribution of PCV13 to the influenza seizures signal. Harvard Pilgrim Health Care Institute collaborated with its colleagues at Southern California Kaiser and CDC to provide comparable estimates of risk for influenza (+/- other vaccines), influenza + PCV13 (+/- other vaccines), and PCV13 (+/- other vaccines). A self-controlled study design was used and the seizures definition was harmonized for influenza and PCV13 protocols. The study age groups included: 6 through 11 months of age, 12 through 23 months of age, and 24 through 59 months of age. Similar ICD9 codes (780.3*) were used for convulsions or seizures, the setting were in-patient or emergency department, the risk window was 0 to 1 day, the comparison window was 14 to 20 days, and a first adverse event in 42 days criterion was applied to increase sensitivity. In order to provide an estimate of the public health impact, the attributable risk was estimated from results of the self-controlled design.

Among 6 through 11 month old children, from August 2005 through April 2010 vaccines administered included 264,327 doses of PCV7; 90,689 doses of TIV + PCV7; and 103,303 doses of TIV. From May 2010 through January 2011 vaccines administered included 46,842 doses of PCV13; 13,390 doses of TIV+ PCV13; and 15,581 doses of TIV. Other vaccines may have been given concomitantly, including DTaP. A small excess risk was observed for seizures following TIV + PCV13 vaccine in the current season with an attributable risk of 19 per 100,000 doses, which was not statistically significant as evidenced by the confidence interval that crossed zero.

Among 12 through 23 month old children, from August 2005 through April 2010 vaccines administered included 240,088 doses of PCV7; 62,457 doses of TIV + PCV7; and 210,069 doses of TIV. From May 2010 through January 2011 vaccines administered included 58,023 doses of PCV13; 14,258 doses of TIV+ PCV13; and 34,109 doses of TIV. The excess risk of febrile seizures in the TIV + PCV13 (+/- other vaccines) is significantly elevated at 61 per 100,000 doses (95% confidence interval: +13 to +109 per 100,000 doses).

Among 24 through 59 month old children, no evidence was observed for excess risk in any of the vaccine groups. In summary, the largest excess risk was noted for TIV + PCV13 (+/- other non-TIV, non-PCV vaccines) for 12 to 23 month old children (attributable risk 61, 95% CI: +13 to +109 per 100,000 doses or approximately 1 in 1640 vaccines).

In conclusion, Dr. Lee recapped that a new increase in risk for febrile seizures was identified in the 2010-2011 season following influenza vaccination. The relative risk was substantially different from prior seasons. Upon review of seizure cases, concomitant PCV13 (and DTaP) vaccination was frequently noted. PCV13 vaccine became available for use in April 2010. No excess risk was observed for TIV (+/- other non-TIV, non-PCV vaccines) or PCV13 vaccines (+/- other non-TIV, non-PCV vaccines). Significant excess risk for febrile seizures on days 0 to 1 following vaccination was noted for TIV + PCV13 (+/- other non-TIV, non-PCV vaccines) for 12 through 23 month old children. However, contributions by other concomitant vaccines cannot be ruled out. The attributable risk of 61 per 100,000 doses can be compared to excess risk of febrile seizures of 43 per 100,000 doses for MMRV versus MMR + V.

Several limitations remain. A chart confirmation rate of approximately 80% was assumed among in-patient and emergency department cases; however, this is believed to be a reasonable assumption given the multiple prior studies in VSD using a similar definition. Out-patient visits for seizures on days 0 to 1 were not included due to the low positive predictive value noted for seizures in out-patient settings ranging from 2% to 20% in prior studies. The contribution of other concomitant vaccines (e.g., DTaP given concomitantly with TIV and PCV13) or other time-varying confounders needs further exploration.

Wrap-Up

Frank DeStefano, MD, MPH
Immunization Safety Office
Division of Healthcare Quality Promotion,
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention (CDC)

Dr. DeStefano pointed out that fever following vaccination in young children is a common event. Fever following vaccination can potentially increase the risk for febrile seizures in children. Whole-cell pertussis vaccines, measles-containing vaccines, and the 2010 Southern Hemisphere CSL TIV have been associated with an increased risk of febrile seizures. Febrile seizures in general and following vaccination have a good prognosis, but are still frightening to parents and caregivers. The preliminary results from the VSD suggest that 2010-2011 TIV vaccine used in the US is not associated with a significantly increased risk of febrile seizure in children 6 through 23 months of age unless administered concomitantly with PCV13. The possible contribution from other concomitantly administered vaccines remains to be determined. Preliminary analyses indicate that the risk of febrile seizure for concomitant TIV and PCV13 vaccination (+/- other vaccines) is likely comparable in magnitude to the risk after MMRV compared to MMR + V administered separately.

In terms of the next steps, Dr. DeStefano emphasized that this is a work in progress and these are preliminary results. Influenza vaccine safety will continue to be monitored until the end of the influenza season, at which time and end-of-season analysis will be conducted. He would like to see tighter confidence intervals; however, because it was unlikely that many more cases would be accumulated before the end of April, he did not believe the results would change appreciably. Chart reviews will be conducted on febrile cases in the VSD investigation and attributable risk estimates will be updated based on those chart reviews. The possible role of other concomitant vaccines will continue to be assessed as well. ACIP work groups will continue to be apprised of new information as it becomes available. The General Recommendations Work Group will consider additional information on febrile seizures following vaccination in coordination with other ACIP work groups as appropriate.

Discussion Points

Dr. Marcy said he would make the same speech he made after the MMRV decision. If going by the numbers of 1 in 1600, and knowing that busy pediatric practices see about 200 neonates per year, there will be 1 additional seizure every 8 years. From 48 to 90 febrile seizures will be observed due to other causes. For family physicians, a third of whose practice is children, there will be 1 every 24 years. The relative risk and attributable risk, as noted, are completely different. For the practitioner, it is almost negligible.

Dr. Sawyer reported that the MMRV Work Group engaged in extensive discussion and some disagreement about what the policy implications of relative risks on this order of febrile seizures should be. This resulted in encouragement for providers to consider separating those vaccines. He cautioned ACIP not to make a similar recommendation with regard to separation of PCV13 and influenza vaccine unless a careful analysis is done of the implications of that, including missed doses of PCV13. He would hate to see them challenge the coverage rates for PCV13 over the concern of a slight increased risk of febrile seizures.

Dr. Temte asked whether medically attended fevers were assessed for the CSL vaccines and PCV13.

Dr. DeStefano responded that PCV13 was not assessed yet this year in terms of medically attended fever as was done for MMRV for which the medically attended fever graph that almost superimposed on the febrile seizure graph. It is known from the pre-licensure trials data that 30% to 40% of children who receives PCV7 or PCV13 experienced low grade fever and high grade fever was rare. TIV vaccines, in general, tend to have much lower fever occurrence. In a few studies, it has not even been above placebo occurrences. A randomized double-blind controlled trial of simultaneous TIV and PCV7 vaccination conducted by Jansen in 2008 found that fever $\geq$38C for at least one day was more common in TIV+PCV7 compared to HepB+placebo, but not compared to TIV+placebo. This study was comprised of children 18 through 72 months old selected by general practitioners in and around Utrecht, Netherlands; used a risk window of 7 days; and compared 194 TIV+PCV7, 183 TIV + placebo, and 19 Hep B + placebo [Jansen et al. Pediatr Allergy Immunol. 2008;19:552-8].

When PCV13 was considered alone or together with other vaccines, Dr. Baker wondered if it was for any dose.

Dr. Lee responded that they did not have the ability to capture that in real-time per se. In most of the 12 through 23 month olds, it should be their 4th dose. It is possible that some of them are caught in the transition between PCV7 and PCV13.

Dr. Cieslak asked whether receipt of TIV vaccine was more likely to cause or prevent febrile seizure, noting that fever is present in 20% of influenza cases.

Dr. Lee responded that they did not have rates of fever following influenza-like illness in the VSD, nor was she aware of real-time surveillance of fevers following influenza-like infections.

Dr. Englund reported that in a 2001 paper in *Pediatrics* from Hong Kong, fever was prospectively assessed in a hospital and it was found that during the influenza season, 40% to 50% of all children admitted with febrile seizures were influenza-positive based on lab results. Throughout the year, 20% to 30% of all febrile seizure admissions were due to influenza. It would be interesting from the VSD perspective to know how many febrile seizures are prevented due to administration of the influenza vaccine.

While he understood that the selection of ICD-9 codes 780.3* was to cast a wide net and then narrow it down, Dr. Gorman (NIH) inquired as to whether 780.31, which is specific for febrile seizures, would have made any methodological data more predictive (e.g., more likely to be above 12%).

Dr. Lee replied that Dr. Shui specifically assessed this in her paper for the ambulatory setting. The problem is the Day 0 seizures code picks up a lot of cases of children who had a prior or existing seizure disorder who happened to be vaccinated on that day, which is the greatest reason for a problem with the positive predictive value.

Thinking about the end-of-season analyses, Dr. Gorman inquired as to whether Dr. Lee could give them any sense of how many of the RCAs that have had a signal of this magnitude and this duration are overturned by end-of-season analyses.

Dr. Lee said she thought influenza was one of the more difficult issues to study because of the confounding by indication, which is why they tend to utilize the self-control design. That said, there are still some limitations in that influenza is seasonal, vaccination is seasonal, and febrile seizures can also be seasonal. There always remains the uncertainty of potential residual confounding. Even with the observational data they have, she thinks they have done the best they can do for the moment given the preliminary data.

Dr. Kimberlin requested clarification about how this all transpired. Beginning with the signal in Australia through the studies in the U.S., it seemed that there was a self-fulfilling prophecy.

Dr. Lee responded that while VAERS data relies on passive reporting, the VSD is comprised of healthcare encounter data. In the out-patient, there could potentially be some bias, but in the emergency department and in-patient setting it improves the specificity of the febrile seizures definition. Healthcare encounter data is less susceptible to reporting bias per se because people are presenting for healthcare encounters and it has nothing to do with enhanced reporting.

Robert Malone (RW Malone MD LLC) said that in speaking with industry colleagues, he had heard the speculation that various serotypes may be more reactogenic. He wondered whether it might be possible to examine that variable, and also rather than focusing just on fever, to assess other variables or symptoms associated with reactogenicity as a function of serotype over time for influenza.

Dr. Lee replied that one of the first questions that came to mind was whether febrile seizure was related to the H1N1 component of the vaccine. What they found reassuring was that for historical TIV and the 2009-2010 monovalent inactivated vaccine, the relative risk elevation was very different this season than in prior seasons for H1N1 or for a variety of other TIV vaccines. That said, it may be different next season.

Dr. Baker summarized that no change was anticipated in the recommendations based on the data available; however, more data will be forthcoming later in 2011.

Dr. Zahn (NACCHO) pointed out that this was an extraordinary database of children being vaccinated and at least some medical events. He wondered if real-time efficacy of vaccine and uptake within that population could be determined from these data.

Dr. DeStefano responded that uptake of vaccine can be determined pretty much in real-time, at least in these managed care organizations. There are on-going projects that are sponsored by different sources to try to assess effectiveness using these types of data.

Influenza

Introduction

Wendy Keitel, MD, Chair
Chair, ACIP Influenza Work Group

Dr. Keitel reported that over the last few months, the Influenza Work Group continued with conference calls every other week. One issue addressed during this period was antiviral agents for the treatment and chemoprophylaxis of influenza, about which the work group members made some very thoughtful and important contributions. The *Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza* statement was published in the *MMWR* following final review by the workgroup members [*MMWR*, January 21, 2011, Vol. 60(RR-1)]. The work group has been briefed by manufacturers with data for several products that are in the development pipeline. It is likely that during the June or October 2011 meeting, some of these data will be presented to the full ACIP membership. The work group is beginning discussions prompted by recent statements and past literature regarding management of individuals who have egg hypersensitivity. This will possibly require a vote during the June 2011 ACIP meeting. During this session, updates will be presented on influenza activity, influenza vaccine distribution and coverage, statement on use of antivirals, and influenza vaccine and egg allergies.

Influenza Activity Update

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

Dr. Grohskopf presented a brief overview of international influenza activity for this season based on data from WHO surveillance reports. For the Northern Hemisphere for the current year temperate countries, in Europe activity is generally increasing (44% of sentinel specimens were influenza-positive in Week 6). Of these, 48% of sentinel samples are influenza B and 44% are 2009 H1N1. Canadian activity is currently decreasing from an earlier peak, and most viruses are influenza A(H3N2). North Africa and Middle East activity has mostly already peaked and is currently a mixture of 2009 H1N1 and influenza B. For Asia, within China, activity is decreasing from an earlier peak, and there is currently a transition from influenza A(H3N2) to 2009 H1N1. The rest of the region is mostly past peak of activity. For tropical countries in Asia, Singapore and Hong Kong, respiratory disease activity is above epidemic threshold with mostly 2009 H1N1. In South China, there is increasing activity and mostly 2009 H1N1, with 94% of surveilled specimens influenza-positive in Week 5. In the Tropical Americas there has been low activity. Sub-Saharan Africa has had mostly low activity, although there has been some increased activity in Madagascar. Within the Southern Hemisphere temperate climate countries, there has been little activity since the end of winter influenza season in that part of the globe. In general for specimens that have been tested, particularly with regard to H3 viruses, there is a reasonably good match with the vaccine strains that were selected for this season.

Of 644 US viruses antigenically characterized at CDC since October 1, 2010, essentially since the beginning of the season, 85 (13%) were characterized as Influenza A(H1N1). Of these, 100% were A/California/7/2009-like, which is the A(H1) component of the current trivalent seasonal vaccine. 348 (54%) were characterized as Influenza A(H3N2), of which 345 (99%) were A/Perth/16/2009-like, which is also a component of the current seasonal vaccine. 211 (33%) were characterized as Influenza B of which the vast majority (199; 94%) were Victoria lineage. Most of these (198, 99%) were further characterized as B/Brisbane/60/2008-like, which is consistent with the current vaccine selection, and 12 (6%) were further characterized as Yamagata lineage. With regard to antiviral resistant testing, of the specimens tested in the US there continues to be high-level resistance to adamantanes that persists among Influenza A isolates. A(H1N1), A(H3N2), and B virus isolates tested remain susceptible to neuraminidase inhibitors (oseltamivir or zanamivir).

During the week of October 16, 2010 (Week 41, 2010), close to the beginning of the influenza season, there was not a great deal of influenza activity as would be expected. Approximately half of states reported no activity and the other half reported sporadic activity. By the week ending December 4, 2010 (Week 48, 2010), there was an appreciable increase in activity. Almost all states were reporting at least sporadic activity, 12 reported local activity, and 3 states reported regional activity (e.g., Georgia, Kentucky, and Virginia). For the week ending February 12, 2011 (Week 6 of 2011), the vast majority of states reported widespread activity or at the very least, regional influenza activity. The percentage of visits for influenza-like illness (ILI) reported by the US Outpatient Influenza-like Illness Surveillance Network (ILINet) is summarized weekly. At Week 6, the portion of outpatient visits that were reported to be due to ILI was somewhat above the national baseline of 2.5%.

The viruses associated with characteristics of influenza-positive tests results are reported to CDC by US WHO / NREVSS Collaborating Laboratories. These laboratories receive a large

number of samples from the US. Of the 9448 specimens tested during Week 6, 3306 were influenza-positive. There was a fairly good mix of the different strain, with 21% B strains and 40% H3 strains. An increase was observed in the proportion of H1N1 strains over the course of time, particularly during the period from December through January. For the week ending 02/12/2011, surveillance data for pneumonia and influenza mortality collected by the 122 U.S. Cities Surveillance System reflected mortality of 8% thought to be due to pneumonia and influenza to be 8.5%, which is slightly above the epidemic threshold for that period of time of 8%. Confirmed influenza-associated pediatric deaths for children under 18 years of age has been a reportable event since 2004. For the current 2010-2011 season, a total of 35 pediatric deaths have been reported. Of those, approximately one-third (n=13) were due to B viruses, approximately 25% (n=9) were H3, approximately 20% (n=7) were due to H1N1, and the remaining 6 were not further characterized.

In summary, key points are that Influenza A(H3N2), A(H1N1), and B strains continue to co-circulate in the US and globally. Recently characterized strains appear to be well-matched to the recommended 2010-2011 seasonal vaccine. Recently circulating viruses remain susceptible to neuraminidase inhibitors. In the US, influenza activity remains high in recent weeks. There has been an increase in the proportion of influenza A viruses identified as A(H1N1) since the beginning of the US season.

Discussion Points

Dr. Meissner requested clarity regarding whether the 644 isolates that were typed was the total received by CDC or a representative sample of the total, and whether these reflected what was occurring everywhere in the US.

Dr. Grohskopf responded that her understanding was that this was a nationally representative sample.

Dr. Bresee (SME) confirmed that in effect, this was a nationally representative sample. It clearly represents all of the viruses that are tested positive. CDC receives a systematic sample from states and characterizes all of those eventually. There is a lag in what the agency can characterize in the lab, but all that are received are ultimately characterized. Antiviral resistance testing is done one those samples as well. Every state is meant to send some samples every two weeks or every month, depending upon the state, and the amount CDC receives is meant to be proportional to the size of the state.

Mid-Season Influenza Vaccination Coverage

Cindy Weinbaum, MD, MPH
National Center for Immunization & Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Weinbaum reported that approximately 163 million doses of influenza vaccine were distributed in the US this season, with the cumulative number of doses distributed by month rising higher faster than in any previous season [Biologics data]. About 17% of the total number of doses were in the federal and state budgets. Based on weekly surveys conducted throughout the season, by the end of January 2010, estimated vaccine coverage among children 6 months to 17 years of age was approximately 40%; whereas, this year it was about 45% [NIS sample frame, CDC unpublished data]. Billing claims from physician offices, which

are utilized to assess trends, were higher this season than for the last two seasons [SDI, unpublished data used by permission]. The number of claims to Medicare Part A and B were also higher this season than in previous seasons [CMS, unpublished data].

Rapid Flu Surveys were conducted in a two-week time period at the beginning of November 2010. The surveys assessed "already vaccinated" and "already vaccinated + definitely intend to be vaccinated" because last year these two combined matched the total vaccinated by the end of the season. The intent was to repeat the survey at the end of March 2011 in order to have a better estimate of coverage. The overall estimate for vaccine coverage in mid-November 2010 was approximately 33%, with about 43% already vaccinated and the remainder definitely intend to be vaccinated. For adults over the age of 65, these percentages were considerably higher than in past years at 64% already vaccinated and 75% already vaccinated + definitely intend to be vaccinated. By race and ethnicity, there is still a difference between Hispanic, Non-Hispanic White, and Non-Hispanic Black populations. The following table reflects the totals during the first two weeks of November 2010:

Group	Already Vaccinated % (95% CI)	Already Vaccinated + Definitely Intend % (95% CI)
Overall	32.8 ± 2.4	42.6 ± 2.6
By age group		
All children (6m-17years)	30.6 ± 5.0	42.9 ± 5.3
All adults	33.5 ± 2.5	42.5 ± 2.7
≥ 65 years	64.3 ± 4.8	74.0 ± 4.4
By race/ethnicity		
Hispanic	25.4 ± 6.3	35.9 ± 6.6
Non-Hispanic, White only	35.8 ± 2.8	45.3 ± 3.0
Non-Hispanic, Black only	27.1 ± 7.2	35.7 ± 8.0

As reported in the Rapid Flu Survey this season, for children the predominant locations for receipt of vaccination include doctors' offices, clinics, and hospitals. For adults, the distribution of places of vaccination is more varied with about 20% reporting workplace vaccination and a total of about 20% who were vaccinated in a pharmacy, drugstore, super market, or other type of retail establishment [http://www.cdc.gov/flu/pdf/vaccination/rapidflusurvey.pdf].

To estimate influenza vaccination coverage among pregnant women in the US during the 2010-2011 influenza season, an internet panel survey was conducted via internet in mid-November 2010. By that time, 45% of pregnant women had already received influenza vaccination. Overall, 49% of pregnant women were or definitely intend to be vaccinated this influenza season. The most common place of vaccination for pregnant women included doctor's office (57%), pharmacy or drugstore (12%), workplace (8%), and hospital (7%) [http://www.cdc.gov/flu/pdf/accination/DingInternetPanelSurveyPregnantWomen.pdf].

The same type of internet panel survey was conducted among approximately 2000 healthcare personnel in the US in mid-November 2010. By mid-November 2010, 56% of healthcare personnel received influenza vaccination. Overall, 62% of healthcare personnel were already or definitely intended to be vaccinated this influenza season. The most common place of vaccination was at work (79%). Coverage varied by work setting, with 40% among healthcare personnel working in settings other than hospitals, physician's offices, or long-term care facilities and 68% among healthcare personnel working in hospitals. Coverage also varied by occupation, with 47% among medical technicians, assistants, and aides and 78% among physicians, dentists, nurse practitioners, and PA.

To summarize, Dr. Weinbaum combined a number of sources of data in order to reflect the "big picture" of coverage before the pandemic year, during the pandemic year, and so far this season. This is reflected in the following table:

Group	2008-09 (%)	2009-10 (%)	2010-11* (%)
Overall	[1] 33	[3] 41	[6] 43
6 mos-17 years	[1] 29	[3] 44	[7] 45-48
≥ 65 years	[1] 66	[3] 70	[6] 74
Pregnant women	[2] 6-20	[4] 42-51	[6] 49
Healthcare personnel	[1] 53	[5] 62	[6] 62

1. NHIS estimates, online at: http://www.cdc.gov/vaccines/stats-surv/nhis/2009-nhis.htm
2. MMWR , July 29, 2010 / 59(Early Release);1-62
3. BRFSS/NHFS estimates, online at: http://www.cdc.gov/flu/professionals/vaccination/coverage_0910estimates.htm
4. MMWR, December 3, 2010 / 59(47);1541-1545 and CDC unpublished data
5. MMWR, April 2, 2010/59(12);357-362
6. RFS and internet panel estimates, online at: http://www.cdc.gov/flu/professionals/vaccination/vaccinecoverage.htm
7. Unpublished data, CDC

*Projected 2010-2011 coverage (already vaccinated + those who answered they'd definitely intend to get vaccinated)

While not all of these data sources are directly comparable to each other, overall estimated coverage for the US appears to have increased from 33% in the 2008-2009 season to about 43% project for 2010-2011. That increase holds up for children 6 months to 17 years of age, persons over the age of 65, and healthcare personnel. For pregnant women the sources are more varied, but the coverage estimates this year and during the 2009-2010 season are more similar in terms of the methodology was used.

Discussion Points

Dr. Baker thought 45% of 4 million women in part of a year seemed like a lot of people getting influenza vaccine in terms of assessing safety. That type of data could be reassuring to improve coverage even more. She congratulated women themselves for being advocates and obstetrical care providers for doing a good job.

Dr. Chilton whether any data were available yet pertaining to how the universal recommendation has affected coverage of those previously considered high risk groups among children and adults.

Dr. Weinbaum replied that these data would be available at the end of the season.

Dr. Baker reminded everyone that the universal recommendation only covered 15% more of the population. There has been improvement in children, but there remains a long way to go.

Ms. Hayes (ANA) asked whether they interviewed currently pregnant women.

Dr. Weinbaum reiterated that the data from this season were from the internet panel survey, which is supposedly a representative sampling of the U.S. population, of whom only pregnant women were considered for this survey. During two weeks in November 2010, these women were asked about pregnancy during the time that vaccine was available.

Dr. Schaffner (NFID) noted that despite the very nice distribution or uptake by week, it really continued to look by mid-November the "air was out of the immunization balloon" in that coverage did not seem to improve after mid-November. He inquired as to whether there is a distinction between the number of doses in children.

Dr. Weinbaum responded that this is at least one-dose coverage. At end-of-season, one- and two-dose coverage among children will be assessed.

Antiviral Agents for Treatment and Chemoprophylaxis of Influenza

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

Dr. Uyeki reminded everyone that, as Dr. Keitel reported at the beginning of this session, approximately a month before this meeting the "ACIP Statement on Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza" was published in the *MMWR* [MMWR 2011, Volume 60 (#RR-1) January 21, 2011]. The "Table Summary of Antiviral Resistance Among Influenza Viruses Worldwide, December 2010" is included in this publication. As reflected in this table, the use of adamantanes is not recommended because of the high prevalence of resistance among circulating influenza A viruses (2009 H1N1, H3N2); however, the circulating A viruses to remain susceptible to oseltamivir and zanamivir. Influenza B virus infections also remain susceptible to oseltamivir and zanamivir. In terms of treatment guidance, it is recommended that oseltamivir or zanamivir be given for treatment or chemoprophylaxis of influenza A or B virus infections. Empirical antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who has severe, complicated, or progressive illness; or requires hospitalization; or is at higher risk for influenza complications; or is not at high-risk if early treatment can be given based on clinical judgment. Initiation of therapy should not be delayed while waiting for results of diagnostic testing if clinically indicated [ACIP Guidance for Use Antiviral Agents; http://www.cdc.gov/flu/ professionals/antivirals/ guidance/; Updates on antiviral resistance can be found at: http://www.cdc.gov/flu/weekly/].

Groups at higher risk for influenza complications include the following:

- Persons <2 or ≥65 years of age;
- Persons with the following conditions:
  - → chronic pulmonary (including asthma),
  - → cardiovascular (except hypertension),
  - → renal, hepatic, hematological (including sickle cell) disease,
  - → neurological, neuromuscular, or metabolic disorders (including diabetes mellitus);
- Immunosuppression, including that caused by medications or by HIV infection;
- Women who are pregnant or postpartum (2 weeks)
- Persons younger than 19 years of age who are receiving long-term aspirin therapy;
- American Indians and Alaskan Natives;
- Persons who are morbidly obese (body-mass index ≥40);
- Residents of nursing homes and other chronic-care facilities.

Zanamivir dosing for treatment of influenza A and B for those 7 years of age and older is 10mg (two inhalations) twice daily. Zanamivir is not FDA-approved for those <7 years of age. Chemoprophylaxis dosing for influenza A and B for those 5 years of age and older is 10mg (two inhalations) once daily, and is not FDA-approved for those <5 years of age. Zanamivir is not recommended for persons with underlying airways disease due to the risk of bronchospasm. Administration requires correct use of an inhalation device [*Source: MMWR 2011, Volume 60 (#RR-1), p.7, Table 2*].

Oseltamivir dosing for treatment if influenza A and B for those 13 years of age and older is 75mg twice daily. Those 1 through 12 years of age should be dosed by weight. Those >40kg receive an adult dose. Chemoprophylaxis dosing for influenza A and B for those 13 years of age and older is 75mg once daily. Those 1 through 12 years of age should be dosed by weight. Those >40kg should receive an adult dose. Oseltamivir is not FDA-approved for children age <1 year. Oseltamivir was used during the pandemic under an Emergency Use Authorization (EUA). Although data are limited, there are some data from observational studies. Although the EUA expired in June 2010, ACIP recommendations still allow for use in children down to birth at the same dosing that was recommended during the pandemic, which was 3 mg/kg twice daily for treatment. Chemoprophylaxis is not recommended for those <3 months of age, while dosing is 3 mg/kg/day for those 3 through 11 months of age [*Source: MMWR 2011, Volume 60 (#RR-1), p.7, Table 2*].

With regard to duration of treatment and chemoprophylaxis, for therapy the recommended course is 5 days. Longer courses may be considered for persons who remain severely ill after 5 days of treatment. For chemoprophylaxis, the recommended course is 10 days following household exposures and 7 days after most recent exposure in other situations. For control of outbreaks in long-term care facilities and hospitals, prophylaxis for a minimum of two weeks and up to 1 week following last exposure is recommended.

Discussion Points

Dr. Meissner noted that children under the age of 5 years are at greater risk of complications over all in terms of office visits. With that in mind, he wondered why treatment was not recommended for children under 5 years of age as emphatically as it is for children under 2 years of age.

Dr. Uyeki responded that in assessing the epidemiology studies in terms of hospitalizations and mortality, it is pretty clear that the risk increases with younger age. There is a substantially higher risk in those children who are less than 2 years of age. It is actually even greater for those who are less than 6 months of age. It is not intended to say not to treat children 2 to 5 years of age who are otherwise healthy. Treatment can be given based upon clinical judgment. The evidence base for these recommendations, in terms of out-patient studies, is primarily from placebo-control RCTs for seasonal influenza. For hospitalized patients, data are from epidemiological or observational studies for seasonal influenza and 2009 H1N1. There are no published RCTs of antivirals for hospitalized patients. This is the best evidence base to date, and this reflects recommendations that were made during the pandemic and that are recommended on the CDC website for this season.

Dr. Baker indicated that it has been her experience that most pediatricians are oseltamivir for treatment since the supply is ample.

Dr. Kimberlin (AAP) thought that last year when they were initially going to suggest less than 5 years of age, a lot of pediatricians felt that few children would get treated so they preferred to have the option to use clinical judgment in the 2 to 5 year old age group. Many pediatricians treat children with positive results, but there are so many RSV and other overlapping infections, they wanted to have clinical judgment.

It was Dr. Baker's impression that more rapid influenza testing was being done by pediatric practices.

Dr. Chilton wondered whether the rapid influenza tests being done in pediatric offices were of any value.

Dr. Baker replied that these tests certainly are of some value in terms of the middle of the season, but they are imperfect.

Dr. Uyeki added that because of the limitations of the rapid influenza diagnostic test, especially the sub-optimal sensitivity, compared to the gold standard tests such as RT-PCR viral culture, empirical treatment based on clinical judgment has been recommend, particularly for those at high risk because of the potential for false negatives even during peak influenza activity. There is definitely concern about the inaccurate interpretation of the results of rapid influenza diagnostic tests. Information specifically tailored to the use of influenza rapid diagnostic tests to help guide interpretation is posted on the CDC website.

Dr. Baker indicated that as an anecdote, validation of rapid testing is being done Texas Children's Hospital. They test about 400 specimens a week during this season of the year. Influenza is outranking RSV. The sensitivity for influenza A is about 63% and is now falling. For influenza B sensitivity is terrible, so a negative test is not reliable. A positive test is pretty reliable if done in the peak of the season based on PCR as the comparator.

Dr. Katz (IDSA) noted that the data presented showed that mortality last year was 8 times what it was so far this year. He wondered whether any of the data regarding the increased use of vaccine or use of antivirals could be attributed to this.

Dr. Baker thought that could be better answered with end-of-season data.

Dr. Schuchat indicated that the sources of interim mortality data presented were pneumonia and influenza excess mortality. The last two weeks were way above the epidemic threshold, and it was way too early to know what the end-of-season mortality data would show. In terms of pediatric mortality, there were already 35 pediatric deaths. During the June 2011 ACIP meeting, they should be able to present more information about these deaths. A number of these were children with no underlying conditions and a number were not vaccinated. It is too soon to say whether this season will have fewer deaths than other seasons. There is still a long way to go in terms of preventable complications.

Influenza Vaccine and Egg Allergies

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

Dr. Grohskopf offered a brief introduction of the topic of influenza vaccine and egg allergies that the work group planned to present further data on during the June 2011 ACIP meeting. Hypersensitivity to egg is cited as a contraindication to the receipt of influenza vaccine in package inserts of most of the U.S.-marketed vaccines. With regard to vaccination for influenza in this population, the current ACIP influenza vaccine statement references to vaccination of persons with egg allergy include the following [Centers for Disease Control and Prevention. Prevention and Control of Influenza With Vaccines. MMWR 2010;59:1-62]:

- Contraindications and Precautions for Use of TIV:

  > "TIV is contraindicated and should not be administered to persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine unless the recipient has been desensitized. Prophylactic use of antiviral agents is an option for preventing influenza among such persons."

- Considerations When Using LAIV:

  > "Do not administer LAIV to the following groups: persons with a history of hypersensitivity, including anaphylaxis, to any of the components of LAIV or to eggs…"

Egg proteins may elicit severe allergic reactions in individuals with hypersensitivity to eggs, particularly those with IgA-mediated immediate-type hypersensitivity. Despite the fact that depending upon the report 0.5% to 1% of the population reports some degree of allergy to eggs, anaphylactic reactions to influenza vaccine are reported relatively infrequently. One published review of VAERS data noted 4 reports of death due to anaphylaxis, not specifying anaphylaxis due to egg, following influenza vaccine between 1990-2005 [Vellozzi C, et al. Vaccine 2009;27:2114-20]. Many individuals who report that they are allergic to eggs may not be allergic to eggs or may have a much milder allergic reaction and do not perhaps have a history of anaphylaxis. Concern about having an allergy to egg may discourage someone from seeking vaccine or a healthcare provider administering vaccine. Published protocols for vaccinating egg-allergic persons exist and involve approaches such as skin testing with the vaccine preparation itself. Should there be no reaction, administration of the vaccine by a 2-dose or multi-dose protocols is recommended.

Within the last few months, several documents have been published that review recent literature and research regarding influenza vaccine and egg allergies. These offer some guidance or advice on what to do with this particular population in terms of influenza vaccine. NIH recently released a large guidance document on the diagnosis and management of individuals with food allergy, which includes a good section on vaccines and a small section within that on influenza vaccines. The American Academy of Allergy, Asthma, and Immunology (AAAAI) issued a statement this past fall. The American Academy of Pediatrics (AAP) also recently issued a document. The specifics included in these documents differ to some degree, but there are some common themes. In general, skin testing with vaccine is considered to be poorly predictive of reaction based on recent studies and is, therefore, not considered useful. There is discussion about trying to confirm whether someone has egg-allergy with an actual egg challenge, but not with skin testing to vaccine. For egg-allergic persons without history of anaphylaxis, the thinking in these documents is that influenza vaccine can be given by either a single-dose or two-step (10% / 90%) approach, with observation following each dose. These documents all emphasize the importance of the availability of appropriate resuscitation equipment in the environment in which influenza vaccine may be given to someone who has an egg allergy. They tend to recommend that the vaccine with lowest ovalbumin content available be used. A point that is very relevant is that while each of these documents point out to one degree or another that there are studies in which individuals who have an actual history of anaphylaxis have been given the vaccine safely, the sample size of the individuals in the study pools is relatively small. The thinking is that it is perhaps not prudent to recommend the same protocol for those who do have a history of anaphylaxis as for those with less severe allergy.

The egg protein that is most commonly measured in vaccine preparations is ovalbumin. There are several egg proteins present in the vaccine. There is an ELISA assay available to measure ovalbumin, which is typically taken as a surrogate for the total amount of egg protein in a vaccine dose or in a concentration cited as µg/mL. Most vaccine manufacturers will give data regarding the ovalbumin content of vaccine in the package insert or can supply that information if requested. This is important because it links to the basis in the literature for the guidance described in the documents just mentioned. Two recent analyses of ovalbumin concentration in vaccine lots from several manufacturers demonstrated levels <1.2 µg/mL[1,2]. The µg/mL is somewhat higher than is seen in MMR vaccine. The 1.2 µg/mL threshold is somewhat important in that it is a level that has previously been demonstrated to be well-tolerated by egg-allergic individuals when administered as a two-step graded challenge.[3] A retrospective study of egg-allergic (without history anaphylaxis) individuals administered vaccine in a two-step graded challenge noted that 4% (7/171) developed systemic symptoms and 17% reported less severe, localized symptoms.[4] A prospective study of a squalene-adjuvanted, low ovalbumin (<0.03 µg/mL) H1N1 vaccine demonstrated vaccine safely administered as a single, age-appropriate dose in 393 egg allergic persons without a history of severe reaction; and by a 2-step graded challenge in 72 persons with either a history of severe cardiovascular or respiratory symptoms from egg, or uncontrolled asthma. There were no reports of anaphylaxis in this group, noting that the number of those with history of anaphylaxis was significantly smaller than those who did not have that history.[5] [1. Li JT et al, J Allergy Clin Immunol 125: 1412-1413; 2. Waibel KH et al. J Allergy Clin Immunol 125:749-751; 3. James JM et sl. L Pediatr 133: 624-628; 4. Chung EY et al. Pediatrics 125: e1024-1030; 5. Gagnon R et al. J Allergy Clin Immunol 126: 317-323/].

To date, the work group has engaged in initial discussions regarding potential additions / changes to statement for next season, and has begun to make plans for further workgroup discussion with technical experts outside the workgroup. No change was proposed to the language at this time; however, the workgroup felt that this was an issue that warranted further discussion given that there are also other guidance documents. The plan is to engage in further discussion with technical experts, including those at NIH and AAAAI. The work group will also review new study data. At least one RCT is currently on-going. An update will be presented during the June 2011 ACIP meeting.

Discussion Points

Dr. Marcy pointed out that the availability of resuscitation equipment in an office did not mean that it would be used properly. This concerned him, given that most pediatricians may not be good at resuscitating, epinephrine may be outdated, equipment may be stored in a back room and dusty, et cetera.

Dr. Grohskopf replied that this is a concern. Not all clinicians are going to have the same degree of comfort or same degree of experience with resuscitation, depending upon how far out of post-graduate training they are. Allergists may have a completely different perspective about this, which is one reason the work group thinks it is important to speak with different experts. AAAAI has allergists so they may feel somewhat different than pediatricians or internists. Since these guidance documents are published and the current ACIP statement does point out correctly that history of anaphylaxis would be a contraindication, they want to ensure that the widest number of clinicians needs to have something that they are comfortable with reading / interpreting.

Dr. Fryhofer (ACP and Practicing Physician) emphasized that guidance on specifically what practitioners should have in their office would be very helpful.

Dr. Duchin reminded everyone that the VFC program includes very clear guidance on what is expected of participating providers in the context of recognizing and managing adverse reactions, including anaphylaxis. It is an expectation that all participants in that program must be able to resuscitate if necessary.

Dr. Judson noted that he had more experience with penicillin allergies than egg allergies, but the rates in STD clinics for true penicillin anaphylactic reactions are approximately 1 to 2 in over 100,000. If people are asked whether they are allergic to something, the vast majority do not actually have true type 1 allergies. He thought the same was true with regard to egg-allergy. Every clinic can have epinephrine available, which is probably more important than a respirator in a closet. Almost anyone can give epinephrine with a minimum of training.

Dr. Turner (ACHA) noted that it is argued that being able to eat and consume cooked eggs does not rule out the possibility of anaphylaxis from injection because the protein is broken down with cooking.

Dr. Grohskopf responded that she had heard that, but she had also heard physicians say that those who can eat eggs should be able to tolerate the vaccine. There is definitely going to be some denaturization of the protein and the molecule is not going to be the same shape, but this is probably a question that should be posed to the allergists.

Dr. Baker reminded everyone that most medical doctors do not go to the hospital anymore. That is increasingly a job that is taken care of by hospitalists and sub-specialists. Whether those in the field are up to date on something besides injecting epinephrine was doubtful. She does not respond when a code is called in the hospital because she is not recently certified and does not feel comfortable doing so, and there are plenty of others in that setting who are prepared to respond.

Dr. Chilton indicated that he works in hospital and is ready, but he has not had to respond. He thought they should not overstate the risk of anaphylaxis. The data presented during this session indicated that there has been one VAERS-reported death for approximately every 400 million doses of influenza vaccine distributed over the past 15 years. That is not a very large number.

Dr. Baker stressed that it is in the mind of the public, which is another important point to consider.

Dr. Keitel commented that in reviewing these documents, there was clear indication that vaccines are stratified according to the amount of ovalbumin content. However, that is not a required characteristic for the lot release. There are some vaccines for which the ovalbumin content may not be known. If recommendations are going to move forward based on the amount of ovalbumin, that will have to become routine.

Regarding the public's concern, Dr. Jenkins indicated that just 20 minutes earlier on Medscape Pediatrics, an email said, "Flu shots okay for people with egg-allergy" and the source was AAAAI.

Dr. Baker indicated that this document recently received a lot of attention. Allergist offices are completely different. They desensitize or test and are completely equipped to feel comfortable with this sort of potential risk.

Dr. Katz reminded everyone that two years ago and one year ago at these meetings, he tried to get enhanced interest and statement from their cherished friends in the pharmaceutical industry about when they planned to move away from eggs. He requested input regarding the status of the enhancement of cell culture vaccines or genomic-developed vaccines and the movement away from egg vaccines.

Dr. Baker thought everyone agreed and wanted better vaccines. Work is on-going in vaccine development.

Proposed Recommendations

Lisa Grohskopf, MD, MPH
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Dr. Grohskopf reported that during this ACIP meeting, no changes were being proposed to the statement. Annual influenza vaccination continues to be recommended for all persons age 6 months and older. No changes to the groups recommended for annual influenza vaccination were proposed at this time. Groups considered at higher risk for severe illness include children <5 years, (particularly those <2); adults 65 years and older; and adults and children who have high risk conditions (e.g., asthma; neurological and neurodevelopmental conditions; chronic lung disease, including asthma; heart disease; blood, endocrine, liver, kidney, and metabolic disorders; weakened immune systems due to disease or medication; people younger than 19 years old who are receiving long-term aspirin therapy; pregnant women; severely obese persons; and Alaska Natives/American Indians).

The WHO met recently and recommended strains for the Northern Hemisphere for 2011-2012 for inclusion in vaccines. These are the same strains as were recommended for the 2010-2011 season, including the following:

- A(H1N1): A/California/7/2009-like
- A(H3N2): A/Perth/16/2009-like
- B: B/Brisbane/60/2008-like

The FDA Vaccine and Related Biologic Products Advisory Committee (VRBPAC) planned to convene a meeting on February 25, 2011 at which time they were to review the WHO recommendation.

Topics for the June 2011 ACIP meeting include confirmation of vaccine strains for 2011-2012, review of any new manufacturer data (e.g., new vaccine formulations, package insert changes), review of any new safety information, update on guidance related to influenza vaccine and egg allergies, and vote on any proposed changes to statement for 2011-2012 season.

Herpes Zoster (HZ)

Introduction

Paul R. Cieslak, MD, Chair
ACIP Herpes Zoster Work Group

Dr. Cieslak reminded everyone that Zostavax® was licensed for persons ≥60 years of age on May 26, 2006, and was recommended by ACIP for persons ≥60 on October 25, 2006. In 2010, Merck completed a Zostavax® efficacy and safety trial in persons 50 through 59 years of age and FDA approval is anticipated. During this session, ACIP members were presented with a review of zoster and its epidemiology, the Shingles Prevention Study, post-licensure efficacy data, post-licensure safety data, and Merck's Zostavax® Efficacy and Safety Trial (ZEST) data on 50 through 59-year-olds). An ACIP vote is anticipated in June 2011 based on the pending indication for Zostavax® in persons 50 through 59 years of age.

Overview of Herpes Zoster and Herpes Zoster Vaccine

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Given the potential FDA approval of Zostavax® in persons 50 through 59 years of age, and the fact that ACIP had not reviewed the herpes zoster vaccine statement in several years, during this session, Dr. Harpaz reported on the clinical manifestations of herpes zoster (herpes zoster, zoster, shingles), the epidemiology and burden of herpes zoster, herpes zoster vaccine (HZV) and the ZEST study and field assessments of HZV, ACIP zoster recommendations, HZV uptake, barriers to HZV uptake, and key remaining questions.

Herpes zoster is a reactivation of varicella zoster virus (VZV), leading to crop of blisters in a dermatomal distribution. Following infection (varicella), VZV establishes a permanent latent infection in dorsal root ganglia along entire neuraxis. Years to decades later VZV reactivates, though subclinical reactivation may occur as well. VZV virions reappear and spread to the skin via peripheral nerves.

The primary manifestation of herpes zoster is a vesicular rash in a dermatomal pattern (e.g., an area of skin supplied by sensory nerve fibers coming from one nerve root). The rash is unilateral with 1 to 3 adjacent dermatomes. There may be a few scattered lesions elsewhere. In terms of frequency of involvement of different dermatomes, the rank order (most to least frequent) is thoracic; followed by lumbar, trigeminal, and cervical; followed by sacral or other cranial dermatomes. With respect to duration, macules and papules form over 5 to 7 days that evolve to vesicles followed by crusts. The full process resolves over approximately 5 to 25 days. Some of the consequences of the rash can be secondary infections; scarring and changes in pigmentation; VZV transmission to susceptible children, causing varicella; and fever and regional adenopathy. Herpes zoster is perhaps 1/5th as contagious as varicella.

Key symptoms may include headache, photophobia, and malaise; however, the primary symptom is pain. Pain can be excruciating and has been compared to childbirth and kidney stones. The pain has been described as aching, burning, stabbing, and shock-like and can be continuous or paroxysmal. It is often associated with altered or painful sensitivity to touch provoked by trivial stimuli (e.g., bed sheets, a breeze). There can be an exaggerated response to pain and unbearable itching. Pain starts prior to rash onset in approximately 84% of cases. It begins with abnormal skin sensation, itching, or tingling and precedes rash by 1 to 5 days, though sometimes it can be weeks or more. On occasion, rash never develops (e.g., zoster sine herpete). Unexplained pain leads to diagnostic dilemmas and work-ups (e.g., cardiac, appendix). By the time of rash onset, pain is present in approximately 89% of cases.

The most important complication of herpes zoster is post-herpetic neuralgia (PHN). PHN is prolonged, sometimes incapacitating, pain after rash resolves. There are variable definitions of "prolonged." PHN may persist months or sometimes years. PHN prevention involves prompt treatment with antivirals with or without steroids once the rash develops. While this treatment may shorten pain duration, it does not conclusively reduce the risk of PHN. PHN treatment involves multiple modalities, including tricyclic antidepressants, anticonvulsants, topical agents, opioids, intrathecal corticosteroids, nerve blocks, hypnosis, relaxation techniques, cognitive

therapy, and acupuncture. The results tend to be partial, inconsistent and can lead to important side effects, especially in the elderly.

The impact of PHN on quality of life is comparable to congestive heart failure, diabetes, and depression. Potential physical impacts include chronic fatigue, anorexia and weight loss, physical inactivity, and insomnia. Potential psychological impacts include anxiety, difficulty concentrating, and depression / suicidal ideation. Potential social impacts include fewer social gatherings and change in social role. Functionally, PHN interferes with activities of daily living (e.g., dressing, eating, travel, bathing, cooking, shopping) [Schmader KE. Clin Infect Dis 2001;32:1481-6]. Dr. Harpaz shared this quote from a patient with PHN, "Doctor, I sure hope you can help me with this pain. It is so bad it has changed my whole life. I am unable to do any of the things I used to do."

Another common complication of herpes zoster can be involvement of the ophthalmic division of trigeminal nerve, which occurs in approximately 15% of herpes zoster cases. Untreated, 50% to 70% go on to develop acute ocular complications. These, in turn, can progress to chronic complications with reduced vision or even blindness. There are also some less common complications. Neurologic complications may include encephalitis, myelitis, optic neuritis, cranial and peripheral nerve palsies; hearing impairment, vertigo, loss of taste sensation; and diaphragmatic paralysis, neurogenic bladder, and colonic pseudo-obstruction. Oral complications include osteonecrosis of the alveolar bone with exfoliation of teeth. In those who are immunocompromised, complications are more common and more severe. Dissemination is a generalized rash with or without visceral involvement (e.g., pneumonia, encephalitis, hepatitis). Mortality is rare in healthy persons. Deaths occur primarily among those who are immunocompromised.

With regard to the epidemiology of herpes zoster in the US, the annual rate is approximately 4 per 1000 population per year. There are about 1 million cases in the U.S. annually, and rates in other countries are comparable. Age-adjusted rates appear to be increasing, with the lifetime risk of developing herpes zoster at about 30%. Repeated episodes of herpes zoster do occur, with the risk of recurrence being comparable to the risk of the first episode. Risk factors for herpes zoster include age (the dominant factor driving incidence and burden in the population); immunosuppression, which is less common but influential due to the magnitude of risk (e.g., hematological malignancies, bone marrow transplant, or HIV infection increase the risk of herpes zoster up to 50-fold compared to age-matched controls). Age and immunosuppression are thought to be risk factors because of impact on VZV-specific cell-mediated immunity (CMI), which otherwise prevents reactivation from progressing to clinical herpes zoster.

Other risk factors for herpes zoster include gender, with a 30% increased risk in females; race, with a 2-fold increased in whites versus blacks; and diabetes, for which studies show a variable increase in risk from no effect to 50%. Early varicella (*in utero* or during infancy) increases the risk of pediatric herpes zoster. There are conflicting results with regard to varicella exposure, but the weight of evidence suggests reduced risk of herpes zoster for those who were exposed to varicella. Stress has also been reported as a risk factor. Pesticide exposure seems to pose an increased risk for those who reside near a disposal site. Chronic diseases (e.g., cardiac-, lung-, renal-disease, hyperlipidemia, hypertension, osteoarthritis, allergic rhinitis have been reported to increase the risk of herpes zoster. One study showed increases ranging from 10% to 50%. Depression and mental illness increase the risk from 20% to 50%; trauma may increase risk for the short-term at the site of an injury (e.g., a local phenomenon—not a systemic one). Ethnicity seems to be a factor, with the risk being lower in Hispanics. An IL-10 polymorphism increases the risk of herpes zoster by approximately 50%. Family history can

also play a role in risk. However, it is not understood what distinguishes most of the approximately 1 in 4 of seemingly healthy persons who develop herpes zoster during their lifetime, and the approximately 3 in 4 who do not.

In the U.S., the proportion of herpes zoster patients who develop PHN varies by definition, setting, age, and study design, with ranges from 8% to 70% in different studies. The Olmsted County study (Yawn, Mayo Clin Proc 2007) suggested that 10% of herpes zoster patients will have ≥90 days of pain and that 18% of patients will have ≥30 days of pain. That translates to 100,000 to 200,000 thousand PHN cases per year. Risk factors for PHN include gender (risk may be greater among women with herpes zoster), and dermatome (possibly increased following ophthalmic herpes zoster. However, of those with herpes zoster, age is the key risk factor for developing PHN. Prolonged pain is rare in herpes zoster patients less than 40 years of age (>60 days), and increases approximately 27-fold in herpes zoster patients over 50 years of age. Age thus increases the risk of herpes zoster and its progression to PHN.

Dr. Edgar Hope-Simpson was a practitioner, keen observer, and theoretician who had a large general medical practice in the United Kingdom. He compiled data on herpes zoster from 1947 to 1972 for 321 patients. The rates increased dramatically after about the age of 50. Dr. Hope-Simpson showed that for patients who progressed to PHN, the rate began rising around the age of 60. Looking at the role of age and severity in zoster in another study, these 60-year old data from Olmstead County show the frequency patients with zoster that report pain as a function of age. These data show that the proportion of persons with zoster experiencing any pain increases dramatically with age. Of those with pain, the proportion who go on to have prolonged pain increases as well [de Moragas JM, Arch Dermatol 1957;75:193-6

In terms of the burden of herpes zoster, direct medical costs may include outpatient visits, emergency department visits, and hospitalizations; consultations with specialists (neurologist, ophthalmologist, ID); and / or medications and procedures to treat herpes zoster, prevent PHN, and control pain. Indirect costs include deaths and / or absenteeism / reduced productivity. There may also be pain and suffering, depending upon the duration and intensity of the pain; and physical and social disability, depression, and / or poor quality of life. For most vaccine-preventable diseases, pain and suffering are essentially ignored in economic analyses, but for herpes zoster, they make up most of the disease burden, particularly in the older, largely retired population. Contagiousness may also contribute to the burden of cost to contacts and to society. The specific burden in the U.S. is 12,000 to 19,000 hospitalizations with an average length of stay of 5 to 7 days; approximately 3 ambulatory visits per episode of herpes zoster; greater than 10 ambulatory visits per episode of PHN with pain ≥90 days; approximately 1/3 of herpes zoster episodes involving ≥1 visit to a specialist; and work loss per episode of herpes zoster of approximately 3 to 7 days [Merck, unpublished, presented at ACIP, June 2006].

Regarding the Shingles Prevention Study (SPS), the scientific basis for a vaccine is the epidemiologic evidence that suggests that herpes zoster risk is increased in the elderly and immunosuppressed which is attributed to declines in VZV-specific CMI. Inactivated VZV reduces zoster burden in immunosuppressed persons which was shown in two very nice studies from Stanford. High doses of live-attenuated VZV vaccine stimulates CMI in older adults shown in a study from the University of Colorado. The approach was to use a high-potency attenuated VZV to ameliorate or prevent HZ in VZV-infected individuals. Methodologically, the study was a double-blind, placebo-controlled, multi-center trial. Collaborators included the VA system, NIH, and Merck. The investigators enrolled over 38,546 healthy subjects ≥60 years old who were randomized to receive the vaccine versus placebo. The vaccine consisted of an OKA-VZV formulation that is also used in the chickenpox vaccine (titer at least 14X > VARIVAX®). The

primary efficacy endpoints included incidence of zoster, the burden of illness (BOI: HZ incidence X intensity X duration), and the incidence of PHN. Median follow-up was about 3 years.

The results of the Shingles Prevention Study were published in the *New England Journal of Medicine* (*NEJM*) in June 2005. Mike Oxman was the study chair and Myron Leven was the principal investigator. In terms of the findings, vaccine efficacy was 51.3% (44.2-57.6) for zoster incidence, 66.5 (47.5-79.2) for PHN incidence (≥90 days), and 61.1% (51.1-69.1) for burden of illness. With respect to the results by age, while vaccine effectiveness declines with age going down to about 20% among persons >79 years of age, the efficacy for PHN is better retained, going down to about 40% among persons in that age cohort. It is particularly important to reach person over 80 years of age, given that they are the ones at greatest risk of progressing to PHN, are the most vulnerable to zoster and PHN, and have the hardest time seeking medical management and tolerating medications. Using progressively more prolonged definitions for PHN from 30 days to 6 months, the vaccine is most effective (75%) at preventing the most prolonged forms of PHN. With regard to vaccine efficacy versus functional status, vaccine recipients were approximately 66% better able to conduct activities of daily living (ADL) than the placebo group. Most of that effect was due to prevention of herpes zoster itself. However, even when restricting the analysis to subjects who developed herpes zoster, interference with ADL was reduced among vaccine recipients approximately 30% compared to placebo recipients.

The vaccine appears to be safe. No patterns were observed to suggest a causal link to serious adverse events. Varicella-like rashes were seen in approximately 0.1% of subjects in the vaccine and placebo groups. There was an excess of local injection-site reactions in 48% of the vaccine recipients (N=3345) compared to 17% (N=3271) of the placebo group. In terms of duration of vaccine efficacy, the confidence limits become increasingly wide with progressive follow-up. While it seems that protection persists for some time following vaccination, it is difficult to draw firm conclusions from the data regarding longer-term trajectories [Source: Data presented by Ken Schmader at IDSA in 2008].

Regarding cost-effectiveness, data from various cost-effectiveness analyses were published with the ACIP statement a couple of years ago. Based on data from the CDC analysis generated by Ismael Ortega-Sanchez, zoster vaccine is expected to prevent about 58,000 cases of zoster; 32,000 cases of PHN; 285,000 outpatient visits; 28,000 emergency department visits; and 6,000 hospitalization days per million vaccinees over their lifetimes. The costs per QALY loss averted based on these assumptions ranges from $35,000 to $55,000. Four other cost analyses have been conducted, yielding widely-ranging cost per QALY of $27,000 to $112,000 [MMWR Recomm Rep. 2008;57(RR-5):1-30].

With regard to effectiveness and safety in field settings, while HZV proved safe and effective in the SPS, there is a particular reason to validate these results in field settings. SPS subjects were healthier and less diverse than the US population. HZV has stringent freezer storage requirements. A larger study is needed to reveal safety signals in this first live vaccine targeted to seniors, particularly given the high background incidence of new medical events occurring in that population that introduces noise that can mask adverse events. Effectiveness in field settings was supported by a study by Tseng published in JAMA in 2011, a Merck-sponsored safety in field settings study presented by Roget Baxter at IDSA in 2010, and VAERS unpublished data and VSD unpublished data.

Based on the burden of zoster and the results of the SPS, the FDA licensed Zostavax® in May 2006 and the ACIP followed with recommendations several months later in October 2006. In terms of some of the key elements of the ACIP statement, the vaccine is recommended for all

adults ≥60 without contraindications, including persons >80, persons who are frail, and persons with chronic illnesses. The vaccine is not intended for treating people who already have zoster, and it is recommended regardless of whether a person reports a history of zoster. It is not necessary to screen for varicella history or check titers before administering the vaccine. The vaccine must be stored at ≤5°F. Immunosuppression is a contraindication for HZV, and it is not recommended for persons who received varicella vaccine.

While this is a vaccine that appears to be safe and the disease is terrible and frightening, vaccine uptake in the US population ≥ 60 years of age has not been optimal. Based on data from 2007-2009, vaccine coverage increased from 2% in 2007, to 7% in 2008, to 10% in 2009. A number of barriers to uptake have been identified. HZV is the most expensive adult vaccine, with a catalogue price of approximately $161.50. That is over 4 times the cost of pneumococcal vaccine, and 10 to 20 times the cost of influenza vaccines. There are also very high up-front inventory costs for providers, placing them at considerable financial risk. HZV must be stored at freezer temperature (≤5º F). Zostavax® is the only freezer-requiring vaccine for adults, and many adult providers are not equipped to handle frozen vaccines. This was identified as a barrier for 36% of adult providers [Hurley, Annals 2010]. This also means that providers must take on added financial risk (e.g., expiry, freezer failure), although Merck has a program to share part of that risk. Merck has a refrigerator-stable formulation licensed in the U.S., Australia, and Europe, but it is currently not marketed. There are also other barriers in physician practice settings, such as Medicare Part D, because the relationship of drug plans is with pharmacies, not physicians. As a result HZV vaccination by physicians usually entails the patient paying the full price up front and filing a claim, or the physician referring the patient to pharmacy for vaccination, or the patient obtaining the HZV at the pharmacy for transport and vaccination at their doctor's office (e.g., brown-bagging). CDC considers brown-bagging to be unacceptable for a frozen vaccine. Regardless, these and other approaches add administrative complexity for providers and patients. Other barriers in physician and pharmacy settings are the non-reimbursed costs (e.g., deductibles, co-pays, donut hole), which often represent approximately 25% of the total cost, which amounts to more than full cost for other vaccines.

Moreover, there have been repeated production problems with bulk material for zoster and varicella vaccines that occurred in 2008-2009 and 2010-2011 that are on-going, which have been disrupting supplies. The potential impacts of disruptions on vaccine uptake are considerable. Disruptions frustrate providers who must answer for lack of availability, potentially leading them to stop offering HZV. Patients may never get vaccinated due to missed opportunities. Most importantly, there may be limited provider- or patient-level marketing and promotion, so most providers and patients are unfamiliar and uncomfortable with HZV. Disruptions may also hinder public-sector activities and goal-setting relating to HZV, particularly given that the public sector does not want to over-promise a vaccine that is not going to be available.

There are also some generic adult barriers. Provider barriers include competing priorities with chronic disease and acute care needs, little emphasis on vaccines during training, and financial barriers. Patient barriers include lack of awareness, lack of physician recommendation, and fragmented care (e.g., many providers; primary care via specialists). System barriers include no comprehensive financing system, no institutionalized well adult visits, and no counterpart to the school entry gate-keeping function.

Unanswered questions regarding herpes zoster include the following:

- Why do approximately 25% of seemingly healthy persons experience herpes zoster during their lives whereas the other approximately 75% do not? What unrecognized risk factors exist for herpes zoster?

- Why have age-specific herpes zoster rates increased in multiple settings prior to, or in the absence of, varicella vaccination? This suggests increases in unrecognized HZ risk factors. Will these increasing trends continue?

Unanswered questions regarding HZV include the following:

- What is the duration of protection provided by HZV?

- Among persons 50 through 59 years of age, do the burden of herpes zoster and the performance of HZV call for expanded use of HZV?

- Is there a role for HZV in persons with immunosuppressive conditions or treatments?

Herpes Zoster Vaccine in Older Adults and Risk of Subsequent Herpes Zoster Disease

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Department of Research and Evaluation

Dr. Tseng described an observational study at Southern California Kaiser Permanente evaluating herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease, emphasizing that the original clinical trial, the Shingles Prevention Study (SPS), was not fully generalizable. The study question was, "How does the vaccine perform in a real-world setting?" The SPS selected population was highly motivated and was comprised of 40% females, 2% African American, and just 1.4% Hispanic. The SPS participants were healthy and ambulatory, likely had heightened awareness of herpes zoster, and had a history of varicella or 30+ years of residence in the US. It excluded patients with chronic pain syndromes, cognitive impairment, severe hearing loss, major underlying illness, and various other concurrent treatments, vaccinations, or conditions and persons with prior herpes zoster. The age-specific mortality in the SPS trial population was less than half of that reported for the general population. Those with prior herpes zoster make up 10% to 20% of the target population and may be the ones who are most interested in receiving the vaccine, at least if the episode was serious. As noted, zoster vaccine requires freezer storage and careful monitoring of the freezer. In the SPS, approximately 1% to 2% of the study population had to be excluded from the analysis because they received a vaccine that had been compromised by freezer temperature deviation. If this occurred in the clinical trial, it would seem likely that it would occur in real-life settings also. Another limitation relates to the relevance of ascertainment of herpes zoster outcomes. The SPS trial conducted vigorous active case finding to identify even the mildest case of herpes zoster. In contrast, the current study was restricted to finding cases of herpes zoster that were clinically relevant for which patients sought medical attention.

Kaiser Permanente Southern California (KPSC) represents a very large and diverse population receiving services from many different physicians and centers, with many practice styles. There are more than 3.4 million members in the Southern California Region; 57,000 employees and staff; 5,300 physicians; 13 medical centers; and 150 medical offices. Members are ethnically diverse, with more than 250 different ethnicities who speak about 117 different languages. The Kaiser study was conducted from 01/01/2007 through 12/31/2009 and was comprised of community-dwelling adults 60 years of age and older who were followed passively using electronic health records. Of the vaccinated cohort, 75,761 members were age-matched (1:3) to 227,238 unvaccinated members. To improve comparability and be consistent with clinical recommendations and data from clinical trials, immunocompromised populations were excluded (e.g., HIV, leukemia or lymphoma diagnoses within one year before the index date until the end of follow-up, or having immunosuppressing agents dispensed within one year before the index date). The outcome of interest was incident herpes zoster and ophthalmic herpes zoster defined by ICD-9 codes (053.XX and 053.2X, respectively; in any position) from hospital, outpatient, and emergency department settings during the study period. The study had approximately four times more vaccinated persons than in the original clinical trial.

To assess comparability between vaccinated and unvaccinated groups, 13 indicator conditions were selected that were likely to be comparable to herpes zoster in terms of severity, access to / healthcare seeking, and documentation, but with no plausible association with herpes zoster. They expected that if the two groups were comparable, the incidence of these conditions should be similar between groups. A conventional statistical approach was used to calculate the incidence. Incidence (/1,000 person-years) was calculated by dividing the number of herpes zoster cases by the total number of person-years. The 95% confidence intervals (CIs) were estimated assuming occurrence of herpes zoster follows a Poisson distribution. Hazard ratios (HRs) and 95% CIs were estimated for age, sex, race, and chronic co-morbid diseases using Cox proportional hazards regression models.

There were 227,283 unvaccinated subjects of whom 118,506 (52.1%) were female and 108,771 (47.9%) were male; and 75,761 vaccinated subjects in the study of whom 42,822 (56.5%) were female and 32,939 (43.5%) were male. In the unvaccinated population there were 69,585 (30.6%) subjects aged 60-64; 60,498 (26.6%) aged 65-69; 46,278 (20.4%) aged 70-74; 32,934 (14.5%) aged 75-79; and 17,988 (7.9%) aged ≥80. In the vaccinated population, there were 23,195 (30.6%) subjects aged 60-64; 20,166 (26.6%) aged 65-69; 15,426 (20.4%) aged 70-74; 10,978 (14.5%) aged 75-79; and 5,966 (7.9%) aged ≥80. The mean standard deviation was 69.6 (6.8%) for each cohort. In the unvaccinated population, there were 122,050 (53.7%) Whites; 27,905 (12.3%) African Americans; 15,496 (6.8%) Asians; 362 (0.2%) Native American / Multiple; 9176 (4.0%) Other; and 52,294 (23.0%) Unknown. In the vaccinated group there were 45,435 (60.0%) Whites; 4,729 (6.2%) African Americans; 6,599 (8.7%) Asians; 87 (0.1%) Native American / Multiple; 2,125 (2.8%) Other; and 16,786 (22.2%) Unknown.

In terms of healthcare utilization, which can be an important confounder, the vaccinated group tended to be somewhat heavier users of outpatient services that patients with shingles would typically use. With respect to emergency department visits, the vaccinated and unvaccinated groups were fairly well-matched. Among the unvaccinated subjects, 78.1% made no emergency department visits, 13.2% made one visit, and 8.6% made two or more visits. Among the vaccinated subjects, 80.7% made no emergency department visits, 13.3% made one visit, and 6% made two or more visits. Of the unvaccinated subjects, 87.8% were not hospitalized, 8.1% were hospitalized one time, and 4.1% were hospitalized two or more times. Of the vaccinated subjects, 89.9% were not hospitalized, 7.5% were hospitalized once, and 2.6% were hospitalized two or more times. Though fairly matched, the mean number of hospitalizations

was slightly higher in the unvaccinated group and there was no evidence that they were much sicker or frailer than the vaccinated group. The two groups were also fairly matched in terms of chronic diseases. Of the unvaccinated subjects 13.8% had heart disease, 22.1% had diabetes, 2.2% had lung disease, 14% had kidney disease, and 1.5% had liver disease. Of the vaccinated subjects, 12.2% had heart disease, 19.4% had diabetes, 1.7% had lung disease, 12.5% had kidney disease, and 1.4% had liver disease.

The adjusted odds ratio was .45 (0.42 - 0.48) and vaccine effectiveness is simply the inverse of the rate ratio or 55%. This is remarkably similar to the results of the SPS for which the vaccine efficacy was 51%. In terms of vaccine effectiveness by age group, the adjusted rate ratio ranged from .40 to .50. Vaccine effectiveness was observed for all age groups, including persons over 80 years of age. This stands in marked contrast to the results of the SPS, for whom the vaccine was observed to be 20% efficacious in persons over 80 years of age. As a secondary finding, zoster incidence in the unvaccinated group increased dramatically with age as expected. The vaccine was also observed to be similarly effective for females (7%) and males (5.5%). In the unvaccinated group, incidence was higher in females (14.9%) compared to males (10.8%), confirming data that has been seen in many other studies. Effectiveness was similar across racial groups as well. For African Americans or Asians, the point estimate of adjusted hazard ratios were smaller, but were not significantly different from that in Whites. Vaccine effectiveness remained high in persons with a variety of chronic conditions. This is an important finding that was observed but not fully explored in the SPS. This suggests that physicians may not need to worry that defects in functional immunity would prevent the vaccine from providing benefits to chronically ill patients.

The investigators also tried to estimate the cumulative risk of herpes zoster by herpes zoster vaccination status following vaccination using the Kaplan-Meier method. The 34-month cumulative risk of herpes zoster after vaccination is about 2.1% compared to 3.5% in the unvaccinated group. In the comparison of the adjusted hazard ratios of the 13 indicator conditions and herpes zoster in a study of cohorts by herpes zoster vaccination status, none of the conditions had a rate ratio as small as that for herpes zoster. In fact, 7 of them were significantly larger than one. Herpes zoster vaccine recipients had reduced risks of ophthalmic herpes zoster (HR=0.37; 95% CI, 0.23-0.61) and hospitalizations coded as herpes zoster (HR=0.35; 95% CI, 0.24-0.51).

The study has some limitations. There is the issue of generalizability, given that the study was conducted in one region of the US and the study population is fully insured. The study is not designed to assess severity or duration of symptoms among herpes zoster cases, assess the effectiveness of the vaccine against PHN, or to capture any decline in protection. Misclassification is possibly because of the use of electronic data, and residual confounding is possible because the risk factors for herpes zoster among those who are immunocompetent is not fully understood. It is not clear whether these factors relate to the vaccine.

In summary, these data complement the results of the original clinical trial. Herpes zoster vaccine is associated with a reduced the risk of herpes zoster in a community setting with its mixed population and routine clinical practices. The vaccine was also associated with reduced risks of ophthalmic herpes zoster and hospitalizations potentially-attributable to herpes zoster. These potential benefits extended to persons of all ages for whom the vaccine is recommended, and to persons with chronic diseases.

Safety of Zoster Vaccine in Adults:
A Vaccine Safety Datalink Study

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Dr. Tseng described the VSD zoster vaccine safety study, which aimed to examine a large cohort of adults who received the herpes zoster vaccine, Zostavax®, for evidence of any increased risk of pre-specified adverse events (AEs) following vaccination. The study period was from January 1, 2007 through December 31, 2008 in a population of adults ≥50 years of age who received the zoster vaccine during the study period in one of the 8 managed care organizations in the VSD study.

Two self-controlled analysis methods were utilized in this study: 1) Case-centered approach, and 2) Self-controlled case series analysis. The case-centered approach is a method developed by a statistician in the VSD group that compares the observed probability of vaccination-in-the-risk-window versus the expected probability of vaccination-in-the-risk-window under the null hypothesis that the vaccine is really safe. Vaccine recipients experiencing pre-defined adverse events were restricted to those that occurred within 1 year of vaccination. For example, suppose 10 adverse events were identified within 1 year after receiving the vaccine, 10% of the vaccine doses were used in the risk window period, 90% of the doses were used in the remote follow-back period, it is expected that 1 adverse event had a vaccination record in the recent follow-back period vs. 9 adverse events that had a vaccination record in the remote follow-back period. The expected case split in this example would be 1/9 (1 vs. 9). What if the observed case split was 3/7 or 4/6? Are they unusual? A statistical method is used to test whether these events are unusual. The self-control case series (SCCS) compares relative adverse event incidence in the risk window to the post-vaccination control windows by conditional Poisson regression. A 90-day washout period is set between the risk window and the compared window. Each individual's observation time is split into successive time intervals determined by changes in exposure status and by the start and end of the observation period.

Pre-specified events for Group 1 included stroke and cerebrovascular diseases. Pre-specified events for Group 2 included five cardiovascular events (e.g., acute myocardial infarction, acute pericarditis, acute myocarditis, cardiomyopathy, and heart failure defined as heart failure code plus cardiomyopathy code). Pre-specified events for Group 3 included meningitis, encephalitis, and encephalopathy. Pre-specified events for Group 4 included Ramsey-Hunt Syndrome, and Bell's Palsy. Pre-specified events for Group 5 included serious reactions of either cellulitis and infection or inflammation or allergic reaction. For the first 3 groups, adverse events were identified from in-patient and emergency settings and only cases representing the first episode in the past 12 months were included. The pre-specified risk window for these groups was 1 to 42 days, with 3 13-day risk intervals examined within the 42 days to determine whether the risk varied within the 42 days: 1-14 days, 15-28 days, and 29-42 days. For Groups 4 and 5, events were identified from out-patient and emergency department settings. The risk window was 1-14 days for Group 4 and 1-7 days for Group 5.

There were over 192,000 vaccinated individuals from the 8 VSD sites included in this study, about 70% of whom were from the two largest sites. Approximately 60% of the vaccinees were female (N= 112,953) and about 40% were males (N= 79,507). Of the vaccinees, 6832 (3.6%) were 50-59.99 years of age; 103,042 (53.5%) were 60-69.99 years of age; 65,562 (34.1%) were 70-79.99 years of age; and 17,031 (6.7%) were 80 years of age and older.

Using the case-centered analyses and the self-controlled case series analyses, no increased risk was observed for stroke; acute myocardial infarction; acute pericarditis; cardiomyopathy; heart failure; meningitis, encephalitis, and encephalopathy; or Ramsey-Hunt syndromes and Bell's palsy. There were 5 cases with ICD-9 codes indicating acute myocarditis within 42 days of vaccination. The relative risk was very large; therefore, the VSD site principal investigators were asked to review each of these diagnoses. None of these 5 cases were confirmed by chart review. There was a slightly increased risk of cellulitis and infection by the case-centered method, but the larger sample size increased the power of the test. Both methods identified an increased risk of inflammation or allergic reaction in Days 1-7, with a relative risk of 2.40 (2.11, 2.73) for the case-centered analysis and 2.25 (1.80, 2.82) for the self-controlled case series analysis.

In order to further understand the nature of the reactions, a medical record review was conducted of 118 cases from KPSC. Of these, 31 were clearly attributable to unrelated causes, 16 were vaguely and inadequately described, and 71 were determined to be the result of a reaction to the zoster vaccine. Of the 71 cases, 59 (83%) complained of a localized inflammatory response and 11 (15%) presumably allergic, pruritic, urticarial, macular, or papular rashes were described. Of the 11, 9 were diffuse, 1 consisted of an urticarial eruption surrounding the site of injection, and 1 was manifest as unilateral eyelid swelling. A single patient was described as having a zosteriform rash "left T4...a few hours after getting the shingles vaccine." No patients whose records were reviewed reported signs or symptoms suggestive of anaphylaxis. Mortality was also assessed using the case-centered analysis only because the self-controlled case series method is not suitable for analysis of deaths as an outcome. No increased risk of mortality was observed within the 42 days following vaccination, and the relative risk was 0.31 (0.23, 0.40), most likely suggesting the healthy vaccinee effect. The increased risk of inflammation or allergic reaction 1-7 days following vaccination was further examined by age group, and it was found that the elevated risk decreased as vaccination age increased. The relative risk was 9.50 (2.21, 40.79) in those 50-59 years of age; 3.00 (2.18, 4.13) in those 60-69 years of age; 1.59 (1.10, 2.30) in those 70-79 years of age; and 0.62 (0.26, 1.48) in those ≥ 80 years of age.

There are some study limitations. The events and risk period were pre-specified, given that this is a new vaccine and the possible adverse events and risk periods are largely unknown. No investigation was made of non-specific events (e.g., fever, generalized rash, et cetera) because of the non-specific ICD-9 codes for these conditions. Misclassification of disease status is possible because the use of electronic data. There are generalizability issues as well because the subjects were from the 8 managed care organizations in the VSD, and are most likely a fully insured population and represent subjects who used the vaccine at a relatively early stage after vaccine licensure.

In conclusion, the data provide reassurance that the zoster vaccine is generally safe and well-tolerated. There is a small increased risk of vaccine-site inflammatory reactions or generalized allergic reactions. The elevated risk of local reaction among the 50 through 59 years group needs further investigation.

Discussion Points

For the effectiveness study, Dr. Baker requested clarification regarding how Hispanics were categorized as she did not see a separate category for Hispanics.

Dr. Tseng replied that the race / ethnicity variables are self-reported based on members' self-report data. There are a variety of selections for them to use to self-report.

Dr. Baker asked what the rationale was for not including PHN in the effectiveness study.

Dr. Tseng responded that they need to determine a way to use the electronic data to identify and validate PHN.

Dr. Sawyer requested clarification on the methodology in the safety study regarding why Group 4 (Ramsey-Hunt Syndrome, Bell's Palsy) had an exposure window of 1-14 days and the other neurologic group, Group 3 (meningitis, encephalitis, and encephalopathy) had an exposure of up to 42. He wondered whether a longer window might be appropriate for Group 4 since this vaccine is more slowly replicating than some of the more traditional vaccines the VSD may assess for these types of complications.

Dr. Tseng clarified that the risk windows were pre-specified, and there is no sound biological evidence for defining these outcomes. Some are them are conventional in the VSD for other vaccine-related adverse events.

Noting that Kaiser physicians have a choice about who they offer the vaccine to, Dr. Judson noted that the match was in terms of the other criteria, but there could still be a healthy person bias.

Dr. Tseng responded that a healthy person bias was possible. The investigators tried to adjust for chronic conditions and healthcare utilization patterns to account for those differences. However, confounding is still possible.

Dr. Judson inquired as to the problem with production at Merck (e.g., yield, potency, reliability).

Dr. Baker responded that there would be a later presentation pertaining to this, and requested that this question be held until that time.

Ms. Ehresmann noted that for acute myocarditis in the safety study, there is a relative risk of 19.44 and the confidence interval does not include 1.0. That was startling compared to all of the other data presented, so she wondered if there was an explanation for this.

Dr. Tseng replied that the code for that condition is not very good. Most chart reviews did not confirm that diagnosis, or the condition occurred several years ago.

Dr. Keitel followed up to Dr. Tseng's reply by asking what diagnoses were found upon chart review to be misclassified as myocarditis.

Dr. Marcy replied to Dr. Keitel indicating that there were numerous diagnoses. There were congestive heart failure in people who had had myocardial infarctions and so forth, but none were actually myocarditis.

Dr. Meissner was intrigued by the comment that the age-adjusted rates of zoster appear to be increasing. The possibility of such an increase was one of the reservations regarding routine varicella vaccination, due to reduced exposure to varicella. CDC data have shown nicely that rates of zoster declined during the first decade following licensure of varicella vaccine in 1995, but those rates were falling even before licensure.

Dr. Harpaz responded that there have been a number of studies to show this in the U.S. and elsewhere. In the U.S., a study is being conducted to go back to 1945 that was presented at IDSA showing that there had been an increase back to 1945. There are data from independent studies in three Western provinces in Canada, each of which shows an increase before varicella vaccine. There have also been increases shown in Taiwan, Japan, and Europe. There is no explanation at this point. A study was recently published that looked back to 1991 and showed no difference in zoster rates as function of varicella vaccine uptake. It is fair to say that persons exposed to varicella might be at reduced risk of zoster, but this effect is not enough to explain declines in zoster rates observed in the general population. There is no evidence that varicella vaccination has been accelerating the increase in zoster rates. If anything, the rate of zoster increase has declined over the last decade.

Dr. Jenkins requested clarification about whether someone who received varicella vaccine should not be given zoster vaccine.

Dr. Harpaz responded that this was correct. The rationale is that children are vaccinated with OKA-VZV based vaccine, which establishes a latent infection. The best data show that rates are considerably lower for reactivation of the OKA VZV as compared to reactivation of wild-type VZV in age-matched children who have experienced chickenpox. Therefore, our best guess is that as these vaccinated children age and become elderly, zoster rates would continue to be low. Furthermore, it does not make sense to give an OKA-VZV based vaccine that becomes latent in order to prevent reactivation by another latent OKA-VZV based vaccine. We will continue to follow and review the data over time.

Dr. Gorman (NIH) asked whether there was any sampling of other datasets to assure them of the quality of the rest of the data pertaining to myocarditis. That is, when the chart review was done on the diagnosis of myocarditis, he wondered whether random sampling was done of the other diagnoses to check their validity.

Dr. Tseng responded that they did not.

Vaccine Adverse Event Reporting System (VAERS): Assessment of Reports after Receipt of Zostavax®

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Zostavax® was licensed in May of 2006 for the prevention of herpes zoster in individuals 60 years of age and older. It is a live-attenuated, single dose, subcutaneous injection. It was Recommended by the ACIP in October of 2006 for all adults 60 years and older who do not have any contraindications [http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm132873.htm].

As noted earlier, the main pre-licensure clinical trial was the Shingles Prevention Study with approximately 38,000 individuals. Injection site reactions and headache were the most common adverse reactions that were higher in vaccine recipients. Injection site reactions were 48% for Zostavax® versus 17% for placebo. Headache was 1.4% in vaccine recipients versus 0.8% in placebo. In a safety sub-study of approximately 6600 individuals, cardiovascular events such as CHF were more frequent in those receiving Zostavax®, with 0.6% in vaccine recipients versus 0.4% in placebo. In terms of post-marketing safety, the 3 main strategies are passive surveillance using VAERS, VSD, and Merck-sponsored observational studies with different safety endpoints.

VAERS is a spontaneous passive surveillance system primarily used to identify potential signals for further investigation. It does not assess causality. VAERS serves as the US “early warning” system for potential vaccine safety concerns. VAERS is co-managed by CDC and FDA. VAERS encourages reports from healthcare providers of clinically significant adverse events after vaccination and accepts reports from anyone. VAERS has both strengths and limitations. Strengths include the ability to rapidly detect signals and rare adverse events. In this way VAERS generates hypotheses for further study. The VAERS data are available to the public via the internet. Limitations of VAERS include several reporting biases such as underreporting, differential reporting, and stimulated reporting. In addition, there is inconsistent data quality and lack of an unvaccinated comparison group. Signs and symptoms on each VAERS report are coded using the Medical Dictionary for Regulatory Activities (MedDRA). Reports may have multiple MedDRA codes and may include vaccines that are given simultaneously. MedDRA uses an internationally standardized terminology and has been clinically validated.

The objectives of this analysis were to summarize U.S. VAERS safety surveillance data for Zostavax® from 2006-2010; and to detect potential safety signals that might be associated with Zostavax® in the post-licensure setting. The methods included a descriptive analysis of reports to VAERS; clinical review of death reports and selected other serious cases where medical records were available; and data mining to detect disproportionate reporting in the VAERS database for adverse events after receipt of Zostavax®. Empirical Bayesian data mining, which is conducted by the FDA, complements other methods for monitoring VAERS data [Bate, A. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiology and Drug Safety. 2009:18: 427-436]. This identified adverse events reported more frequently than expected after Zostavax®, compared with other vaccines in the VAERS database. The Empirical Bayesian Geometric Mean (EBGM) is the point estimate for disproportionality. Any Zostavax® adverse event pairs with reporting proportions at least twice that of all other vaccines are further evaluated. The lower bound of the 90% confidence interval of the EBGM is defined

as the EB05 and is used to make this determination. If EB05 is greater than or equal to 2, it is further evaluated. An EB05 greater than or equal to 2 does not demonstrate that the vaccine caused the adverse event.

This analysis included primary U.S. reports to VAERS following Zostavax® received between July 1, 2006 and December 31, 2010. Cases are categorized as serious or non-serious based on reported outcome. A report is defined as serious if it is reported as life-threatening or results in death, in-patient hospitalization or prolongation of an existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect.

With regard to the crude reporting rates for total and serious reports to VAERS after Zostavax® by year, 2006-2010, there has been a steady decrease in both the number of total and serious reports over time. This pattern is often seen with new vaccines. The reporting rate of serious reports has ranged from its peak in 2007 at 8.9 per 100,000 net doses distributed to its low in 2010 at 2.3 per 100,000 net doses distributed. There were a total of 7,330 reports during the study time period, with 458 (6.25%) serious cases. Of the cases, 70% were females. The majority of reports were from the manufacturer (50%). Of those reporting, 10% had simultaneous vaccination, the majority of which were influenza, pneumococcal, or tetanus-containing vaccines. The median age was 67 with a range of 0-97 years, and the median onset interval between vaccination and adverse event was 2 days with an inter-quartile range of 0-7 days.

Regarding the age distribution of total and serious reports to VAERS after Zostavax® from 2006 through 2010, as expected from vaccine indication, the most frequent reports were from the 60-69 year age group, followed by the older age groups. There were also reports in younger age groups, the vast majority of which were classified as non-serious events. Many of these were inappropriate administration or given off-label. If adverse events were reported, their safety profile was similar to that of the older age group. There were 13 serious reports in those less than 60 years of age, with an age range of 20-59 years of age. In the 60 years and older age group, the most frequent MedDRA codes reported after Zoster vaccine were reviewed for non-serious and serious non-fatal reports. Herpes zoster was the most frequently coded event. Local reactions and pain were also common. The serious group had more frequent constitutional symptoms.

FDA data mining compared Zostavax® to all other vaccines in the VAERS data base and found these MedDRA terms to be significant based on the EB05 criteria. Again, they are all related to herpes zoster or injection site reactions. Given that herpes zoster was the most frequent term, the reports were characterized. It is important to keep in mind that the efficacy of Zostavax® in the prevention of herpes zoster is 51% overall, with approximately 64% in the 60-69 year age group, and declining thereafter. There were 1328 total reports of herpes zoster, with 128 (9.6%) classified as serious, and 67% from females. The most frequent reporter type was the manufacturer, with 58% of the reports. Only 4% had simultaneous vaccination. The median age was 71 years, with a range of 60-96 years. The median onset interval from vaccination to adverse event was 8 days, with an inter-quartile range of was 2-69 days.

There were 122 serious, non-fatal herpes zoster reports, of which 77% were reported by the manufacturer, 72% did not have any additional medical records, 62% were female, 78% reported a history of chronic disease, and 10% reported a history of immune compromise The median age was 73 years, and the median onset was 36 days. Of the reports, 7% mention a previous history of shingles, 2% mention the possibility of shingles at the time of vaccination, 2 reports mention zoster contacts, 61 (50%) report hospitalization (30 with other medical conditions, 18 mention shingles related to admission, 12 with unknown or unrelated reasons for admission), 58 (48%) reported permanent disability or thought the condition was disabling, and 13 (11%) mentioned lab testing (of these 2 were VZV negative, 10 were +VZV wild type, 1 was +VZV with no typing).

There were 38 reports to VAERS of death after Zostavax® administration. Of these, 55% were female, 63% were manufacturer reports, 5 individuals received simultaneous vaccination (e.g., PPV23(2), TIV, Td, Tdap), the median age was 76 years, with a range of 60-93 years, and the median time to death was 17 days, with a range of 0-204 days. In total, 33 of these death reports had adequate information for review, and 5 manufacturer reports were excluded due to lack of information (e.g., 2 were hearsay reports, 3 could not obtain adequate follow-up). Based on review of medical records, death certificates, and autopsy reports of cardiovascular deaths (which include stroke) accounted for 64% of the reports, followed by other infectious disease and neurological disease. This pattern is expected in this age group due to high prevalence of chronic disease such as cardiovascular disease and diabetes. One death was reported by the manufacturer of an 82-year-old female with a history of diabetes, asthma, and heart attack that had a potential relation to zoster infection. The death certificate stated the cause of death as 1) viral encephalitis, and 2) chicken pox. Of note, the patient's unvaccinated husband had shingles, which triggered her to inquire about the vaccine. The interval between vaccination and death was 29 days. Per the report, her spinal tap was consistent with viral meningitis; however, there was no additional information.

In summary, the most frequently reported adverse events after Zostavax® were herpes zoster, injection site reactions, pain, and rash. VAERS data do not show any unexpected patterns for adverse events after Zostavax®, and there were no cardiac terms that signaled. Surveillance is challenging due to the high prevalence of co-morbid conditions among those 60 years and older. As with all US licensed vaccines, CDC and FDA will continue to monitor the safety of Zostavax®.

Zostavax® Update

Janie Parrino, MD, Director
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Dr. Parrino presented data from two of the studies in the Merck Zostavax® program: 1) P020, a Phase IV General Safety Study; and 2) P022 ZEST Efficacy and Safety Trial in 50 to 59 year olds.

P020 was a Phase IV trial to evaluate the safety and tolerability of Zostavax® in people ≥60 years of age. The purpose of P020 was to accumulate additional safety data in individuals ≥60 years of age. A safety evaluation was conducted in this age group in the pivotal efficacy study, the SPS, which enrolled 38,546 individuals ≥60 years of age. In the SPS, adverse experiences were assessed from Day 1 to 42 post-vaccination. The SPS included an overall study and an adverse event monitoring sub-study (AEMS). In the adverse event monitoring sub-study, post-

vaccination safety evaluation included a vaccination report card (VRC). A VRC was not used with the monitoring cohort. In terms serious adverse events in the overall study population and the AEMS, examples of serious adverse experiences are events that resulted in hospitalization, prolongation of hospitalization, deaths, cancer, life-threatening events, or events that resulted in persistent or significant disability. In the AEMS, there were more reports of serious adverse events in the Zostavax® group with 64 subjects versus 41 in the placebo group, with a relative risk of 1.53 and the confidence interval excludes 1.0. However, in the overall study the number of subjects reporting serious adverse events wass 255 in the Zostavax® group and 254 in the placebo group, with a relative risk of 1.01.

The P020 study design is a randomized (1:1), double-blind, placebo-controlled, age-stratified study that includes 11,999 individuals ≥60 years old. Of these, approximately 85% are 60 to 79 years of age and approximately 15% are ≥80 years of age. These individuals were followed only for SAEs. There was a primary safety follow-up period from Days 1-42 post-vaccination and a secondary safety follow-period for Days 1-182. No VRC was used in this study. Subjects with an SAE were instructed to contact study site immediately if they experienced an event they thought might meet SAE criteria. At 6 weeks, 4 months, and 6 months, the study staff telephoned study participants to inquire about any unreported SAEs, utilizing a pre-specified script.

The P020 study objectives were to evaluate the general safety of Zostavax® in people ≥60 years of age. This was done by assessing the relative risk of developing SAEs following administration of Zostavax® or a placebo. The primary measurement was based on the 42-day post-vaccination time period and the study was considered a success if the lower bound of the 95% confidence interval of the relative risk was ≤1 or if the point estimate of the relative risk was ≤1.25. The relative risk was also assessed for the secondary measurement of 182 days post-vaccination.

In terms of the baseline characteristics in the study, the Zostavax® (N=5**983)** and placebo groups (N=5997**)** were very similar. The mean age in both groups was about 70.5, and the target was reached of 15% of subjects being 80 years of age or greater. There were more females enrolled in the study, with 58.7% in the Zostavax® group and 58.8% in the placebo group. Race was predominantly White, with 96.3% in the Zostavax® group and 96.2% in the placebo group.

With regard to SAEs in the follow-up period, nearly everyone had safety follow-up in the study. There were 84 reports of SAEs in the Zostavax® group compared with 67 in the placebo group. Two vaccine-related SAEs were reported in the Zostavax® group. One was an episode of sciatica and the other was an episode of uveitis. With regard to the uveitis, after the study physician made the determination that this was vaccine-related, he received additional information. The patient's clinical presentation progressed and was eventually diagnosed as Crohn's Disease. The investigator thought that perhaps the uveitis was due to the Crohn's Disease after receiving that information. For the secondary safety follow-up period from Day 1 to 182, which includes the information from Day 1 to Day 42, there were 340 subjects with SAEs in the Zostavax® group compared to 300 in the placebo group. The vaccine-related SAEs in the Zostavax® were the two already mentioned that occurred during the primary safety follow-up period. There was another SAE that was determined by the study investigator to be vaccine-related, which was an episode of lumbar radiculopathy. In terms of the subjects who died for the Day 1-182 time period, there were 24 subjects in the Zostavax® group compared with 17 subjects in the placebo group who had a fatal event with onset during that 6 month time period.

Regarding the number of subjects reporting one or more serious adverse experiences post-vaccination, the relative risk from Day 1-42 post-vaccination Zostavax® to placebo was 1.26, so the lower bound at 0.91 is less than or equal to 1 and meets the pre-specified study success criteria. From Day 1-182 post-vaccination, the relative risk was 1.13. Based on an analysis of age or region trends for risk of SAEs during the primary safety follow-up time period, the 95% confidence intervals for each sub-group contains 1, indicating that there was no significant difference in the Zostavax® and placebo groups for each sub-group. There were no statistical trends observed with regard to treatment difference in SAE risk among age groups or within regions as evidenced by the large p-values and overlapping confidence intervals.

The conclusions from P020 are that the estimated risk of SAEs in the Zostavax® group was not statistically different from the placebo group for the Day 1-42 or Day 1-182 post-vaccination time frames. While Dr. Parrino did not present data during this session on the specific SAE terms, those data are available and show that the Zostavax® and placebo groups had similar safety profiles in terms of types of SAEs Day 1-42 and Day 1-182 post-vaccination time profiles. The safety profiles in this study for the Zostavax® and placebo groups are similar to previous clinical studies. The overall relative risk in this study is similar to that in the SPS. The relative risk of 1.53 from the SPS AEMS was not repeated in P020.

Protocol 022 is a Phase III clinical trial to evaluate the efficacy, immunogenicity, safety, and tolerability of Zostavax® in individuals 50 to 59 years of age. The primary difference between P004 (SPS) and P022 (ZEST), aside from the age differences, is that there were differences in the efficacy endpoints. The co-primary efficacy endpoints in SPS were vaccine efficacy on PHN and vaccine efficacy on herpes zoster burden of illness. The secondary endpoint was vaccine efficacy on the incidence of herpes zoster. In ZEST, the primary endpoint was vaccine efficacy on herpes zoster. No data were collected on PHN in this study. Due to the incidence of PHN in this age group, a much larger study would have been required. SPS used a modified intent to treat (MIIT) population. This included people who had been randomized and had been in the study for 30 days who had not developed confirmed herpes zoster during that 30-day time period. ZEST used an intent to treat (ITT) population, which included all randomized subjects. The herpes zoster case follow-up time was 6 months for SPS and 21 days for ZEST.

There was also a difference in the immunogenicity assays utilized between the two protocols. Three immunogenicity assays were utilizes in SPS (e.g., gpELISA, ELISPOT, and RCF). All three were found to correlate with efficacy; however, the GMT and foldrise combination from the gpELISA results correlated best with efficacy. gpELISA was used for the immunogenicity assays for ZEST. Regarding safety follow-up time, all AEs were collected in the SPS from Day 0-42. Day 0 was the day of vaccination in SPS. From Day 42 post-vaccination to the end of the study, only vaccine-related SAEs and deaths were collected. In addition, in the adverse event monitoring sub-study, hospitalizations were also collected. For ZEST, vaccination date was Day 1. From Day 1-42 post-vaccination, all adverse experiences were collected. From Day 43 to Day 182 post-vaccination, all SAEs continued to be collected. From Day 182 to the end of the study, only vaccine-related SAEs and deaths were collected. The follow-up time for SPS was a median of 3.1 years compared to 1.3 years for ZEST.

With respect to P022, the primary objective was to assess the impact of Zostavax® on the incidence of herpes zoster, while the secondary objectives were to assess the immunogenicity and overall safety and tolerability of Zostavax®. P022 was a randomized (1:1), multi-center (with sites globally), double-blind, placebo-controlled study that enrolled 22,439 varicella history-positive, herpes zoster history-negative subjects 50 to 59 years of age. This was an event-driven study in which subjects followed for herpes zoster occurrence for approximately ≥1 year

post-vaccination, based on the time to accrue 96 confirmed herpes zoster cases. Subjects were instructed to call the study site for symptoms suggestive of herpes zoster, and monthly contacts were made through an Interactive Voice Response System (IVRS). All subjects were actively contacted at end of the study. All subjects with suspected herpes zoster were entered into the herpes zoster case follow-up. All suspected cases were adjudicated in a blinded fashion by a Clinical Evaluation Committee (CEC). Final herpes zoster case determination was based on the results of lesion PCR. If there were missing or inadequate PCR result, final determination was made by CEC decision.

In terms of follow-up of suspected herpes zoster cases, subjects were asked to notify the study site for rash or other symptoms suggestive of herpes zoster. Lesion specimens were collected for PCR during the first evaluation. The subjects were contacted roughly every 3 days (+/-1 day) for 21 days beginning on day of the initial rash visit to assess evolution of clinical signs and symptoms and administer questionnaires, including the Zoster Brief Pain Inventory (ZBPI), which was also utilized in SPS, and the Work Productivity Questionnaire (WPQ). Information on work loss was only collected for subjects who reported a case of herpes zoster and not the entire study cohort.

The primary analysis was on the reduction of incidence of herpes zoster, and an ITT analysis was used that included all randomized subjects. Exploratory analyses included vaccine effect on herpes zoster pain, Severity-by-Duration Scores of herpes zoster pain, and worst pain in the last 24 hours. There were also analyses based upon evaluation of the Quality of Life. Questions were included to address activities of daily living interference in the ZBPI questionnaire, and work interference was assessed using the WPQ.

With regard to how Severity-by-Duration scores of herpes zoster pain are calculated, the Severity-by-Duration score of herpes zoster pain is analogous to the burden of illness that was conducted in SPS. The important difference is that the analysis in SPS has a 6-month follow-up time period. Similar to both, this evaluation is sensitive to the incidence, duration, and severity of herpes zoster pain. This is a population measure, and the was the area-under-curve (AUC) is calculated is that it is a sum of areas determined by multiplying average of two consecutive herpes zoster “worst pain in the past 24 hours” score on the pain response curve by the number of days between scores. For example, an AUC score of 56 may represent any combination such that the average severity-by-duration score is 56, for example a pain score of 4 out of 10 for 14 days, followed by a score of 0 of out of 10 the other 7 days; or a pain score of 7 out of 10 for 8 days, followed by a score of 0 out of 10 the other 13 days; or a pain score of 2 out of 10 for 19 days, followed by 9 out of 10 the other 2 days.

Regarding the baseline characteristics for the results of this study population, the Zostavax® and placebo groups were very similar. There were more females enrolled in the study (62%), the mean age was about 55, and race was predominantly White at 94%, with 4.2% Black. Approximately 90% of study subjects reported prior medical conditions, with data collected about years back. The most frequently reported prior medical condition was hypertension (20%); 10% to 20% reported drug hypersensitivity, hypercholesterolemia, seasonal allergy, depression, osteoarthritis, and gastroesophogeal reflux disease; and 5% to 10% reported hysterectomy, back pain, hypothyroidism, hyperlipidemia, insomnia, headache, migraine, asthma, arthralgia, obesity, and type 2 diabetes mellitus. These are not really unexpected given the age group in the study.

With respect to the primary objective results (e.g., incidence of confirmed herpes zoster cases), there were 30 confirmed cases in the Zostavax® compared to 99 in the placebo group. The

total follow-up time in terms of person years was 15,043 in the Zostavax® compared to 15,010 in the placebo group. The estimated incidence rate of herpes zoster per 1000 person-years was 1.994 in the Zostavax® compared to 6.596 in the placebo group. This resulted in a vaccine efficacy in terms of herpes zoster at 69.8%. The lower bound was 54.1%, keeping in mind that the success criterion was for the lower bound to be greater than 25%. It was expected that the vaccine efficacy would be 54% or higher based upon the 59 to 60 year old age group in SPS. This study reached 69.8% (54.1%, 80.6%).

In terms of the exploratory objectives for the entire randomized population, the relative reduction in mean herpes zoster pain severity-by-duration score was 73.0% (52.7%, 84.6%), and this is analogous to burden of illness measure from SPS. At 73.0% this is consistent with the reduction incidence of herpes zoster observed. This was also as expected based on the results in the SPS study. The exploratory efficacy analyses have been conducted on confirmed cases to evaluate clinical characteristics and quality of life measures in subjects who developed herpes zoster. The two vaccination groups were similar with regard to the various outcomes assessed. There was no significant vaccine effect above and beyond vaccine effect on reduction in herpes zoster incidence in the entire study population. Again, these results were as expected based on the findings from SPS. The similarity between the two vaccination groups for these analyses demonstrated that Zostavax® prevented herpes zoster cases across the spectrum of disease severity. In subjects 50 to 59 years of age who received one dose of Zostavax®, Zostavax® significantly reduced the incidence of herpes zoster in 30 versus 99 confirmed herpes zoster cases respectively. This resulted in a vaccine efficacy of 69.8% (95% CI: 54.1%, 80.6%), and demonstrated an estimated 73.0% (95% CI: 52.7%, 84.6%) relative reduction in the mean herpes zoster pain severity-by-duration score consistent with the reduction in the incidence of herpes zoster.

With regard to immunogenicity, all subjects had blood samples drawn at Day 1 and 6 weeks post-vaccination. However, samples were only tested on a 10% pre-specified randomly selected sub-cohort and subjects with suspected cases of herpes zoster for VZV antibody titer by gpELISA. The immunogenicity hypothesis for the study was the secondary hypotheses that Zostavax® would elicit a higher VZV-specific GMTs at 6 weeks post-vaccination compared to placebo. The statistical criterion corresponds to the lower bound of the 2-sided 95% CI on the GMT ratio [Zostavax® / placebo] being >1.4. There were approximately 1100 subjects in each of the two groups. The estimated GMT in the Zostavax® group was close to 664 compared to close to 289 in the placebo group. This results in a GMT ratio of 2.3 (2.2, 2.4). The lower bound on the 95% confidence interval at 2.2 is greater than 1.4, which was the statistical criterion, and the p-value reflects a statistically significant finding. In summary of the immunogenicity results, compared with placebo, Zostavax® induced a significantly higher VZV gpELISA antibody response at 6 weeks post-vaccination with an estimated GMT ratio (Zostavax® / Placebo) of 2.3 (95% CI: 2.2 to 2.4).

Turning to the safety results in the study, subjects were followed for adverse experiences for 6 weeks post-vaccination and for serious adverse experiences for 6 months (182 days) post-vaccination. Subjects were asked to record adverse experiences from Day 1 to 42 post-vaccination on a VRC. Subjects were also contacted at 4 and 6 months post-vaccination to collect serious adverse experiences using the same telephone script that was used in Protocol 020. All vaccinated subjects were included in analyses. The primary safety endpoint was incidence of serious adverse experiences observed during the 42-day follow-up period in each vaccination group. Of the subjects in the Zostavax® group, 73% reported an adverse event compared to 42% in the placebo group. This difference is driven primarily by the different rates of inject site adverse events, which were 64% in the Zostavax® group compared with 14% of

placebo recipients. It was known from earlier studies in people 50 to 59 and people 60 and above that the 50-59 year old age group tended to report higher injection site adverse event, so this was not unexpected. Based on the data from SPS, the overall study showed 48% reporting of injection site adverse events, but the 50-59 year old age group was about 57%.

With regard to non-injection site or systemic adverse events, there were 35.4% in the Zostavax® group compared with 33.5% in the placebo group. This was actually a statistically significant different. All of the specific adverse event terms were not different between the two groups, except for two (e.g., pain in the extremity and headache). When headache is removed from the analyses, the difference goes away, so it appears that the difference in report for systemic adverse advents was primarily attributed to the adverse event of headache. All of the injection site adverse events are considered to be vaccine-related. The non-injection adverse events, by investigator assessment, were 6.7% in the Zostavax® group compared to 4.7% in the placebo group. Serious adverse events were similar at 42 days post-vaccination with 0.6% in the Zostavax® group compared with 0.5% in the placebo. At 182 days post-vaccination, serious adverse events were 2.1% in the Zostavax® group compared with 1.9% in the placebo group. There was one vaccine-related serious adverse event of anaphylactic reaction reported in the Zostavax® group. Similar mortality rates were observed as well, with 1.18 deaths per 1000 person years in Zostavax® group and 1.90 deaths per 1000 person years in the placebo group.

In subjects 50 to 59 years of age who received one dose, Zostavax® was generally well-tolerated. Compared with the placebo group, Zostavax® recipients had no statistically significant difference in rates of non-injection site VZV-like rashes. Vaccine strain VZV was not detected in any rashes that were PCR positive for VZV. The VZV strain could not be determined for one subject with a varicelliform rash in the Zostavax® group. The safety profile demonstrated in this population is consistent with the known safety profile of the vaccine.

In conclusion, in subjects 50 to 59 years of age who received one dose of Zostavax®, Zostavax® significantly reduced the incidence of herpes zoster. Zostavax® induced a significantly higher VZV gpELISA antibody GMT at 6 weeks post-vaccination, and was generally well-tolerated.

Discussion Points

Dr. Keitel asked whether the antibody levels were assessed in the 50-59 year old age group for whom serum samples were collected for patients who subsequently developed zoster in the vaccine group.

Dr. Parrino replied that they did, and what they found was that those who did not develop confirmed cases of herpes zoster had higher GMTs than subjects who did. That held true for both the Zostavax® and placebo groups.

Vaccine Supply

Dr. Jeanne Santoli
Vaccine Supply and Assurance Branch
Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Santoli offered an update on the vaccine supply for adult hepatitis B vaccine, adult hepatitis A vaccine, MMRV vaccine, zoster vaccine, discontinuation of Tripedia and TriHIBit, supply constraints and updates related to specific presentations, and the CDC vaccine supply page.

Merck is not currently distributing its adult hepatitis B vaccine. Dialysis formulation returned to market in August 2010. The adult formulation is anticipated to be available in the third or fourth quarter of 2011. Production and supply of GSK's adult hepatitis B vaccine and hepatitis A/hepatitis B combination vaccine currently are sufficient to meet demand for routine adult usage of adult hepatitis B vaccine.

Merck does not anticipate its adult hepatitis A vaccine to be available until sometime in 2012. Production and supply of GSK's adult hepatitis A vaccine and hepatitis A/hepatitis B combination vaccine currently are sufficient to meet demand for routine adult usage of adult hepatitis A vaccine.

Supply of MMRV, ProQuad®, is expected to be depleted by late February to early March 2011. This is a known product outage and there have been communications with Merck. Merck has an adequate supply of both M-M-R II® and VARIVAX® to meet current demand for MMR and varicella vaccination.

In December, Merck filled a majority of existing backorders of zoster vaccine. Merck will have less product available in the early part of 2011 than previously anticipated. Merck will release doses of Zostavax® more regularly in 2011, but as inventory is building, backorders are still anticipated to occur.

In 2011, sanofi pasteur announced that they will discontinue the supply of Tripedia® (DTaP) and TriHIBit® (DTaP-Hib). Supplies are expected to last through the second quarter of 2011. "Dear Doctor" letters have been sent directly to providers. CDC has also communicated to immunization grantees. Alternative DTaP and Hib products will continue to be available from sanofi pasteur (e.g., DTaP, Hib, and DTaP-IPV-Hib).

GSK anticipates intermittent supply constraints for individual presentations of Infanrix® vials through March 2011, Kinrix® syringes through April 2011, and Engerix B® pediatric vials through April 2011. In all cases, alternative products, presentations, and brands are available to meet overall market demand. Cervarix® vials will be discontinued as of September 2011; however, pre-filled syringes will continue to be available.

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

Discussion Points

Dr. Marcy inquired as to whether MMRV was to be discontinued or would just not be available after March.

Dr. Santoli responded that the issue with MMRV has to do with the varicella bulk issue. Merck has indicated that the priority is on varicella and zoster, and that MMRV would be a third priority. As those issues continue to evolve, they will be able to provide more information about when MMRV would be available again. She invited their colleagues from Merck to offer any additional information.

Dr. James Robinson (Merck) added that Merck is equally as frustrated with its current performance with the varicella product supply. They have been prioritizing the infant supply, which is why that has been in good supply. Zostavax® is a much higher dose, so it takes more bulk does to make a single dose of Zostavax®. This has been the challenge to keeping it in full supply. He has been personally involved with the issues of production and improving production. They are encouraged in that they were able to clear backorders last year, and have had improved supply. However, they have not been able to build an inventory because demand continues to be as high as supply. Until they can build inventory, there will be periodic outages. However, they do expect this to be resolved in the second half of 2011. With regard to MMR+V, Merck wants to ensure that the individual components are available so that people can be protected. Because the combination vaccine also requires a higher bulk dose of varicella, the best way to get the highest number of total doses out is to keep the separate products available. As supply improves, they will continue to consider other opportunities to supply the different products. Merck has also made significant investment into new varicella manufacturing facilities. The sterile fill facility is already approved by FDA for VARIVAX®. A bulk facility is currently being validated, which will allow Merck to significantly increase its varicella supply over the next couple of years. Merck does not plan to discontinue MMRV. It is just temporarily not available until supply improves.

Public Comment: February 23, 2011

Dr. Judy Bernbaum
Children's Hospital Of Philadelphia

I am Dr. Judy Bernbaum, Professor of Pediatrics at the University of Pennsylvania and Director of the Neonatal Follow-Up Program at Children's Hospital in Philadelphia—a position I've held for the last 36 years. I have been involved in this position in direct patient care of high risk and preterm infants. I was surprised this morning by the announcement that the RSV Work Group had disbanded. Since last June, it was reported that at this very meeting, the work group was moving forward with formulating Synagis® guidelines. Now we have lost the transparency process and opportunity for public forum. As a high risk pediatrician, I am concerned about this population of infants contracting RSV and the potential sequelae they may face immediately as well as in the future. It is for these reasons that many of my colleagues and I call into question the 2009 AAP guidelines for the use of Synagis®. These new guidelines were developed based on expert opinion rather than any robust randomized clinical trial. Such clinical trials provided the basis for the initial guidelines.

I am here actually representing a group of experts from around the country, including neonatologists, intensivists, pulmonologists, and those such as I am, who direct neonatal follow-up programs. Each of us has had extensive firsthand experience in providing direct patient care to preterm infants, including those 32 to 36 weeks. We've drafted a document that outlines our position, which is outside for your review on the table outside this room. We have concerns specifically about the scientific basis from which the following changes were made, including the age eligibility criteria, the truncated dosing schedule, and the limitation in the number of risk factors. We are concerned that these changes place preterm infants at considerable risk. In addition, these new restrictions may disproportionately affect minority and low income patients who we know already have a higher incidences of risk factors. We feel this represents a form of healthcare rationing. Without strong data to support the Committee on Infectious Disease (COID) recommendations, we are reluctant to recommend to our pediatric colleagues that they accept any changes that differ from the 2006 guidelines.

Our group, experts in our own right, who represent prominent physicians in our field, are calling for the CDC to make RSV a reportable disease in order to improve the accuracy of RSV prevalence data, and to support an effort to rigorously investigate the scientific merit of these changes with a robust randomized clinical trial to either justify or rescind the current untenable recommendations regarding prophylaxis against RSV in our most vulnerable populations. Thank you.

Dr. Stanley Plotkin
VaxConsult and Sanofi Pasteur

I simply want to inform you that a new website has been developed by the College of Physicians of Philadelphia, the oldest medical society in the US. This is called "This History of Vaccines," www.historyofvaccines.org. It chronicles the development of vaccination from pre-Jennerian variolation practices to the defeat of polio in the Western Hemisphere, the approaches to novel vaccines and vaccine delivery. The site aims to increase public knowledge and understanding of the way vaccines work, how they have been developed, and the role they have played in the improvement of human health. In addition, it may be useful for historical material and lectures, and I am addressing that to the audience here. Timelines step the visitor through the development of vaccines for smallpox, diphtheria, yellow fever, measles, rubella, pneumococcal disease, and others. Articles on topics such as the history of anti-vaccination movements, the role of the military in vaccine development, and cultural perspectives on vaccination are also present. There is a media gallery of over 400 images and videos from the history of medicine, including interviews with Maurice Hilleman, Sam Katz, Hilary Koprowski, C. Everett Koop, D.A. Henderson, Baruch Blumberg, Robert Austrian, and myself. The general public will benefit from the multi-media activities showing how vaccines work, demonstrating host postulates, the principles of herd immunity describing the types of vaccines and how they are made, and illustrating risks from vaccination in context with other types of risks. Finally, there is an epidemic simulation game that challenges players to develop capacity to create vaccines, while at the same time avoiding and controlling epidemics. So I repeat, this is www.historyofvaccines.org.

Dr. Paul Mendelman
LigoCyte Pharmaceuticals, Inc.

Hi, thanks. Dr. Paul Mendelman, Chief Medical Officer at LigoCyte Pharmaceuticals. We heard earlier today that within a few days, the United States of America in terms of a planet is going to have a disappearance of the Japanese Encephalitis Vaccine for children under 17 years of age. Access to vaccines is really important, and it's very simple to do. I urge my Novartis and Intercell friends, and this committee to urge them as well—I've done it at Merck when I was there. I've done it at Aviron, MedImmune, now known as AstraZeneca—you write a protocol and a consent form and you hire a CRO to outsource it just like was done for varicella vaccine for children with leukemia. Before varicella was ever licensed, the CRO was hired, they dealt with it, they got the vaccines out there, the children got vaccinated. There is no indication for immunocompromised hosts for the varicella vaccine. With the JEV, providers can get the safety data at Intercell that will add to their safety database with these small studies that they are already planning to do to show that the vaccine is safe and immunogenic. Thank you.

February 24, 2011

Unfinished Business

Dr. Carol Baker
Chair, ACIP

Dr. Baker called the meeting to order. She indicated that there was no unfinished business from the previous day, except that she was informed that several questions were raised about the zoster presentation late in the afternoon. She instructed those with questions about the zoster presentation to direct them to Dr. Rafael Harpaz during the morning break.

Agency Updates

Health Resources and Services Administration (HRSA)

Responding to a question that arose the previous day about JE vaccine and its possible coverage under the Vaccine Injury Compensation Program, Dr. Geoffrey Evans reminded everyone that there are two prerequisites for a vaccine to be covered under that program. First, it has to be recommended by CDC for routine use in children. Second, it has to have an excise tax imposed. The program covers about 95% of vaccines shipped in the US. Those not covered include JE, yellow fever, and typhoid (under the cover of traveler's vaccines and not recommended for routine use in children). Licensing is irrelevant regardless of whether an IND or licensure application is submitted. The IND issue arose during the effort to deliver H1N1 product rapidly in the U.S. A vaccine has to be recommended for routine use by CDC. In terms of the circumstances that arose with JE vaccine, that criterion would not be satisfied.

Regarding the *Bruesewitz v Wyeth* decision rendered on February 22, 2011, under the National Childhood Vaccine Injury Act, a claim must be filed with the program. It must either be dismissed after 240 days or dismissed by the court if someone is compensated. Compensation must be rejected before being permitted to pursue legal remedies in the civil court system at the state or federal level. The act also specifies what was thought to be fairly clear, but that

became an issue in the Supreme Court hearing in terms of what types of suits can be brought. Two areas that were highlighted in the act were the theories that were pursued during the 1980s when there was a liability crisis. There were hundreds of vaccine lawsuits at that time alleging injury by design defects. The lawsuits alleged that the plaintiffs were not warned adequately that there was a safer product. These two allegations (design defect and lack of warning) were precluded by the act, but the language was ambiguous according to some and that was the basis for the suit that was brought. The Bruesewitz family filed a claim alleging design defect in 1992. The special masters issued a decision rejecting entitlement for the family, who then pursued a lawsuit against Wyeth that was also not successful. Because there were some inconsistencies, a split among federal and state courts as to whether plaintiffs could sue manufacturer for design defects, the Supreme Court accepted the case. Both sides provided arguments on the meaning of the language of the act dealing with design defect claims and what Congress meant by the phrase "unavoidably unsafe." Additionally, the Supreme Court invited the government to provide its own brief as the agency responsible for administering the statue that was at issue. The 6 to 2 decision on February 22, 2011 held that both the language and the structure of the vaccine act preempted all design defect claims. It is now settled law that plaintiffs are precluded from bringing these types of claims against manufacturers in civil court. It does not mean that other types of claims cannot be brought.

National Institutes of Health (NIH)

Dr. Richard Gorman reported that the National Center for Clinical Research (NCCR) is being revised by Drs. Collins and Dr. Guttmacher. Probably of most interest to ACIP is that the Clinical Translational Science Awards (CTSA) will now be moving to the new National Center for Advancing of Translational Science (NCATS), one of the new centers designed by Dr. Collins. The National Institute for Substance Abuse and Addiction (NISAA) is being created, which will take over the portfolio of the National Institute for Drug Abuse (NIDA) and the National Institute for Alcohol Abuse and Alcoholism (NIAAA). Those two institutes' portfolios will be distributed to appropriate institutes or centers. The National Institute of Child Health and Human Development (NICHD) is undergoing a strategic science visioning under Dr. Guttmacher. A series of public meetings will be convened over the next couple of months, each of which will result in a White Paper on the various areas of the NICHD portfolio (e.g., pediatrics, drugs, and therapeutics). For the National Institute of Allergy and Infectious Diseases (NIAID), a series of town hall and informational meetings will be convened regarding the re-competition and the redesign of the HIV and non-HIV networks.

National Vaccine Program Office (NVPO)

Dr. Bruce Gellin indicated that during the NVAC meeting the previous week, the long overdue updated National Vaccine Plan (NVP) was released. ACIP members were provided with a copy and it is available on NVPO's website. The plan was first written in 1994, since which there have been drastic changes. The updated plan provides a 10-year roadmap, which happens to coincide with the Decade of Vaccines, which is getting a lot of coverage as well. He encouraged everyone to review the plan and to determine where they fit, because it is a national not a federal plan. Everyone's support will be required to achieve the goals of the plan. In addition, a shorter more user-friendly version of the document describing the vaccine safety system has been developed. While it is not yet on the NVPO website, it soon will be posted there.

The HHS Assistant Secretary for Health has led a seasonal influenza effort over the past year, with a focus on increasing demonstration projects for use in pregnant women, healthcare workers, and occupational settings and to try to reduce disparities. That project is currently under evaluation. ACIP heard some encouraging data from Dr. Cindy Weinbaum the previous day, and more will be presented about this during the Influenza Summit in May 2011 in terms of lessons learned and moving forward.

National Vaccine Advisory Committee (NVAC)

Reporting on behalf of Dr. Birkhead, Dr. Gellin indicated that the Vaccine Safety Working Group has been developing the draft report regarding the vaccine safety system. There will be an opportunity for stakeholders and the public to review and comment on this report. The Adult Immunization Working Group also has a draft report that will be available soon for review and comment. Stakeholder meetings are planned in Denver and Chicago. There is also a focus on healthcare workers and influenza vaccination in terms of reaching the Healthy People 2020 goals of 90%.

Food & Drug Administration (FDA)

Dr. Wellington Sun reported on some noteworthy approvals that occurred since the last ACIP meeting in October 2010. Gardasil® has a new indication for anal cancer for 9 to 26 year old males, which would be discussed later in the afternoon. They heard the previous day about the JE vaccine booster approval indications. There is also a confirmation study of one of the seasonal vaccines, AGRIFLU, in which a clinical endpoint RCT confirmed efficacy. This is the second seasonal vaccine that has been approved under accelerated approval, which simply means that it is done using serologic endpoints. Under that approval mechanism, FDA requires the sponsor to conduct a clinical endpoint study. An advisory committee meeting is scheduled for February 25, 2011 for annual strain selection, and another is scheduled for April 2011 that will be devoted to the subject of conjugated meningococcal vaccines.

Veterans Affairs (VA)

Dr. Linda Kinsinger reported that the VA has had another successful influenza vaccine campaign, and continues to promote a campaign that they titled, “Infection, Don’t Pass It On.” This campaign is directed toward patients and employees and regards hand washing, good respiratory hygiene, et cetera. The VA set a goal to have 80% of the employees vaccinated against seasonal influenza, although they do not yet know whether they have reached that goal. Some high dose influenza vaccine was made available to facilities that wished to use it, although they do not yet have information on the number of doses administered. Currently, only influenza and pneumococcal vaccines are available without any co-pay to Veterans. The VA is working to make all vaccines available with no co-pay, but that is a long process that requires regulation change.

Indian Health Services (IHS)

Dr. Amy Groom offered a brief update on influenza in the IHS patient population. Last year in response to H1N1, IHS developed a surveillance system based on patient data collected via IHS electronic health records. This was continued through the current season. Weekly reports are posted on the IHS website, with data included on about 60% of the IHS patient population. IHS is tracking influenza-like illness (ILI) as well as vaccine coverage, and is working with the FDA to monitor potential adverse events. Some coverage data were available as of the

previous week. IHS has administered approximately 390,000 doses of influenza vaccine and has achieved a coverage rate of about 30% for the overall population 6 months of age and older. Coverage is approximately 35% among children 6 months to 17 years of age, while adult coverage is approximately 30%. Some preliminary healthcare personnel data are also available. IHS has achieved a 71% coverage rate among its 28,000 healthcare workers. They are not pleased with that coverage, especially given that the VA has set a goal of 80%. Currently under consideration is mandatory influenza vaccination of all employees who work in IHS facilities.

Department of Defense (DoD)

Dr. Jesse Giebe said that it was a privilege and a pleasure to be a part of ACIP, and that he looked forward to learning a lot and providing input from DoD. At this time, he had nothing to report from the DoD.

Evidence Based Recommendations

Jon Temte, MD, PhD, Chair
Evidence-Based Recommendations Work Group

Dr. Temte reminded everyone that the Evidence-Based Recommendations Work Group (EBRWG) was initially established in 2003. He said he learned something new at every ACIP meeting. During this meeting, he learned that the bell that rings them into every ACIP meeting has an inscription on it. Dr. Katz presented this bell to the committee in October 1993. It is inscribed with the phrase, "May the ACIP recommendations always ring clear." The EBRWG was formed to try to assure that ACIP's recommendations are clear and evidence-based. Dr. Temte recognized the members of the EBRWG and acknowledged the hard work of everyone involved, emphasizing that the CDC staff lead, Dr. Faruque Ahmed, was very instrumental in helping to bring this to fruition.

The terms of reference for the EBRWG were to develop a uniform approach to making explicit the evidence base for ACIP recommendations. On October 28, 2010, ACIP voted unanimously to adopt a methodology to assist in the development of clear and uniform evidence assessment and reporting for future ACIP recommendations based on a modification of the Grades of Recommendation Assessment, Development and Evaluation (GRADE) methodology. The EBRWG has now officially disbanded following the completion of the specified terms of reference set forth by ACIP.

With regard to additional evidence-based recommendation activities, emphasis has been placed on maintaining communication and parallel tracks with international vaccine colleagues, including WHO's Strategic Advisory Group of Experts (WHO-SAGE). Drs. Temte and Ahmed were fortune enough to attend a meeting in Berlin in November 2010, the International Workshop on Procedures for the Development of Evidence-Based Recommendations for Immunization. This was a very interesting and worthwhile meeting where they learned about what a number of our colleagues, especially in the European countries, are doing in terms of evidence-based recommendations and setting agendas for the future for possible cooperation in evidence reviews. Several EBRWG publications are also being finalized, including an article based on the final work group document, a guidance document for other work groups and CDC

staff to be posted on ACIP website, and a concise *MMWR* publication (notice to readers or policy note) linking readers to the guidance document.

To maintain evidence-based activities pertaining to vaccine recommendations, a Simultaneous Individual Consultation Group on Evidence-Based Methods has been established to initiate the implementation of evidence-based methods for vaccine recommendations. The first issues this group will address include zoster vaccine for adults less than 60 years of age, HPV vaccine for boys, and hepatitis B vaccine for diabetics. The other emphasis of this group will be the education of CDC staff and ACIP work group members on the methodology.

Immunization in the United Kingdom

Professor DM Salisbury, CB
Director of Immunisation, Department of Health
London, United Kingdom

Dr. Salisbury noted that he was at a considerable disadvantage in having to speak after the well-deserved accolade to Dr. Katz. During this session, Dr. Salisbury reported on United Kingdom immunization coverage up to and including 2011 with regard to the schedule, infant immunization coverage, MMR, influenza vaccination, and HPV vaccination.

The UK immunization schedule differs from the U.S. schedule. For example, the UK administers only 2 doses of pneumococcal conjugate vaccine (PCV) to young infants, followed by a third dose when they are 12 to 13 months of age. That is, the UK uses one fewer doses. The schedule is as follows:

When	What	How many
2 months	DTaP/Hib/IPV PCV	One injection One injection
3 months	DTaP/Hib/IPV MenC	One injection One injection
4 months	DTaP/Hib/IPV PCV MenC	One injection One injection One injection
12 – 13 months	Hib/MenC PCV MMR	One injection One injection One injection
3 years 4 months	DTaP/IPV or dTaP/IPV MMR	One injection One injection
Girls 12 – 13 years	HPV	Three injections
13 – 18 years	Td/IPV	One injection
Influenza	All over 65 years All pregnant women Medical risk factors and carers	One injection One injection One or two injections

In terms of coverage, Dr. Salisbury shared data for the period July through September 2010 reflecting immunization coverage for all antigens by 12 months, 24 months, and 5 years of age by Strategic Health Authorities (SHAs) and country (England, Wales, Scotland and Northern Ireland). These data were for all children who reach a particular birthday during that quarter. He emphasized that these data are actually for every child in the country—not just samples. For the England SHAs, Wales, Northern Ireland, Scotland, and the United Kingdom, by 12 months of age vaccine coverage for was over 90% for each of DTaP/IPV/HIB3, MenC2, and PCV2. By 24 months of age vaccine coverage was over 90% for each of DTaP/IPV/HIB3, MenC2, and Hib/MenC and over 88% for PVC booster and MMR1. By 5 years of age vaccine coverage was over 90% for each of DTP/Pol3, Hib3, MenC, and MMR1 and over 84% for MMR2 and DTaP/IPV. Routine coverage figures are updated every quarter, and the data are available about a month to six weeks after a quarter has ended. Tracking the same cohorts allows them to determine which children are not vaccinated, observe trends, and project future immunization coverage.

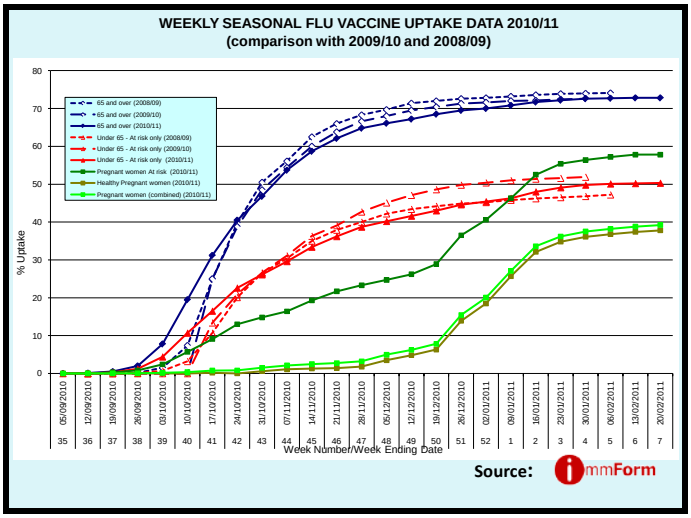
For an MMR catch-up campaign, new software was sent to all general practitioners that identifies which children aged 5 to 18 in their practice databases have not received either zero, one, or two doses of MMR so that they can notify them for catch-up. This program has been in place for about two years now, and there has been a progressive decline in the number of children who have received zero doses and the number of children in this cohort who have had 2 doses of MMR has been progressively rising. Two types of surveillance are being conducted for measles. Statutory notifications of measles are required when a doctor believes that a child has measles. A case definition is not utilized. It is sufficient simply to consider that the child might have measles to report it. However, since the mid to late 1990s, salivary surveillance has been used to confirm suspected cases of measles. There have been very high completion rates of sampling for saliva in suspected cases of measles. Over the last year, there have been very few cases apart from an increase that was linked to transmission at social gatherings of traveling families.

An uptake survey process called ImmForm is used to collect data. This was set up in 2004 to replace a fragmented, paper-based, labour-intensive process. This was designed, built, and is hosted by the Informatics Team in the DH Immunisation Branch. The ImmForm service has brought local and national processes together, saving time, providing information in easily accessible formats, and saving money. It provides a bulk upload process for approximately 50% of general practices. A further 15% use semi-automated processes. Since 2007, weekly and monthly influenza and pneumococcal vaccine uptake data, pandemic flu vaccine coverage, MMR catch-up, and school-based HPV vaccination data have been collected. This system provides data for the NHS, with validated and timely data for management of the National Immunisation Programme, whilst reducing the front-line burden for collecting and managing data. Near real-time data allows programs to be adjusted mid-course, if necessary.

Using ImmForm for seasonal influenza vaccination for 2010-2011, weekly data have been received from 50% of general practices, while monthly data have been received from 100% of practices in England. The response rate is 96.2% response rate, with 7980 or 8293 practices reporting. A total of 52,217,430 general practice-registered patients aged over 6 months have been surveyed. Of these, 65.5% have been submitted via automated or semi-automated methods. Automated data for the week ending each Sunday are available to DH between Monday and Wednesday and are published on Thursdays. Monthly data are usually published within a month of the end of the survey. Anonymized data are reported by risk factor (e.g., over 65, medical conditions, pregnant with risk factors, pregnant healthy, et cetera). In addition, practitioners can use the ImmForm process to order vaccine for any of the centrally provided

vaccines through this system. Thus, this system is used to track coverage and for ordering and distributing vaccine.

Dr. Salisbury shared several screen shots of the system to illustrate what these data may be used for (e.g., national uptake, regional uptake, uptake by PTC, individual GP uptake). The uptake reports show number of practices total, number of forms completed, number of practices reporting, vaccine uptake for those aged 65 and older, all patients under 65 years of age, and those under 65 years of age with medical risk factors. The regional report breaks this down for localities (e.g., the individual districts within the region), while the GP report breaks it down by specific practices. Hence, they can identify performance down to the individual practice level. The Department of Health receives these data every week for the entirety of each country, with data measured in almost real time. The following example illustrates how the data are used for seasonal influenza vaccination:



In November 2010, for under 65 with medical risk factors, the Department of Healthy began to observe that the trajectory was falling away from previous years. This information was sent back to the coordinators at the local level, along with their current performance data, and they were told to identify and work with their lower achieving practices to improve their immunization coverage. This is the first year that all pregnant women have been routinely vaccinated rather than just those with medical risk factors. When it was observed coverage was not increasing sufficiently, pressure was increased to vaccinate these women, particularly through the media. This effort effectively doubled the coverage of pregnant women, especially those with risk factors. For all pregnant women, 40% uptake has been achieved. One of the consequences of the pressures on performance and media reporting of the seriousness of H1N1 in 2010 was that shortages of seasonal flu vaccine started to be reported. In response, the Department of Health released H1N1 monovalent vaccine from the central store. On January 6, 2011 the decision was taken to release this vaccine to any provider who wanted to use it. By the next day, the ImmForm process was adapted to receive orders for H1N1 vaccine. By the following Monday, deliveries began directly to practices with practices receiving vaccine either the day of ordering or the next day. The Health Department was able to produce daily maps to determine exactly who is ordering vaccine, how much and when it was ordered and delivered.

The Department of Health manages a school-based HPV vaccination program through which schools are visited three times per year by teams of public health nurses to vaccinate all girls 12 to 13 years of age. Coverage is measured by local providers using the ImmForm system with national and local data being published monthly. The first cohort to be vaccinated was in 2008 / 2009. By the end of that year, first dose coverage reached approximately 88%, second dose coverage was about 85%, and third dose coverage was just under 80%. During the second year of the program, pandemic influenza led to a decreased coverage due school absences. Additionally, the catch-up program for four cohorts of older girls ages 13 through 18 years was running simultaneously.

The Department of Health also undertakes regular surveys of parental attitudes as a further means of assessing immunisation acceptance, rejection or relevant factors in parental decision making. Each year, approximately 1000 mothers are interviewed about what they know about vaccines, where they get their information, whom they trust, who they want to receive information from, whether they are satisfied with the program, and their perceptions of disease seriousness and vaccine safety. Data on perceptions of safety of MMR over the previous decade showed a decline in perceptions of safety that followed the media reporting surrounding claims of links between MMR vaccine, autism and bowel disease reaching a nadir in about 2002/3. Since that time there has been a gradual restoration of parental confidence in safety of MMR. The reporting of confidence in MMR safety has been a reliable proxy for immunization coverage. Recently, perceptions of risk of MMR have waned such that MMR is not seen as carrying any different risk than other childhood vaccines: this displacement effect seems to be associated with concerns over the safety of H1N1 vaccine. UK experience has shown that there are always concerns about safety when vaccines are new and that it takes a few years for a new vaccine of any type to be accepted as safe compared with the other vaccines.

In conclusion, Dr. Salisbury recapped that coverage is measured through processes that are very extensive for all immunization programs. The system is automated as much as possible in order to obtain data in real time for use in program management. In addition, input is acquired from parents so that their views are reflected in the way that the immunization program is implemented.

Discussion Points

Dr. Keitel requested information about how the UK incentivizes or compels general practitioners to provide this information.

Dr. Salisbury responded that they do not incentivize or compel anybody to provide any information. The fact that GPs are customers for the information systems means that they are party to the data being collected. The data are anonymised and since their collection is automated, nothing specific is required by the GPs.

Referring to the decreased fear about MMR due to increased concern about pandemic influenza vaccine, Dr. Meissner asked whether Andrew Wakefield's impact had disappeared and whether that was the reason there was more confidence.

Dr. Salisbury clarified that over time confidence in the safety of MMR has changed for a number of reasons: the tone and balance of media reporting; scientific confidence in the safety of MMR

and lack of evidence of harm; parents are more confident, because care providers have been more effective in communicating to their patients about the safety and value of MMR.

Dr. Jenkins requested further information about the methods for engaging parents and acquiring their input.

Dr. Salisbury replied that they have conducted about 34 of these surveys over the years, using market research to interview around 1000 mothers of young children. The focus is primarily on mothers because fathers make less impact on the decision-making. The surveys are done by face-to-face computer-assisted interviews rather than by telephone, and they are conducted on a random basis that covers all demographic groups. A standardized set of questions is administered, and the interview lasts approximately an hour. These surveys result in a major resource of information that allows the health department to assess decision-making, consent, et cetera. In addition, small group work using focus groups is done before introducing a new vaccine or changing a policy to obtain more in-depth information.

Dr. Duchin requested clarification about whether this exchange of information is all done by the government in the UK.

Dr. Salisbury responded that he has a team within the Department of Health that manages the immunization program. There is a sub-group that deals with informatics, a group that deals with vaccine purchase and supply, a communications group, and a policy group. The team had been increased to cope with pandemic influenza, but the core program is run by approximately 25 to 30 people. The epidemiological and other data are collected and analyzed by the Health Protection Agency on the Health Department's behalf to support the immunization program. The data that had been presented represented a mix of the Health Department's in-house data and data from the Health Protection Agency.

Dr. Duchin observed that having the government intimately involved in the collection of data and delivery of healthcare services seemed to be producing a very good result in the UK. He wondered whether this was causing any problems for citizens in any way.

Dr. Salisbury indicated that parents responded in the surveys that health professionals and the National Health Service (NHS) are the most trusted sources of advice on immunization. Parents recognize that family and friends may not give them the most accurate information. The figure for primary care, health professionals, general practitioners and the nurses who work with them was of the order of 87% to 88% trust. Trust for the National Health Service was almost as high. They trusted the government at about 57% or 58%. Trusting family and friends was 49%, and trusting the media was 21%. The media is hugely influential, but they are not necessarily trusted for the advice they give.

Regarding the delivery model, Dr. Sawyer noted that the US has explored school-based immunizations with mixed success, largely because of the lack of personnel to administer them. He asked who in the UK school setting delivers the vaccines.

Dr. Salisbury replied that the Immunization Program has access to school health nurses who are part of the local area public health provision. They have been invaluable in delivering school-based programs. For the HPV program, teams of nurses go into schools and are extraordinarily good at carrying out this program. They have been used for campaigns in schools on other occasions as well, such as the delivery of the Meningitis C vaccine in schools.

Dr. Chilton pointed out that one of the most salient differences between rates in the UK and the US was observed in HPV, especially HPV3. He wondered what barriers the UK encountered and how they overcame them to deliver HPV in schools.

Dr. Salisbury responded that they met with extraordinarily few barriers. They had worried about barriers in advance of the HPV vaccine program launch, such as acceptability in different communities. Before they started the program, a significant amount of research was done with parents. They began with a view that they would vaccinate in the final year in primary school at about ages 10 to 11. Parents were not comfortable with the notion of vaccination against a sexually transmitted disease for primary school age children, so the age range was shifted to the second year of secondary school at ages 12 to 13. That was much more acceptable to parents and to the girls themselves. The Department of Health also offered meetings with representatives of the faith communities before starting the program in order to identify whether there were any ethical or religious issues for different faith communities. There was concern that the first year of immunization for HPV in schools was going to coincide with Ramadan. The issue was not about receiving an immunization during Ramadan, rather it was about the girls fasting and whether they may faint. The solution was to permit those schools with a high proportion of girls in particular communities to start their programs when they thought it was best locally. There was little overt opposition to the program, probably due to promotion of the program based on the benefits of preventing cervical cancer. Most people viewed the prevention of cervical cancer as a worthwhile goal.

Human Papillomavirus Vaccines (HPV)

Introduction

Eileen F. Dunne, MD, MPH
ACIP HPV Vaccine Work Group

Dr. Dunne reminded everyone that in October 2009, the FDA licensed the quadrivalent HPV vaccine for males 9 through 26 years for prevention of genital warts. ACIP stated that HPV vaccine may be given to males 9 through 26 years for prevention of genital warts, but did not include the vaccine in the routine immunization schedule for males. ACIP voted to include HPV vaccine for eligible males in the VFC. In December 2010, the FDA included the indication for prevention of anal cancer in females and males.

Data presented during the HPV vaccine session during the October 2010 ACIP meeting included HPV vaccine uptake in females; relevant programmatic issues for vaccine implementation; quadrivalent HPV vaccine clinical trial data in males; provider knowledge, attitude, and practices on male HPV vaccination; updates on cost-effectiveness of male vaccination; and consideration for HPV vaccination recommendations in males. In addition, requests were made by ACIP members for additional information. This included updates and clarification of the burden of HPV-associated cancers in the US, information on anal HPV infection and anal cancers, cost-effectiveness modeling with different assumptions, and healthcare use by young men who have sex with men (MSM).

As a reminder about the reason for focusing on young adolescents for HPV vaccination, Dr. Dunne reported data from a population-based survey, the National Survey of Family Growth (NSFG), which provides information on the percentage of adolescents who have had vaginal sex, by age, for both females and males. According to these data, both females and males have an increasing prevalence of ever having vaginal sex. At age 18, 70% of females and 62% of males have had vaginal sex [Mosher et al., 2005; Vital and Health Statistics: No. 362].

Young women acquire HPV infection soon after sexual debut. About 40% of young women will have acquired any HPV infection within 24 months after sexual debut, and this increases with time [Winer R, Am J Epidemiol, 2003;157]. Similar to females, males also acquire HPV rapidly. In a study of young men who have sex with women who were sampled at genital sites for HPV DNA, 24 months after enrollment, over 50% of young men had acquired any HPV [Partridge, JID 2007]. Although HPV can lead to cancers and other diseases, most infections clear. Many studies have demonstrated this rapid clearance of HPV in females. Recent studies have demonstrated the same thing in men. A study of clearance of any HPV and clearance of HPV 6, 11, 16, 18 in males showed that HPV is cleared rapidly in males, as in women, and most men had cleared any HPV infection by 24 months [Giuliano AR, JID 2008;198].

With regard to the overview of the important diseases / cancers caused by HPV types 16, 18, 6, 11, in addition to cancers, an important burden of low and high grade intraepithelial neoplasias, such as cervical intraepithelial neoplasias, are caused by HPV 16 and 18. According to some estimates, there are about half-million cases of CIN each year, and 30% to 50% may be attributed to HPV 16 or 18. These cervical abnormalities are detected through routine cervical cancer screening. HPV 6, 11 can cause low grade intraepithelial neoplasias, and over 90% of genital warts and recurrent respiratory papillomatosis [Clifford GM, BJ Ca 2003, Munoz Int J Cancer 2004; Brown J Clin Micro 1993; Carter Cancer Res 2001; Clifford Cancer Epi Biomarkers Prev 2005; Gissman Proc Natl Acad Science 1983; Kreimer Cancer Epidemiol Biomarkers Prev. 2005; and Insinga RP et al. American Journal of Obstetrics and Gynecology 2004].

Regarding the natural history of HPV infection to cervical cancer, initial HPV infection occurs soon after sexual debut and most of these infections clear within 2 years. However, some of these HPV infections can lead to abnormalities like low grade changes in the cervix, or cervical intraepithelial neoplasia 1 (CIN 1). Oncogenic HPV infections can persist and lead to cervical cancer and cervical pre-cancers (CIN 2/3) over years to decades. Cervical cancer screening programs often detect cervical diseases early, before it leads to cancer. However, it is important to note that cancer screening programs do not exist for a number of the other HPV–associated cancers.

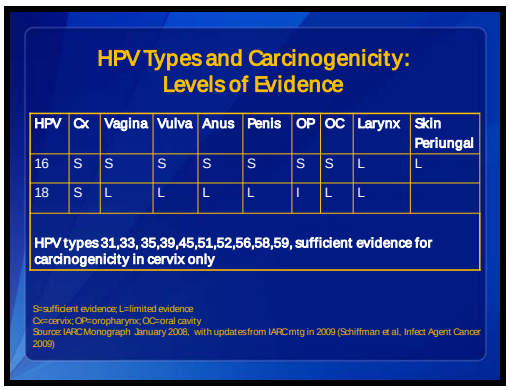
Although the natural history of cervical HPV infection leading to cervical pre-cancers and cancers is well-characterized, there are important HPV natural history knowledge gaps. Little is

known about the natural history of HPV infection in other anatomic sites, such as natural history of infection to development of cancer of the oropharynx. Although most sexually active persons will acquire HPV, less is known about determinants of progression to disease / cancer. Persistent oncogenic infection, immunosuppression, or HIV infection all can contribute to progression, but other host and viral factors are poorly characterized. Data are unclear on the role of natural immunity in preventing HPV infection. Some studies describe protective immunity to type specific infection, while others do not.

Burden of HPV-Associated Cancers in the United States

Mona Saraiya, MD, MPH
Division of Cancer Prevention and Control
Centers for Disease Control and Prevention

Dr. Saraiya reported on the burden of HPV associated cancers in the US. The International Agency of Research on Cancer (IARC), which is an arm of WHO, invited experts in 2005 and most-recently in 2009 to determine if and which type of HPV was a carcinogen based on variety of evidence. Their conclusion regarding levels of evidence are reflected in the following table:



HPV Types and Carcinogenicity: Levels of Evidence

HPV	Cx	Vagina	Vulva	Anus	Penis	OP	OC	Larynx	Skin Periungal
16	S	S	S	S	S	S	S	L	L
18	S	L	L	L	L	I	L	L	

HPV types 31,33, 35,39,45,51,52,56,58,59, sufficient evidence for carcinogenicity in cervix only

S=sufficient evidence; L=limited evidence
Cx=cervix; OP=oropharynx; OC=oral cavity
Source: IARC Monograph January 2008, with updates from IARC mtg in 2009 (Schiffman et al, Infect Agent Cancer 2009)

HPV 16 has sufficient evidence for almost all of these cancers except for pharyngeal and skin and periungal cancers. HPV 18 has only been found to have sufficient evidence for cervical cancer, and the other HPV types also have only been found to have sufficient evidence for cervical cancer only. For oral cavity cancer, even though HPV DNA has been detected, whether HPV is etiologic remains unclear. Several studies report weak but significant associations between HPV seropostivity or oral HPV infection and oral cavity and laryngeal cancer. However, most studies estimate that HPV may play a role of 3% at most for oral cavity cancers. It is really difficult to determine a cause-effect relationship and the possible role of anatomic misclassification of the primary tumor site for these findings.

Summarized literature from US studies that have examined tissues from these cancers to determine whether HPV is present are reflected in the following table:

Cancer	Any HPV % (95% CI)	HPV 16/18 % (95% CI)
Cervical	96 (95-97)	76 (NA)
Vaginal	64 (43-82)	56 (35-76)
Vulvar	51 (37-65)	44 (30-58)
Anal	93 (86-97)	87 (82-91)
Penile	36 (26-47)*	31 (22-42)
Oropharyngeal	63 (50-75)	60 (47-72)

It is important to note that HPV DNA prevalence or positivity does not necessarily mean that that is the percent attributable to that cancer or causes that cancer. Cervical cancer has the most evidence because it is based on more evidence than just HPV positivity. All of the other cancers are more likely based on the HPV DNA positivity. There are other causes for particular cancers, such as smoking and alcohol. For vulva cancers, there are some chronic disease conditions as well. The percentage estimates will increase as more data become available for recent studies. It is important to keep in mind that these percentages are going to be combined with the actual number of cancer cases from the U.S. to estimate the burden of HPV associated cancers. For example, for anal cancer, 93% are HPV positive and 87% are due to HPV16 / 18 of all anal cancers.

"Oral cavity" and "pharynx" are the terms often used in cancer registries / official cancer registry data. Oropharynx represents approximately 20% of all oral cavity / pharynx cancers among females and approximately 37% among males. Given that people tend to use these terms interchangeably, Dr. Saraiya clarified the definitions. Head and neck cancer is a broad overall category that includes the nasal cavity, sinuses, lips, oral cavity, salivary glands, throat, and larynx. Within the head and neck cancers, there are oral cavity cancers that include the lips, labial and buccal mucosa, anterior two-thirds of the tongue, retromolar pad, floor of the mouth, gingiva, and hard palate. The pharynx includes the nasopharynx (the upper part of the throat behind the nose), oropharynx (the middle part of the pharynx), and hypopharynx (the bottom part of the pharynx). It is the oropharynx that is the concern with regard to HPV-associated cancers. The oropharynx includes the palatine and lingual tonsils, posterior one-third (base) of the tongue, soft palate, and posterior pharyngeal wall. Cancer registry data uses the broad categories "oral cavity" and "pharynx" cancers. Therefore, it is often not possible to know the specific subset without further analyses.

Cancer registries in the U.S. have been in existence since 1973, beginning with the National Cancer Act, which called for the creation of the Surveillance, Epidemiology and End Results program (SEER) to be funded through the National Cancer Institute (NCI). At that time, the program collected cancer incidence and survival data from 5 state cancer registries and 4 metropolitan areas, covering about 10% of the US population. Today, SEER collects cancer

data for about 26% of the population. Although SEER was intended to be population-based and representative of the U.S. as a whole, there remained a need for a more comprehensive cancer registry program covering the remainder of the US. In 1992, the National Program of Cancer Registries (NPCR) was established through Public Law, and is funded through CDC's Division of Cancer Prevention and Control (DCPC). NPCR collects cancer incidence data only and covers 96% of the US population. At the outset, 36 states covered by NPCR already had existing registries, but 13 had no such infrastructure. With the creation and implementation of NPCR in addition to SEER, all states now have central cancer registries. NPCR focuses only on incidence, but there is a lag time of 22 months by the time an initial cancer is diagnosed to the time it appears in the cancer registry because a great deal of work must be done with respect to quality assurance, de-duplication, et cetera. There is additional reporting delay on both of these systems of approximately 8 to 12 months.

In the U.S., there is a need for real-time data, so the American Cancer Society (ACS) provides estimates for the US using projected data. This requires a complex modeling scheme that takes into account screening prevalence, smoking prevalence, and age cohort studies. The data sources used are from 1995 to 2006. More importantly, for HPV-associated cancers, these data do not allow for examination of sub-sites that are potentially HPV-associated. Although the overall total numbers are similar for NPCR- and SEER-reported cancer cases and ACS data, specific sites vary substantially. Counts for cervical cancer vary by 9%, vulvar by 16%, and female breast cancer by 12%. Although anal cancer for males is similar, for females there is a 14% difference. Oropharyngeal cancer cannot be compared directly as oropharyngeal is grouped together with oral cavity estimates. Penile cancer cannot be compared with vaginal cancer because vaginal cancer is grouped together with other female genital cancers in the ACS estimates. To determine HPV-associated cancers on an annual basis, it is necessary to conduct a sub-specific analysis rather than relying on estimated data.

With respect to how HPV cancers rank among female cancers in the U.S., in the 1950s and 1960s, the picture would have been different with cervical cancer being one of the most common cancers. However, screening improved treatment of pre-cancerous lesions, which has changed the picture. Cervical cancer, the most common HPV-associated cancer, was the 13th most common cancer among females in the U.S. in 2007, followed by oral cavity and pharynx, remembering that just a subset of these are considered to be HPV-associated. Vulvar and anal cancers ranked 21st and 23rd respectively, and vaginal cancer was quite rare at an estimated rank of 33. For males, oral cavity and pharynx cancers ranked 8th in the US during 2007. The next most common cancer with any association to HPV was anal cancer, which was the 26th most common cancer, and ranked just below male breast cancer. Penis cancer was even rarer, with an estimated ranking of 31 [NPCR/SEER database, 2010 submission year].

Estimated HPV and HPV 16/18-associated cancers for both sexes from 2004 to 2007 were updated from data shown by Dr. Markowitz during the October 2010 ACIP meeting which reflected data from 1998 to 2003. These are surveillance data from cancer registries, so they do not have information on HPV status. The point is to try to estimate the number of HPV cases. The average annual number of cases from 2003 to 2007 is defined by histology and anatomic site. The estimated numbers due to any HPV based on any HPV 16 / 18 is based on the percentage in the literature. Overall, there are approximately 25,000 HPV-associated cancers adding these two together, approximately 22,000 cancers of which are due to HPV 16 and 18 in the US. Dr. Markowitz's data showed a total of 19,000 due to HPV and 17,000 due to HPV 16 / 18. The 2004 to 2007 estimates are believed to higher because more recent data were used that had higher population coverage. The U.S. data were updated on the percent of HPV positivity, which actually reflect the increasing trend [Watson M et al. Cancer 2008. Data

source: National Program of Cancer Registries and SEER, covering 83% coverage of US population. + Gillison ML, et al. Cancer 2008].

According to trends in potentially HPV-associated cancers for females from 1973 to 2007 using SEER 9 data and covering about 9% of the population, cervical, vaginal, and oropharyngeal cancers declined during the time period, while anal cancer increased approximately 2% per year. It is important to note that potential HPV-associated cancers are called "potential" because they are derived from pure cancer registry data. In the same data for males, anal cancer increased about 3% a year and oropharyngeal cancers increased about 1% per year, while penile cancer decreased.

In conclusion, cancers associated with HPV include cervical, vaginal, vulvar, anal and oropharyngeal cancers. "Head and neck" cancers have an important burden, but the oropharynx is the only site strongly associated with HPV. Cancer Registries and data are a valuable resource, but it is important to know where the data come from and that there is a lag period of approximately 2 to 3 years. There are approximately 25,000 HPV-associated cancers and approximately 22,000 HPV 16/18-associated cancers. There is a trend of increasing oropharyngeal cancers, especially in men, and anal cancers in men and women.

Anal HPV infection, AIN, and Anal Cancer

Joel Palefsky, MD, FRCP(C)
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Dr. Palefsky is trained in infectious diseases and is the founder and director of the UCSF Anal Neoplasia Clinic, which was the first clinic devoted to the detection and prevention of anal cancer by screening for and treating AIN. He is also the Founder and Chair of NCI AIDS Malignancy Consortium HPV Working Group, a Member of the Board of the American Society for Colposcopy and Cervical Pathology (ASCCP), and a Member of the Board of the HPV and Anal Cancer Foundation. He is also a recipient of grant funding from Merck and Company, a member of several of Merck's scientific advisory committees, and an investigator on the Merck 020 protocol. He is also a board member of Pharmajet Incorporated and Aura Biosciences.

During this session, Dr. Palefsky discussed the biological similarity between anal and cervical cancer; the demographics and risk factors for anal cancer; and the epidemiology of anal HPV infection and high-grade anal intraepithelial neoplasia (AIN).

For the epithelium, with many layers of stratified epithelium and some keratin, the thought is that HPV first sets up infection in the basal cell layer. To get through those layers of keratin and many layers of keratinocytes, it is thought that some sort of breach is required in the epithelium. That can occur in a number ways, including trauma, which is a mechanism thought to be particularly germaine in the setting of anal HPV infection. Typically, the early regions of the HPV genome are expressed first, which are important for viral replication. As the cells mature, late gene expression occurs, including capsid formation and the formation of infectious virions, which are then shed or spread potentially to other areas of the epithelium or potentially to sexual partners.

The anal canal has many similarities to the cervix and this is what much of the approach to diagnosis and treatment of AIN is based upon. That includes the fact that the primary site of the HPV infection in the anus is an area called the transformation zone, which is also discussed in

the context of the cervix. In the cervix, this is where the squamous epithelium of the exocervix meets the columnar epithelium of the endocervix. In the anus, this is where the squamous epithelium of the anus meets the columnar epithelium of the rectum. The anorectal junction is therefore biologically similar to the cervical transformation zone. However, it is internal and cannot be seen through perianal visual inspection. Similar methods to those used in the cervix are used to establish levels of disease (e.g., cytology by inserting swabs, high resolution endoscopy, biopsies of visible lesions).

The spectrum of disease that occurs in the anal canal is similar to what occurs in the cervix, moving from low-grade disease (e.g., CIN or AIN1), which is not considered precancerous, through high-grade disease (CIN2/3, AIN2/3). AIN 2/3 are considered to be the cancer precursor and show the same morphologic changes seen in the cervix. The thought, just like in the cervix, is that this lesion may remain for a long time, perhaps decades, before ultimately the cells cross the membrane to become an invasive cancer. The thought again, just like in the cervix, is that that period of time offers an opportunity to detect the lesion and potentially treat it before progression occurs. Dr. Palefsky shared several photographs to illustrate what some of the lesions look like. It would never be said that anal and cervical cancer are the same disease because they are in different sites, but they are about as biologically similar as two different sites can be and they have the same profile of HPV infection. The great majority of the cancers are HPV 16-related, and there is very little difference in the proportion of HPV positivity between men and women. Anal cancer is essentially the same disease in men and women.

As Dr. Saraiya pointed out, ACS produces estimates for the number of new cases. In 2010, they estimated that there would be about 5260 cases. Dr. Palefsky emphasized that in the US general population, anal cancer is still predominantly a disease of women compared with men. In addition, the mortality rate tends to be somewhat on the low side compared with the overall incidence rate, because often times these cancers are diagnosed at early stages and are amenable to combined radiation and chemotherapy. While that is great news, he also stressed that it is still a bad outcome because, while the treatment is often successful, the radiation in particular is inducing a very high degree of morbidity. There is typically a lot of pain, bleeding, and very severe symptoms for many years—even after successful therapy.

With respect to the incidence change in anal cancer between women and men, anal cancer is increasing by about 2% per year, somewhat more in men. This has also been shown in some of the Scandinavian registries, with an increase in both men and women. In terms of who progresses to anal cancer, it is believed that HPV is necessary, but insufficient. Some of the risk factors for anal cancer reflect the risk of getting HPV. Amongst the risks is the number of sexual partners. It is not necessary to engage in receptive anal intercourse to get anal cancer; however, according to a review of the data over a long period of time, anal receptive intercourse is perhaps the most efficient of getting anal HPV. Current smoking has been associated just like in the cervix. One difference from the cervix is that chronic irritation (typically in the form of chronic hemorrhoids, fissures, and fistulas) is a well-known risk factor [Daling JR et al. *Cancer*. 2004;101:270-289; Holly EA et al. *J Natl Cancer Inst.* 1989;81:1726-31]. Other HPV-associated cancers are also associated with anal cancer, not surprisingly, and it may well reflect the fact that people are getting HPV shed from some of those other sites or there is a common exposure. These include cancers of the cervix and the vulva. In the last few decades, immunosuppression has taken on an increasingly important role as a risk factor. One of the most common forms of immunosuppression is HIV, but other forms of immunosuppression may also be important, such as those seen in solid organ transplants [Palefsky JM et al. *Obstet Gynecol Clin N Am*. 2009;36:187-200].

Although the incidence of anal cancer is low in the general population of men, it is important to understand that there are some risk groups that are at particularly high risk of anal cancer. Of these, probably the risk is the highest among MSM and even higher amongst HIV-infected MSM. It is difficult to determine the number of cases of male anal cancer contributed to by MSM because the registry data do not include information on sexual orientation. The best estimate using a variety of calculations is that the proportion of cases among men contributed by MSM is almost certainly more than 50%, though the exact percentage is not known. Putting that into the context of cervical cancer, cervical cancer prior to cervical cytology screening was 40-50/100,000[1]. Cervical cancer is currently 8/100,000 and anal cancer among HIV- MSM is up to 37/100,000[2] [[1]Qualters JR, Lee NC, Smith RA, Augert RE. MMWR 1992, 41:1-15; [2] Daling JR, Weiss NS, Hislop TG, et al. N Engl J Med 1987, 317:973–977].

Adding in HIV, it appears as though that risk has increased even more. In HIV-positive men, the increase is about 38-fold higher than the general population of men, and HIV-positive women are at a 37-fold higher increased risk of anal cancer compared with the general population of women. The risk is even higher among individuals who reported a history of receptive anal intercourse, but it is also increased significantly amongst those who have never had receptive anal intercourse (e.g., men who acquired HIV through injection drug use). In that group, the increase is about 5- to 6-fold, while it is about 60-fold in people who have a history of receptive anal intercourse.

In the era of highly active antiretroviral therapy (HAART), it would seem that the incidence of anal cancer would drop with the immune reconstitution that results from this treatment regimen. However, for a number of reasons, it appears that the trend is in the opposite direction. The following relatively recent papers show high incidences of anal cancer in HIV-positive MSM:

- 75/100,000 person-years among HIV+ MSM since 1999
  - → Piketty C, Selinger-Leneman H, Grabaret S, et al. *AIDS*. 2008;22:1203-1211

- 78/100,000 person-years among HIV+ MSM since 2000
  - → Patel P, Hanson H, Sullivan S, et al. *Ann Intern Med*. 2008;10(148):728-736

- 137/100,000 person-years among HIV+ MSM since 1996
  - → D'Souza G, Wiley D, Li X, et al. *J Acquir Immune Defic Syndr*. 2008;48(4):491-499

Turning to the underlying cause of HPV infection, population-based data pertaining to the prevalence of anal HPV among MSM who were HIV-positive and HIV-negative show that 57% had anal HPV positivity in any one sampling, and about one-third of them had a cancer-causing HPV type. Of the HIV-positive MSM, 88% had anal HPV, with about 70% having a cancer-causing HPV type. It is believed that with repeated testing, that number would probably go even higher [Chin-Hong et al. *Ann Int Med*. 2008;149;300-6]. Women have a surprising degree of anal HPV infection as well. The earliest studies were conducted in the most immune-suppressed and highest risk group of women. Data for either HIV-positive or HIV-negative women at high risk for HIV suggest that for both groups, regardless of CD4 count, anal HPV infection is more common than cervical HPV infection. This has been found repeatedly in a variety of populations ranging from very healthy to high-risk women. All of these studies essentially show that anal HPV infection, if not more common, is at least about the same rate as cervical HPV infection [Palefsky JM et al. *J Infect Dis*. 2001;183:383-391].

In an example from Hawaii, cervical and anal HPV testing was conducted in 1566 healthy women. Of these, 13% were anal HPV-positive and cervical HPV-positive, 14% were anal HPV-negative and cervical HPV-positive, 14% were anal HPV-positive and cervical HPV-negative, and 59% were anal HPV-cervical and HPV-negative. Thus, anal and cervical infection were found at about the same rate in this group [Modified from Hernandez BY et al. *Cancer Epidemiol Biomarkers Prev*. 2005;14:2550-2556]. In some slightly higher risk women, such as those who attend a planned parenthood clinic, some unpublished studies show that 60% have anal HPV infection and 50% have cervical HPV infection. Regarding men who report never having had receptive anal intercourse, a study of prevalence of anal HPV infection among Tampa men who have sex with women in the "HPV in Men Study," shows that men who are putatively heterosexual in Tampa have HPV infection as well. This is lower at 13%, but still occurs. Most importantly, about 9% or so have type 16 or 18, so it is less common in men with no history of receptive anal intercourse, but by no means unheard of [Nyitray, A et al. *J Infect Dis.* 2010; 201:1498–1508]. In terms of the natural history of HPV infection in the anal canal, a study from Montreal showed that the cumulative incidence of HPV 16 and 18 is higher than for type 6, but the clearance rates are somewhat slower for HPV 16 versus 6—not statistically significant. It appears that HPV 16 is being picked up faster and clearing at about the same rate [De Pokomandy et al. *JID* 2009; 199: 965-73].

Among both men and women, it is believed that receptive anal intercourse is a risk factor for anal HPV infection. This is not a requirement, but it is a risk factor. Fingers, toys, and perhaps other mechanisms may also lead to the spread of HPV to the perianal area and potentially to the intra-anal area. In the case of men, that spread may occur from other genital sites (e.g., perianus, penis, and scrotum) and in women perhaps it occurs from the perianus, vulva, vagina, and cervix. A number of lines of evidence support the relationship of AIN3 being a precursor to cancer, just as observed with high-grade cervical disease being the precursor to cervical cancer. Consistent with that, the same profile of HPV is seen in the high-grade lesions as in cancer, with HPV 16 being overwhelmingly the most important HPV type in AIN 2/3, with the smattering of some of the other HPV types. The profiles in the cancers and the AIN 2/3 are very similar [Hoots, BE et al. *Int J Cancer*. 2009;124:2375-2383].

In terms of what is known about AIN, in the same population-based study in San Francisco, anal cytology and high resolution endoscopy with biopsies were done. It was found that in the HIV-negative MSM, 35% had AIN of any kind and a quarter had a high-grade lesion. Of the HIV-positive men, 57% had AIN of any kind and 43% had a high-grade lesion. These numbers are enormous, particularly compared to a population-based study of cervical disease in healthy women in San Francisco or anywhere else, in which the percentages with CIN or high-grade CIN would be substantially lower [Chin-Hong et al. *Ann Int Med.* 2008;149;300-6].

A study of AIN in HIV-positive and HIV-negative women in the Women's Interagency HIV Study (N=657) the same rates of CIN and AIN were found. That was true in positive and negative women. Not surprisingly, more AIN was found in the HIV-positive women [Hessol NA et al. *AIDS*. 2009;23:59-70]. AIN is increasingly being recognized in healthier women, not just HIV-positive or high risk women. In a recently published study of AIN in women with CIN / VIN / VAIN, 12% had AIN of any kind and 8% had a high-grade lesion. This has stimulated a lot of interest to assess women in dysplasia clinics across the country.

As described previously the incidence of anal cancer is increasing in men and women, and the rates are particularly high in MSM and other immune-suppressed people. This raises the question regarding the best ways to prevent anal cancer. Based on the cervical model, treatment of AIN 2/3 should reduce the risk of anal cancer. However, screening and treating AIN 2/3 is very challenging. Particularly in the case of immunosurpressed people, large lesions are found that are often multi-focal. No data are currently available to show that treatment of these high-grade lesions prevents cancer; however, it is anticipated that such studies will be designed. There are no national screening and treatment guidelines in place. Consequently, very few people with AIN 2/3 are screened and treated. That, in part, reflects the fact that there are no guidelines and that the expertise to perform high resolution endoscopy is still somewhat limited. The treatment and diagnostic algorithms are still not finalized.

In conclusion, anal cancer and its precursor (AIN 2/3) are biologically similar to cervical cancer. Anal cancer is a growing problem in the general population and in select risk groups. The incidence is highest in MSM, particularly HIV-infected MSM. The proportion of cases among men contributed by MSM is almost certainly greater than 50%, but the exact percentage is not known. Dr. Palefsky emphasizes that anal HPV infection is remarkably common in all segments of the population. Screening for AIN is still not the standard of practice for a number of the reasons mentioned. The treatment of AIN 2/3 is possible, but it is challenging. Clearly, alternative methods to prevent anal cancer are needed.

HPV Vaccine Cost-Effectiveness Updates and Review

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Dr. Chesson reported that the cost-effectiveness of vaccines is often assessed in terms of cost per quality-adjusted life year (QALY) gained by vaccination. QALYs account for both the quality of life and length of life, and a QALY can be thought of as one year of life in perfect health. When calculating QALYs, death is given a value of 0 and one year of life in less than perfect health is given a value between 0 and 1 QALY, depending upon the severity of the health issue.

In the U.S., the cost per QALY gained from childhood vaccines is as follows: DTaP <$0 (cost-saving), Hib <$0 (cost-saving), MMR <$0 (cost-saving), Polio <$0 (cost-saving), Varicella <$0 (cost-saving), Influenza (LAIV) ≈ $10,000, Hepatitis A ≈ $10,000 to $30,000, and Meningococcal (MCV4) in toddlers ≈ $120,000 to $230,000 [Ekwueme (2000); Zhou (2005), Zhou (2005); Cochi (1985), Zhou (2004, 2005); White (1985), Zhou (2005); Thompson (2006), Zhou (2004,2008); Preblud (1985), Prosser (2006), Das (1999); Rein (2007), Shepard (2005), Ortega-Sanchez (February 2010 ACIP) respectively). The first 5 have been shown to be cost saving whether considered individually or as a group.

The cost per QALY gained by selected adolescent vaccines in the U.S. is as follows: Hepatitis B, college freshmen <$0 (cost-saving) to ≈ $10,000; Hepatitis A, college freshmen <$0 (cost-saving) to ≈ $15,000; HPV, 12-year-old girls ≈ $3,000 to $45,000; Influenza, 12- to 17-year-olds, high risk ≈ $10,000; Tdap, all 11-year-olds ≈ $25,000; Meningococcal (MCV4), 1-dose, all 15-year-olds ≈ $120,000; Influenza, 12- to 17-year-olds, healthy ≈ $140,000; Meningococcal (MCV4), 2-dose, all 11 & 16-year-olds ≈ $160,000; and Meningococcal (MCV4), 1-dose, all 11-year-olds≈ $280,000 [Ortega-Sanchez et al. *Pediatrics* (2008), except HPV and MCV4; Elbasha (2007) and Kim (2008), respectively] were published after the cutoff date for inclusion in the Ortega-Sanchez review. Estimates for MCV4 were presented by Ortega-Sanchez, October

2010 ACIP]. HPV vaccination of 12 year old girls compares favorably to these other vaccines. Note that some vaccination strategies have cost per QALY estimates of over $100,000 to $200,000.

It is known that the routine vaccination of 11-12-year old girls in the US is a good use of public health resources. This is a finding that is consistent across a range of published models, provided that there is sufficient duration of vaccine protection. In contrast, there is more uncertainty and less precision in the estimates of the cost-effectiveness of vaccination of adult women and vaccination of males. The cost-effectiveness of male vaccination depends on vaccine coverage of females. The most favorable scenario for male vaccination is when coverage of females is low. Male vaccination is less cost-effective as female coverage increases. The reason for this is that with high female coverage, the impact of male vaccination on HPV-related diseases in females is limited because the high female coverage leaves little room for benefit of reduced transmission from vaccinated males to unvaccinated females. Also, males are protected indirectly through female vaccination; that is, female vaccination could prevent HPV transmission to males. Thinking of this in terms of "buy one, get one free," if female vaccination is paid for and coverage is high, male protection is achieved as a bonus. In this scenario, vaccinating males would mean paying for a benefit that had already been obtained as an indirect benefit of high coverage with female vaccination.

The cost-effectiveness of HPV vaccination depends upon the health outcomes that are included in the analysis. As one might expect, the most favorable scenario for vaccination is when all of the potential health outcomes that could possibly be prevented with the vaccine are included in the analysis. HPV vaccination of MSM appears cost-effective based on the first and only study to address this issue. Dr. Jane Kim found that the cost per QALY estimate for vaccinating MSM was consistently less than $50,000 over a range of assumptions about age at vaccination and the degree of exposure to the HPV vaccine types prior to vaccination [Kim JJ. Lancet Infect Dis. 2010;10:845-52. QALY: quality-adjusted life year]. The estimates for male vaccination cost-effectiveness are more uncertain than female vaccination. Male vaccination could be cost-effective, particularly if coverage of females is low. The two most recently published studies provided cost per QALY estimates of $24,000 and $62,000 in scenarios where female coverage was less than or equal to 50% [*$24,000 per QALY is from Merck model (Elbasha & Dasbach, 2010) with effective coverage (all 3 doses) by age 18 of ≈40% and ≈25% for females and males, respectively. $62,000 per QALY is from Kim et al. (2009) with 50% 3-dose coverage of girls and boys by age 12]. However, male HPV vaccination might not be cost-effective, and this could hold true even if coverage of females is low. For example, when male vaccination is compared to a strategy of increased coverage of females or if males vaccinated have mostly vaccinated sex partners.

In terms of male HPV vaccination cost-effectiveness, estimates are available from several U.S. and one UK study. The study by Taira and colleagues (2004) included only cervical outcomes. The studies Elbasha (2007) and Jit (UK, 2008) included cervical outcomes and genital warts. The most recent studies by Kim (2009), Elbasha (2010), and Chesson (preliminary) have included cervical outcomes, genital warts, non-cervical cancers attributable to HPV, and recurrent respiratory papillomatosis (RRP). Within a given study, as coverage increases, the cost per QALY gained by male vaccination increases; however, the degree to which this increases varies across the models. Also, for a given coverage scenario, the cost per QALY estimates can vary substantially across models. This is most pronounced in the higher coverage scenarios where the models do not agree as much. In the lower coverage scenarios, there is much more agreement across the models.

The Chesson et al model was updated since the October 2010 ACIP meeting using more current and higher estimates of non-cervical cancers attributable to HPV 16 and 18 that Dr. Saraiya presented. [Updated percent of vaginal, vulvar, oropharyngeal, anal, and penile cancers attributable to HPV 16/18 based on Gillison (2008)]. As a result, the updated estimates have a lower cost per QALY, indicating that male vaccination appears to be more favorable than it did before. For example, at the 50% coverage level, the new estimate is $43,000 per QALY, which is about 20% less than the previous estimate. The coverage estimates refer to 3-dose female coverage by age 26. We do not have data on 3-dose coverage of females by age 26, but it is known that 3-dose coverage of 13 to 17 year olds is about 27% and 1-dose coverage is about 44%. Taking into account that these females have additional years to be vaccinated through catch-up vaccination, the coverage scenario of about 50% by age 26 is reasonably consistent with current coverage in the US. The updated results of the Chesson et al model are as follows: the cost per QALY gained by vaccination of 12-year-old boys with all health outcomes included is $24,000 at 20% to 45% coverage; $43,000 at 50%; $84,000 at 70% to 75% coverage; and $192,000 at 80% to 90% coverage.

The cost per QALY gained by HPV vaccination can vary depending upon what outcomes are included in the analysis. One important difference between the Merck model and the Chesson model is that the Merck model assesses vaccination of males 12 through 26; whereas, the Chesson model focuses on vaccination of 12-year-old males. If catch-up vaccination of males were included in the estimates, the cost per QALY estimates for male vaccination would be somewhat higher than what is shown here for the Chesson et al . model.

As more health outcomes are included in the analysis, the cost per QALY gained decreases. When including only cervical outcomes, the cost per QALY gained by male vaccination is over $100,000 in both models. When all health outcomes are included, the cost per QALY is about $24,000 in the Merck model and just over $42,000 in the Chesson model. Vaccine efficacy has been demonstrated for cervical disease, vulvar and vaginal cancer, genital warts, and anal cancer. The cost per QALY gained when including only cervical disease is $182,400 in the Merck model and $115,400 in the Chesson model. When including the outcomes of cervical disease + vulvar and vaginal cancer + genital warts + anal cancer, the cost per QALY gained for male vaccination is about $50,000 in the Merck model and almost $70,000 in the Chesson model.

Based on three modeling scenarios, one from the Merck model and two from the Chesson model under two different coverage assumptions, as coverage increases not only does the cost per QALY gained by male vaccination increase, but also the degree of the uncertainty in the estimates seems to increase as well. The cost per QALY gained by vaccination of 12-year-old boys can vary depending on vaccine costs Male vaccination appears more favorable in the lower vaccine cost scenarios. Even in the sensitivity analyses, the vaccine is much more likely to be favorable from a cost-effectiveness standpoint with a lower cost per dose.

Dr. Chesson reminded everyone that during the October 2010 ACIP meeting, three main issues were raised about which the members wanted more information: 1) 1- and 2-dose efficacy assumptions, 2) genital wart quality of life assumptions, and 3) accounting for trends in cancer incidence. In terms of 1- and 2-dose efficacy assumptions in the three most recent models, the Merck model is the only one that includes some protection for those who receive 1 or 2 doses of the vaccine. They assumed that protection after 1 and 2 doses of the vaccine would be 23% and 45% that of the 3-dose vaccination, respectively [Elbasha & Dasbach, 2010]. The Kim et al model assumed that everyone vaccinated would receive all 3 doses [Kim et al 2009], and the

Chesson model assumed no protection in the base case for those who did not receive all 3 doses. When efficacy is included for those who receive 1 dose or 2 doses, it could have two different impacts on male vaccination that work in opposite directions. First, male vaccination might appear more cost-effective due to the benefits in males who receive 1-dose or 2 doses, their sex partners, their partners' partners, and so on. However, male vaccination might appear less cost-effective because the effective female coverage is higher (1-dose coverage is higher than 3-dose coverage) and male vaccination appears less favorable as female vaccine coverage increases. However, the Merck model found that when they took away their assumptions of 1- and 2-dose efficacy, the cost per QALY estimates did not change substantially.

In terms of genital wart QALY assumptions, the Merck model and the Kim model assume that genital warts would reduce quality of life in the short-term by about 9% and the Chesson model by about 6.5%. Average duration of genital warts was assumed to be 8.5 months in the Merck model, 3.0 months in the Kim model, and 5.8 months in the Chesson model. The average number of QALYs lost per case of genital warts was therefore about 0.064 in the Merck model, 0.023 in the Kim model, and 0.031 in the Chesson model [Sources for quality of life weights: Merck; Kim et al.: Myers et al. (2004 Int'l Papillomavirus Conference) survey of 150 female volunteers in Duke University Medical Center study; Chesson et al: Average of 2 sources: Expert panel (IOM 2004 report) & Woodhall (2008) survey of 81 subjects in UK with history of genital warts; Sources for duration of genital warts: Merck: Winer (2005), median duration of 5.9 months, which corresponds to 8.5 months mean; Kim et al.: Insinga (2003) study of claims data from private health plans; Chesson et al.: Average of 2 sources: Expert panel (IOM 2004 report) and Woodhall (2009) study of 189 subjects in UK with genital warts].

With regard to how the impact of the genital wart quality of life assumptions affect the cost per QALY gained by male vaccination, during the last ACIP meeting, Dr. Judson suggested that a lot of people with genital warts do not know they have them and for some it is just a minor nuisance. He might be more willing to focus on the assumption that there is no impact of genital warts on quality of life. Dr. Turner noted that a lot of the college patients he sees are devastated by genital warts and would rank it just above death, so he might be more willing to look at the assumption that there is a higher impact on quality of life. In general though, the genital warts assumptions do not have that great an impact, at least for the Merck model with a base case coverage of 40% and the Chesson model with a base case coverage of 50%. The bulk of the QALYs gained by vaccination are from preventing morbidity and mortality related to cervical and other cancers.

It was also noted that if recent trends in cancer incidence were to continue in the absence of vaccination, the models might over-estimate the benefits of HPV vaccination in preventing cancers that would have declined over time anyway. Conversely, the models might under-estimate the benefits of HPV vaccination in preventing cancers that would have increased. Accounting for recent trends over the past 20 to 30 years did not have major impact on male vaccination cost-effectiveness [Chesson et al model]. The impact of accounting for decreasing trends in some cancers (e.g., cervical) is offset by impact of accounting for increasing trends in other cancers (e.g., anal).

To summarize, with regard to the additional modeling results requested by ACIP, the cost-effectiveness estimates for male vaccination did not change substantially when allowing for efficacy of incomplete vaccination (under base case coverage assumptions; 23% and 45% relative efficacy after 1 and 2 doses, respectively); when varying quality of life impact of genital warts (with the possible exception of high coverage levels or when not including all outcomes);

and when incorporating trends in cancer incidence (with the possible exception of allowing trends continue for 50 to 100 years rather than 25 as in the model, or when applying greater annual percentage changes in cancer incidence).

To summarize the updates to the models and the sensitivity analyses, a higher percentage of non-cervical cancers attributable to HPV was applied in the Chesson model. As a result, the male vaccination cost per QALY estimates were about 20% lower than previously presented ($43,000 at 50% female coverage by age 26; $84,000 at 70% female coverage by age 26). In probabilistic sensitivity analyses (all outcomes included), the cost per QALY estimates ranged from $26,000 to $59,000 in the Chesson model with 50% female coverage by age 26, and $53,000 to $113,000 in the Chesson model with 70% female coverage by age 26. This is very consistent with the range of estimates with the Merck model at a similar coverage. Vaccine costs are important. The cost per QALY gained by male vaccination appears much more favorable with lower cost per dose for the vaccine.

There are several limitations and uncertainties, including the following:

- Limited data to inform models (e.g., natural history of HPV)
- No vaccine efficacy data for some outcomes included in analysis (e.g., oropharyngeal cancers; RRP)
- Models examining routine male vaccination focus on heterosexual transmission of HPV (direction of resulting bias on estimated cost-effectiveness of routine male vaccination unclear)
- Probabilistic sensitivity analyses have not included all model parameters (may not reflect the full range of plausible results)
- Male vaccination catch-up strategies not yet examined in detail

In conclusion, male vaccination becomes less cost-effective as female coverage increases. Uncertainties in these estimates, such as future coverage of females, preclude precise estimates of cost-effectiveness of male vaccination. At current female coverage levels, male vaccination could be cost-effective. All available models suggest potentially favorable cost-per-QALY estimates when female coverage is ≤ 50% by age 26 years. However, plausible scenarios exist in which male vaccination is not cost-effective even at current female coverage levels (e.g., compared to strategy of increased female coverage). Vaccine costs are an important factor in affordability and cost-effectiveness of male vaccination. With lower cost, male vaccination is more likely to be cost-effective over a wide range of scenarios (e.g., higher female coverage).

HPV Vaccine For Males

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Dr. Markowitz reminded everyone that the purpose of this session was to provide ACIP with additional information needed for decision-making about HPV vaccine for males. Two vaccines are licensed for use in the U.S. The quadrivalent vaccine was licensed in June 2006, and ACIP recommended the vaccine for routine use in females 11 or 12 years of age. In 2009, the bivalent vaccine was licensed for use in females, and ACIP revised the recommendations to state that either vaccine could be used for routine vaccination of females. Also in 2009, the quadrivalent vaccine was licensed for use in males based on data showing efficacy against genital warts, and ACIP provided guidance that the vaccine may be used in males. The

quadrivalent and bivalent vaccines are included in the VFC program for females, and the quadrivalent vaccine is included in the VFC program for males.

Since October 2009, the workgroup has continued to review data related to HPV vaccine for males. Information has been presented during several ACIP sessions. In October, new vaccine efficacy data in males was reviewed showing high efficacy for prevention of vaccine HPV type-related anal pre-cancers as well as previously available data in males. Vaccine safety updates were presented, including data from clinical trials and an update from the VSD rapid cycle analysis. A presentation was also offered on HPV vaccine coverage in females and program issues. Data were also presented from a national provider survey regarding provider acceptability of male vaccination and practices, which found high acceptability of male vaccination among providers—although it was lower than for females. There was also a presentation on cost-effectiveness, which was updated during this session by Dr Chesson.

Given the importance of coverage in this discussion, Dr. Markowitz briefly reviewed data presented during the October 2010 meeting as to estimated vaccination coverage among adolescents 13 through 17 years of age, as measured by the National Immunization Survey-Teen from 2006-2009. Similar to coverage for Tdap and meningococcal conjugate vaccine, HPV coverage has steadily increased each year. In 2009, coverage in 13 through 17 year old females was 44% for one dose and 27% for three doses. Coverage with at least one dose varied by state. In 2009, initiation ranged from a low of 20% to over 50%. In some states, vaccine initiation was over 60%. There were also variations in the increases in vaccine initiation by state between 2008 and 2009. Some states had as much as a 25% increase over that one year period, while others had more modest increases.

HPV vaccination among females is increasing in the U.S., but remains low and there is wide variation in coverage by state. In October 2010, various challenges of HPV vaccination were discussed, including access to and financing of vaccine, provision of vaccine including provider recommendation, acceptance of vaccine by parents, and completion of the series. Projects to identify effective strategies for increasing adolescent vaccination coverage are on-going, and these were reviewed in October as well.

During this session, data requested by ACIP in the October 2010 meeting were further reviewed. Burden of HPV-associated cancers in the U.S. includes cervical as well as a variety of non-cervical cancers. Approximately 21,000 HPV 16/18-associated cancers occur annually and about 1/3 of those are in males. Estimates of the percentage of cancers at some non-cervical sites have increased. Anal cancer incidence is increasing, with incidence being highest among MSM. The update on cost-effectiveness modeling included a revision of the model using a higher percent of non-cervical cancers attributable to HPV, which resulted in a change in male vaccination cost per QALY of ≈ 20%. Cost-effectiveness models show that at current coverage levels, male vaccination could be cost-effective. However, male vaccination is less cost-effective as female coverage increases, and is less cost effective even at current coverage levels compared to a strategy of increased female coverage.

During the October 2010 ACIP meeting, ACIP members also requested information on healthcare use by young MSM. While data are not available on healthcare use in young adolescents, there are some data on males 18 through 26 years of age. Data on healthcare use by young gay, bisexual, and other MSM were obtained from the 2008 National HIV Behavioral Surveillance system (NHBS). NHBS is an anonymous, cross-sectional survey conducted in 21 US cities that uses venue-based sampling. This analysis included males 18 through 26 years of age. Overall, 89% had used clinical healthcare within the last 12 months

and 75% visited a healthcare provider. Disclosure or "being out" to any other person was reported by 92% of males, of whom 61% were "out" to a healthcare provider. One of the limitations of this survey is that the venue-based methodology might have selected males who are more likely to have disclosed their sexual orientation. While the high percentage of males who had used a clinical health service might suggest that vaccine could be delivered in the population, even in this population only 60% had disclosed to a healthcare provider.

Since the October 2010 ACIP meeting, the work group has reviewed the new data presented to the ACIP and continued to discuss issues related to male vaccination. As presented before, the options being considered are to, 1) recommend routine vaccination of males at ages 11 or 12 with catch-up, with or without a specific guidance or recommendation for MSM, or 2) retain current guidance stating that males may be vaccinated, but vaccination of males are not included in routine schedule, with or without a specific guidance or recommendation for MSM. Most work members favor a recommendation for routine vaccination of males, but there is no consensus of the work group to date. There is also no consensus about guidance or a specific recommendation for vaccination of MSM. Support of specific guidance for MSM depends upon the working group members' opinions about routine vaccine recommendations.

Among work group members who support routine vaccination, reasons for support include safety and efficacy of the vaccine in males, burden of disease, and issues of equity. Protection of MSM was also a reason for some to support routine vaccination. In addition to protecting heterosexual males and their female sex partners, some felt that routine vaccination of males is the best way to reach MSM at an age when they could most benefit, and would eliminate need for disclosure of sexual orientation. Some work group members also felt that there would be programmatic benefits. Most members who supported a routine vaccination felt that it is cost - effective to vaccine males in U.S. at current coverage levels in females, and that it would remain cost-effective into the foreseeable future given challenges with increasing coverage in the U.S.

Among work group members who did not support a routine recommendation for males, some felt that there are programmatic challenges at state and local levels and that the cost of HPV vaccine prohibits reaching even all females. Most of the burden of disease is in females and priority should be given to vaccinating females, which would also impact male disease. Most members who did not support a routine recommendation for males felt that for protection of MSM, there should be a recommendation for MSM rather than making a routine recommendation for males. Those not supporting a routine recommendation did not feel that it is cost-effective to vaccinate males.

Cost or cost-effectiveness impacted considerations for most work group members. Many members were concerned about the vaccine cost. However, work group members considered cost-effectiveness differently. Those who supported routine recommendations for males tended to consider cost-effectiveness at current coverage when vaccination appears cost-effective in the models. Those who did not support males vaccination assumed coverage would increase and tended to consider cost-effectiveness at higher coverage levels when there is more uncertainty about cost-effectiveness of male vaccination and when the cost per QALY is high. Of members who are not in support of a routine recommendation for males, most would support if the vaccine price was lower.

Regarding considerations for MSM, work group members recognized that there is a high burden of HPV-related disease in this group. Members acknowledged that there are programmatic challenges in reaching MSM at an age when they would benefit most without a routine recommendation. For those males who have disclosed their sexual orientation, many work group members felt that HPV vaccine could be recommended or strong guidance provided. While the most benefit would occur if vaccine is given before sexual debut, a recent model found that vaccination into the 20s appears to be cost-effective for MSM, even after taking into account prior exposure. Some work group members expressed concern about stigma if there is a specific recommendation for MSM. The group has had some informal discussions with a few MSM providers, and it appears that there is support for at least some specific guidance for vaccination of MSM. Of course, a routine recommendation would make this less important.

Dr. Markowitz reiterated that the purpose of this HPV session was to provide additional data to the full ACIP membership so that all members would have more complete understanding of the issues and background data before making a policy decision. The work group members feel that the quadrivalent HPV vaccine is safe and effective in males, and there is increasing support for use of the vaccine within the medical community. Addressing cost would be important for the work group members to reach consensus. Future work group plans are to further consider HPV vaccine use in males, including implications of catch-up vaccination. They will also continue to review data from vaccine trials and other data related to all aspects of the program as they become available. When the HPV vaccine ACIP statement is revised, the evidence-based format will be used.

Discussion Points

Dr. Baker inquired as to whether condoms are protective against transmission and whether there are any data about this.

Dr. Markowitz replied that there are some data showing that condoms, if used consistently and appropriately, can provide some protection against HPV infection. While protection is not 100%, they do offer some protection.

Dr. Judson noted that condoms are variably and partially effective depending upon storage and proper use with every single encounter. Therefore, it is difficult to answer this question “yes” or “no.”

Dr. Markowitz agreed that the data are not as strong for HPV as for other sexually transmitted infections.

Dr. Duchin requested clarification regarding how the duration of protection figured into the conclusions presented. He also wondered how increasing the use of the bivalent vaccine would affect outcomes related to genital warts.

Dr. Markowitz responded that models handle duration of protection differently. The Chesson model assumed that there was no waning of protection.

Dr. Chesson added that for female vaccination, he thought that 30 years was the cutoff listed in one review paper to say without hesitation that female vaccination is cost-effective. The Chesson model assumed lifelong protection, which is the best case assumption in many of the models. Waning protection does impact cost-effectiveness. It gets tricky in terms of male

vaccination because male vaccination can help fill in the gaps that female vaccination leaves. Sometimes when the vaccine has less desirable attributes, male vaccination can become more cost-effective; for example, if the duration of the vaccine is shorter, male vaccination might actually be able to add more value because there is a lot of room for improvement. In the UK study by Jit and colleagues, the cost per QALY gained by male vaccination increased greatly as the duration of vaccine protection increased. It is counter-intuitive in terms of male vaccination. He offered to discuss this in further detail during the June 2011 ACIP meeting.

Given that duration of protection can sometimes be unpredictable, Dr. Duchin wondered whether a shorter duration of protection would drastically change the conclusions.

Dr. Chesson replied that if duration of protection was 10 years, in one situation it would not change the cost-effectiveness estimates if it was assumed that a booster dose could be available for most people. If duration of protection was assumed to be 10 years with no booster, protection would be gone and that could have a major impact on cost-effectiveness estimates.

Dr. Coyne-Beasley pointed out that the model assumption of 50% coverage is greater than what there is currently. Also, HPV vaccination is more cost effective than meningococcal and influenza vaccines, particularly as other outcomes are added (e.g., anal cancer, penile cancer, oropharyngeal cancer). That is, is it true that the quadrivalent vaccine is not any more expensive than influenza and meningococcal vaccine. A lot is discussed in isolation, but in terms of the entire platform of adolescent vaccines, it did not appear to her to be any more expensive than other vaccines—assuming 50% vaccine coverage. She also wondered whether decrease in or elimination of health disparities was taking into consideration in any of the models. There has been an emphasis on reducing health disparities in terms of smallpox, polio, and more recently measles.

Dr. Markowitz replied that 50% coverage is the base case and is really the coverage by age 26. What was used in the model was not 50% coverage at age 12; it was something closer to the 27% coverage observed in the 2009 the National Immunization Survey). It may be a misnomer to call that the base case, but it was selected to determine how the Chesson model compared to the Merck model and some other models. That is not ideal coverage—it is current coverage. In terms of disparities, different models have assessed what would occur. That really depends up the program. If males and females are vaccinated who are going to get Pap smears anyway, and males would be vaccinated who are partners of those females, this will worsen disparities. The issue of disparities really depends upon whether the vaccines can be delivered to females at high risk of cervical cancer or to everyone.

Given how much lower the GMTs are for the single dose and the fairly rapid decline, Dr. Judson wondered how the 23% protection was determined.

Dr. Chesson replied that his understanding was that it was based on the relative efficacy for one or two doses observed for hepatitis B vaccine.

Dr. Temte's understanding was that in the last 4 years of the HPV program, the U.S. has been very effective in providing this vaccine to the people who probably need it the least. There has been a disparity in the uptake of this vaccine among people who have actually had pretty good access to care, while far less vaccine is distributed to people who have less access to care. He was curious how this affected the modeling to have an expensive vaccine administered to a group of people in which the benefit is less than for other groups.

Dr. Chesson indicated that Kim / Goldie model showed that if people who are vaccinated are also those who are screened, the cost per QALY of female vaccination increases substantially. It is possible that male vaccination could be a way to reach females who do not have access to care, depending upon how there is mixing among the males and females.

Dr. Markowitz] I just want to correct it. In the data that we heard in October 2010 from NIS showed that in terms of vaccine initiation, there were not a lot of disparities. Initiation of HPV vaccine is very similar by socio-economic status and race and where the disparities showed up was actually in completion. There were some disparities seen in completion of the 3 dose series, but in terms of initial initiation, it looks like we are doing an OK job on that.

Responding to Dr. Coyne-Beasley's question, Dr. Englund indicated that the figures Dr. Chesson showed for cost-effectiveness comparing HPV vaccine to other vaccines, the cost-effectiveness for HPV was for females only. She also emphasizes what was briefly mentioned by Dr. Markowitz that the pediatrician and adolescent medicine members of the HPV work group feel very strongly that screening at a young age for potential MSM is impossible, so this should not be on the table as an adolescent approach.

Dr. Coyne-Beasley agreed. It is known that the vaccine is most effective prior to sexual contact. By the time a male identifies as MSM, sexual contact has likely already occurred. At age 11 and 12 when vaccine is being recommended, many young people have not declared their sexual orientation.

Dr. Middleman (SAM) agreed, pointing out the data that was presented about males self identifying was 18 to 26 year olds. Self-identification does not necessarily address younger adolescents who are exploring their sexuality and may not end up being those who would typically be categorized as heterosexual versus homosexual. There is a lot of experimentation during adolescence, which is an extremely important point to keep in mind.

Dr. Cieslak pointed out that there are now two indications for HPV vaccine in males, although he did not believe they had seen cost-effectiveness analyses of just two indications. He wondered whether it was still the case that driving the cost-effectiveness picture are indirect effects in females. He wondered what percentage of the QALYs saved in the models was accrued to females versus males.

Dr. Chesson replied that while he did not have these data with him, he could provide a breakdown of how QALYs accrue for female vaccination and the incremental impact of male vaccination. As he recalled, a primary benefit of male vaccination was prevention of cervical cancer, but it was not the majority of the benefit. For example, another important component of the QALYs for male vaccination was prevention of oropharyngeal cancers.

Dr. Schuchat noted that while among the routine recommendations being considered was a routine 11 to 12 year old recommendation with a catch-up; however, the CDC economic model did not appear to incorporate catch-up. If that recommendation was to be considered for future votes, it would be very helpful to this added to the model.

Dr. Chesson responded that the model is set up such that they could do this fairly easily, and that this could be presented during the June 2011 ACIP meeting.

Dr. Meissner asked whether the work group discussed the programmatic issue of uptake of the vaccine by males; that is, if the uptake in females is 27% after 3 or 4 years and they have serious well-recognized cervical cancer, he wondered what would motivate vaccination of boys.

Dr. Markowitz replied that this has been discussed by way of assessing the national provider survey, which showed fairly high support of providers to recommend the vaccine for males. There have also been a variety of smaller, though not national studies, assessing parental acceptability. A literature review was conducted that was presented to the work group. Numerous studies have evaluated parental acceptability, which is lower than acceptability for females, but it is still fairly high. These data can also be presented to the full ACIP membership. Clearly, there are going to be challenges to vaccinating males and females with current strategies for providing vaccine.

Dr. Schuchat thought the contrast between Dr. Salisbury's presentation and the HPV presentation was fairly striking. Even in the UK, where every general practitioner is connected electronically to their health department, they are not trying to use providers to deliver teenage vaccines—they are going into schools. She was also struck by healthcare access of the self-identified MSMs in the 18 to 26 year old group. Their history of a healthcare encounter in the past year is much higher than the average adolescent's, male or female. As they consider recommendations for teens, she emphasized the importance of continuing to think about the opportunity to reach teens in venues where they actually are, such as schools.

Hepatitis B Vaccine

Introduction

Mark Sawyer, MD, Chair
ACIP Hepatitis Work Group

Dr. Sawyer reminded everyone that in 2009, the Hepatitis Working Group was asked to review data from hepatitis B outbreaks among adults with diabetes in institutional care to determine whether vaccination is appropriate. This review was initially requested by National Association of County and City Health Officials (NACCHO) because of the continuing public health burden of hepatitis B outbreaks.

The work group has met by teleconference 29 times, presented at 4 ACIP meetings in 2009 and 2010, and at a Healthcare Infection Control Practices Advisory Committee (HICPAC) meeting in 2010. Among the issues they have been discussing are defining the role of infection control to prevent hepatitis B among persons with diabetes; age-related responses to hepatitis B vaccine; and seroprevalence of hepatitis B infection among adults with and without diabetes, by demographic and risk characteristics.

A number of parallel infection control activities have been undertaken as well in response to this initial challenge. CDC, with FDA and CMS, held 2 stakeholder meetings to improve infection control oversight, and the regulation of devices used in diabetes care and management; and CDC updated its guidance for infection control among persons with diabetes, now posted on the website. In September 2010, CDC and FDA issued clinical advisory and product alerts for use of finger-stick devices, glucose meters, and insulin pens; and the FDA revised its evaluation and approval process for blood glucose monitoring devices, with greater focus on preventing infection.

During this session, ACIP members heard a summary of some of the latest national diabetes statistics for the U.S.; information pertaining to the incident risk of acute hepatitis B infection among adults with and without diabetes, and a review the anticipated next steps for the Hepatitis Work Group,

In conclusion, Dr. Sawyer acknowledged the four CDC divisions that have contributed to the Hepatitis Working Group activities: Division of Viral Hepatitis, NCHHSTP; Healthcare Quality Promotion, NCPDCID; Diabetes Translation, NCCDPHP; and Immunization Services, NCIRD.

National Diabetes Statistics

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Ms. Burrows reported that recommendations for the diagnosis of diabetes released by the American Diabetes Association (ADA) in January 2011 included a fasting blood sugar level of ≥126 milligrams per deciliter (mg/dL) after an overnight fast, a 2-hour blood sugar level ≥200 mg/dL after a 2-hour oral glucose tolerance test (OGTT), or a hemoglobin A1c level ≥6.5%. People with undiagnosed diabetes have laboratory values in the diabetic range, but report not ever being told that they have diabetes. Pre-diabetes refers to an emerging condition in which individuals have blood glucose or A1c levels higher than normal—fasting plasma glucose 100–125 mg/dL, 2-hour plasma glucose (OGTT) 140–199 mg/dL, or Hemoglobin A1c 5.7%–6.4%—but not high enough to be classified as diabetes. People with pre-diabetes are at increased risk of developing type 2 diabetes [American Diabetes Association. Diabetes Care, Suppl 1. Jan 2011].

The National Diabetes Surveillance System provides resources documenting the public health burden of diabetes and its complications in the United States. This surveillance system includes trends in prevalence of diagnosed diabetes in the civilian non-institutionalized population using data of self-reported diabetes from the NHIS. Survey respondents were considered to have diabetes if they responded "yes" to the question, "Have you ever been told by a doctor or health professional that you have diabetes?" Women who indicated that they had diabetes only during pregnancy were not considered to have diabetes. Adults who reported being diagnosed with

diabetes were then asked at what age they were diagnosed. Incidence is calculated on the basis of duration of diabetes less than one year or the number of adults who reported that they were diagnosed within the past year. Data from the National Diabetes Surveillance System (NDSS) show the trend in diagnosed diabetes among adults in the US to have risen from 3.5% in 1980 to 8.0% in 2008. Since 1990, the prevalence began to increase more rapidly [CDC. Diabetes Data and Trends: National Diabetes Surveillance System, www.cdc.gov/diabetes/statistics. Data from the National Health Interview Survey].

Diabetes disproportionately affects U.S. racial ethnic populations. After adjusting for population age differences, national survey data indicate that, among adults, 7.1% of non-Hispanic Whites, 8.4% of Asian Americans, 11.8% of Hispanics, and 12.6% of non-Hispanic Blacks had diagnosed diabetes. Prevalence varies among Hispanic subgroups, with higher percentages in Mexican Americans (13%) and Puerto Ricans (14%). Of the adult population receiving care from IHS in 2009, and after adjusting for population age differences, 16% of American Indian and Alaska Native (AI / AN) adults had diagnosed diabetes. Prevalence varies by American Indian group, with higher percentages among American Indian adults in Southern Arizona where about one-third had diagnosed diabetes [Age-adjusted based on 2000 U.S. standard population. Source: National Diabetes Fact Sheet, 2011. Data from the National Health Interview Survey and the Indian Health Service].

In terms of the distribution of age at diagnosis of diabetes among cases ages 18 to 79 years diagnosed with diabetes in the past year, in 2008, 68% of the adult incident cases were diagnosed between the ages of 40 to 64 years[1]. Men and women born in the US in 2000 have a high risk of developing diabetes sometime in their lifetime. If current trends continue, 1 in 3 Americans will develop diabetes sometime in their lifetime. The risk is higher for women and for minority populations, with 40% to 50% estimated to develop diabetes during their lifetime[2] [[1]CDC. Diabetes Data and Trends: National Diabetes Surveillance System www.cdc.gov/diabetes/statistics. Data from the National Health Interview Survey; [2]Narayan et al. JAMA, Oct 2003].

Relevant to the considerations of this working group, Ms. Burrows reviewed the proportion of people who self-monitor their diabetes in the context of the proportion of people using insulin or oral medication. Among adults with diagnosed diabetes (type 1 or type 2), 12% take insulin only and 14% take both insulin and oral medication. Thus, about one-quarter or 5 million adults with diagnosed diabetes receive insulin. The remaining includes nearly 60% of adults taking oral medication only and 16% reporting no insulin or oral medication [National Diabetes Fact Sheet, 2011, and National Health Interview Survey, 2007–2009].

To determine trends in the percentage of adults with diabetes who checked their blood glucose at least daily using data from the Behavioral Risk Factor Surveillance System (BRFSS), survey respondents were asked, “About how often do you check your blood for glucose or sugar? Include times when checked by a family member or friend, but do not include times when checked by a health professional.” Regardless of the mode of treatment, whether insulin or oral medication, more than 60% of adults with diagnosed diabetes checked their blood glucose at least daily. This percentage increased to 86% in adults in 2009 who checked their blood glucose at least monthly [Diabetes Data and Trends: National Diabetes Surveillance System, www.cdc.gov/diabetes/statistics; Behavioral Risk Factor Surveillance System www.cdc.gov/brfss].

Recommendations for hepatitis B vaccinations include people with end-stage renal disease (ESRD) or on hemodialysis and people with chronic liver disease. The National Diabetes Surveillance System does not include surveillance data on people with diabetes and chronic liver disease. ESRD, which requires dialysis or transplantation for survival, is the end of the spectrum (or stage 5) of chronic kidney disease (CKD). Based on guidelines from the National Kidney Foundation Kidney Disease Outcome Quality Initiative, earlier CKD stages are defined as either kidney damage (for stages 1 and 2) or glomerular filtration rate (GFR) < 60 ml/min for 3 months or more (for stages 3 to 5). All individuals with kidney damage are classified as having chronic kidney disease, irrespective of the level of GFR. Kidney damage is defined as pathological abnormalities or markers of damage, such as macro- or microalbuminuria. Conversely, all individuals with GFR <60 ml/min for more than 3 months are classified as having chronic kidney disease, irrespective of the presence or absence of kidney damage [National Kidney Foundation. Am J Kidney Dis, Suppl 1. Feb 2002].

Using 1999-2004 data from the National Health and Nutrition Examination Survey (NHANES), the age-adjusted prevalence of CKD among adults with diagnosed diabetes was 40% for CKD stages 1-5: nearly 20% for CKD stage 1, about 11% for CKD stage 2, about 8% for CKD stage 3, and 1% for CKD stages 4-5 [Age-adjusted based on the 2000 U.S. standard population. Source: Saydah et al. MMWR, Mar 2007].

With good care, fewer than 10% of patients with type 2 diabetes develop kidney failure. Depending upon the age at onset of diabetes and glycemic control, lifetime risk of ESRD among people with type 2 diabetes ranges from 0.1% to 5.0%. Diagnosing CKD at an early stage of the disease can prevent or delay ESRD. However, nearly 50,000 or 44% of cases initiating treatment for ESRD in 2008 had diabetes listed as the primary cause of kidney failure [Brenner et al. N Engl J Med, Sep 2001, and Vijan et al. Ann Intern Med, Nov 1997].

To summarize, about 18 million adults (8%) have diagnosed diabetes. Nearly 2 million adults were newly diagnosed in 2010. About 2/3 of new cases were among people aged 40–64 years with a mean age at diagnosis of 53 years. The total estimated costs of diabetes in 2007 were $174 billion, with approximately $116 billion in direct medical costs and about $58 billion in indirect costs (e.g., disability, work loss, premature mortality, and other indirect costs) [CDC. Diabetes Data and Trends: National Diabetes Surveillance System, www.cdc.gov/diabetes/statistics, and National Diabetes Fact Sheet, 2011].

According to 2008 county-level estimates of diagnosed diabetes among U.S. adults, wide sections of the Southeast and Appalachia have high rates of diagnosed diabetes. In many counties in those regions, rates of diagnosed diabetes exceed 10%. Hand-in-hand with obesity, diabetes is a big problem that is likely to get bigger before it gets smaller www.cdc.gov/diabetes/statisticsnrios@cdc.gov.

Incidence of Acute Hepatitis B among Adults With and Without Diabetes

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Ms. Reilly presented estimates of the incidence of acute hepatitis B among adults with and without diabetes using case report data from four Emerging Infections Program (EIP) sites. With respect to the morbidity and mortality associated with acute hepatitis B in adults, an estimated 30% of acute cases are symptomatic, while the remainder have atypical symptoms or

are not symptomatic but are still at risk for developing chronic infection. Symptomatic patients generally are debilitated for 1 to 4 months, and 28% to 43% are hospitalized[1]. The overall case fatality rate for reported cases ranges from 0.5% to 1%, but varies with age. In 21 hepatitis B outbreaks in long-term care facilities with residents having a mean age in the 70s, the case fatality rate was approximately18%[2]. Acute symptomatic and asymptomatic infection is followed by the development of chronic hepatitis B in 5% to 10% of young adults; however, chronic infection has been confirmed in 45% or more elderly adult residents of long-term care [[1]NNDSS 2007; Sentinel Counties 2002-2005; Emerging Infections Program Sites, 2005-2007; [2]CDC published and unpublished data].

In recent years, surveillance for viral hepatitis has been maintained from two systems. Cases of acute viral hepatitis are voluntarily reported by all state and territorial health departments to CDC's National Notifiable Diseases Surveillance System (NNDSS). In addition, 10 EIP sites form a network of health departments, with the goal of conducting enhanced surveillance for emerging infectious diseases, and routinely report cases of acute viral hepatitis to CDC. NNDSS and EIP sites use the CSTE case definition to determine confirmed cases, which is defined as meeting both the clinical case definition and laboratory criteria for diagnosis. A clinical case has acute illness with a discrete onset of symptoms and jaundice or elevated ALT levels. Laboratory criteria for a confirmed case are either Immunoglobulin M (IgM) antibody to hepatitis B core antigen positive or hepatitis B surface antigen positive, and anti-HAV negative, if performed. Note that asymptomatic, unrecognized, unconfirmed, and unreported cases would not have been included in national reporting.

Higher rates of acute hepatitis B might be expected from the EIP sites due to enhanced surveillance, compared with the voluntary national case reporting to the NNDSS. Therefore, the incidence of acute hepatitis B by age group from NNDSS for 2007 was compared to the 10 EIP sites for 2005-2007. However, national estimates from 2007 NNDSS data were remarkably similar to those from the EIP sites from 2005 to 2007 [ACIP Hepatitis WG Presentation on HBV Surveillance, October 15, 2009].

Diabetes status of acute hepatitis B cases is not collected for national surveillance and is not included in the standard questionnaire of the EIP sites; however, 4 of the 10 EIP sites (Colorado, Connecticut, New York City, and Oregon) collected information on diabetes status of acute hepatitis B cases and were the sites that provided data for this study. These four sites covered a population of approximately 14 million people, or about 30% of the population in the overall EIP network. In Connecticut, Colorado, and New York City, diabetes information was determined with the initial case interview. In Oregon, diabetes information was collected retrospectively during year 1, with the case interview starting in year 2. Cases were interviewed for potential risk factors falling within 6 weeks to 6 months of hepatitis B symptom onset, and for history of diabetes using the question, "Have you ever been told by a doctor that you have diabetes?" Pregnancy-related diabetes and pre-diabetes were considered "no" for purposes of this study. Diabetes data on acute hepatitis B cases were available from all 4 of the EIP sites for 2009 and 2010. New York City also provided diabetes data on cases reported in 2006 to 2008. Only confirmed acute hepatitis B cases were included. Cases were excluded from this analysis if they were less than 23 years of age (~3%) because school vaccination laws suggested substantial coverage with hepatitis B vaccine in this age group. Cases that had missing diabetes information were also excluded.

For the study population denominator, data were used from the BRFSS and New York City's Community Health Survey (CHS). Both surveys collect information on a broad range of chronic and behavioral risk factors. BRFSS collects state-based data and CHS collects data for New York City. The information is self-reported by non-institutionalized individuals who live in households with landlines only. The surveys used the same language for determining diabetes status as was used in the EIP sites. Weighted results of self-reported diabetes status among persons aged 23 years and older were used to determine the study population denominators by diabetes status. Weighting the data corrected for differences in the probability of selection due to non-response and persons not reached, and adjusted for variables of age, race, and gender between the sample and the entire population, allowing for generalization of the findings to the population.

The average annual incidence of acute hepatitis B among persons with diabetes was estimated by calculating the number of acute hepatitis B cases with diabetes divided by 2 (for the 2 years of data collection in 2009 and 2010). This result was divided by the number of adults with diabetes in the catchment area. The result was then multiplied by 100,000 to determine the average annual incidence per 100,000 population. We used the same approach to calculate the average annual incidence of acute hepatitis B among persons without diabetes. We assumed a Poisson distribution to calculate 95% confidence intervals around the incidence estimates. The rate ratio, comparing acute hepatitis B incidence among persons with and without diabetes, was calculated by dividing the average annual incidence of acute hepatitis B among persons with diabetes by the average annual incidence of acute hepatitis B among persons without diabetes. To determine if the incidence among persons with diabetes was significantly different than the incidence among persons without diabetes, a rate ratio test was performed assuming both rates followed a Poisson distribution. The null hypothesis for this test is a rate ratio equal to one. Therefore, a p-value of less than 0.05 suggests that the true rate ratio is not equal to 1 and the two rates are significantly different.

In terms of study population demographics by EIP site using data from the 2009 BRFSS and 2009 New York City CHS, the average age of the study population was about 50 years and approximately 50% of the population was male. Race and ethnicity varied across the sites. In particular, there were different distributions of race and ethnicity in New York City compared to the other sites. For example, only 40.6% of the New York City population was White non-Hispanic compared to 72% to 83% in the other states. Also of note, Colorado and New York City's populations were more than 18% Hispanic, and Oregon's population was only 0.3% Black non-Hispanic and 11.3% other [Behavioral Risk Factor Surveillance System Survey Data, 2009. NYC Community Health Survey, 2009, Prepared by Bureau of Epidemiology Services, Feb 2011].

Regarding the study population diabetes prevalence by age group and EIP site for 2009, BRFSS and CHS data highlight the difference in diabetes prevalence in the study population between younger and older adults, and suggest that approximately 5% of adults aged 23-59 years and 18% of the population aged 60 years and older had been diagnosed with diabetes. Across sites, diabetes prevalence ranged from 6.3% in Colorado to 10% in New York City. Of the 14 million persons in the study population, 8.4% had a reported history of a diabetes diagnosis. The proportion of adults age 18 years and older diagnosed with diabetes was similar to that reported by Ms. Burrows from 2008 national prevalence data, which estimated that 8% of adults aged 18 and older have been diagnosed with diabetes [Behavioral Risk Factor Surveillance System Survey Data, 2009. NYC Community Health Survey, 2009, Prepared by Bureau of Epidemiology Services, Feb 2011].

During 2009 to 2010, the four EIP sites had 326 reported acute hepatitis B cases age 23 years or older. Of these 326 cases, 226 had diabetes information; 34 (15%) of cases with diabetes information reported history of a diabetes diagnosis; 192 (85%) of cases with diabetes information reported no history of diagnosed diabetes; 100 cases (31%) of the total case reports were excluded from the study for missing diabetes information. In terms of acute hepatitis B study case demographics by EIP site, the average age of the study cases was about 46 years and approximately 65% of the study cases were male. Similar to the study population denominator, there were variations by race and ethnicity across the sites; however, compared to the study population, cases had a slightly younger mean age, a larger proportion of males, and larger site-specific populations of Black non-Hispanics with the exception of Oregon. Also assessed for the excluded cases were age, sex, and race / ethnicity. No significant differences were found between the study cases and excluded cases [Provisional Data, CDC].

With regard to diabetes status of acute hepatitis B cases by age group, site, and overall, Ms. Reilly presented data highlighting the difference in diabetes prevalence among hepatitis B cases between younger and older age groups. Of acute hepatitis B cases 23 through 59 years old, 12.4% had been diagnosed with diabetes whereas only 5.2% of the study population in this age group carried that diagnosis. Of reported acute hepatitis B cases age 60 years and older, 30.3% had been diagnosed with diabetes whereas only 18% of the study population reported a diabetes diagnosis. Across sites, diabetes prevalence ranged from 11.7% in New York City to 25% in Connecticut. Overall, EIP case report data indicated that approximately 15% of acute hepatitis B cases with diabetes status had been diagnosed with diabetes whereas the proportion of the study population with diabetes was 8.4% [Provisional Data, CDC].

Groups currently recommended for adult hepatitis B vaccination include persons with two or more opposite sex partners in a six month time period; MSM; persons with history of sexual contact with a person with hepatitis B; injection drug use (IDU); and persons with a history of household contact with a person with hepatitis B. The proportions of acute hepatitis B cases reporting risk factors were calculated for cases with available risk information for each factor. Of all reported cases, 52.8% (which includes those excluded from the analysis) and 46.5% of study cases had either no history of these risk factors or the risk factor information was unknown. The proportion of cases with “diabetes” as a potential “risk factor” fell within the range of proportions observed for other risk factors, at 15% [Provisional Data, CDC].

Comparing the risk factors for acute hepatitis B cases by diabetes status, in every diabetes status category, more than half of acute hepatitis B cases had no reported risk factors or risk was unknown. The percentage of cases with no or unknown risk factor information was 61.8% for cases with diabetes, 54.7% for cases without diabetes, and 68% for cases with unknown diabetes status. Comparing cases with and without diabetes, risk factors were reported less often among cases with diabetes than without diabetes, or at about the same rate, but none of the differences by risk factor and diabetes status were statistically significant. The only factor that differed significantly across all three groups was the proportion of cases with reported IDU: 2.9% IDU was reported among cases with diabetes, 6.9% was reported among cases without diabetes, and 27.3% was reported for cases with unknown diabetes status. Considering the available data, IDU appeared to be an important risk factor for cases that were excluded for lack of diabetes status, but not for cases with diabetes [Provisional Data, CDC].

Recalling that New York City had data on diabetes status of acute hepatitis B cases going back five years, from 2006 through 2010, annual incidence of acute hepatitis B was estimated by year, using 2009 population data as the denominator. Variation in the number of hepatitis B cases with diabetes was observed by year ranging from 3 to 10, and in the number of cases without diabetes ranging from 43 to 79. The annual acute hepatitis B incidence varied from 0.5 to 1.8 per 100,000 among persons with diabetes, and from 0.9 to 1.6 per 100,000 for persons without diabetes. The rate ratio by year ranged from 0.5 to 2.1 for hepatitis B incidence among persons with diabetes compared to persons without diabetes, and was only statistically significant in 2009 [Provisional Data, CDC]. To determine factors that might have influenced the variation in incidence by year and diabetes status, additional analyses are planned. Factors being considered include vaccine coverage, race and ethnicity, demographic changes in the population, changes in case interview procedures and in the proportion of cases with diabetes status, hepatitis B risk factors, and cases excluded because of missing diabetes status.

Returning to the data from all 4 EIP sites, incidence was estimated for acute hepatitis B infections among adults with and without diabetes by EIP site and overall from 2009 to 2010. In both Colorado and Connecticut, the incidence of acute hepatitis B among persons with diabetes was approximately four times higher than for those without diabetes. New York City and Oregon data did not show significant differences for acute hepatitis B incidence between persons with and without diabetes during 2009 and 2010. The overall incidence of acute hepatitis B among adults with diabetes was 1.4 per 100,000. Hepatitis B incidence was 1.9 times higher in persons with diabetes than among persons without diabetes, which was significant at a p-value of 0.01 [Provisional Data, CDC].

With respect to the estimated incidence of acute hepatitis B infections among adults with and without diabetes by age group from 2009 through 2010, for both age groups, hepatitis B incidence was at least 2 times higher among persons with diabetes than among persons without diabetes. The rate ratio was statistically significant for adults age 23 to 59, but not for the 60 years and older age group, in which only 33 total cases were reported [Provisional Data, CDC]. The incidence estimates obtained from the 4 EIP sites for 2009 through2010 were compared with the incidence estimates from a catalytic model that was presented to ACIP in June 2010 by Dr. Dale Hu. The catalytic model estimated an acute hepatitis B annual incidence of 1 to 4 per 100,000 adults with diabetes for reported cases, and 22.7 per 100,000 adults with diabetes for all cases, which accounted for underreported, unrecognized, and asymptomatic cases. The estimate from the 4 EIP sites was 1.4 cases of acute hepatitis B per 100,000 adults with diabetes. The catalytic model estimated that the annual number of hepatitis B infections among adults with diabetes is approximately 4000 per year, or about 10% of the estimated 40,000 total annual cases of hepatitis B infection among adults 25 years and older in the US. An estimated 10% of all reported cases of acute hepatitis B from EIP sites had diabetes, and the percentage was 15% of reported cases when information on diabetes status was known [Catalytic model presented at ACIP June, 2010. CDC, unpublished data; Provisional Data, CDC].

There were some study limitations. The BRFSS and the CHS data used to represent the study population excluded institutionalized adults. Therefore, the total population with or without diabetes within each location may have been underestimated, resulting in an overestimate of the incidence of acute hepatitis B, particularly in older age groups. However, the estimated incidence is more likely an underestimate because the denominator data included non-susceptible persons by virtue of vaccination or prior hepatitis B infection, leading to an overestimate of the susceptible population. The study was limited to confirmed cases, excluding probable and unrecognized cases. Additionally, unreported cases would not have been included. Cases without diabetes information were also excluded, which accounted for

30% of all reported cases. It is unknown what proportion of these cases would have had diabetes. Although the 10 sites of the EIP roughly represent the US population on the basis of demographic characteristics and health indicators, only 4 out of the 10 sites were used. Thus, the estimates from the 4 study EIP sites might not be representative of the US population.

In conclusion, the incidence of acute hepatitis B was significantly higher among adults with diabetes than without diabetes overall, and for ages 23 through 59 years. For ages 60 years and older, incidence of acute hepatitis B was also higher among adults with diabetes than without diabetes, but the difference was not statistically significant. Annual incidence from reported hepatitis B cases among adults with and without diabetes substantially underestimates the actual incidence, given that unrecognized, asymptomatic, and unreported cases were not accounted for. The 4 EIP sites providing data for this analysis are continuing surveillance for diabetes status of reported acute hepatitis B cases, and the analysis will be updated to include several months of 2011 data. In the meantime, potential factors influencing the differences in incidence across EIP sites and years will be explored, such as vaccine coverage, race and ethnicity, hepatitis B risk factors, and cases excluded due to no follow-up interview.

Next Steps

Trudy Murphy, MD
NCHHSTP / CDC

Dr. Murphy reported that the Hepatitis Work Group continues to collaborate on work by CDC and partners on infection control initiatives. Several additional tasks are planned, including completing cost-effectiveness analyses; summarizing the results of on-going hepatitis B vaccine seroprotection studies among residents of assisted living facilities with an outbreak of hepatitis B; presenting the estimates of current vaccination coverage among persons with diabetes and some implementation strategies for a potential hepatitis B vaccination program among adults with diabetes to ACIP; and completing an evidence-based GRADE categorization for any proposed recommendations.

Discussion Points

Dr. Keitel noted that in Dr. Burrows' presentation, there was a striking increase in the incidence of diabetes after almost a 10-year period when it appeared that the rate was flat. She wondered whether Dr. Burrows had any explanation, whether anyone mapped body mass index (BMI), and whether it mapped with BMI or any other known risk factors for diabetes.

Ms. Burrows replied that there are some unpublished data showing trends in the prevalence and incidence of diabetes together with the prevalence of obesity, which reflect that the rise in obesity occurred about 10−15 years before the rise in diabetes.

Dr. Keitel asked whether the prevalence of pre-diabetes in the adult population and the risk for progression to diabetes were known, given that this is another population moving into the risk population at an increasing rate.

Ms. Burrows responded that about 1 of 3 (35%) of adults in the US have pre diabetes (i.e., are at risk of developing diabetes). More than 100 million adults have either diabetes or pre-diabetes in the US.

With regard to the data about acute hepatitis B cases 2009 to 2010, Dr. Judson said he would guess that people with no diabetes information in their medical chart would be far less likely to have diabetes than those who did have information. One way to assess that would be add the 100 cases that were excluded back into the denominator for the cases without diabetes. He also observed that those in the more sexually active age, 23 through 59, would have higher rates of IDU and sexual contact than those who were over 60. That difference seemed to attenuate in cases of over 60 with or without diabetes.

Dr. Keitel asked if it was known whether a patient with diabetes would be more likely to have asymptomatic infection and what the risk was for development of chronic hepatitis B among patients with diabetes.

Dr. Murphy responded that the data on risk of developing chronic hepatitis suggests the rates could be related to age rather than related to diabetes, or could be related to both. Although seroprevalence of past hepatitis infection is higher for people with diabetes than people without diabetes across age groups, information on the rates of developing chronic hepatitis among persons with diabetes is primarily from older adults in outbreak settings where the rates of chronic infection are very high. Since diabetes is more common in older adults than younger adults, it is difficult to separate the two factors, age and diabetes.

Regarding the epidemiologic analysis, Dr. Schuchat observed that it was striking that the New York City 4-year analysis had a pretty flat risk of acute hepatitis B with diabetes. She wondered in additional analyses whether the investigators could assess excluded cases by geographic area to determine whether there was some difference, and to assess for the one year with risk in New York City whether there were any recognized outbreaks during in a particular institution or practice.

Ms. Reilly thought this was a great suggestion. CDC would like to examine excluded cases by site to determine whether there were any differences. She also thought it was a great suggestion to assess the 2009 NYC data in more depth in terms of the significant difference between persons with diabetes and without. The investigators plan to talk to their colleagues at the EIP sites to find out whether they have any insight regarding potential outbreaks in NYC in 2009.

Dr. Cieslak noted that a potential confounder he worries about is access to healthcare. People who are diagnosed with diabetes presumably presented to a healthcare provider. Given that 70% of hepatitis B cases are asymptomatic, he wondered whether the proportion of people who had contact with a healthcare provider were more likely to have their hepatitis B diagnosed through liver function tests.

Ms. Reilly responded that differences in the cases were not assessed in terms of access to healthcare. However, perhaps they can acquire further information from the sites regarding this.

Pneumococcal Conjugate Vaccine (PCV 13)

Introduction

Dr. Michael S. Marcy, MD
Chair, ACIP Pneumococcal Work Group

Dr. Marcy indicated that a 23-valent polysaccharide vaccine is recommended for use in the U.S. for the prevention for pneumococcal disease in adults. The effectiveness of this vaccine in preventing invasive pneumococcal disease has been demonstrated, but the vaccine has not been effective in preventing non-invasive pneumococcal pneumonia in the elderly and adults with co-morbid and immunocompromising conditions. In addition, there is evidence of waning immunity and hypo-responsiveness to revaccination with the vaccine, further limiting the benefits of this vaccine.

The use of 7-valent pneumococcal conjugate vaccine has dramatically reduced the incidence of invasive pneumococcal infections in children, as well as the burden of disease among adults through indirect effects, so called herd immunity. However, reductions in the burden of non-invasive pneumonia among adults have not been documented. The burden of invasive pneumococcal disease, although reduced, remains high among adults, especially among the elderly and among adults with co-morbid conditions.

These data raised questions about the remaining opportunities for prevention of pneumococcal infections in adults and the role of pneumococcal conjugate vaccine for adults. A 13-valent pneumococcal conjugate vaccine was licensed for use in children last year and is expected to be licensed for use among adults around the fourth quarter of this year. The Pneumococcal Working Group has engaged in several conference calls considering the potential use of this vaccine in adults.

During this session, two economic models were presented, and the manufacturer provided an update on the status of PCV13 licensure and presented the results of the Phase 3 studies on the safety and immunogenicity of PCV13 in adults. The investigators at the University of Pittsburgh, in collaboration with CDC, have developed a model evaluating the cost-effectiveness and public health impact of different immunization strategies using PCV13 and / or PPV23 in a cohort of adults 50 years of age and older. The manufacturer was scheduled to present results of a model evaluating the public health and economic impact of routine PCV13 vaccination of adults 50 years of age and older (this presentation was postponed to June 2011 meeting).

Safety and Immunogenicity of PCV13 In Adults

Dr. Peter Paradiso
Pfizer Vaccines

Dr. Paradiso reminded everyone that it was one year ago during the ACIP meeting that Prevnar 13® was licensed for use in infants and young children. During the course of the year since then, Pfizer has completed the Phase III studies and have submitted an application to FDA proposing to expand indication for Prevnar 13® to include prevention of pneumococcal disease in adults 50 years of age and older caused by the serotypes in the vaccine.

As this committee is well aware, there are currently recommendations for the use of pneumococcal polysaccharide vaccine in risk populations (adults with chronic or immunocompromising conditions), as well as age-based recommendations for the use of the pneumococcal polysaccharide vaccine. The vaccine is currently recommended for all persons 65 years of age and older. The recommendation is for one dose in the majority of those subjects, and immunization rate has been reported to be about 60% to 70%. That has been fairly constant over the last 10 years or more. In addition, recommendations for high risk individuals 50 through 64 years of age that now cover about 40% to 50% of that age group. With the recent inclusion of smokers and asthmatics, that percentage went up from approximately the low 30% range into the 40% to 50% range. At this time, although the immunization rates are still lagging in the 50 through 64 year old population, the recommendations are already quite broad in this age group. As Dr. Marcy said, with these recommendations and current uses of the vaccine, there is still a significant burden of disease that is preventable by vaccination.

Pneumococcal disease in older adults exerts a significant clinical burden. In the 50 to 60 year old age group, there are an estimated 11,207 cases of invasive pneumococcal disease (IPD); 33,749 cases of non-bacteremic pneumococcal pneumonia (NPP) requiring in-patient care; 104,494 cases of NPP requiring outpatient care only; 1762 IPD-related deaths; and 2086 NPP-related deaths in those requiring inpatient care. In those $\geq$ 65 years of age, there are an estimated 18,155 cases of IPD; 164,852 cases of NPP requiring in-patient care; 199,526 cases of NPP requiring outpatient care only; 4415 IPD-related deaths; and 17,081 NPP-related deaths in those requiring inpatient care [Weycker D et al. *Vaccine.* 2010;28:4955-4960]. Clearly, NPP remains a significant cause of morbidity and mortality in the U.S. Mortality rates have not really changed in the case of pneumonia in adults. There is a significant increase in the burden with age that really begins in the 50 year old range that continues to increase throughout the lifetime. Obviously, there are considerable adverse sequelae that occur as a result of pneumonias and invasive disease.

For the 13-valent vaccine in adults, the regulatory pathway that Pfizer has taken in agreement with FDA is to demonstrate non-inferiority of the functional opsonophagocytic (OPA) response of PCV13 compared to PPV23 in pneumococcal vaccine-naïve and previously vaccinated adults. The regulatory pathway will be Accelerated Approval (601.41) to address an unmet medical need in adults >50 years of age. This is an approval process on the basis of antibody response to PCV13 in comparison to the polysaccharide vaccine (PPV23). Pfizer also agreed to conduct a confirmatory follow-up trial post-licensure, with pneumonia as the primary endpoint. Data will be submitted as a post-approval supplement. That trial is currently on-going, but will not be completed for a while.

One of the benefits observed in conjugate vaccines in younger age groups and older populations is predominantly an ability to stimulate a T-cell immune response. A fair number of studies have tried to examine this; however, these are difficult studies to conduct. Andy Pollard, of the Oxford Vaccine Group at the University of Oxford agreed to let Dr. Paradiso present data from a study in which Dr. Pollard assessed adults 50 to 70 years of age who had received either the conjugate or the polysaccharide vaccine to examine the change and frequency of antigen-specific memory B-cells one month post-vaccination compared to at the time of vaccination. In the polysaccharide vaccine group, there was a reduction in memory B-cells after vaccination; whereas, in those who received a 7-valent conjugate vaccine there was an increase. Again, these studies are difficult to do and not all of the studies have consistently shown this result. However, it is important to point out that different mechanisms are employed in inducing an immune response to a polysaccharide versus a conjugate vaccine. The polysaccharide vaccine

contains 25 micrograms per serotype and the conjugate vaccine for 12 of the 13 serotypes has only 2 micrograms.

Two studies were conducted in the last 10 years in Africa in very high risk HIV-positive populations of adults. One of the studies was with polysaccharide vaccine conducted in Uganda, and the other was in Malawi with the 7-valent conjugate vaccine. Both studies were conducted by Neil French. The contrast is pretty clear with the polysaccharide, for which they were not able to demonstrate efficacy in this high risk population. In fact, there seemed to be a higher incidence of disease in the vaccinated population than in the unvaccinated. In contrast, with the conjugate vaccine, even in this high-risk population of HIV-infected adults, that there was efficacy against invasive disease that was significant. There was also a trend toward reduction in all-cause pneumonia, although that reduction did not achieve significance [French N et al. *Lancet*. 2000;355:2106-2111; French N et al. *N Engl J Med.* 2010;362:812-822]. These data offer some confidence, in addition to the Phase 3 trial data, that there is a potential benefit with the conjugate vaccine.

Pfizer Phase 3 studies evaluated the functional immune response to PCV13 compared to PPV23 in naïve and previously immunized with PPV23 adults ≥50 year of age. They assessed non-inferiority of the PCV13 response to the polysaccharide as the primary outcome, and superiority or statistically significantly higher responses in either group (vaccine naïve or pre-immunized with PPV23) as the secondary outcome. Also evaluated were the sequential administration of PCV13 and PPV23, the compatibility of PCV13 with TIV, and the overall safety profile of PCV13. Dr. Paradiso clarified that while they conducted studies with the sequential use of the two vaccines, they are not seeking a sequence licensure. They are seeking a license for PCV13 vaccine for the prevention of pneumococcal disease. The data are simply informative about how these vaccines might be used.

Subjects in these studies were healthy adults or immunocompetent adults with chronic, stable medical conditions. The number of subjects by age in the six Phase 3 studies who were vaccinated with PCV13 at any dose included 2616 (46.2) 50–64 year olds, 646 (11.4) 65–69 year olds, 1139 (20.1) 70–74, 760 (13.4) 75–79, and 506 (8.9) ≥80 for a total of 5667 (100.0) subjects. A fair number of PCV13 recipients had co-morbid conditions, including 790 (16%) with chronic pulmonary diseases, 700 (14%) with diabetes mellitus, 575 (11%) with cardiovascular diseases, 100 (2%) with renal and urinary disorders, and 30 (1%) with chronic liver disease, including alcoholic liver disease and alcoholism. Across studies, 37%–56% of adults ≥65 years of age had one or more chronic medical condition, while 17%–26% of adults 50–64 years of age had one or more chronic medical condition. In terms of the number and percentage of PCV13 recipients with a smoking history 1790 (~46%) had any smoking history and 385 (~11%) were smoking within the last 6 months.

Pivotal non-inferiority comparisons were made in Study 004 in pneumococcal vaccine naive adults, and Study 3005 in PPV23 immunized adults. Dr. Lisa Jackson was the principal investigator on both of these studies. Study 004 was in 50 through 64 year olds who were naïve to vaccination and the 3005 study were in adults over 70 who had previously been immunized with the polysaccharide vaccines, but not within the last 5 years.

Study 004 was conducted in U.S. adults who were vaccine naïve. There were two primary cohorts: 60 throough 64 years of age and 50 throough 59 years of age. The 60 through 64 year old cohort subjects were randomized to receive either PCV13 (n = 370) or PPV23 (n = 370). The 50 throough 59 years of age cohort received PCV13 (n = 370). For the primary end points, the 60 throough 64 year old conjugate group was compared to the 60 through 64 year

old polysaccharide group. As polysaccharide vaccine is not recommended for 50 throough 59 year old adults, the response in 50 through 59 year olds receiving conjugate was compared to the response in 60 through 64 year olds receiving conjugate vaccine.

The 60 throough 64 year old vaccine naïve adults achieved non-inferiority for all of the serotypes, and there was a statistically significantly higher response for 8 out of the 13 serotypes. Because 6A is present in the conjugate vaccine but not in the polysaccharide vaccine, this serotype has a different end point (proportion achieving greater than four-fold increase in OPA titers) . Among adults 50 through59 years old, non-inferiority criteria were met for all serotypes, and the response to 9 of 13 serotypes was statistically significantly greater for the 50 through 59 year olds versus the 60 through 64 year olds. This trend has been observed in the course of Pfizer's studies across the age groups. There is an age-dependence of the immune response, with the highest responses in the youngest group (50-59 year olds). The average age of the difference is about 10 years (52 to 62 range in difference of age). In Study 004, immune response in 60 through 64 year old high-risk subjects was also assessed. The data show that in each of the groups with co-morbid conditions, and even though the numbers are small because only about 20% have co-morbid conditions in this age group, the response is comparable across those groups. It does not seem that any of those comorbid conditions contribute to a dramatic reduction in antibody response.

The conclusions from Study 004 are that PCV13 induces a response in naïve 60 through 64 year olds that is non-inferior to PPV23 for all serotypes, and is statistically significantly greater for 8 of the 13 serotypes. The response to PCV13 is generally higher in 50 through 59 year olds compared to 60 through 64 year olds for 9 of the 13 serotypes.

In Study 3005 a response to PCV13 versus PPV23 was assessed in PPV23-exposed subjects ≥70 years of age in the U.S. and Sweden. Approximately 60% of U.S. adults over 65 years of age fit into the category of having previously been immunized with polysaccharide vaccine. Antibody response was assessed after 1 month. A year later, both groups were boosted with conjugate vaccine. One cohort received PCV13 (n = 462) for both doses, and the other cohort received PPV23 (n = 462) followed by PCV13 (n = 462). Non-inferiority criteria were met for all serotypes, and for 11 of the 13 serotypes, it was statistically significantly higher for the conjugate vaccine versus the polysaccharide. This is consistent with the data in the naïve subjects. Stratified by age (dividing the subjects by 70 through 74, 75 through 79, and over 80), regardless of the age group, for the majority of serotypes, the response was higher for the conjugate vaccine than for the polysaccharide vaccine.

Due to time constraints, Dr. Paradiso did not have time to show all of the second dose data and titers for each of the scenarios that were used. Instead, he reported on the Serotype 1 because it is indicative of most of the serotypes studied. As observed in the previous comparisons, after the second dose of conjugate vaccine, the titer achieved is comparable to the first dose. There is a waning between doses and immunity is renewed with the second dose. A boost is not observed with the second dose. However, if the polysaccharide is given first, there is a clear blunting in the response to a subsequent conjugate vaccine. This was observed for all 13 serotypes in the vaccine. This pattern of polysaccharide followed by conjugate is consistent throughout all of Pfizer's trials regardless of the population or regardless of the previous immunization status.

Conclusions from Study 3005 are that PCV13 induces a response in previously immunized >70 year olds that is non-inferior to PPV23 for all serotypes, and the response is statistically significantly higher for 11 of the 13 types. Superior responses to PCV13 were seen throughout the age range over 70 years. A second dose of PCV13 one year later induced a response comparable to the initial dose of PCV13. Immunization with PPV23 significantly blunts a subsequent response to PCV13.

In Study 3010, sequential vaccination in PPV23-naïve US subjects 60 through 64 years of age was assessed. Those who received PCV13 (n = 480) were subsequently given either PCV13 (n = 240) or PPV23 (n = 240) a year later, while those who initially received PPV23 (n = 240) were subsequently given PCV13 (n = 240) a year later. While the response in this group to the initial vaccination is higher than in the older group, not as consistent a pattern was observed to the second dose of vaccination. For serotype 1 and serotype 23, the conjugate has a better response. Prior polysaccharide vaccine results in a lower response than the conjugate without the polysaccharide, which is again consistent with all of the Pfizer data. For serotype 1, the second dose a year after receiving the conjugate vaccine shows an increase, but not as high as observed after the initial dose. For serotype 23, there is a mix within the serotypes. In this group that is younger and actually achieves a better response overall, a second dose a year later may not be the right interval.

The proportion of patients achieving a response above the lower limit of quantification (LLOQ) was also used (instead of titers > 1:8 used in pediatric studies) to compare the responses in the two arms. This endpoint is not really a correlate and was probably too easy an outcome for adults, in which case PCV13 / PCV13 was non-inferior for 11 of the 13 serotypes and PCV13 / PCV13 was statistically significantly higher for 3 of 13 serotypes. Adults who responded more poorly with the first dose had a higher response with the second. Those who responded very well with the second dose tended not to go as high with the second dose.

The conclusions for Study 3010 are that a dose of PCV13 does not blunt the response to a subsequent dose of PPV23. A dose of PPV23 significantly blunts the response to a subsequent dose of PCV13. At year one, response to a second dose of PCV13 was blunted for some serotypes. Percent responders was non-inferior for 11 of the 13 serotypes. To investigate this question further, Study 004 was extended to call the subjects back 3 to 4 years after the first dose to receive conjugate and polysaccharide in a varying schedule. In addition, this trial includes an arm of 18 through 49 year olds. While Pfizer is not seeking licensure at this time for this age group, they are collecting the data needed for subsequent expansion of the indication.

Study 3001 examined the compatibility of the use of the conjugate vaccine with the TIV. One study was conducted in the U.S. and one was conducted in Europe. The designs of the US and European studies were similar. The U.S. study assessed 50 through 59 year olds and the European study assess those over 65 years. The key objectives were to determine whether the immune response to trivalent inactivated influenza vaccine (TIV) administered concomitantly with PCV13 was non-inferior to TIV alone; and whether immune responses to PCV13 administered concomitantly with TIV was non-inferior to PCV13 administered 1 month after TIV. This study follows subjects for 5 years and is currently at about the halfway point. Annual blood draws are being done to examine waning or sustaining immunity. These subjects will be boosted at 5 years, and then the response to PCV13 will be examined.

The conclusions for Study 3001 for PCV13 with TIV in 50 through 59 year olds concomitant administration of PCV13 and TIV is non-inferior to TIV or PCV13 alone, as measured by IgG response to PCV13 and HAI response to TIV. Systemic adverse events associated with concomitant administration of PCV13 and TIV are comparable to TIV or PCV13 alone. Local reactions associated with concomitant administration of PCV13 and TIV are comparable to PCV13 alone. These data will be the basis for a request for supporting simultaneous administration of these vaccines.

In terms of the overall safety data for this program in which there were numerous other trials not shown during this session, there were approximately 4000 subjects who were naïve to the polysaccharide vaccine, about 2000 subjects overall who contributed to the safety database in previously immunized, and approximately 6000 adults over the age of 50 have been immunized. In summary, PCV13 has demonstrated an acceptable safety and reactogenicity profile. PCV13 is comparable to PPSV23 in unvaccinated subjects. PCV13 has an acceptable safety and reactogenicity profile when administered with trivalent inactivated influenza vaccine. No increase in local or systemic reactogenicity is observed when PCV13 is administered after vaccination with either PPSV23 or PCV13. While Dr. Paradiso did not have time to go through all of the safety data during this session, he said he would be happy to review this during a future ACIP meeting.

In terms of the overall benefit of PCV13 in adults, when administered as the first pneumococcal vaccine to adults ≥ age 50 years, PCV13 may provide the immunologic advantages associated with conjugate vaccines. PCV13 could be recommended for all adults ≥50 years of age regardless of previous history of vaccination with PPV23 (e.g., adults naïve to PPV23 vaccine, adults who have previously received PPV23 vaccine, and adults with an unknown vaccine history).

On-going PCV13 studies in adults, for which data will be available over the next couple of years, include adults 18 through 49 years of age, HIV positive adults >18 years of age with and without previous PPS23, bone marrow transplant (HSCT) patients >18 years of age, antibody persistence studies (up to 5 years), and a community-acquired pneumonia trial in adults (CAPiTA). CAPiTA is an on-going placebo-controlled efficacy trial in the Netherlands, which is a follow-up commitment to FDA to examine the impact on pneumococcal pneumonia.

Discussion Points

Dr. Baker noted that OPAs are done a variety of ways. She was concerned with the use of GMTs without confidence intervals, and the data can look good for adults with GMTs only.

Dr. Paradiso responded that he did not have time to show all of the data during this session, but would be happy to do so during another ACIP meeting. These data will be presented at a meeting in Europe, where all of the numbers will be available.

Dr. Baker said she would appreciate seeing the confidence intervals and the duration of protection data during a future ACIP meeting.

Dr. Paradiso replied that they are conducting follow-up. While he could not promise an exact date, as soon as they have the requested data he will share it with the ACIP membership. The experience Pfizer has about duration of immunity is in the pediatric population. There have been numerous trials in the pediatric population. In two studies, one in Gambia and one in

South Africa, children were immunized at a very young age and received three doses of vaccine. They were not boosted in the second year of life. In those children, antibody wanes very dramatically by 12 months of age. The impact on invasive disease and pneumonia was dramatic in those populations. One overall reduction in the 20% range in Gambia was close to 40%. A follow-up study in South Africa shows that protection actually persisted out to 5 years post-vaccination. This is actual protection, not antibody titer. With these vaccines, OPAs offer only a picture of the magnitude of the response, not necessarily the quality of the response.

Dr. Baker noted that the pediatric population has an inherent advantage with conjugate vaccines, given that they have a limited period of risk. The peak attack rate was in 6 to 24 month olds, so the risk definitely goes down with time. Even in an efficacy trial, the older the children get, the better the protection is going to look.

Dr. Keitel was intrigued by the B-cell studies. Since there is an apparent drop among subjects who received purified polysaccharide vaccine, that means they were primed to those antigens before they were vaccinated. The fact that there is a drop suggests that the memory B-cells were either tolerant or depleted by means of apoptosis or some other mechanism. She wondered whether there was in vivo mechanism to explain this. She also wondered whether these results were tied to the antibody responses following vaccination.

Dr. Paradiso clarified that this was Andy Pollard's study in the U.K. During their lifetime, these adults were likely exposed to pneumococcus. It is noy well understood why this reduction in memory cells is observed, but one theory is that that a large amount of polysaccharide attaches to memory cells and reduce their availability to be stimulated a month later. Whether that is the answer it is not known, but it is a way that future hypo-responsiveness has been explained. Dr. Paradiso indicated that he would find out if more data are available on this topic.

Dr. Chilton asked to what degree the 10 or 11 types that are not in PCV13 contribute to disease in adults, and where they have observed replacement of vaccine type serotypes with others as was seen with PCV7 when it was first used in children.

Dr. Paradiso replied that the PCV13 covers about 75% of what PPS23 covers. The additional 11-serotypes cover more disease but .the serotypes that are in PCV13 are the predominant ones. It is too early to know whether there is any impact of vaccination with PCV13 vaccine, especially in this adult population. All they have are the studies done in immunogenicity.

Dr. Schuchat asked what age group was enrolled in the community-acquired pneumonia trial being carried out in the Netherlands and what the timeline is for results.

Dr. Paradiso responded that the trial is in over 65 year olds. It is a randomized placebo controlled-trial with 85,000 subjects who are being followed. The endpoint is case-driven. It will probably be a couple years before there are enough cases. The study will assess both bacteremic and non-bacteremic pneumonia endpoints.

Dr. Schuchat wondered where the pneumonia indication for those under 65 would come from.

Dr. Paradiso responded that the label shown is essentially the label that is on the polysaccharide vaccine. The accelerated review process indicates that if non-inferiority is

demonstrated to what is currently licensed, this would be sufficient for licensure, assuming that they agreed to follow-up in an efficacy trial to demonstrate efficacy against pneumonia.

Cost-Effectiveness of PCV13 Vaccination of Adults ≥ 50 Years of Age

Richard K. Zimmerman, MD, MPH
Kenneth J Smith, MD, MS
University of Pittsburgh School of Medicine, Pittsburgh, PA

Dr. Zimmerman indicated that they are assessing the issue of public health impact as well as cost-effectiveness. He believes that modeling studies can help with the cost-effectiveness, and more importantly they can help assess public health impact. In terms of background, there are approximately 25,000 pneumococcal disease deaths per year in the US, most of which are due to non-invasive pneumonia. PCV13 protects against pneumonia and IPD, and PPV protects against IPD. The optimal strategy for PCV13 and / or PPV in adults is unknown in terms of the public health impact and cost-effectiveness.

Zimmerman et al examined several possible strategies. When conducting cost-effectiveness modeling, it is necessary to begin with no vaccination. They then reviewed the current U.S. strategy for those at 65 years of age, which is one dose of polysaccharide vaccine. For those younger than 65 who have a high-risk condition, the strategy is one dose of polysaccharide vaccine at diagnosis plus a second dose at age 65, with at least a 5-year interval between doses. In terms of the current U.S. adult vaccination recommendation, consideration was also given to substituting PCV13 for PPV23, PCV13 at age 50 and PPV23 at age 65, PCV13 at ages 50 and 65, and PCV13 at ages 50 and 65, then PPV23 at age 75.

The design is a Markov model with the cycle length of 1 year that assesses a 50-year-old cohort that mirrors the U.S. population and is followed up for life. The recommendations of the Panel on Cost-Effectiveness in Health and Medicine are followed using the societal perspective and discounting it 3% per year. The public health outcomes are cases and deaths prevented, and the economic outcomes are costs and QALY. The Markov model begins with a person who is healthy. This person may develop invasive infection, recover from the invasive infection, and return to being a healthy person. Alternatively, they might have invasive infection, perhaps meningitis, become disabled, and potentially die from a disability—the terminal state of the model. The person could also develop a non-invasive infection, such as pneumonia, and return to health or become disabled. Alternatively, this healthy person could be vaccinated. However, there also could be vaccine failures for either invasive or non-invasive, which would lead to disability. A person with a high-risk disease (e.g., chronic lung disease, chronic heart disease) can become infected (non-invasive or invasive infection), they can recover or they can be vaccinated. Again, vaccine failures could lead to disability. There is an exact similar part of the tree that has immunocompromised persons, because the investigators felt that they were substantially different from the person with chronic heart or lung disease.

Cost-effectiveness of vaccination is the cost associated with vaccine in 2006 U.S. dollars plus the cost of pneumococcal disease. The effectiveness equals the QALYs in terms of the utility of health states (0=death to 1=perfect health) multiplied by the time spent in those states. Decision-tree modeling expertise came from the University of Pittsburgh Section of Decision Science, vaccine policy expertise was from the University of Pittsburgh Department of Family Medicine, pneumococcal disease expertise came from CDC. An iterative process was used, with multiple presentations to CDC on data inputs and assumptions.

The ABCs data were segmented by age; healthy, co-morbid illness, or immunocompromised; PPV23 serotype coverage, and PCV13 serotype coverage. These data were adjusted to produce hypothetical "no vaccine" rates using the model of Fry et al [Fry AM, Zell ER, Schuchat A, Butler JC, Whitney CG. Vaccine 2002;21:303-11]. Data were used from the National Hospital Discharge Survey and from the National Inpatient Sample for co-morbid illness groups. For the regular population who are not infected, US Mortality tables were used. Expert Delphi panels were used for the age- and co-morbidity-stratified PPV23 and PCV13 vaccine effectiveness estimates. A number of ACIP work group members were used as panel members.

Estimates by the Delphi panel for the effectiveness against invasive pneumococcal disease were 90% one year post-vaccination in healthy 50 year olds. With increasing years away from vaccination, the expert group recommended that effectiveness estimates be lowered. Each of these effectiveness estimates has a range around it. For 65 year olds, a decreasing set of estimates were used for effectiveness against invasive disease. The same was done for those who are immunocompromised, the values for which are much more sobering. The worst-case scenarios all include zero. Effectiveness estimates against non-invasive pneumococcal pneumonia follow the same pattern in terms of years since vaccination, healthy 50 year olds, starting at 74 and going down, with a range around those (the worst-case to best-case scenario). For non-invasive pneumococcal pneumonia, the group's estimates are substantially lower than against invasive disease.

Putting this into the context, Kaiser PCV7 efficacy trial in children, pneumonia effectiveness was reduced by 20%* for x-ray defined pneumonia of any infiltrate versus 73% efficacy for consolidation of 2.5^{+} centimeters versus 87% efficacy against bacteremic pneumonia. In terms of the effectiveness against pneumonia, this depends upon which definition of pneumonia is used. To put this in context, 73% is not dissimilar to what the expert group determined. For the Kaiser trial in children, the efficacy against invasive disease was 97%. The working group dropped the efficacy estimates from invasive disease to non-invasive pneumonia. Note that a 25% reduction in IPD efficacy is 73% (97.4-0.75) [* *PIDJ* 2002: 21:810-5; † 39th ICAAC as cited in ACIP recommendations in *MMWR* 2000; 49: (RR09)].

Dr. Smith reviewed how invasive pneumococcal disease in adults was modeled in the face of herd immunity from pediatric PCV7 use. There is a very well-documented effect from PCV7. The modelers would postulate some similar type of effect from the use of childhood PCV13 on adult invasive pneumococcal disease rates. They modeled changes in IPD rates based on changes in rates and changes in serotype distribution. IPD rate changes from herd immunity and replacement disease were modeled based on observed changes post-PCV7 in a study last year from the CDC group. Decreases have been modeled in adult age-specific IPD rates from the four new carried serotypes in the PCV13, and increased adult age-specific IPD rates caused by non-vaccine serotypes were modeled (i.e. replacement disease). Ranges were used for future IPD cases based on 95% confidence intervals from the same study [*Pilishvili* et al. JID 2010; 201: 32-41].

For serotype-specific changes from herd immunity, diminished relative likelihoods of disease from PCV13 serotypes over the first 1 to 5 years after the licensure of the PCV13 for children were modeled. Those assumptions were varied in sensitivity analyses and included assessment of longer-term serotype changes. In terms of modeling non-invasive pneumococcal pneumonia rates, National Discharge Survey data were used, with an assumption that 30% of hospitalized pneumonia cases were due to pneumococcous [Metersky et al. Chest 2010; Carbonara et al. Curr Opin Pulm Med 2009]. Age and co-morbidity specific rate ratios were used to derive a conversion factor for the number of cases for various age and co-morbidity groups. Those IPD rate ratios were applied to the non-invasive pneumococcal pneumonia rates to calculate hospitalized non-invasive pneumonia rates by age and co-morbidity. It was also assumed that the likelihood of PCV serotypes causing hospitalized non-invasive pneumonia was the same as that seen in invasive pneumococcal disease. Non-hospitalized pneumonia was not modeled, given that estimating age and co-morbidity specific outpatient pneumonia rates and serotype epidemiology was extremely difficult. This was done with the understanding that by not modeling outpatient pneumonia, they were biasing the model against PCV13 strategies.

In terms of extrapolating estimates of non-invasive pneumococcal pneumonia to all-cause pneumonia prevention, using the base case estimates in the first year after PCV13 vaccination in adults, it was estimated that 10.6% of all hospitalized pneumonia cases would be prevented in healthy 50 year olds, and that 10.2% of those cases would be prevented in healthy 65 year olds. For herd immunity effects in non-invasive pneumococcal pneumonia, herd immunity effects were not modeled in the base case analysis based on no statistically significant changes in pneumonia cases observed post-PCV7 in patients aged 50 and older from Grijalva et al [Lancet 2007;369:1179]. Point estimates for observed versus expected rates were modeled in the sensitivity analysis based on the same Grijalva et al study.

In the base case analysis, 100% vaccine uptake was assumed; however, in sensitivity analyses decreased uptake and differential uptake between age- and comorbidity-based vaccination strategies was assumed, and the main scenario used observed vaccine uptake with age-based (60.1%) and comorbidity-based (33.9%) vaccination rates based on observed data for the pneumococcal polysaccharide vaccine from NHIS 2008. Private sector vaccine and administration costs were used. Inpatient costs for pneumococcal disease were used from the Healthcare Cost and Utilization Project (HCUP), and quality of life utility values were used from the medical literature.

In sensitivity analyses, all parameters were varied individually in a one-way sensitivity analysis, and all parameters were varied simultaneously over distributions in a probabilistic sensitivity analysis. A number of scenarios were examined. The main scenario, mentioned earlier, was designed to be a worst-case scenario for PCV13 against non-invasive disease, using worst-case PCV effectiveness values against non-invasive pneumonia, base case effectiveness against invasive disease for both vaccines, and observed age- and co-morbidity-based vaccine uptake. A number of other scenarios were also examined, varying serotype likelihood, herd immunity effects, and delays in replacement disease.

In terms of base case public health impact results, the model estimates that for 50 year old cohorts, about 11% will be hospitalized with non-invasive pneumococcal disease throughout their remaining lifetime. Vaccinating with PCV13 at age 50 and PPV at age 65 would decrease the number of cases by about 5700 in the approximately 4.3 million 50 year olds in this cohort. Substituting PCV13 for PPV23 in the present recommendations will prevent about 18,000 cases of non-invasive pneumonia. Giving PCV13 at ages 50 and 65 would decrease the number of

cases by about 33,000. Fewer cases of invasive pneumococcal disease were prevented despite greater relative risk reductions due to the much lower incidence of IPD. In the base-case scenario, the number of cases of non-invasive pneumonia prevented far outweighs the number of IPD cases prevented; once again, based on the relative likelihood of non-invasive disease versus invasive disease. In the worst-case scenario, the number of non-invasive disease cases prevented still outweighs the number of IPD cases in the three strategies where PCV13 is given at age 65.

The cost-effectiveness analysis results show those strategies that were non-dominated. In the base case, the costs per person for pneumococcal disease and vaccination were about $1,300. Vaccinating with PCV13 at ages 50 and 65 cost about $14,000 per QALY gained compared to no vaccination. The incremental cost of the next strategy, which added PPV23 at 75, was greater than $500,000 per QALY due to minimal gains in effectiveness. In the worst-case scenario, the present recommended strategy represented by 65 and younger high risk and the strategy substituting the PCV13for PPS23 in the present recommendations were no longer dominated, with incremental cost-effectiveness ratios of $35,000 for the present strategy and about $47,000 per QALY gained for the substituted strategies. In this analysis, the PCV at 50 and 65 years was much more expensive at more than $180,000 per QALY gained.

In terms of the sensitivity analyses, vaccine efficacy was by far the most important strategy with the most variation of the efficacy value. Vaccine price had modest effects, and only when the price was a good bit higher than the value used in the base case analysis. Other parameter values, when varied individually, had relatively modest effects on the analysis. If herd immunity effects were allowed to decrease the number of non-invasive pneumonia cases, that increased the incremental cost-effectiveness ratio of PCV13 at age 50 and 65 years to about $20,000 per QALY compared to $14,000 in the base case analysis. If greater herd immunity effects on invasive pneumococcal disease were modeled, that only very modestly changed the incremental cost-effectiveness ratio for that strategy (PCV13 (50 and 65) cost $14,576/QALY). Modeling long-term serotype changed the results relatively minimally (PCV13 (50 & 65) cost $14,617- $14,774/QALY). Modeling the 5-year delay in full replacement decreased the incremental cost-effectiveness ratio of that strategy to about $13,000.

Based on a probabilistic sensitivity analysis in which all of the parameter values were varied over distributions 3000 times, if the cost-effectiveness acceptability threshold is $25,000 or greater, PCV13 given at 50 and 65 years would be favored. That same analysis using observed age and co-morbidity based vaccine uptake shows that PCV13 substituted for PPV23 in the present recommendation strategy would be favored at cost-effectiveness ratios of $25,000 to $50,000, but at ceiling ratios greater than $50,000, the PCV13 given at 50 and 65 years would again be favored.

There are several limitations with this study. Expert panels were used to estimate vaccine effectiveness. Because a 50-year-old cohort was used, effects cannot be estimated on the entire population. The childhood PCV13 herd immunity projections were based on observed changes pre- and post-PCV7. The actual effects from childhood PCV13 are as yet unknown. Non-hospitalized pneumonia was not considered in the model; thus, the cost-effectiveness ratio for PCV13 could be slightly overestimated.

In conclusion, PCV13 strategies were found to be highly cost-effective for a 50-year-old cohort compared to the present adult PPV23 recommendations under base case assumptions. In addition, scheduled PCV13 at ages 50 and 65 years were favored over other strategies except

when vaccine efficacy is low. In this case, PCV13 substituted for PPV23 in the current recommendations may be more favored.

Discussion Points

Dr. Keitel noted that Slide 25 displayed the public health impact using the base case scenario, but in Slide 28 demonstrated the results of cost-effectiveness analyses using the base case and the worst case scenarios. She wondered if there was an analogous slide for the worst-case scenario to 25.

Dr. Smith replied that this was in the supplemental slides on Slide 52.

Dr. Whitley-Williams (NMA) requested clarification about whether 100% coverage was assumed for this model.

Dr. Smith replied that in the base case analysis, 100% coverage was assumed.

Dr. Whitley-Williams (NMA) wondered how less than 50%, if not 40%, coverage rates of pneumococcal vaccine in the current population would impact the model. She thought it would be useful to see the results at different coverage rates.

Dr. Smith indicated that they did assess various coverage rates. Basically, when the coverage rates are decreased, the result is a proportionate decrease in cases. A decrease in coverage rates does raise the incremental cost effectiveness ratio slightly, but going down to 50%, the incremental cost effectiveness ratio for the 50 and 65 year old strategies does not go over $20,000 per QALY gained.

Dr. Baker indicated that due to fairly strict rules and regulations about having a quorum and given the time, Dr. David Strutton's presentation on the public health and economic impact of PCV13 in U.S. adults aged 50 years and older would be postponed until the June 2011 ACIP meeting.

Public Comment: February 24, 2011

John Grabenstein, PhD
Senior Medical Director
Adult Vaccines, Merck Vaccines

Dr. Grabenstein indicated that his professional responsibilities at Merck Vaccines in Pennsylvania involve pneumococcal vaccines. While he thought the last hour had been a good beginning to a comparison of two vaccines for adults, he was struck by the literature not cited. He also noted that time matters. He reminded everyone that Dr. Baker pointed out that some of the analyses shown were at the 1-month interval. However, there are published data at 6 months and 12 months after vaccination that the workgroup should take into account. A recent review by Musher would take them through that. The workgroup should also consider a very important recent article from the Alaska Public Health Department by Hammitt that shows no evidence of hypo-responsiveness related to the third and fourth doses of PPV23 vaccine. Two articles from David Goldblatt's group, on which Baxendale is the lead author, show no difference

in memory B-cells between polysaccharide and conjugate pneumococcal vaccines. The meta-analysis by Moberly of 2008 renders a finding of about 75% efficacy. That is in the process of being updated to include the Moriyama study from Japan that shows 64% efficacy of 23-valent vaccine against pneumonia in a nursing home setting. In terms of efficacy for PPV23 vaccine, two years ago the Pneumococcal Workgroup chose 20%, 50%, and 80% and did not choose 0% to get a better sense of what the true efficacy of pneumococcal polysaccharide vaccine might be. He would say that a 0% efficacy rate is not supported by the literature.

Dr. Baker reiterated that the Pfizer presentation regarding cost-effectiveness of PCV13 vaccine would be presented during the June 2011 ACIP meeting, which would be followed with a summary statement by the workgroup chair, Dr. Marcy. She also announced that if there were any suggestions from ACIP members, liaisons, or the audience regarding how ACIP meeting could be better run, they should submit these to Dr. Pickering at lpickering@cdc.gov.

Certification

I hereby certify that to the best of my knowledge, the foregoing Minutes of the February 23-24, 2011 ACIP Meeting are accurate and complete.

Date

Dr. Carol Baker, Chair
Advisory Committee on
Immunization Practices (ACIP)

Attendees

US Citizens			
Last	**First**	**Country**	**Organization**
Alexa	Pamela	United States	Pfizer
Allen	Curtis	United States	Pfizer
Allred	Stephen	United States	Get A Flu Shot.com
Ambrose	Karita	United States	Novartis Vaccines and Diagnostics
Arnett	Samantha	United States	The National Academies
Arrindell	Deborah	United States	American Social Health Association
Ashley	Don	United States	Pfizer Pharmaceuticals
athar	heba	United States	CDC
Ault	Kevin	United States	Emory University School of Medicine
Baker	Carol J.	United States	Baylor College of Medicine
Bandell	Allyn	United States	MedImmune
Bardi	Janna	United States	Washington State Department of Health
Bargatze	Robert	United States	LigoCyte Pharmaceuticals, Inc.
Baylor	Norman	United States	FDA, Office of Vaccines Research and Review
Beaman	Ann	United States	Avalon Catering
Berman	Taryn	United States	Ruder Finn
Bernbaum	Judy	United States	Children's Hospital Of Philadelphia
Berns	Abby	United States	National Association of County and City Health Officials
Bibila	Dora	United States	Merck & Co, Inc.
Blalack	Gary	United States	GlaxoSmithKline
Bleser	William	United States	National Vaccine Program Office
Bobinsky	Marcella	United States	NH Immunization Program, Div. of Public Health Services
Bodenstein	Carl	United States	Pediatrix Medical Group Neonatology of WA
Bozof	Lynn	United States	National Meningitis Association, Inc.
Bradley	Kimberly	United States	Novartis Vaccines
Brady	Micahel	United States	AAP COID
Bresnitz	Eddy	United States	Merck & Co., Inc
Brewer	Katherine	United States	American Nurses Association
Campbell-Welsh	Gay	United States	GA DPH
Campos-Outcalt	Doug	United States	American Academy of Family Physicians
Carter	Laura	United States	Avalon Catering
Cary	Donna	United States	Sanofi Pasteur
Center	Kimberly	United States	Pfizer Vaccine Research
Chaney	Mike	United States	GA Chapter, American Academy of Pediatrics

Cheek	Jim	United States	Indian Health Service
Chester	Barry	United States	Pfizer
Chilton	Lance	United States	University of New Mexico (ACIP member)
Cieslak	Paul	United States	Oregon Public Health Division
Clark	Liana	United States	Merck & Company, Inc.
Clark	Liana	United States	Merck & Company, Inc.
Claxton	Isabelle	United States	GSK Vaccines
Clover	Richard	United States	University of Louisville
Coelingh	Kathleen	United States	MedImmune
Colwell	Chrisopher	United States	Becton Dickinson
Conner	Penny	United States	Georgia Department of Community Health
Constantino	Tor	United States	MedImmune
Conway	Catherine	United States	Avalon Catering
Cooper	Louis	United States	National Network for Immunization Information
Counard	Catherine	United States	Village of Skokie
Coyne-Beasley	Tamera	United States	University of North Carolina
Cullison	Mark	United States	Merck and Co., Inc.
Curry	David R	United States	Center for Vaccine Ethics and Policy/UPenn
Dalrymple	Donald "Dack"	United States	Dalrymple & Associates, LLC
Damm	Zachary	United States	Country Doctor Community Health Clinic
Decker	Michael	United States	sanofi pasteur
DeNoon	Daniel	United States	WebMD
Deora	Ami	United States	BRG
Dickson	Najla	United States	Sanofi Pasteur
Dinovitz	Richard	United States	RCDVaccine, LLC
Donnelly	John	United States	Pfizer
Duchin	Jeffrey	United States	ACIP Member
Dudgeon	Matt	United States	CDC
Duncan	Lorraine	United States	Oregon Immunization Program
Dutta	Amlan	United States	Merck
Egge	Steve	United States	Merck & Co, Inc.
Ehresmann	Kristen	United States	Minnesota Department of Health
Eisenbart	Valerie	United States	University of Illinois
Elward	Alexis	United States	Hospital Infection Control Practice Advisory Committee
Englund	Janet	United States	Seattle Children"s Hospital/Univ. Washington
Erkman	Brett	United States	Great Point Partners, LLC
Etkind	Paul	United States	National Association of County and City Health Officials
Evans	Geoffrey	United States	Division of Vaccine Injury Compensation, HRSA
Feinberg	Mark	United States	Merck & Co., Inc.
Fernandez	Carrie	United States	Pfizer

Fill	Mary-Margaret	United States	CDC Epidemiology Elective for 4th year Medical Students
Fletcher	Andrea	United States	Emory University RSPH
Fortner	Angela	United States	Northeast Georgia Medical Center
Foster	Stephan	United States	Liaison Representative for ACIP
Friedland	Leonard	United States	GSK
Fryhofer	Sandra	United States	American College of Physicians
Fye	Jessica	United States	JPMorgan Securities
Gaffoglio	Diane	United States	Nancy Lee & Associates
Gall	Stanley A	United States	The American College of Obstetricians & Gynecologists
Gargano	Lisa	United States	Emory University
Gaskins	Diana	United States	retired
Gastanaduy	Paul	United States	Emory University Rollins School of Public Health
Geddes	Cathy	United States	Pfizer
Gellin	Bruce	United States	National Vaccine Program Office
Goddard	Kristin	United States	Department of Health and Human Services, National Vaccine Program Office
Goldstein	Michael	United States	Merck
Gordon	Lili	United States	Pfizer
Goveia	Michelle	United States	Merck
Grabenstein	John	United States	Merck & Company, Inc.
Granville	Chanel	United States	CDC Epidemiology Elective Program
Greenberg	David	United States	sanofi pasteur
Grogg	Stanley	United States	American Osteopathic Association
Groom	Amy	United States	CDC
Grunstra	Ron	United States	Pfizer Pharmaceuticals
Gurtman	Alejandra	United States	Pfizer
Hackman	Jeff	United States	Intercell
Hahn	Christine	United States	Council of State and Territorial Epidemiologists
Halsey	Neal	United States	Johns Hopkins Bloomberg School of Public Health
Hannan	Claire	United States	Association of Immunization Managers
Haupt	Richard	United States	Merck Research Labs
Hayes	Carol	United States	American Nurses Association
Hazelwood	Kim	United States	Georgia DPH, Pharmacy
Henry-Wallace	Stephanie	United States	Cambridge Communications
Hewlett	Dial	United States	Pfizer
Heyward	William	United States	Dynavax Technologies
Hinman	Alan	United States	Task Force for Global Health
Holcombe	Julie	United States	Pfizer Pharmaceuticals
Hosbach	Philip	United States	sanofi pasteur
Howe	Barbara	United States	GlaxoSmithKline
Huber	Helen	United States	South Carolina Department of Environmental Control Immunization Division

Hughes	Carol Rene	United States	StayWell Health Management
Hughes	Jim	United States	Emory University
Hull	Harry	United States	HF Hull & Associates
Humphrey-Franklin	Donelle	United States	Ga Division of Public Health
Hunter	Margie	United States	Dekalb Medical Services
Israel	Zimra	United States	Pfizer
Janssen	Robert	United States	Dynavax Technologies
Janusz	Cara	United States	Pan American Health Organization
Jenkins-Woodard	Renee	United States	Howard University
Jimenez	Jeanne	United States	NAVAL BRANCH HEALTH CLINIC
Johnson	David	United States	Sanofi Pasteur
Johnson	Amy	United States	Cambridge Communications
Johnson	Erica	United States	APCO Worldwide
Judson	Frank	United States	University of Colorado School of Public Health
Kagan	Stephen	United States	Pfizer
Kanaras	John	United States	Merck & Co., inc.
Katz	Samuel	United States	Infectious Diseases Society of America
Kaye	Bronwen	United States	Pfizer
Keitel	Wendy	United States	Baylor College of Medicine
Kent	Charlotte	United States	Centers for Disease Control - Division of STD Prevention
Kimak	Lee Ann	United States	Pfizer
Kimberlin	David	United States	AAP Red Book
Kinsinsger	Linda	United States	VHA National Center for Health Promotion and Disease Prevention
Kitchen	Chester	United States	Merck & Company, Inc.
Kozak	Waldemar	United States	Novartis Vaccines & Diagnostics
Kozycki	Christina	United States	Medical College of Georgia
Krishnarajah	Shanthy	United States	GlaxoSmithKline
Kuter	Barbara	United States	Merck
Labenita	Maribel	United States	Avalon Catering
LaMarca	Lou	United States	Pfizer
Landry	Sarah	United States	National Vaccine Program Office
Lawson	Herschel	United States	Retired CDC
Lease	Christian	United States	Novartis Vaccines
Leger	Marie-Michele	United States	American Academy of Physician Assistants
Lewin	Clement	United States	Novartis Vaccines and Diagnostics
Li	Xiaoming	United States	Merck Research Laboratories
Lievano	Fabio	United States	Merck & Co., Inc.
LONG	DERYL	United States	WELLSTAR HEALTH SYSTEMS
Lurvey	Robert	United States	University of Illinois College of Medicine
Maes	Lanne	United States	American Red Cross

Makari	Doris	United States	MedImmune
Malhame	Melissa	United States	Dynavax Technologies
Malone	Robert	United States	RWMalone MD LLC
Marcy	Stephan Michael	United States	Advisory Committee on Immunization Practices
Maroko	Robert	United States	Pfizer
Masaquel	Anthony	United States	MedImmune
Mazur	Marie	United States	CSL Biotherapies
McCormack	Trudi	United States	American Red Cross, Environmental, Health & Safety deiv
McKinney	William	United States	University of Louisville
McLaughlin	John	United States	Pfizer, Inc.
Meade	Bruce	United States	Meade Biologics LLC
Meigs	Wendy	United States	Meningitis Angels
Meissner	Cody	United States	Tufts University School of Medicine
Mendelman	Paul	United States	LigoCyte Pharmaceuticals, Inc.
Middleman	Amy	United States	Baylor College of Medicine
Milley	Frankie	United States	Meningitis Angels
Moeller	Karl	United States	Campaign for Public Health
Montero	Jose	United States	New Hampshire Department of Health and Human Services
Moore	Kelly	United States	Tennessee Department of Health
Morgenstern	Diana	United States	Pfizer
Mulligan	Mark	United States	Emory University - School of Medicine
Musey	Luwy	United States	Merck & Co.
Myers	Martin	United States	National Network for Immunization Information
Neloms	Stacey	United States	SRA International
Netoskie	Mark	United States	Americas Health Insurance Plans (AHIP)
Neuman	William	United States	Pfizer Pharmaceuticals
Nicholson	Jennifer	United States	Emory University Rollins School of Public Health
Norman	James	United States	Georgia Institute of Technology
Offit	Paul	United States	Children"s Hospital of Philadelphia
Ouyang	sherry	United States	Pfizer
Owen	Bill	United States	MedImmune
Palefsky	Joel	United States	UCSF
Papandrikos	Konstantinos	United States	Sanofi Pasteur
Paradiso	Peter	United States	Pfizer
Parrino	Janie	United States	Merck & Co., Inc.
Pennisi	Eugene	United States	Pennisi Consulting
Peter	Georges	United States	Warren Alpert Medical School of Brown University
Peterson	Diane	United States	Immunization Action Coalition
Petrucelli	Michael	United States	MedImmune
Plotkin	Stanley	United States	VaxConsult and Sanofi Pasteur

Poland	Gregory	United States	Mayo Clinic
Quinn	Jane	United States	GlaxoSmithKline
Quinn	Carrie	United States	primary care pediatrician
Randolph	Edgar	United States	Emory University
Read	Jennifer	United States	National Vaccine Program Office
Redwood	Lyn	United States	SafeMinds
Rennels	Margaret	United States	GlaxoSmithKline
Richardson	Vesta	United States	National Center for Child and Adolescent Health, Ministry of Health, Mexico
Richmond	heather	United States	medi
Ripley	Millicent (Mea)	United States	Avalon Catering
Rizzo	Christopher	United States	MedImmune LLC
Robertson	Corey	United States	sanofi pasteur
Robertson	Jeff	United States	Pfizer Pharmaceuticals
Robins	Jennifer	United States	Avalon Catering
Robinson	James	United States	Vaccine Product & Technical Operations
ROSENBAUM	SARA	United States	DEPARTMENT OF HEALTH POLICY
Rousculp	Matthew	United States	MedImmune, LLC
Rue-Cover	Alison	United States	none - private citizen
Ruth	Laura	United States	Fuld
Saddier	Patricia	United States	Merck & Co., Inc.
Saltalamacchia	Charles	United States	CDC Epidemiology Elective Fellow
Saslow	Debbie	United States	American Cancer Society
Sato	Reiko	United States	Pfizer Inc.
Sawyer	Mark	United States	University of California San Diego
Schaffner	William	United States	Vanderbilt University School of Medicine
Schmader	Kenneth	United States	American Geriatrics Society
Schutt	Robert	United States	Sanofi Pasteur
Scott	Laura	United States	Families Fighting Flu
Scott	Daniel	United States	Pfizer Vaccine Research
Searfoorce	Amy	United States	Glaxosmithkline
Seifert	Harry	United States	GlaxoSmithKline
Sheffield	Tamara	United States	Intermountain Healthcare
Shelton	Jerry	United States	The Dunn Group
Sherner	Jim	United States	Pfizer
SIEVERT	ALAN	United States	GA CHAPTER, AAP
Smearman	Erica	United States	Emory University School of Medicine
Smith	Susan	United States	Medscape
Smith	Kenneth	United States	University of Pittsburgh
Smith	Parker	United States	Parker Smith Photography
Snow	Vincenza	United States	Pfizer Vaccines

Spaulding	Ann	United States	Emory University
Steinberg	Nina	United States	Ruder Finn
Stevens	Hilary	United States	Epi Elective Program
Stone	Alanna	United States	Emory University School of Medicine
Strutton	David	United States	Pfizer Inc.
Stuerke	Stacy	United States	Merck Vaccine Division
Sullivan	Gina	United States	GlaxoSmithKline
Sun	Wellington	United States	Center for Biologics Evaluation and Research
Sylvester	Gregg	United States	Pfizer Inc
Talkington	Kathy	United States	ASTHO
Temte	Jonathan	United States	ACIP
TenEyck	Carolyn	United States	MedImmune
Thistle	Kirsten	United States	APCO
Thomas	Lonnie	United States	Henry Schein, Inc
Thompson	Brad	United States	Pfizer
Tobar	Peter	United States	MediMedia Educational Group
Trofa	Andrew	United States	GlaxoSmithKline
Tsai	Theodore	United States	Novartis Vaccines
Tucker	Miriam E.	United States	Pediatric News
Turner	James	United States	American College Health Association
Vaupel	Christine	United States	GlaxoSmithKline
Velicer	Christine	United States	Merck Research Laboratories
Vicari	Andrea	United States	Pan American Health Organization
Vigliarolo	Peter	United States	Cooney Waters
Vogt	Kathleen	United States	Georgia Research Alliance
Wallace	Fred	United States	Dunn Group
Wambold	Deb	United States	Merck & Co., Inc.
Warner	Amy	United States	Take Care Health
Warren	Thomas	United States	Johnson & Johnson
Wexler	Deborah	United States	Immunization Action Coalition
Whitley-Williams	Patricia	United States	National Medical Association
Wighton	Timothy	United States	GlaxoSmithKline
Wilson	Paul	United States	Intercell USA
Wood	Laurel	United States	Alaska Immunization Program
Wu	Lauren	United States	National Vaccine Program Office
Yamada	Eileen	United States	CDPH
Yarn	Sandra	United States	GA-AAP
Yatsko	Joan	United States	Pfizer
Yeh	Michael	United States	Novartis Vaccines & Diagnostics
Yendell	Stephanie	United States	University of Minnesota- Epi Elective Student

Zahn	Matthew	United States	Louisville Metro Public Health and Wellness
Zavolinsky	Jennifer	United States	Every Child By Two
Zimmerman	Richard	United States	University of Pittsburgh
Non-US Citizens			
Last	**First**	**Citizenship**	**Organization**
Ajuma Mary	Sule	Nigeria	Kogi State Government
Bae	Geun-Ryang	South Korea	Division of VPD control and NIP, Korea Centers for Disease Control and Prevention
BASHIR BOLAJI	ADEMOSU	Nigeria	BAYELSA STATE MINISTRY OF HEALTH
Biehn	Brant	Canada	Dynavax
Brakel	Tom	Netherlands	Federated Kaufmann Fund
Cho	Heeyeon	South Korea	Division of VPD control and NIP, Korea Centers for Disease Control and Prevention
DODOO	HARRY	Ghana	WORLD IN NEED INTERNATIONAL
Dubischar-Kastner	Katrin	Germany	Intercell AG
El Zein	Majed	Czech Republic	Internal Revenue,IRS US
EZINNE DORA	EMERUE	Nigeria	BAYELSA STATE MINISTRY OF HEALTH
FLOREZ	JORGE	Colombia	IMMUNOPROTECTION
Guerra	Fulvia	Panama	Caja de Seguro Social
ILORI	ADESEUN	Nigeria	APIN,NIGERIA
JAMES	PETER	Ghana	WORLD IN NEED INTERNATIONAL
KAFAYAT BAYONDE	IKUMOGUNNIYI	Nigeria	BAYELSA STATE MINISTRY OF HEALTH
Kamiya	Hajime	Japan	National Institute of Infectious Diseases Infectious Disease Surveillance Center
Langley	Joanne	Canada	NACI
LeBlanc	John	Canada	Dalhousie University
LeBlanc	Daniel	Canada	Dalhousie University
Lester-Swindell	Mark	United Kingdom	Pfizer Inc
Lewis-Bell	Karen	Jamaica	Ministry of Health
Maduhu	Ibrahim	Tanzania	Expanded Program on Ummunization
Makino	Tomohiko	Japan	Johns Hopkins School of Public Health
MERCY	OKOMAYIN	Nigeria	BAYELSA STATE MINISTRY OF HEALTH
Mike Unyime	Anthony	Nigeria	Kogi State Government
Okabe	Nobuhiko	Japan	National Insitute of Infectious Diseases, Japan
Okada	Kenji	Japan	NIID, Japan
Nowenoni Marian	Fiakpa	Nigeria	BAYELSA STATE MINISTRY OF HEALTH
Perez	Gonzalo	Brazil	Merck & Company, Inc.
Poulin	Danielle	Canada	PHAC, CIRID, Director of Immunization Division (ID)
Schodel	Florian	Germany	Philimune LLC

Seet	Bruce	Canada	GlaxoSmithKline
Smith	Ning	China	Kaiser Permanente Southern California
Speranza	Noelia	Uruguay	Ministerio de Salud Pública
Suárez Castaneda	Eduardo	El Salvador	Ministerio de Salud
Tan	Litjen	Singapore	American Medical Association
Terry Nosakhare	OGBEBOR	Nigeria	BAYELSA STATE MINISTRY OF HEALTH
TOME-ABARCA	FERNANDO	Honduras	INSTITUTO INTERAMERICANO DEL NIÑO
Tseng	Hung Fu	China-Taiwan	Kaiser Permanente, Southern California
Yasuda	Naoyuki	Japan	Ministry of Health, Labour and Welfare
York	Laura	Canada	Pfizer