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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
June 19-20, 2013
Atlanta, Georgia

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MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Centers for Disease Control and Prevention

1600 Clifton Road, NE, Tom Harkin Global Communications Center (Building 19), Kent "Oz" Nelson Auditorium

Atlanta, Georgia 30333

June 19-20, 2013

Wednesday, June 19, 2013

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
8:00 am to 8:30 am	**Welcome & Introductions**		Dr. Jonathan Temte (ACIP Chair) Dr. Larry Pickering (Executive Secretary, ACIP)
8:30 am to 8:45 am	**Agency Updates** - CDC, CMS, DoD, DVA, FDA, HRSA, HIS, NVPO, NIH		
8:45 am to 10:30 am	**Japanese Encephalitis Vaccine** - Introduction - Safety and immunogenicity of JE-VC in children - GRADE evidence for JE-VC in children - Recommendations for use of JE-VC in children	Information & Discussion **Vote**	Dr. Joseph Bocchini (ACIP, WG Chair) Dr. Katrin Dubischar-Kastner (Intercell Biomed.) Dr. Marc Fischer (CDC/NCEZID) Dr. Marc Fischer (CDC/NCEZID)
10:30 am to 11:00 am	*Break*		
11:00 am to 11:45 pm	**General Recommendations on Immunization** - Overview - Preventing and managing adverse reactions	Information & Discussion	Dr. Jeff Duchin (ACIP, WG Chair) Dr. Andrew Kroger (CDC/NCIRD)
11:45 pm to 1:00 pm	*Lunch*		
1:00 pm to 3:30 pm	**Pertussis Vaccines** - Introduction - Pertussis in the United States and Tdap vaccine effectiveness - Tdap revaccination: safety and immunogenicity - Decision and cost effectiveness analysis: a second dose of Tdap - Work group conclusions on a second dose of Tdap - Maternal Tdap and cocooning: experiences from Australia and the United Kingdom	Information & Discussion	Dr. Mark Sawyer (ACIP, WG Chair) Dr. Anna Acosta (CDC/NCIRD) Dr. Jennifer Liang (CDC/NCIRD) Dr. Mark Messonnier, Dr. Hajime Kamiya (CDC/NCIRD) Dr. Jennifer Liang (CDC/NCIRD) Dr. Peter McIntyre (National Center for Immunization Resrch & Surv., Australia) Dr. David Salisbury (Department of Health, United Kingdom)
3:30 pm to 4:00 pm	*Break*		
4:00 pm to 5:15 pm	**Human Papillomavirus (HPV) Vaccines** - Introduction - Merck pregnancy registry for quadrivalent HPV vaccine - Plans for updated ACIP statement - HPV vaccine impact monitoring	Information & Discussion	Dr. Joseph Bocchini (ACIP, WG Chair) Dr. Fabio Lievano (Merck) Dr. Eileen Dunne (CDC/NCHHSTP) Dr. Lauri Markowitz (CDC/NCHHSTP)
5:15 pm to 5:30 pm	**Public Comment**		
5:30 pm	**Adjourn**		

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Thursday, June 20, 2013

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
8:00 am to 8:15 am	**Unfinished Business**		Dr. Jonathan Temte (ACIP Chair)
8:15 am to 10:45 am	**Rotavirus Vaccines: Update on Intussusception** - Introduction: intussusception following RV5 and RV1 - VSD data - VAERS data - PRISM data - Australian data - Summary and review of risk: benefit in the United States	Information & Discussion	Dr. Marietta Vázquez (ACIP, WG Chair) Mr. Eric S. Weintraub, MPH (CDC/NCEZID) Ms. Penina Haber, MPH (CDC/NCEZID) Dr. Katherine Yih (Harvard Pilgrim Health Care Institute) Dr. Peter McIntyre (National Center for Immunization Resrch. & Surv., Australia) Dr. Margaret Cortese (CDC/NCIRD)
10:45 am to 11:15 am	*Break*		
11:15 am to 11:45 am	**The Role of Retail Pharmacies/Pharmacists in Vaccine Delivery in the United States**	Information & Discussion	Mr. Mitchel C. Rothholz, RPh, MBA (American Pharmacists Association)
11:45 am to 11:50 am	**Vaccine Supply**	Information & Discussion	Dr. Jeanne Santoli (CDC/NCIRD)
11:50 am to 12:00 pm	**Herpes Zoster Vaccine** - Update on Herpes Zoster Work Group activities	Information	Dr. Jeff Duchin (ACIP, WG Chair)
12:00 pm to 1:00 pm	*Lunch*		
1:00 pm to 3:00 pm	**Influenza** - Introduction - Epidemiology/surveillance update - H7N9 update - Preliminary data on 2012-2013 vaccine effectiveness - Vaccine safety update - FluLaval Quadrivalent: GSK's inactivated quadrivalent seasonal influenza vaccine manufactured in Quebec - 2013-2014 recommendations	Information & Discussion **Vote**	Dr. Wendy Keitel (ACIP, WG Chair) Dr. Lyn Finelli (CDC/NCIRD) Dr. Dan Jernigan (CDC/NCIRD) Dr. Mark Thompson (CDC/NCIRD) Dr. Tom Shimabukuro (CDC/NCEZID) Dr. Varsha Jain (GlaxoSmithKline) Dr. Lisa Grohskopf (CDC/NCIRD)
3:00 pm to 3:15 pm	**Public Comment**		
3:15 pm	**Adjourn**		

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACA	Affordable Care Act
ACCV	Advisory Commission for Childhood Vaccines
ACHA	American College Health Association
ACIP	Advisory Committee on Immunization Practices
ACIR	Australian Childhood Immunisation Register
ACOG	American College of Obstetricians and Gynecologists
ACP	American College of Physicians
AE	Adverse Events
AFP	American Family Physicians
AHIP	America's Health Insurance Plans
AMA	American Medical Association
ANA	American Nurses Association
aP	Acellular Pertussis
APhA	American Pharmacists Association
APTR	Association for Prevention Teaching and Research
AST	American Society of Transplantation
ASTHO	Association of State and Territorial Health Officials
BMBL	Biosafety in Microbiological and Biomedical Laboratories
BMT	Blood and Marrow Transplantation
CDC	Centers for Disease Control and Prevention
CIN	Cervical Intraepithelial Neoplasia
CISA	Clinical Immunization Safety Assessment
CMS	Centers for Medicare and Medicaid Services
CO_2	Carbon Dioxide
COI	Conflict of Interest
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Database
CPT	Current Procedural Terminology
CRS	Congenital Rubella Syndrome
DBT	(India) Department of Biotechnology
DFO	Designated Federal Officer
DHS	Department of Homeland Security
DoD	Department of Defense
DRR	Daily Reporting Ratio
DSMB	Data Safety Monitoring Board
DTaP	Diphtheria, Tetanus, and Pertussis
DVA	Department of Veterans Affairs
HER	Electronic Health Record
EIP	Emerging Infections Program
EIP	Emerging Infections Program
EMA	European Medicines Agency
EMR	Electronic Medical Record
EPS	Enhanced Pertussis Surveillance
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GBS	Guillain–Barré Syndrome
GMCs	Geometric Mean Concentrations
GMTs	Geometric Mean Titers
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HAART	Highly Active Antiretroviral Therapy
HAI	Hemagglutination Inhibition Assay
HCUP	Healthcare Cost and Utilization Project
HHS	(Department of) Health and Human Services
Hib	*Haemophilus influenzae B*
HIPAA	Health Insurance Portability and Accountability Act
HPV	Human Papillomavirus
HRSA	Health Resources and Services Administration
HUI®	Health Utilities Index®
IAC	Immunization Action Coalition
IDSA	Infectious Disease Society of America
IgG	Immunoglobulin G
HIS	Indian Health Service
IIS	Immunization Information System
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
ILINet	Influenza-Like Illness Surveillance Network
IOM	Institute of Medicine
ISO	Immunization Safety Office
ISTM	International Society of Travel Medicine

JAMA	*Journal of the American Medical Association*
JE	Japanese Encephalitis
JEEV	Vero cell culture-derived JE vaccine
JE-MB	Inactivated Mouse Brain-Derived JE Vaccine
JE-VC	Vero Cell Culture-Derived JE Vaccine
LAIV	Live Attenuated Influenza Vaccine
LEEP	Loop Electrocautery Excision Procedure
LLR	Log Likelihood Ratio
MACDP	Metropolitan Atlanta Congenital Defects Program
maxSPRT	Maximized Sequential Probability Ratio Test
MCV4	Meningococcal Conjugate Vaccine
MMR	Measles, Mumps, Rubella
MMWR	*Morbidity and Mortality Weekly Report*
MN	Micronuclei Assay
MSM	Men Who Have Sex with Men
NACCHO	National Association of County and City Health Officials
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
NCHS	National Center for Health Statistics
NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
NHANES	National Health and Nutrition Examination Survey
NHFPC	National Health and Family Planning Commission (China)
NHIS	National Health Interview Survey
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NIP	National Immunisation Program (Australia)
NIS	National Immunization Survey
NIS-Teen	National Immunization Survey-Teen
NMA	National Medical Association
NNDSS	National Notifiable Diseases Surveillance System
NVAC	National Vaccine Advisory Committee
NVP	National Vaccine Plan
NVPO	National Vaccine Program Office
NVSN	National Vaccine Surveillance Network
NVSS	National Vital Statistics System
OMB	Office of Management and Budget
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
PIDS	Pediatric Infectious Diseases Society
PPE	Personal Protective Equipment
PRISM	Postlicensure Rapid Immunization Safety Monitoring System
PRNT	Plaque Reduction Neutralization Test
QALY	Quality-Adjusted Life Year
RCA	Rapid Cycle Analysis
RCT	Randomized Controlled Trial
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAEs	Serious Adverse Events
SARS	Severe Acute Respiratory Syndrome
SCCS	Self-Controlled Case-Series
SCRI	Self-Controlled Risk Interval
SID	State Inpatient Databases
SME	Subject Matter Expert
Td	Tetanus-Diphtheria
Tdap	Tetanus and Reduced Diphtheria Toxoids
TGA	Therapeutic Goods Administration (Australia)
UCSD	University of California, San Diego
US	United States
US Flu VE	US Influenza Vaccine Effectiveness Network
USPHS	US Public Health Service
USPSTF	US Preventive Services Task Force
VA	Department of Veterans Affairs
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Effectiveness
VFC	Vaccines for Children
VICP	National Vaccine Injury Compensation Program
VRBPAC	Vaccine and Related Biologic Products Advisory Committee (FDA)
VSD	Vaccine Safety Datalink
VTE	Venous Thromboembolism
VTrckS	Vaccine Tracking System
WG	Working Group
WHO	World Health Organization

Welcome and Introductions

Dr. Jonathan Temte
Chair, ACIP

Dr. Larry Pickering
Executive Secretary, ACIP / CDC

Dr. Temte called the June 2013 Advisory Committee on Immunization Practices (ACIP) meeting to order, welcoming those present. He turned the floor over to Dr. Pickering for opening remarks.

Dr. Pickering welcomed everyone to the ACIP meeting. He indicated that the proceedings of this meeting would be accessible to people not in attendance via the World Wide Web, and he welcomed those who could not attend the meeting in person.

He then recognized several others in the room who were to be present throughout the duration of the ACIP meeting to assist with various meeting functions: Felicia Betancourt, Natalie Greene, and Reed Walton.. Dr. Pickering emphasized that there would be a full agenda, and noted that handouts of the presentations were distributed to the ACIP members and were made available for others on the tables outside of the auditorium. Slides presented during this meeting will be posted on the ACIP website approximately two weeks after the meeting concludes, the live webcast will be posted within four weeks following the meeting, and the meeting minutes will be available on the website within 90 days following this meeting. Minutes of the February meeting are posted on the ACIP website. Members of the press interested in conducting interviews with ACIP members were instructed to contact Jamila Howard Jones, who was in attendance, for assistance in arranging the interviews.

At this time, Dr. Pickering thanked ACIP voting members Wendy Keitel, Mark Sawyer, and Sara Rosenbaum who would be rotating off of the committee at the end of June. Given that Sara Rosenbaum was not able to attend this meeting, she was recognized during the February ACIP meeting. During the June meeting, Drs. Keitel and Sawyer were recognized for their incredible contributions to ACIP over the last four years. Dr. Pickering noted that they were present during a transformative time in this committee's history, and, among other important milestones, helped oversee the integration of the Grading of Recommendation Assessment, Development and Evaluation (GRADE) process for evidence-based recommendations that has improved—and will continue to improve—the transparency and effectiveness of the ACIP process. He thanked each of these members for their time and commitment, as well as their ability to make their thoughts known in a way that was respectful of everyone on the committee and in the room. Dr. Temte then shared the following information about each departing member:

Dr. Wendy Keitel

Dr. Keitel couples wisdom, knowledge, and passion and has been a wonderful resource for ACIP. She chaired the Influenza Working Group (WG) from 2010 through 2013, and served as a member of the Influenza WG from 2009 through 2010 and the Pneumococcal Vaccines WG from 2010 through 2013. Dr. Keitel is a Professor in the Department of Molecular Virology and Microbiology at Baylor College of Medicine. Her research interests include vaccine development and evaluation, with an emphasis on prevention of respiratory infections and other emerging diseases. She has been involved in pre-clinical and clinical stages of vaccine development, and her recent activities have focused on live attenuated and inactivated influenza virus vaccines, including H1N1 and candidate vaccines for H5, H7, and H9. She is also interested in exploring immunization of pregnant women to protect both the mother and the infant against influenza and pertussis. Reviewing her CV and publications reveals interesting information such as "Prenatal Passive Transfer of Maternal Immunity in Asian Elephants (*Elephas Maximus*)" and an interesting article titled "Perspectives on Human Microbiome Research Ethics." She brings forth an incredible background of knowledge and integrates it beautifully into ACIP's vaccine policy work. Her ACIP publications are as follows:

- Prevention and Control of Influenza with Vaccines: Interim Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2013. May 10, 2013. MMWR 62(18):356.
- Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine for Adults with Immunocompromising Conditions: Recommendations of the Advisory Committee on Immunization Practices (ACIP). October 12, 2012. MMWR 61(40):816-819.
- Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP) — United States, 2012–13 Influenza Season. August 17, 2012. MMWR 61(32):613-618.
- Licensure of 13-Valent Pneumococcal Conjugate Vaccine for Adults Aged 50 Years and Older. June 1, 2012. MMWR 61(21):394-395.
- Prevention and Control of Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2011. August 26, 2011. MMWR 60(33):1128-1132.
- Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). January 21, 2011. MMWR(RR-01):1-24.
- Prevention of Pneumococcal Disease Among Infants and Children --- Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine. December 10, 2010. MMWR 59(RR-11):1-18.
- Updated Recommendations for Prevention of Invasive Pneumococcal Disease Among Adults Using the 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV23). September 3, 2010. MMWR 59(34):1102-1106.
- Update: Recommendations of the Advisory Committee on Immunization Practices (ACIP) Regarding Use of CSL Seasonal Influenza Vaccine (Afluria) in the United States During 2010-11. August 13, 2010. MMWR 59(31):989-992.
- Licensure of a High-Dose Inactivated Influenza Vaccine for Persons Aged ≥65 Years (Fluzone High-Dose) and Guidance for Use --- United States, 2010. April 30, 2010. MMWR 59(16):484-486.

- Licensure of a 13-Valent Pneumococcal Conjugate Vaccine (PCV13) and Recommendations for Use Among Children --- Advisory Committee on Immunization Practices (ACIP), 2010. March 12, 2010. MMWR 59(09)**.**
- Use of Influenza A (H1N1) 2009 Monovalent Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. August 21, 2009. MMWR(Early Release):1-8.

Something people may not know about Dr. Keitel is that she is an avid birder. She is a member of Gulf Coast Bird Observatory and a generous donor to the Houston Area Audubon Society.

Dr. Keitel thanked Dr. Temte for his very kind remarks. She explained that the way she became involved with the Asian elephants was through a call from a representative of the Houston Zoo who said, "We were told that you could make a vaccine for elephant herpes virus." She realized that they knew absolutely nothing regarding what was occurring among the elephants, and certainly vaccine development was a long way down the road. One of the first things she suggested was that they gain some understanding of the loss of immunity because of the age at which the elephants begin dying of this lethal infection, which threatens the worldwide population of elephants. This has been very interesting, as has been all of her other work, particularly at the ACIP. She thanked everyone very much for the opportunity to participate.

Professor Sara Rosenbaum

Professor Rosenbaum is the Harold and Jane Hirsh Professor of Health Law and Policy and Founding Chair of the Department of Health Policy, George Washington University School of Public Health and Health Services. She has devoted her entire professional career to issues of health justice for populations who are medically underserved as a result of race, poverty, disability, or cultural exclusion. She has provided her service to six Presidential Administrations and 15 Congresses since 1977. She is best known for her work on Medicaid, expansion of community health centers, patients' rights and managed care, civil rights in health care, and national health reform. Between 1993 and 1994, Professor Rosenbaum worked for President Clinton directing the drafting of the Health Security Act and designing the Vaccines for Children (VFC) program, which offers near-universal coverage of vaccines for low income and medically underserved children. With respect to ACIP, she has been a member of the Smallpox Vaccine WG from 2012 through 2013, the Herpes Zoster Vaccine WG from 2010 through 2013, and the Evidence-Based Recommendations WG from 2009 through 2010. She has been a tireless ACIP member, who has shared enormous wisdom and knowledge regarding health policy, especially with regard to the Affordable Care Act (ACA). Professor Rosenbaum will be greatly missed as the Consumer Representative for ACIP. Her extremely long list of publications includes pieces as diverse as *US Health Policy in the Aftermath of Hurricane Katrina*, *Vaccinating the Health-Care Workforce: State Law vs. Institutional Requirements*, and *Maternal Care and Liability*. Her ACIP publications include the following:

- New Framework (GRADE) for Development of Evidence-Based Recommendations by the Advisory Committee on Immunization Practices. May 11, 2012. MMWR 61(18):327-327.
- Update on Herpes Zoster Vaccine: Licensure for Persons Aged 50 Through 59 Years. November 11, 2011. MMWR 60(44):1528-1528.

Dr. Mark Sawyer

Dr. Sawyer has served as Chair of the Hepatitis Vaccines WG from 2009 through 2013, Chair of the Pertussis Vaccines WG from 2009 through 2013, a member of the Rotavirus Vaccine WG from 2008 through 2013, a member of the General Recommendations WG from 2009 through 2012, and a member of the MMRV Vaccine Safety WG from 2008 through 2009. He is Professor of Clinical Pediatrics and Pediatric Infectious Disease at the University of California, San Diego (UCSD) School of Medicine and Rady Children's Hospital. He is also Medical Director of the San Diego Immunization Partnership, a partnership between UCSD and San Diego County for Health and Human Services that exists for the purpose of improving immunization delivery in San Diego. Dr. Sawyer is an active and strong voice for pro-immunization policies and cost-effective ways to improve public health, particularly in terms of herd protection . When asked why he went into pediatrics, he quipped, "The reason I went into pediatrics is because adults are obnoxious." An interesting publication of Dr. Sawyer's is "Missed Opportunities to Immunize: Psychosocial and Practice Correlates." Despite the comment he made about sick adults, this makes him sound like a family doctor, so perhaps he can be made an honorary member of the American Academy of Family Physicians (AAFP). Several publications have emerged from Dr. Sawyer's work on ACIP, including the following:

- Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine (Tdap) in Pregnant Women — Advisory Committee on Immunization Practices (ACIP), 2012. February 22, 2013. MMWR 62(07):131-135.
- Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis (Tdap) Vaccine in Adults Aged 65 Years and Older — Advisory Committee on Immunization Practices (ACIP), 2012. MMWR 61(25):468-470.
- Use of Hepatitis B Vaccination for Adults with Diabetes Mellitus: Recommendations of the Advisory Committee on Immunization Practices (ACIP). December 23, 2011. MMWR 60(50):1709-1711.
- Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) in Pregnant Women and Persons Who Have or Anticipate Having Close Contact with an Infant Aged <12 Months --- Advisory Committee on Immunization Practices (ACIP), 2011. October 21, 2011. MMWR 60(41):1424-1426.
- General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). January 28, 2011. 60(RR-02):1-60.
- Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis (Tdap) Vaccine from the Advisory Committee on Immunization Practices, 2010. January 14, 2011. MMWR 60(01):13-15.
- Prevention of Rotavirus Gastroenteritis Among Infants and Children Recommendations of the Advisory Committee on Immunization Practices (ACIP). February 6, 2009. MMWR 58(RR-02):1-25.

Something people may not know about Dr. Sawyer is that he is an avid cellist, about which he has said, "I play cello in a community orchestra. I was never a professional, but I play in a bunch of chamber groups. Just to show how long you can stay in music, in one of my quartets, I am the youngest by 25 years. We get together in the afternoon because the three others cannot stay up too late at night, so I have to sneak out of work to go play with that particular group. It's just a delightful thing you can do forever." ACIP has appreciated Dr. Sawyer's approach. He always knows when someone is wrong, but never tells them. Instead, he very carefully, cautiously, and with kindness coaxes people into the right direction. He has served on ACIP for five years, and his service is greatly appreciated.

Dr. Sawyer thanked Dr. Temte for the kind and interesting remarks that he found on the Internet. He reiterated Dr. Keitel's comments and those of many of his predecessors as they have left this committee to highlight what a privilege it has been to be part of this robust system that is in place to ensure that only the best immunization recommendations come forward from the Centers for Disease Control and Prevention (CDC). It has been great to meet so many people on the committee, among the liaisons, and on the WGs. Most importantly, he acknowledged and personally thanked the CDC staff who have supported the WGs on which he has served and ACIP. Without them, the members really could not do the work they do.

Dr. Pickering once again thanked departing ACIP members and emphasized that ACIP looks forward to working with the new members. He then recognized international visitor, Dr. Li Li, who was in attendance during this meeting. Dr. Li is Director of the China CDC National Immunization Program. With help from the former Director of CDC's Immunization Services Division, Dr. Lance Rodewald, now on long-term assignment from CDC to the World Health Organization (WHO) China, Dr. Li arrived at CDC to learn more about the United States (US) immunization program, including how ACIP works to make evidence-based recommendations. Dr. Li will be in Atlanta for approximately six months, during which time he will rotate through the different divisions that work on immunization related issues and will observe several ACIP WGs and work with the ACIP Secretariat to secure a better understanding of ACIP structure and function. We appreciate the opportunity to interact with Dr. Li during his time at CDC.

Though delegates from the Pan American Health Organization (PAHO) typically attend each ACIP meeting, no delegates were in attendance during this meeting. CDC will host the next delegation during the October ACIP meeting.

Dr. Pickering noted that there would be simultaneous translation services available during the meeting for Spanish-speaking guests, and that ACIP staff at the table in the back of the room could provide headphones for those wishing to take advantage of this service. He also took a moment to provide information for future international visitors to ACIP meetings. Due to changes in Department of Homeland Security (DHS) policy, additional forms will be required for each meeting at the time an international guest registers. When registering, these forms will be provided to international visitors. It is critical that they be completed and submitted as soon as possible following registration. Unlike in the past, no exceptions can be made for late, missing, or unprocessed forms. Felicia Betancourt, CDC's committee management specialist, will be able to help with any questions and concerns about the process. The next ACIP meeting will take place at CDC on Wednesday/Thursday October 23-24, 2013. Registration of meeting attendees is required, and would be open on the afternoon of June 20, 2013 on the ACIP website. Registration for international guests will close a week earlier than in the past on Monday September 30, 2013.

Dr. Pickering then offered the following liaison representative notes:

- The Director General of Mexico's National Center for Child and Adolescent Health, Dr. Ignacio Villasenor Ruiz, will be serving as the new liaison representative to ACIP from the Ministry of Health, Mexico. Gratitude was expressed for the previous representative, Dr. Vesta Richardson, who left the National Ministry of Health to lead the Ministry of Health for the State of Morelos in Mexico.

- Carol Hayes, a public health consultant in the Atlanta area, will be representing the American Nurses Association (ANA) at this meeting and in October. Katie Brewer is taking time off to welcome a new baby in July. Katie has assured ACIP that her infant will be fully immunized, which will make Dr. Baker very happy.

- Sandy Fryhofer, representing the American Medical Association (AMA), has assumed the additional duty of serving as liaison to the American College of Physicians (ACP) in place of Greg Poland.

- Kimberly Martin, the Director of Immunization Policy for the Association of State and Territorial Health Officials (ASTHO), was in attendance to represent that organization in place of José Montero.

- No representatives were present during this meeting from the Association for Prevention Teaching and Research (APTR), the National Medical Association (NMA), or the Indian Health Service (IHS).

To avoid disruptions during the meeting, Dr. Pickering requested those present to turn all cell phones off. He explained that topics presented during the ACIP meeting include open discussion with time reserved for public comment. During this meeting, a time for public comment was scheduled following the afternoon sessions during both meeting days. Time for public comments also may be provided prior to specific votes by ACIP to enable these comments to be considered before any votes. Those who planned to make public comments were instructed to visit the registration desk in the rear of the auditorium to have Felicia Betancourt record their name and provide information about the process. Those who registered to make public comments were instructed to state their name, organization if applicable, and any conflicts of interest (COIs) prior to making their comments.

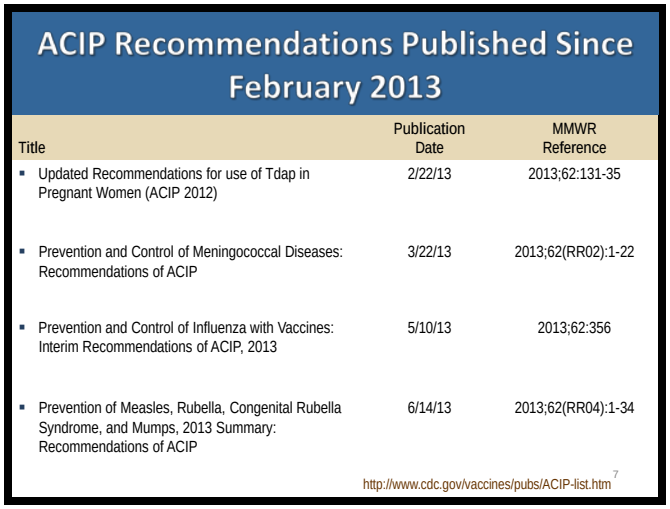
With regard to disclosure, to summarize conflict of interest provisions applicable to ACIP, as noted in the ACIP Policies and Procedures manual, Dr. Pickering indicated that members of the ACIP agree to forego participation in certain activities related to vaccines during their tenure on the committee.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

Applications for ACIP membership are due no later than November 15, 2013 for the 4-year term beginning July 2014. 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: http://www.cdc.gov/vaccines/acip/index.html

Nominations: http://www.cdc.gov/vaccines/acip/committee/req-nominate.html

During every ACIP meeting, an update is provided with regard to the status of ACIP recommendations. Links to these recommendations and schedules can be found on the ACIP website. A listing of recommendations that have been published since the October 2012 ACIP meeting follows:



ACIP Recommendations Published Since February 2013

Title	Publication Date	MMWR Reference
▪ Updated Recommendations for use of Tdap in Pregnant Women (ACIP 2012)	2/22/13	2013;62:131-35
▪ Prevention and Control of Meningococcal Diseases: Recommendations of ACIP	3/22/13	2013;62(RR02):1-22
▪ Prevention and Control of Influenza with Vaccines: Interim Recommendations of ACIP, 2013	5/10/13	2013;62:356
▪ Prevention of Measles, Rubella, Congenital Rubella Syndrome, and Mumps, 2013 Summary: Recommendations of ACIP	6/14/13	2013;62(RR04):1-34

http://www.cdc.gov/vaccines/pubs/ACIP-list.htm 7

ACIP has a policy that every three to five years each recommendation is either renewed, reaffirmed, or rejected. The measles, mumps, and rubella (MMR); *Haemophilus influenzae* B (Hib); and meningococcal statements are the most recent documents to adhere to this policy.

The following resource information was shared pertaining to ACIP:

Next ACIP Meeting: Wednesday – Thursday, October 23-24, 2013
Registration Deadline: Non-US Citizens September 30, 2013; US Citizens October 7, 2013
Registration to watch the webcast is not required.

Vaccine Safety: www.cdc.gov/vaccinesafety/

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

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

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

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

Vaccine Toolkit:
www.cdc.gov/vaccines/conversations

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

Before officially beginning the meeting, Dr. Temte called the roll to determine whether any ACIP members had conflicts of interest. Dr. Pickering declared that there was a quorum of 13 voting members and 7 *ex officio* members. The following conflicts of interest were declared:

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

- The remainder of the ACIP members declared no conflicts.

Dr. Temte reported that in April, he had the pleasure of being in Beijing for an exchange with his department and a general practice department. Dr. Rodewald helped to arrange an opportunity to present to the Chinese CDC on implementation of GRADE into vaccine recommendations. The presentation was enthusiastically received. China is well underway in incorporating GRADE into vaccine recommendations, beginning with a new recommendation for varicella vaccine. This was a wonderful exchange and an enthusiastic reception of an evidence-based process into that country.

Dr. Temte also pointed out some notable anniversaries. It has been 20 years since the inception of the VFC program. The birth of VFC was created by the Omnibus Budget Reconciliation Act of 1993, and has been operating ever since. The National Vaccine Advisory Committee (NVAC) began 25 years ago. Dr. Ornstein could not attend this ACIP meeting, but he is now Chair of NVAC, and was also present during the first meeting 25 years ago on June 8, 1988. Fifty years ago, the 317 Program came into play under the Immunization Assistance Act (P.L. 87-868) passed in 1962 and implemented in 1963 as the federal government began to provide support for state- and community-level immunization programs. The updated *Prevention of Measles, Rubella, Congenital Rubella Syndrome, and Mumps, 2013* was recently published in the *Morbidity and Mortality Weekly Report* (*MMWR*). Of note, this year marks the 50th anniversary of the mumps vaccine culture. Maurice Hilleman first collected and cultured mumps virus from his daughter, Jeryl Lynn, and in what would appear to be a clear violation of Health Insurance Portability and Accountability Act (HIPAA) regulations, he named the strain after his daughter, which is the strain that continues to be used today. Since that time, there has been a marked reduction in mumps in the US. This year also marks the 50th anniversary of the measles vaccine, which was licensed in 1963. This vaccine has prevented an incredible number of illnesses and deaths worldwide. When Dr. Temte began working on vaccine issues in about 2000, there were still approximately 1 million deaths per year of children across the world. The number of deaths declined to approximately 158,000 by 2012 and continues to decline. This has been an impressive implementation of wonderful technology that has been lifesaving across the globe. He expressed gratitude to all who have been involved in measles vaccine development, marketing, testing, and distribution.

Dr. Pickering reminded everyone that they ring the bell at every meeting, the saying on which reads, “May the ACIP recommendations always ring clear.” The bell was donated by Dr. Sam Katz in October 1993. Dr. Katz was the co-discoverer of the vaccine with Dr. Hilleman. Dr. Pickering concluded, “Sam, if you’re listening to us, you’re still with us in spirit. Thank you for all the work that you’ve done.”

In conclusion of this session, Dr. Pickering indicated that the previous day he received a wonderful resource, “The Immunization Resources for Obstetricians and Gynecologists: A Comprehensive Toolkit.” He emphasized that the continued and important immunization of pregnant women is being stressed by obstetricians/gynecologists (OB/GYN), and requested that Laura Riley from the American College of Obstetricians and Gynecologists (ACOG) offer a few comments regarding this toolkit. Dr. Riley shared the website where this toolkit can be obtained, which is www.immunizationforwomen.org. The toolkit is available to anyone who is interested in having it. This incredibly comprehensive toolkit is ACOG’s effort to continue to educate obstetricians/gynecologists about what needs to be done, both during pregnancy and for non-pregnant adult women in an effort to integrate immunization into standard OB/GYN practice. While this has been an uphill battle, the battle is slowly but surely being won, at least in terms of education. One of the additional pieces of information, in addition to committee opinions, there is a nice book on coding, which is particularly important for OB/GYNs as they put this into practice. Also included in the toolkit are laminated cards, tearoff sheets that can be used in offices or clinics.. Information is included on all vaccines, but the Tdap recommendations are included. Tearoff pads of frequently asked questions were fast-tracked and should be available at the end of July 2013. Dr. Riley thanked everyone on the ACOG immunization committee who worked very hard to assemble all of this information.

Agency Updates

Centers for Disease Control and Prevention (CDC)

Dr. Schuchat reported that the public health community in the US and around the world have been dealing with several vaccine preventable disease outbreaks, three of which she briefly reviewed. The largest outbreak of measles in the US since elimination indigenous spread is occurring in New York City in a religious community that does not vaccinate regularly. The health department is managing this. An outbreak of hepatitis A is affecting people who live in Western states, which has been linked to a blend of berries and pomegranate mix that was distributed by COSTCO. The public health representatives in the 8 states that have received the product are managing vaccination of those who have been exposed. The third outbreak is particularly unfortunate and is affecting the Horn of Africa, with a resurgence of polio in Somalia and refugee camps in Kenya. Large scale, aggressive vaccination efforts are underway there. While this is a setback, polio eradication is closer than ever. On a more positive note, the Vaccine Tracking System (VTrckS) for ordering vaccines through the VFC or 317 program has been successfully rolled out to all of the state and city grantees. As of May 2013, 73% of providers in the country are on the system now, either directly or through their registries interacting with the VTrckS system at the state health department. CDC’s target is to get 85% of providers on the system by the end of 2013, and seems to be well on the way to achieving this goal. This has been a multi-year effort with major collaboration between state and local public health and IT experts in Atlanta. Dr. Schuchat thanked everyone who has been involved in moving this effort so far.

Centers for Medicare and Medicaid Services (CMS)

Dr. Hance indicated that CMS is actively working on implementation of the provisions of the ACA related to immunizations. Section 1202 is the primary care payment increase. Every state with the exception of Alaska, which already pays at the Medicare rate, submitted an application before the March 21, 2013 deadline. CMS is in the process of reviewing those applications, and is close to approving 40 of them. That means that providers will soon be able to receive the increase in payment for all primary care services, as well as for vaccine administration. Section 4106 allows states to receive additional federal funds if they choose to cover all US Preventive Services Task Force (USPSTF) recommended services and all ACIP recommended vaccines and their administration for adults. Currently, those are optional services. If states choose to cover all of those services and have no cost-sharing, they can receive an additional 1% of federal funds for those services. Applications have been submitted by 4 states for this provision, once of which has been approved. CMS hopes that as time goes by, applications will be received from many other states. The Final Rule should soon be published that will define the benefit package for the Medicaid expansion populations that will go into effect on January 1, 2014. That will include an emphasis on prevention.

Department of Defense (DoD)

Dr. Geibe indicated that while DoD had no new updates, on behalf of DoD he thanked CDC and ACIP for their ongoing collaborative communication with DoD as it continues to reassess its immunization programs to ensure that they are closely aligned with those of CDC/ACIP. An example would be DoD's recent guidance update and publication by the Office of the Assistant Secretary of Defense for Health Affairs on Japanese encephalitis vaccine in May 2013.

Department of Veteran's Affairs (DVA)

Dr. Kinsinger mentioned several efforts in which DVA is engaged with its federal partners pertaining to electronic health records and immunization. DVA continues to work with its partners in the DoD to develop a joint immunization module for their two electronic health records. That work is ongoing, and probably will be ongoing for a while yet. Ultimately, this will be a wonderful tool when completed. As a result of the adult immunization meetings in May 2013, DVA began working with CDC to determine whether there are ways for VA providers to access non-VA immunization registries in states. DVA is also working closely with the Indian Health Service (IHS) to share ideas about decision support tools for electronic health records.

Food and Drug Administration (FDA)

Dr. Sun noted that since the last ACIP meeting, the Japanese encephalitis vaccine IXIARO® was approved for the pediatric indication of 2 months through 17 years of age. Due to the expiration of JE-VAX®, no Japanese encephalitis vaccines have been licensed for the pediatric population. Approval of IXIARO® in this population fulfills an unmet need. Also approved since the last ACIP meeting was Fluzone® Quadrivalent Influenza Virus Vaccine (QIV), which is the third licensed QIV vaccine in the US. This vaccine has an age indication of 6 months and above. FDA conducted a post-marketing PRISM study of rotavirus vaccine, which is notable in that this is the first instance in which the authority given to FDA by the FDA Amendment Act of 2007 was utilized to require new safety information to be placed in the package insert.

Health Resources and Services Administration (HRSA)

Dr. Caserta indicated that the Advisory Commission for Childhood Vaccines (ACCV) met two weeks before this meeting and produced recommendations for the Secretary. One recommendation of interest is to extend the statute of limitations up to 8 years with no opt out period during that extended period of time. The ACCV also recommended that the Secretary work to expand coverage under the National Vaccine Injury Compensation Program (VICP) to include vaccines that are routinely recommended for categories other than children, such as pregnant women, that are not specifically recommended for routine administration to children. The ACCV also recommended to the Secretary that she should support eligibility to pursue compensation for injuries sustained by a live born infant whose mother received the vaccine while the infant was in utero. In order to further her support, the ACCV recommended that the Secretary take whatever steps are necessary and within her legal authority to accomplish this. In addition, HRSA is very close to publishing its rotavirus table. The agency received a waiver from the Office of Management and Budget (OMB), so it does not need to go through OMB clearance. That should be published within the next few weeks.

Indian Health Services (IHS)

No update was provided.

National Institutes of Health (NIH)

Dr. Gorman reported that NIH has been preparing for H7N9 in terms of developing, testing, and providing a vaccine if and when this becomes an epidemic. In terms of responding to future influenza epidemics, NIH is also working diligently with multiple manufacturing techniques to reduce the reliance on egg-based technology. In a public-private partnership, India has announced positive results from its rotavirus vaccine called ROTAVAC®. The partnership is comprised of NIH, India's Department of Biotechnology (DBT), Bharat Biotech, Stanford University School of Medicine, Bill and Melinda Gates Foundation, and the Research Council of Norway. This will increase the vaccine supply for that particularly important vaccine in that country. The National Institute of Allergy and Infectious Diseases (NIAID) announced the award of an Antibacterial Resistance Leadership Group, which will be meeting for the first time on June 19, 2013 at NIH to begin that particular effort.

National Vaccine Advisory Committee (NVAC)

Dr. Orenstein reported that NVAC met on June 11-12, 2013. This marked the 25th anniversary of NVAC, which convened its first meeting in June 1988. The major focus of the June 2013 meeting was on adult immunization, and there were two major action items. The first is that the Adult Immunization Summit proposed a major revision in the *Standards for Adult Immunization Practices* that NVAC issued in 2003. NVAC is reviewing the draft, which is much more comprehensive and audience-based than the current version. The second action item regards the sorry state of affairs with regard to implementation of adult vaccines. With regard to that issue, NVAC issued a comprehensive set of recommendations in 2011 that was published in 2012, and has asked the National Vaccine Program Office (NVPO) to offer feedback about how the committee could be helpful moving forward. CMS has recommended withdrawal of a requirement for a performance measure for pneumococcal vaccination. NVAC planned to convene an urgent meeting by teleconference on June 21, 2013 to discuss the proposed CMS rule to remove that measure, and whether NVAC should or should not make any recommendations with regard to that. NVAC has formed a WG to address human

papillomavirus (HPV) vaccine uptake to assess what else can or should be done to improve implementation, as well as a vaccine competence/hesitancy WG to address how to improve acceptance of recommended vaccinations. NVAC's Global Immunization WG has proposed a comprehensive set of recommendations to address why it is in humanitarian interests and the best interest of the US to improve global immunization, with a focus on use of current vaccines, regulation, and development of new vaccines to deal with global infectious disease problems. NVAC is commenting on a set of recommendations from its Maternal Immunization WG that focus on improving coverage. The hope is to finalize and vote on those recommendations during the September 2013 NVAC meeting.

National Vaccine Program Office (NVPO)

Dr. Gellin noted that the themes of NVAC often overlap with the themes of NVPO under the umbrella of the National Vaccine Plan (NVP). One of the major themes across that is adult immunizations, and the significant effort of transforming what was the National Influenza Vaccine Summit into an Adult Vaccine Summit with the help of partnerships with CDC and the Immunization Action Coalition (IAC). That has been picked up by the Assistant Secretary for Health as an Interagency Adult Immunization Task Force. In the future, NVPO hopes to develop a freestanding adult immunization plan or strategy that somewhat maps across the goals of the NVP. In the past, ACIP has seen the presentation from the Institute of Medicine (IOM) with the vaccine prioritization decision making algorithm called SMART Vaccines. This is now in another phase, and the report is scheduled to be released publicly at the end of September 2013. If ACIP is interested in hearing more about this, perhaps information can be presented during the October 2013 ACIP meeting.

Japanese Encephalitis Vaccine

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

Dr. Bocchini reminded everyone that currently, there is one licensed and available Japanese encephalitis (JE) vaccine in the US, which is an inactivated Vero cell culture-derived JE vaccine (JE-VC). Since 2009, this vaccine is licensed for use in persons ≥17 years of age. On May 17, 2013, FDA licensed JE-VC (IXIARO®) for use in children 2 months through 16 years of age. IXIARO® is manufactured by Intercell Biomedical, and is distributed in the US private market by Novartis Vaccines. It is indicated for active immunization to prevent disease caused by JE virus. Dosage is 0.25 mL per dose for children 2 months through 2 years of age and 0.5 mL per dose for children ≥3 years of age and adults, and the primary series is 2 doses administered 28 days apart.

There are no efficacy data for JE-VC. Availability of several effective JE vaccines in Asia makes a comparative efficacy trial difficult to perform. However, there is an established immunologic correlate of protection. A JE virus 50% plaque reduction neutralization test ($PRNT_{50}$) titer ≥10 is considered to be protective [Hombach. Vaccine 2005; Markoff. Vaccine 2000]. JE-VC was licensed in adults based on a non-inferiority trial of neutralizing antibody response compared to the licensed inactivated mouse brain-derived JE vaccine (JE-MB). It was licensed based on a proportion of JE-VC recipients who achieved JE virus $PRNT_{50}$ titer ≥10 as indicated as a

correlate of protection. JE-MB had a 91% efficacy in a randomized controlled trial in over 65,000 children in Thailand in the mid-1980s. During the licensing process of JE-VC in adults, safety evaluations were conducted in approximately 5,000 adults in clinical trials. Since licensure, over 300,000 doses of JE-VC have been distributed in the US.

In June 2009, ACIP approved recommendations for use of JE vaccines in US travelers, including JE-VC in adults ≥17 years of age and JE-MB for adults and children ≥1 year of age. In February 2011, ACIP approved recommendations for a booster dose of JE-VC. JE-MB is no longer manufactured or available. An estimated 2,000 to 3,000 doses were distributed to pediatric providers from 2002 through 2009. It is difficult to translate that into the number of children who were immunized because a non-pediatric provider could have given the vaccine to children who were traveling, and JE-MB required three doses for the primary series. As of May 2011, the vaccine was no longer available for children in the US. The options for obtaining JE vaccine for US children outside of the country who were traveling were published in the *MMWR* in May 2011.

The JE Vaccine WG was reactivated in October 2012, and since then has met 13 times to discuss issues related to JE-VC in children. The group reviewed the epidemiology of JE in travelers, as well as JE-VC safety and immunogenicity data. In addition, the group performed a GRADE evaluation and developed proposed recommendations. Two previous presentations have been delivered to ACIP on this topic, one in October 2012 to discuss the WG charge and plans and the second in February 2013 to discuss JE and JE vaccine for travelers.

Safety and Immunogenicity of Japanese Encephalitis Vaccine in Children

Dr. Katrin Dubischar-Kastner
Intercell Austria AG
A Valneva SE Affiliate

Dr. Dubischar-Kastner informed everyone that Intercell had recently completed a merger and formed a new company called Valneva. In the future, the new company's name will be transferred to the vaccine. She then presented data from the following three clinical trials that were conducted leading up to pediatric licensure of IXIARO®:

Study	Design	Number of Subjects
IC51-221: Dose-Confirmation in Toddlers Aged 1 to <3 Years; India[1]	Randomized, Controlled, Open-Label Trial, comparing IXIARO to Korean Green Cross JE vaccine	60
IC51-322: IXIARO in Traveling Children Aged 2 Months to <18 Years; EU, US and Australia[2]	Single-Arm, Open-Label Trial	60
IC51-323: Pivotal Pediatric Trial in Children Aged 2 Months to <18 Years; The Philippines (JEV Endemic Region)[3]	Randomized, Controlled, Open-Label Trial, comparing IXIARO to Havrix®720 and Prevnar 7®	1,867

1. Kaltenboeck et al. Immunogenicity and safety of IXIARO (IC51) in a Phase II study in healthy Indian children between 1 and 3 years of age. Vaccine 2010;28:834-9
2. Dubischar-Kastner et al. Interim Safety and Immunogenicity Data for the Inactivated Japanese Encephalitis Vaccine IXIARO®, IC51, in Children from JE non-endemic countries. Presented at the 4th Northern European Conference on Travel Medicine, June 2012, Abstract P.9. Abstract available at http://nectm.com/wp-content/uploads/BookofAbstracts.pdf
3. Dubischar-Kastner et al. Safety and Immunogenicity of the Inactivated Japanese Encephalitis Vaccine IXIARO®, IC51, in Filipino Children aged 2 months to <18 years. Presented at the 4th Northern European Conference on Travel Medicine, June 2012, Abstract P.9. Abstract available at http://nectm.com/wp-content/uploads/BookofAbstracts.pdf

The objective of Trial IC51-221 was dose-confirmation in children 1 to 3 years of age. The study was conducted in 1 center in Bangalore, India. The study population was comprised of 60 healthy toddlers. The study design was an open-label randomized controlled trial (RCT), with the following treatment groups:

- IXIARO 0.25 mL, i.m. on Days 0 and 28 (N = 24)
- IXIARO 0.5 mL, i.m. on Days 0 and 28 (N = 24)
- Control Group 0.5 mL JenceVac™ (Mouse-brain derived JE vaccine [virus strain Nakayama] produced by Korean Green Cross), given in a 3-dose schedule on Days 0, 7, and 28 (N = 12)

Follow-up was up to 28 days after the last dose, and assessed immunogenicity and safety. Relatively limited pre-existing immunity has been observed at Day 0 before vaccination of about 4% neutralizing antibodies against Japanese encephalitis in both of the IXIARO® groups. On Day 28, 4 weeks after the first dose of IXIARO®, the seroprotection rates ranged from about 60% to 70% and within 4 weeks of the second dose of IXIARO® exceeded 95% in both IXIARO® groups. The geometric mean titers (GMTs) in response to the complete immunization schedule, on Day 56 the half and full dose of vaccine did not differ in terms of immunogenicity and were also very low comparable to the neutralizing antibody titers induced by the 3-dose course of mouse-brain derived vaccine. Based on the immunogenicity data, there was no indication that the higher dose would be of benefit for children 1 to 2 years of age. Regarding safety results for the half and full dose, both doses were well-tolerated. The overall adverse event rates were about 12% in subjects who received the 0.5 mL dose of vaccine and about 20% in subjects who received the full adult dose. The only reaction that was observed in more than one subject was injection site tenderness, and no serious adverse events were reported. Based on the immunogenicity and safety results, the decision was made to carry the 0.25 mL dose forward for development in this age group.

The objective of Phase III Trial IC51-322 was to assess the safety and immunogenicity of IXIARO® in a Japanese encephalitis vaccine naïve, pediatric traveler population in 15 study sites in Australia, Germany, USA, Denmark, and Sweden. This study was a challenge to conduct because of the population that had to be enrolled. Notoriously, travelers tend to present very late for their immunizations; therefore, it was very difficult to recruit children who were able to receive both vaccinations and who would be present for a follow-up visit 4 weeks after the second dose of vaccination. The study population was comprised of 60 children and adolescents 2 months to 18 years of age. The study design was an open-label single-arm trial, with the following treatment groups:

- IXIARO® 0.25 mL, i.m. on Days 0 and 28; <3 Years of Age (N = 5)
- IXIARO® 0.5 mL, i.m. on Days 0 and 28; 3 to <18 Years of Age (N = 55)

The data presented by Dr. Dubischar-Kastner during this session were from an interim analysis that covered 60 children. Follow-up of this study extended to Day 56 and Month 7 for immunogenicity and safety. As expected in this population, no pre-existing immunity was observed (e.g., no child with neutralizing antibodies prior to vaccination). On Day 56 with both doses of vaccine, the seroprotection rate reached 100%. While the data at Month 7 in the interim analysis are limited to 18 subjects who had reached this time point, all of them were able to retain their protective titers. On Day 56, the GMTs were in the range of 200 to 300 with both doses of the vaccine, so there was not lower immunogenicity with the half dose. As expected from the results observed in adults, there was a decline in neutralizing antibody titers between Day 56 and Month 7. The rate of decline in children is comparable to the profile in adults. The

safety analysis was based on 60 subjects who received at least one dose of the vaccine. Overall, the primary endpoint for safety in this trial was the rate of serious adverse events or medically attended adverse events. In total, 3 children (5%) experienced medically attended adverse events.

No serious adverse events occurred through Day 56. The overall rate for any solicited or unsolicited adverse events was 66%. In the children who received the 0.25 mL dose of vaccine, 1 child had an injection site reaction following the first dose and 2 children had injection site reactions after the second dose. The reactions were hardening and redness. Diarrhea is the only solicited systemic symptom that has been observed after both doses. In the children who received the 0.5 mL dose, local reactions following the first dose of vaccine for any injection site reaction was 40% following the first dose and 27% following the second dose. Comparable to the local reactogenicity profile seen in adults, pain and injection site tenderness are the most common reactions and were the only reactions that were observed in more than 10% of the subjects. Solicited systemic reactions were 42% following the first dose and 16% following the second dose. Muscle pain and excessive fatigue were the most common reactions after the first dose, and are the only reactions that were observed in greater than 10% of the subjects. There was a low rate of fever, and fever was very mild.

In summary of Trial IC51-322, IXIARO® was immunogenic, providing protective antibody titers in both dose groups. All 51 subjects developed protective titers at Day 56. GMTs were 216 with the 0.25 mL and 332 with the 0.5 mL dose at Day 56. At Month 7, for the 18 subjects in this interim analysis, titers declined but remained at protective levels. IXIARO® was generally well-tolerated in both dose groups, with an overall adverse events profile comparable with adult data for rates of solicited local adverse events and solicited systemic adverse events, and lower rates for unsolicited adverse events.

The objective of Phase III Trial IC51-323 was to assess safety, immunogenicity and dose-confirmation in a pediatric population in a Japanese encephalitis virus endemic region in 3 study sites in the Philippines. It is important to point out that while the Philippines is endemic for Japanese encephalitis virus, it does not have a licensed Japanese encephalitis vaccine that is included in the national immunization program. Therefore, it was possible to recruit from all ages in this population. The study population was comprised of 1869 children and adolescents 2 months to 18 years of age. The study design was an open-label, randomized, active-controlled trial. The treatment groups included the following:

- IXIARO® 0.5 mL, i.m. on Days 0 and 28 (N = 540)
- IXIARO® 0.25 mL, i.m. on Days 0 and 28 (N = 871)
- Prevnar®7, 0.5 mL, i.m. on Days 0, (28*), 56 and 3rd/4th dose after study (N = 64)
- HAVRIX®720 0.5 mL, i.m. on Days 0 and Month 7 (N = 394)

The two control vaccines were used (Prevnar®7 and HAVRIX®720) because the investigators did not find a vaccine licensed in the US that is approved for the entire age range from 2 months to 17 years of age. The study had a follow-up to Day 56, and at Month 7 for immunogenicity and safety. The primary endpoint of the study was rate of serious adverse events and medically-attended adverse events up to Day 56. Immunogenicity was addressed in a subgroup of patients. IXIARO® was given at all of the ages in both doses on Days 0 and 28. For each of the vaccinations, there is a subject vaccine diary that covers 7 days following vaccinations. The first dose of HAVRIX® was given at the beginning of the study, so there is a subject diary for the first dose. The second dose was given at the last study visit, and there was no additional safety follow-up after 60 minutes following the second dose. Subject diaries for

Prevnar®7 after the first dose and the 28-day dose, if it was administered, are included in the analysis up to Day 56 data. A diary card for the third dose is included in the data analysis up to Month 7. No safety data were collected for the last dose administered at the last study visit.

In terms of the age distribution of the study population, overall 131 children were recruited between 2 months and 1 year of age. The comparator group for these children was comprised of 64 children who received Prevnar®7. The age group from 1 year to below 3 years is the largest cohort in this study. In this group, 640 children received IXIARO® compared to 213 who received HAVRIX®720. The age group 3 to 12 years of age, 300 children received the 0.5 mL licensed dose compared to 100 who received Prevnar®7. There were 240 adolescents who received IXIARO® compared to 80 who received HAVRIX®720.

Regarding the seroprotection results, for the 0.25 mL dose of IXIARO® there was relatively limited preexisting immunity with the younger age group at about 5%. This rate was higher with the 0.5 mL dose for which the age range goes through adolescents. On Day 56 in both vaccination groups, seroprotection rates exceeded 99% for the 0.25 mL dose of IXIARO® and reached 100% with the 0.5 mL dose. At month 7, protection persisted in about 88% who received 0.25 mL dose and about 95% who received the full dose of vaccine. Because of the preexisting immunity, the rate of subjects who achieved seroconversion with $PRNT_{50}$ titers ≥10 with the half dose of vaccine exceeded 96% on Day 56 and about 85% with the full dose. For children 2 years to under 3 years of age who received 2 doses, the GMT was 288 for the 0.25 mL dose and about 200 for the older age group who received the full dose of vaccine. By month 7, the GMTs declined as expected in both age groups.

The safety profile of IXIARO® is comparable to the control vaccine Prevnar®7 for children 2 month to below 1 year of age. As mentioned earlier, the primary endpoint of the study was the rate of subjects with any serious or medically attended adverse events. The rate was comparable for the two vaccines at about 40% for IXIARO® and Prevnar®7. The overall adverse event rate of any solicited or unsolicited adverse event was also comparable between the two vaccine groups at 84% for the IXIARO® group and 87% for the Prevnar®7 group. Through Day 56, there were no serious events in the IXIARO® group and 1 in the Prevnar®7 group. For children 1 to below 18 years of age, safety profile of IXIARO® is also comparable to the control vaccine HAVRIX®720. As expected, fewer serious or medically attended adverse reactions were observed with the older children compared to infants. In this age group, the overall adverse event rate of any solicited or unsolicited adverse event up to Day 56 was also comparable between the two vaccine groups at 16% for the IXIARO® group and 14% for the HAVRIX®720 group. Again, there was no difference in adverse event rates overall for the two study vaccines, with about 60% of children in each group experiencing any adverse event during the trial. The rates are very comparable for serious or adverse events for each group.

For complete follow-up at Month 7, the safety profile of IXIARO® is comparable to the control vaccine Prevnar®7 for children 2 month to below 1 year of age. For children 1 to below 18 years of age, the complete follow-up safety profile of IXIARO® is also comparable to the control vaccine HAVRIX®720. Unfortunately, there was one death during the study of a 12-year old boy who died following suspected bacterial meningitis and pneumonia. The underlying cause of death was believed to be disseminated intravascular coagulation. The death occurred 4.5 months after IXIARO®, and was reviewed by an independent monitoring and safety board. The board concluded that it was very unlikely that the death had anything to do with vaccination.

Turning to solicited local reactions within 7 days after vaccination for infants below 1 year of age, 19% of children had any local reaction after the first dose of IXIARO® compared to 32% who received Prevnar®7. The rates for local reactions were lower for redness, tenderness, swelling, and hardening for IXIARO® compared to Prevnar®7. As observed in other studies, fewer local reactions were seen with the second dose of vaccine, with 8% of children having any local reaction after the first dose of IXIARO® compared to 18% who received Prevnar®7. For children 1 to below 18 years of age, about 14% in the IXIARO® and HAVRIX®720 groups had any local reaction within 7 days after the first dose. None of the solicited local reactions occurred in greater than 10% of subjects overall. Again, with the second dose of IXIARO®, the local adverse events rates declined to about 6% who had any injection site reaction. As mentioned earlier, these follow-up data are not available for the second dose of HAVRIX®720.

Moving to solicited systemic reactions within 7 days after vaccination for infants below 1 year of age, about 40% of children who received IXIARO® or Prevnar®7 experienced any solicited systemic reaction within 7 days after the first dose. The dominant symptom was fever in both vaccine groups at about 24% to 25%, and fever was very mild. After the second dose of IXIARO®, only one child experienced fever of greater than 39.4 °C. The other reactions that occurred in more than 10% of study participants in the IXIARO® group were irritability and diarrhea, and all other reactions were less common. Again, reactions to the second dose occurred at a lower frequency. For children 1 to below 18 years of age, comparable rates were observed in the IXIARO® and HAVRIX®720 groups solicited systemic reactions. The only symptom that occurred in more than 10% of children was fever, and it was mostly of a mild nature with very few children having higher grade fevers.

No serious adverse events occurred up to Day 56 in infants less than 1 year of age after receiving IXIARO®. There was one adverse event of febrile convulsion in the Prevnar®7 group. For children 1 to below 18 years of age, a relatively comparable rate was observed of any serious adverse events up to Day 56 in 6 subjects in the IXIARO® group compared to 4 subjects in the HAVRIX®720 group. The most commonly observed serious adverse events involved infectious diseases. None of these serious adverse events occurred in more than 1 subject. The most commonly observed non-infectious serious adverse event was febrile convulsion. The overall rate of febrile seizures among children between 2 months and under 3 years of age was 1% (8 / 771) of children for the IXIARO® group, 1.6% (1 / 64) in the Prevnar®7 group, and 1.4% (3 / 213) in the HAVRIX®720 group. In terms of the timing of seizures, the overall randomization ratio for the study was 3:1, so more cases were expected with IXIARO® compared to the control vaccines. The temporal distribution does not indicate that there would be any clustering of febrile seizures following vaccination with IXIARO®.

Because the previously used mouse brain-derived Japanese encephalitis vaccine had been associated with hypersensitivity reactions, the rates of hypersensitivity, urticarial, and rash were assessed for IXIARO® within 14 days after vaccination. A total of 9 subjects had any such reactions within 14 days of vaccination with IXIARO®. All of these occurred in children who received the 0.25 mL dose. During the same timeframe, 1 subject in the HAVRIX®720 group had such a reaction within 14 days after vaccination. While this may appear as a difference, due to the different number of doses administered throughout the trial, there is much higher accumulated post-vaccination follow-up time for IXIARO® than for Prevnar®7 or HAVRIX®720. In the IXIARO® group, 3 cases of rash occurred within the 14-day window. All three cases occurred within 7 to 10 days following the first dose of vaccine. None of these children had a reaction following the second dose of vaccination. There was also 1 case of maculo-papular rash and 1 case of popular rash. The maculo-papular rash was believed to be associated with a probable viral infection. The child had a fever at the same time. There were 2 cases of

hypersensitivity. In the child who experienced hypersensitivity 7 days after the second dose, the reaction was not associated with any systemic symptoms. It was self-limited to itching and did not require medical treatment. In the second case of hypersensitivity, the child received the second dose and did not have any subsequent reaction. There were also two reactions of urticaria, one 5 days after the first dose in which the child did not have a reaction following the second dose. The second child had an urticaria reaction 13 days after the first dose, and was not given the second dose. The investigator believed that the underlying reason for this was most likely a viral infection.

In conclusion, the overall safety profile of IXIARO® was comparable to the control vaccines, Prevnar® and HAVRIX®720. The most commonly observed adverse events were in-line with the expected adverse events profile in a pediatric population, and mostly were of mild nature. The adverse event profile in the age group 12 to under 18 years resembled the solicited adverse event profile seen in previous adults trials with IXIARO®. Compared to Prevnar®7, IXIARO® appeared to cause fewer local reactions in the age group under 1 year. IXIARO® was immunogenic in all age groups tested. The seroprotection rate at Day 56 was 99% to 100%. At month 7, seroprotection rate ranged between 85.5% and 100%. In terms of immunogenicity, the GMTs in the age group 12 to under 18 years was comparable to levels typically seen in adults after receiving IXIARO®.

Discussion Points

Dr. Keitel requested a description of the effect of age and preexisting immunity in response to vaccine, and in terms of persistence of antibody, if those with preexisting antibody were more likely have persisting antibody.

Dr. Dubischar-Kastner responded that immunogenicity was determined in a subgroup of 496 children. The youngest age groups developed the highest titers. Titers in adolescents are similar to titers typically observed in adults. On Day 56, there were 100% protection rates throughout all of the age groups in the study. There was a 99% rate in children 2 months to 6 months and 6 months to 12 months, and upward of 100% in the children 1 to 3 years of age and 3 to 12 years of age. There was very good persistence at Month 7 among the youngest age groups at 100% with children below 12 months and 85% in the children 1 to 3 years of age. Persistence appears to be somewhat higher with the older age groups. In terms of GMTs, the best response is observed in the youngest age group of children 2 to 6 months of age. Although a half dose was used in the youngest age group, the titers are best here. Persistence is better in the extremes of age groups, so the very young and older children tend to maintain higher GMTs. In terms of GMTs stratified by preexisting antibodies, immunogenicity was determined in a subgroup of 496 children at Day 56 comprised of 17 children who received the 0.25 mL dose and 79 who received the 0.5 mL IXIARO® who were seropositive for Japanese encephalitis virus compared to a group of 166 children who received the 0.25 mL dose and 71 who received the 0.5 mL who tested negative for Japanese encephalitis virus and dengue. There were lower titers at Day 56 in the children who had preexisting immunity with both the 0.25 mL and 0.5 mL doses of IXIARO®. The changes were lower in the seropositive at baseline compared to the naïve. In terms of the 7 month data, it appears that those who are positive at baseline retain higher GMTs compared to those who are negative at baseline.

Dr. Harrison inquired as to whether there was any effort to blind the individuals collecting the adverse event data in terms of vaccination status.

Dr. Dubischar-Kastner responded that the study was conducted as an open-label, so the safety data and most of the immunogenicity data collection were not blinded. Due to the different number of vaccinations administered in the study, placebo shots would have to have been utilized for the purpose of blinding. This was not considered to be justified based on the very robust endpoints.

Dr. Karron requested information about how the vaccine is supplied for the 0.25 mL and 0.5 mL doses.

Dr. Dubischar-Kastner replied that the vaccine supply would be a single presentation going forward. The vaccine is a very niche product for the age groups below 3 years. It is apparently not routine to give at that age group. The label of the syringe in the future will carry a mark, and there will be a procedure to expel volume up to that mark, and inject the remaining volume as the 0.25 mL in children under 3 years of age.

Dr. Sawyer expressed surprise the high rates of medically attended adverse events. For example, 1 to 18 years olds HAVRIX®720 experienced a 25% medically attended adverse event rate. That vaccine generally has very few side effects. He wondered whether this may be an artifact of instructions given to the participants in terms of whether they should seek medical care, if it related to routine practice in the Philippines, or if Dr. Dubischar-Kastner could comment further about what types of events lead to being medically attended.

Dr. Dubischar-Kastner said it is believed that this is the result of offering free medical care for study participants in a resource-limited country, who are probably biased and more likely to see a doctor if they have any adverse event. The majority of the unsolicited and medically attended adverse events reported in the study included infectious diseases. These included gastroenteritis, as well as children presenting for rabies shots for dog bites.

GRADE Evidence for Japanese Encephalitis Vaccine in Children

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Dr. Fischer reminded everyone that in 2009, JE-VC was licensed for use in adults in the US, Europe, and Australia. In June of that same year, ACIP approved the current recommendations for use of JE vaccines in travelers. Those recommendations included the use of JE-VC in adults 17 years of age and older, and the inactivated mouse brain-derived JE vaccine (JE-MB) for adults and children 1 year of age or older. JE-MB is no longer produced and no JE vaccine has been licensed and available for children in the US for the past 2 years. In May 2013, JE-VC was licensed for use in children 2 months of age and older.

The WG evaluated the evidence for use of JE-VC in children using GRADE methods, which included the following steps:

- ❑ Developing a policy question
- ❑ Identifying and ranking the importance of outcomes
- ❑ Searching and reviewing published and unpublished data
- ❑ Summarizing the evidence for critical outcomes
- ❑ Evaluating the quality of evidence for outcomes

- ❑ Assessing the values related to options and outcomes
- ❑ Reviewing health economic data
- ❑ Assessing considerations for formulating recommendations (e.g., benefits, harms, values, costs)
- ❑ Determining ACIP recommendations and GRADE category

The policy question considered by the WG was, "Should JE-VC be recommended for use in children 2 months through 16 years of age at increased risk of travel-related exposure to JE virus?" The population taken into consideration included children 2 months through 16 years of age traveling to JE-endemic areas. The intervention considered was JE-VC administered as a 2-dose primary series. Regarding the current option, as noted there is no JE vaccine recommended and available for use in children. The WG was surveyed to identify and rank the outcome measures to be evaluated, and the group identified vaccine efficacy to prevent JE and seroprotection at 1 month and 6 months as benefits of critical importance. There are no efficacy data for JE-VC. A JE virus $PRNT_{50}$ of ≥10 is an established immunologic correlate of protection, which was used to evaluate evidence of seroprotection. The harms considered included serious adverse events using the FDA definition and systemic adverse events (e.g., fever, rash, hypersensitivity, urticaria, neurologic, medically attended). Injection site reaction and interference with other vaccines were considered to be important outcomes, but were not included in this GRADE evaluation.

To collect the evidence for the GRADE evaluation, a systematic search and review of the published and unpublished data was performed through which 12 studies were identified that reported primary data relevant to the critical outcome measures in children (n=1) or adults (n=11). The review of the unpublished data included two clinical trials of JE-VC in children, Vaccine Adverse Event Reporting System (VAERS) reports for JE-VC administered from May 2009 through April 2012 to adults in the US or US military personnel, and two clinical trials (one in children, one in adults) of a similar inactivated Vero cell culture-derived JE vaccine manufactured and licensed in India under the trade name JEEV.

The evidence used to evaluate seroprotection at 1 month after vaccination with JE-VC was from 10 studies, including 3 in children and 7 in adults. The 3 pediatric studies included the RCT in children 1 and 2 years of age in India; the RCT in children 2 months through 17 years of age in the Philippines; and the observational study in children 2 months through 17 years of age in the US, Europe, and Australia. The study in the Philippines provided no comparative immunogenicity data, so for this part of the evaluation it was considered observational. Of the 578 children who received JE-VC in the 3 studies combined, 99% were seroprotected at 1 month after the 2-dose primary series. Of the 7 studies in adults based on seroprotection data at 1 month, 5 were RCTs and 2 were observational studies. However, 2 of the RCTs had no comparative immunogenicity data and were considered observational studies for this analysis. The comparator JE vaccines used in the controlled trials included an inactivated mouse-brain derived vaccine from Korea, one from Japan, and the JEEV vaccine from India. Of the 800 adult JE-VC recipients in the 7 studies combined, 98% were seroprotected at 1 month after the 2-dose primary series.

In terms of the effects of a weighted random effects model combining data from the 4 RCTs in children and adults, risk ratios and 95% confidence intervals were calculated to compare seroprotection rates in JE-VC and the comparator JE vaccine recipients. The risk ratios from individual clinical trials were weighted and combined to provide an overall comparison from the 4 studies, stratified by children and adults. Overall, there was no difference in seroprotection rates at 1 month between JE-VC and the other JE vaccines.

The evidence used to evaluate seroprotection at 5 to 6 months after a primary series of JE-VC or comparator JE vaccine in children or adults were from 4 studies, including 2 each in children and adults. For the pediatric studies, follow-up was at 6 months after completing the 2-dose primary series. For the studies in adults, follow-up was at 5 months after completing the 2-dose series, or 6 months after the first dose. Of the 800 JE-VC recipients in the 4 studies combined, 90% still had a $PRNT_{50}$ of ≥10 at 5 to 6 months after the 2-dose primary series. This included 89% of 500 children and 90% of 297 adults. The findings from the one RCT in adults showed that a significantly higher proportion of JE-VC recipients were seroprotected at 5 months following vaccination, compared to subjects who received the mouse brain-derived JE vaccine.

The evidence used to evaluate serious adverse events within 56 days after the first dose of JE-VC or control vaccines was from 13 studies, including 11 clinical trials or observational studies in children or adults and 2 reviews of post-marketing surveillance data in adults. In terms of the data from the 3 pediatric studies, as previously presented, the control vaccine for the study in India was an inactivated mouse brain-derived vaccine from Korea. The control vaccines in the Philippines study were hepatitis A and pneumococcal conjugate vaccine. Serious adverse events were reported in less than 1% of the 1519 children who received JE-VC overall. No serious adverse events were reported during the studies in India or among the children from non-endemic countries. Among the 1411 children who received JE-VC in the Philippines study, 6 serious events were reported. These included 2 febrile seizures and 1 report each of cellulitis, gastroenteritis, pneumonia, and dengue.

In the 7 clinical trials in adults, serious adverse events were reported in less than 1% of 2874 JE-VC recipients within 56 days after the first dose. The control vaccines in the various studies included mouse brain-derived JE vaccine from Japan, Vero cell-derived JE vaccine from India, hepatitis A vaccine, and a placebo of phosphate buffered saline with aluminum hydroxide adjuvant. In terms of the weighted random effects model combining the data from the 7 RCT trials in both children and adults, overall there was no difference in serious adverse events reported in the 56 days after the first dose of JE-VC or the comparison vaccines.

Three studies provided data for serious adverse events within the 6 to 7 months after the first dose of JE-VC or the control vaccines. In the 2 pediatric studies, a total of 1471 children were followed for 7 months after the first dose of JE-VC. Of these, 25 children (2%) had serious adverse events reported. In the study which pooled clinical trial data from adults, 1% of 3558 JE-VC recipients had serious adverse events reported within 6 months after their first dose. Again, there was no difference between JE-VC and comparison vaccine recipient for serious adverse events reported within 6 to 7 months post-vaccination in the 2 RCTs in children or adults.

Two studies evaluated serious adverse events that were reported to passive post-marketing surveillance systems following the receipt of JE-VC in adults. The first was a published study that included reports from the US, Europe, and Australia for April 2009 through March 2010, during which time approximately 250,000 doses of JE-VC were distributed in these areas. The second study included unpublished VAERS data from May 2009 through April 2012, when more than 275,000 doses of JE-VC were distributed in the US alone. Approximately 85,000 doses distributed in the US from May 2009 through March 2010 would be included in both of these surveillance systems. However, there is no overlap in the 13 serious adverse events identified in the two separate analyses. The relatively small number of subjects in the clinical trial limited the ability to detect rare serious adverse events. However, these post-marketing surveillance data for more than 400,000 doses distributed provide some indirect but reassuring data in adults with 1.6 to 3.3 serious adverse events reported per 100,000 doses distributed. There were no

patterns in the timing or types of serious adverse events that were identified in either the clinical trials or surveillance data.

The evidence used to evaluate systemic adverse events following JE-VC was from 9 studies, including 7 clinical trials or observational studies and the 2 reviews of post-marketing surveillance data. Fever within 7 days after a dose of JE-VC was reported in 6% of 3659 subjects in 6 clinical trials, including 9% of about 1500 children and 4% of 2140 adults. When data from the 4 RCTs were combined and weighted using the random effects model, there was no difference in the incidence of fever between recipients of JE-VC or the control vaccines. Rash as a solicited adverse event within 7 days of either JE-VC dose was reported in 2% of all subjects, including 3% in children and 1% in adults. In the 4 RCTs, there was no difference in the incidence between JE-VC and comparison vaccines for rash. Hypersensitivity or urticaria within 56 days after the first dose of vaccine was reported in less than 1% of 3635 JE-VC recipients in the 5 studies combined. In the 3 RCTs, there was no difference in the incidence of hypersensitivity reactions between JE-VC and control recipients. Neurologic adverse events excluding headache were reported in 1% of JE-VC recipients within 56 days of the first dose of vaccine. There were no cases of meningitis, encephalitis, or Guillain–Barré Syndrome (GBS) reported among JE-VC or control recipients. The 5 neurologic events reported following JE-VC included 3 febrile seizures in children 1 to 2 years of age at 2 days, 8 days, and 3 weeks after vaccination; 1 child 2 years of age who had drooling; and 1 child 3 to 11 years of age who had dizziness. There was no difference in the incidence of neurologic adverse events between JE-VC or control vaccines. Medically attended adverse events were reported in 14% of 3714 subjects overall, but ranged from 18% in 1471 children to 12% of 2243 adults. When data from the 3 RCTs were combined and weighted in the random effects model, there was no difference in the incidence of medically attended adverse events between JE-VC and comparison vaccine recipients.

In the two reviews of post-marketing surveillance data, reported incidence of hypersensitivity in adults was 4.5 to 4.7 per 100,000 doses distributed. The 13 hypersensitivity reactions reported to VAERS occurred within 14 days after vaccination. However, 7 occurred after administration of JE-VC alone, while 6 occurred after concomitant administration of JE-VC and other vaccines. Five neurologic adverse events following the administration of JE-VC in adults were reported to VAERS for a total incidence of 1.8 per 100,000 doses distributed. These included 1 report of encephalitis at 39 days after vaccination with JE-VC and 4 other vaccines, and 4 reports of seizures within 5 days after vaccination. Of the JE-VC recipients with seizures, 3 had received other vaccines and for 1 there was no information available.

In addition to the studies of JE-VC in children and adults, the WG reviewed evidence for seroprotection, serious adverse events, and systemic adverse events from an RCT of a similar JE vaccine that is manufactured and licensed in India under the trade name JEEV. JEEV is manufactured by Biological E using technology transferred from Intercell. JEEV is licensed in India for children 1 through 2 years of age and adults 18 through 49 years of age. JEEV and JE-VC use the same virus strain, adjuvant, and virus purification steps; however, no comparability studies have been completed and it cannot be assumed that the two final vaccine products are the same. In one RCT comparing JEEV and a mouse brain-derived vaccine in children 1 through 2 years of age, 92% of the 280 children who received JEEV had protective neutralizing antibodies at 1 month after the second dose. Serious adverse events were reported in less than 1% of recipients, and fever within 7 days after either dose was reported in 11% of children, and rash was reported in 1%. Although JEEV and JE-VC are not identical vaccines, these data provide some additional evidence of immunogenicity and safety of inactivated Vero cell culture-derived JE vaccine in children.

After completing this review and summarizing these data, the WG assessed the quality of the evidence for each of the 4 critical outcomes. The following standard GRADE classifications were used, with the initial evidence type classified based on the study design:

1	RCTs or overwhelming evidence from observational studies
2	RCTs with important limitations or exceptionally strong evidence from observational studies
3	Observational studies or RCTs with notable limitations
4	Clinical experience, observational studies with important limitations, or RCTs with several major limitations

The evidence type for each critical outcome was derived through review of the study design and limitations, including risk of bias, inconsistency, indirectness, and imprecision. For seroprotection at 1 month post-vaccination, 4 RCTs started at evidence type 1, but were downgraded because of indirectness due to the majority of data being in adults, for a final evidence type of 2. The 6 observational studies for seroprotection at 1 month started at an evidence type of 3, and no additional serious limitations were identified. For seroprotection at 6 months, there were 1 RCT and 3 observational studies. The RCT was downgraded to evidence type 2 because of indirectness, and no serious limitations were identified in the observational studies. Other criteria that were considered but had no effect on evidence type included publication bias, strength of association, dose response, and residual confounding.

For serious adverse events, 8 RCTs started with evidence type 1, but were downgraded because risk of bias due to inadequate blinding and indirectness due to the majority of data being in adults, for a final evidence type of 3. Of the observational studies, 5 started at evidence type 3 and were downgraded to evidence type 4 because of indirectness. For systemic adverse events, the evidence provided by 5 RCTs was downgraded to type 2 because of the risk of bias due to inadequate blinding. Of the observational studies, 6 started at evidence type 3 and no serious limitations were identified.

In terms of the overall quality of evidence for JE-VC in children, both RCTs and observational studies were considered. The final evidence type was based on the RCTs, which provided the higher quality of evidence. The overall quality of evidence was classified as type 2 for vaccine safety and vaccine effectiveness, using seroprotection as the endpoint.

After establishing the quality of evidence, the next step was to assess the values and preferences related to management options and outcomes. For most travelers to Asia, the risk for JE is very low but varies based on destination, duration, season, and activities. More than 300 cases of JE were reported among US military personnel during the Vietnam and Korean Wars. However, for the 40 years from 1973 through 2012, only 65 cases of travel-associated JE among people from non-endemic areas have been reported to CDC or published in the literature. Of these, 6 (9%) cases were in children less than 17 years of age. During this timeframe, a median of 1 case was reported per year, with a range of 0 to 6 annual cases. Of the 65 travel-associated cases reported during this time, 20% were fatal and 43% of patients survived with neurologic or cognitive sequelae. Among the 6 pediatric cases, 2 were fatal, 3 survivors had sequelae, and 1 patient had an unknown outcome. For 47 of the 65 of the travel-associated cases, more complete information was available regarding their itineraries and activities. Duration of travel for these cases ranged from 10 days to 34 years, and 64% of the cases were traveling for a month or longer. Of the 17 shorter-term travelers, 13 had a trip duration of 2 to 4 weeks and 4 had traveled for 10 days to 2 weeks. Among the shorter-term

travelers, 4 had known extensive rural exposures, 10 took shorter trips to rural areas, and 3 stayed primarily in coastal areas. No cases were reported among short-term travelers who visited only urban areas.

Of the 65 reported travel-associated cases, 19 occurred in US travelers or expatriates, including 3 of the pediatric cases. However, a JE vaccine has been available in the US since 1993 and it is not known how many cases have been prevented due to vaccination, or how many cases are not diagnosed or reported. In addition, the numbers of susceptible travelers to JE endemic areas is also unknown. These limitations make it difficult to estimate the overall risk of JE among travelers to Asia.

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 for most travelers is very low. However, when JE does occur it has a high morbidity and mortality and there is no treatment. A safe and effective vaccine is available, but the vaccine is 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 importation or spread of the virus.

The WG placed a high value on preventing this life-threatening disease with no treatment options, noting that a survey performed in the US in 2001 found that parents and community members are willing to pay median of $500 to reduce the risk of bacterial meningitis from 21 to 6 per 100,000. Although the rates of disease used in the survey are higher than the risk for JE among all travelers to Asia, these findings support a willingness to pay to prevent serious outcome [Prosser. Pediatrics 2004;113:283]. The WG also placed a high value on educating healthcare providers to help them counsel travelers about JE and JE vaccine, and to inform decisions about JE vaccination based on a traveler's planned itinerary.

The WG also considered the cost of JE vaccine for children. Several studies have demonstrated that using JE vaccine to immunize children in JE endemic countries is cost-saving. However, JE vaccine for all travelers to Asia would not be cost-effective given the large numbers of US travelers to Asia (>5.5 million/year), the overall low risk of disease for most travelers (<1 case per million travelers), and the high cost of JE-VC ($200-250/dose). For some travelers, even a low risk of serious adverse events attributable to the vaccine may be higher than the risk for disease. Therefore, JE vaccine should be targeted to travelers who are at increased risk for disease based on their planned itinerary. The number of US children who travel to Asia and have an itinerary that puts them at increased risk for JE is likely very low. In addition, travel vaccines are usually paid for by the travelers themselves. They are not covered under the VFC program or by most private insurance plans. As a result, the WG decided not to perform a cost-effectiveness study of JE vaccine for US children traveling to endemic areas.

Recommendations for use of Japanese Encephalitis Vaccine in Children

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Dr. Fischer reported that the WG considered the following findings from the GRADE evaluation in formulating its proposed recommendations:

- JE-VC provides high levels of seroprotection in children following a 2-dose primary series
- Serious adverse events are uncommon and rates are similar to those seen with comparison vaccines
- Systemic adverse events also occur at rates similar to comparison vaccines
- A high value is placed on prevention of a serious disease with no treatment and substantial morbidity and mortality
- The low risk of disease, low risk of vaccine-related adverse events, and high vaccine cost warrant targeted vaccination of higher risk travelers

Given these considerations, the WG concluded that JE-VC is effective using seroprotection as the endpoint and safe in children aged 2 months through 16 years, with an overall evidence type of 2. Based on the GRADE evaluation for JE-VC, the WG found no reason to change the existing recommendations that were approved in 2009. Therefore, the WG proposed to extend the current ACIP recommendations for use of JE-VC to include children ≥2 months of age. No other changes were proposed to the existing recommendations.

Therefore, the recommendations and GRADE categories proposed for a ACIP vote were as follows:

> "JE vaccine is recommended for travelers who plan to spend a month or longer in endemic areas during the JE virus transmission season. This includes long-term travelers, recurrent travelers, or expatriates who will be based in urban areas but are likely to visit endemic rural or agricultural areas during a high-risk period of JE virus transmission (Recommendation Category A)."
>
> "JE vaccine should be considered for short-term (<1 month) travelers to endemic areas during the JE virus transmission season if they plan to travel outside of an urban area and have an increased risk for JE virus exposure (e.g., spending substantial time outdoors in rural or agricultural areas, participating in extensive outdoor activities, staying in accommodations without air conditioning, screens, or bed nets). JE vaccine also should be considered for travelers to an area with an ongoing JE outbreak and travelers to endemic areas who are uncertain of specific destinations, activities, or duration of travel (Recommendation Category B)."
>
> "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 (Recommendation Category A)."

Discussion Points

Dr. Temte thanked Dr. Fischer and the WG for an incredibly clear, beautiful presentation of this evidence and recommendation using GRADE. He noted that it almost felt routine, and the presentation made it easy to follow.

Dr. Keitel asked whether the recommendation included any additional comments about the need for booster immunization, and whether there are any data from endemic areas that suggest the primary series is necessary to protect an individual over the long-term.

Dr. Fischer replied that ACIP passed recommendations in 2011 regarding a booster dose for adults, which would remain in place. While there are ongoing studies to assess the issue of a booster dose for children, no data are available at this point. Therefore, only recommendations for the 2-dose primary series were being taken into consideration for the vote during this session. The booster dose for children will have to be addressed later. Duration of protection in endemic areas is more difficult to address because various JE vaccines are licensed and used in Asia, which are different. There is a live attenuated vaccine that appears to provide long-term protection. The most commonly used inactivated vaccines have been mouse brain-derived, and those have required subsequent booster doses. The inactivated Vero cell-derived vaccines have not been used long enough to determine the full duration of protection or numbers of booster doses that may be needed.

Dr. Harrison asked whether there were any data on the immunization status of the travel-related cases.

Dr. Fischer responded that the 65 cases were reported to be vaccinated. Those were all published or were reported to CDC, so there is fairly extensive evaluation of these.

Dr. Harriman wondered whether this vaccine was recommended for certain child travelers in other non-endemic countries.

Dr. Fischer replied that the vaccine is approved for use in Europe and Australia, and is recommended in those countries for use in travelers. The recommendations are slightly different, but it is recommended for pediatric travelers in those countries.

Dr. Duchin requested that Dr. Fischer expand on the rationale that the WG used to derive a Category B recommendation for short-term travelers. Given that 35% of the cases were in short-term travelers, he wondered why that would have the same strength of recommendation as the others.

Dr. Fischer indicated that this related to a discussion several years ago ACIP discussed the vaccine for adults and came to the same conclusion. Essentially two-thirds of the travelers had prolonged duration of travel or were expatriates and one-third had shorter term travel. However, even among the shorter-term travelers there was essentially some type of risk factor in almost all cases identified. A quarter of those shorter-term travelers alone had extensive rural travel, and the others had shorter-term travel to rural areas. Thus, ACIP thought it was important to divide the people who were at highest risk based on duration of travel. This distinction would offer healthcare providers the ability to assess the risk for the largest group of travelers who may be spending shorter periods of time, and distinguish those travelers who are traveling only to urban versus rural areas.

Dr. Duchin pointed out that according to the recommendation, short-term travelers going to high risk areas would still be a Category B.

Dr. Fischer responded that it is a Category B because the healthcare provider has to evaluate the patient's itinerary and assess their activities to make a determination. The vaccine is not recommended for all people who are shorter-term. Instead, providers should consider the vaccine and assess risk factors.

It remained unclear to Dr. Duchin why they would not explicitly state that a short-term traveler going to a high risk area, based on the criteria described, should be Category A.

Dr. Fischer replied that it depended upon how many groups they would want to split out. The previous discussion regarding adults was the same for children, which was to split the recommendation based on the clearest identified risk (e.g., duration of travel) to make a recommendation for all of those travelers, and to allow health care providers to have the information to consider for the other shorter-term travelers and make that determination based on their activities, which is a Category B recommendation.

Dr. Baker stressed that "should be considered" is really difficult for physicians to deal with. She did not disagree with a Category B recommendation based on the GRADE process, but thought the recommendation should be very clear about who is included. Family practitioners need to understand that they should give the vaccine. The term "should be considered" is a waffling phrase, which she receives calls about whenever it is put in the Red Book.

Dr. Coyne-Beasley pointed out that the phrase "during the JE virus transmission season" is used a number of times, but providers may not know when that season is. She suggested perhaps including some guidance about the season timeframe.

Dr. Fischer indicated that seasonal information is provided in the recommendations and in CDC's international health travel recommendations, known as the Yellow Book. The Yellow Book includes a table by country that gives recommendations for the season and the areas of risk, and this is referred to in the published recommendations.

Dr. Turner (ACHA) directed a question to ACIP's insurance representative, pointing out that one of the slides indicated that private insurance plans generally do not pay for travel vaccines. As he understood the ACA, preventive services, including vaccinations, are now supposed to be included. He was not aware that travel vaccines were excluded, and he also wondered about the Medicaid population. Clearly, this raises implications for third-party payers and government agencies if, in fact, they have to cover it. Based on the data, it appears that 1 or 2 cases a year are being prevented.

Dr. Netoskie (AHIP) responded that when travel by the insured is required by the employer, the vaccine is generally covered. However, he was not able to clarify specifically at that time whether the vaccine is covered under ACA.

Dr. Pickering thought the vaccines covered under ACA include those that are recommended in the childhood and adult immunization tables.

Dr. Loehr (AAFP) agreed with Dr. Duchin, and suggested that the paragraph be revised and divided as follows:

> "JE vaccine is recommended for short-term (<1 month) travelers to endemic areas during the JE virus transmission season if they plan to travel outside of an urban area and have an increased risk for JE virus exposure (e.g., spending substantial time outdoors in rural or agricultural areas, participating in extensive outdoor activities, staying in accommodations without air conditioning, screens, or bed nets) (Recommendation Category A)."
>
> JE vaccine also should be considered for travelers to an area with an ongoing JE outbreak and travelers to endemic areas who are uncertain of specific destinations, activities, or duration of travel (Recommendation Category B)."

Speaking as a person with a travel medicine certificate and a travel medicine clinic, Dr. Grogg (AOA) indicated that JE vaccine is not typically reimbursed by insurance because it is rather expensive. Companies will pay for employees who they are traveling to these areas for work-related activities.

Dr. Smith (ACIP Medical Officer) indicated that when first speaking with Dr. Fischer about this, they learned that ACA covers routinely recommended childhood vaccinations, not travel vaccinations. She recently had some personal experience with this when she put her 15-year old daughter on a plane to Nepal where she is now. She investigated this in-depth, including talking with Dr. Fischer, and indeed discovered that the series costs about $500. Private insurance does not pay for this. Her daughter belongs to a large pediatric practice in Atlanta that does not even offer the vaccine, so she contacted a travel clinic to follow-up. She requested comments from Dr. Grogg or Dr. Gershman on the likelihood that a general practicing pediatrician would be called upon to give this vaccine and, therefore, interpret the recommendation or if the child would be more likely to go to a specialized travel medicine clinic that knows how to interpret the situation.

Dr. Grogg (AOA) replied that typically, the child would go to a travel medicine clinic. If a child needs Japanese encephalitis vaccine, they will probably need other vaccines such as yellow fever, which has to be administered by a CDC-certified clinic.

Dr. Sawyer made a motion to accept the recommendation as presented, with the change that Dr. Loehr recommended, that the first sentence become Category A and the second sentence remain Category B.

Dr. Temte pointed out that to be consistent with discussion in the past for wording, the second sentence probably should read, "JE vaccine may be used." They are trying to get away from "should be considered" as a phrase, and under Category B the phrase is "may be used."

Dr. Fischer reminded everyone that the recommendations shown were the actual existing adult recommendations, and they were voting on children. He requested clarity regarding whether ACIP was saying that the recommendations should be changed for adults as well, emphasizing that the review was not completed for that purpose. If the recommendation was changed as reflected in the discussion and motion, that would represent a change from the current recommendations.

Given the discussion, Dr. Harrison wondered why they should not change the first "should be considered" to "is recommended" and make it Category A.

Dr. Schuchat vaguely recalled this being discussed when ACIP was dealing with the adult recommendations. Since some of the discussion was focused on the one-third of cases occurring in people experiencing short-term exposure, she requested a reminder about the denominator and proportion of short-term versus long-term travelers. She thought part of the issue pertained to the focus on a small population for whom there should be adherence and a larger group for which the recommendation should be permissive based upon additional fact-finding.

Dr. Fischer replied that he presented these data in February. While he did not have those data with him during this session, he reminded everyone that there really are not very good data to allow them to distinguish that. Most of the data on travelers are based on entries to Asian countries. CDC conducted a survey at airports where people were asked about their itineraries, their planned duration of travel, and what they were going to do there. Based on that, about a quarter of the travelers surveyed at three airports in the US had either intention of long-term travel, or of spending the majority of their time in rural areas. That was a relatively small survey of hundreds of people. Millions of US travelers enter Asian countries, so that was an attempt to focus in on the people believed to be at truly increased risk of disease. Beyond that, Dr. Fischer knew of no other data that could offer an idea about the denominator and who would meet the higher risk category.

Dr. Temte emphasized that most clinical practices do not keep this vaccine available because it falls within the realm of travel medicine, and that the WG tried to harmonize the childhood recommendation with the preexisting adult recommendation.

Dr. Bocchini reiterated that the WG was very careful not to change the adult recommendations while making the recommendations for children, and felt that the language of the recommendation shown on the screen for a vote was more of a Category B-type recommendation based on the language ACIP now uses to make recommendations. At one point, the WG split these two sentences and had separate recommendations, but then put them back together to be harmonious with the existing adult recommendations.

Dr. Duchin maintained that it would be an improvement to separate short-term travelers at high risk, for whom his impression was that ACIP would recommend the vaccine be given not just "considered."

Dr. Bocchini agreed that they want people to consider the circumstances to make a decision, so over time the language needs to change to reflect that.

Dr. Fischer pointed out that the language addressed a wide range of travelers who have very short-term travel and are going one day to a rural area, versus people who are traveling for two weeks. That was how the WG felt there was variation. Regarding the wording "should be considered," the existing recommendation was voted on prior to the use of the GRADE process language. The wording used was based on the rationale at the time the recommendations were posed.

Dr. Bennett wondered whether this could be addressed partly by creating an algorithm that would be easy to follow and more specific for anyone trying to decide whether to give this vaccine.

Dr. Temte requested clarity about whether the motion was for the recommendation as presented by Dr. Fischer.

Dr. Sawyer thought guidance was still needed on that. He said he made the motion thinking about the childhood recommendation, so he did not consider that the adult recommendation would then be different. Thus, he was not quite sure how to handle that. His personal preference was to change the recommendation for children and adults, but he did not know whether they should or could do this in this session.

As Chair of the Adult Immunization WG, Dr. Coyne-Beasley did not think it would be appropriate to change the adult vaccination recommendation without consulting the WG.

Dr. Temte inquired as to whether there was a willingness to modify the motion.

Dr. Sawyer modified the motion to accept the language as presented for children, and to move this discussion forward in the Japanese Encephalitis WG and the Adult Immunization WG for possibly changing both later. Dr. Campos-Outcalt seconded the motion.

Dr. Duchin indicated that this was not acceptable to him.

Dr. Bocchini mentioned that the next task for the WG would be to update the guidelines to revise the statement for JE vaccination. He thought the comments made and questions raised would help the WG in reformatting this recommendation to read more like the discussion suggested. He thought the algorithm would help as well.

Dr. Loehr (AAFP) asked whether the intent for the vote was to change the wording to “should be considered.” He pointed out that the way the recommendation was phrased it made no comments regarding “adults” or “pediatrics.”

Dr. Bocchini clarified that essentially, they were just extending the age group for the existing recommendations. A Policy Note will be published to indicate that the age group has been extended, but the recommendations remain the same.

Dr. Fischer reminded everyone that when the existing recommendations were passed, two vaccines were licensed for use in the US in different age groups. The age group will be extended in the Policy Note, which will note the licensure. He also pointed out that while it may not be quite the algorithm Dr. Bennett suggested, there is a box that delineates recommendations and other consideration categories that essentially provides that type of detail.

Dr. Duchin expressed confusion and requested clarity. If the language presented applied to both adults and pediatrics, the barrier to changing the recommendation to indicate that short-term travelers at high risk should be vaccinated was unclear. That would cover both populations anyway, and there would be no reason to make the same change for adults.

Dr. Fischer replied that there was not a barrier. What was presented for a vote was to extend the existing 2009 recommendation for use of the vaccine in adults to include use of the vaccine children unless ACIP wanted to have different recommendations for the two age groups. If they voted on that, it would be applied to adults. The recommendations would then need to be

published in that way. Otherwise, CDC would simply publish a Policy Note stating that these recommendations are extended to the use in children.

Dr. Temte believed the comments from Drs. Coyne-Beasley and Campos-Outcalt were appropriate in terms of taking this back to the WG to assess the suggested change to "may be used" and to divide the first sentence, and then return their proposed recommendation about these issues to the full ACIP perhaps during the next meeting.

Dr. Keitel also expressed confusion, because to a certain extent it would depend on whether they all agreed that short-term travelers to high risk areas during the season of transmission would make ACIP say, "You should receive the vaccine." She appreciated Dr. Schuchat's comments about lacking the denominator data, because it may be that almost everybody is short-term, the risk is miniscule, and ACIP would not recommend it.

Dr. Campos-Outcalt pointed out that "high risk" is a relative term and was not sure he would use the term. He would say "higher risk," because it appears that "high risk" is pretty "low risk" regardless. To him, this was a B recommendation for which circumstances and risk should be considered based on the best available data before making a decision about whether to get the vaccine. He did not think he would recommend that everybody who meets the definition should get a vaccine.

Dr. Harrison liked the idea of voting to extend the age range during this session, and readdressing the existing recommendation during the next meeting.

Dr. Bennett requested clarity about the discussion of changing the wording. She was unclear about whether they were voting on the wording as it currently existed or with change.

Dr. Temte responded that they were voting on the wording as presented in the three slides, and that the proposed change to the phrase "may be used" would be addressed during a future meeting.

It was unclear to Dr. Karron why they would not this to "may be used" since that was the kind of language they were hoping to use for the future.

Dr. Temte clarified that the question regarded whether they could live for 4 months with "should be considered," and indicated that he was fine with either decision.

Dr. Bennett thought harmonization was of significant importance for a vaccine that would not be given very often.

Dr. Temte concluded that the nice thing was that they were quibbling over minor language points as opposed to the bigger picture, which he thought was testimony to how nicely the evidence was presented to ACIP by Dr. Fischer.

Vote: JE-VC Vaccination in Children

Dr. Sawyer made a motion to accept the language as presented for children, and to move the discussion forward to the Japanese Encephalitis WG and the Adult Immunization WG for consideration of potential additional changes that will be addressed in a future ACIP meeting. Dr. Campos-Outcalt seconded the motion.

The motion carried with 13 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

General Recommendations

Introduction

Dr. Jeff Duchin
ACIP General Recommendations Working Group Chair

Dr. Duchin reminded everyone that the General Recommendations document is published by the *MMWR* every 3 to 5 years, and addresses a broad range of immunization issues that are relevant to all vaccines as opposed to the vaccine-specific publications. The General Recommendations are intended to address topics that cannot be attributed to a single vaccine, but that are germane to the practice of immunization in general. The General Recommendations are directed to providers who give a large variety of vaccines every day, and who come from variable backgrounds and training (e.g., physicians, nurse-practitioners, nurses, pharmacists, medical assistants, et cetera). The General Recommendations are intended to provide resources through text, tables, and figures that can be used as a handy and easy to interpret reference. The last version was published in January 2011. A number of topics are being revised, including the following:

- ❑ Timing and spacing of immunobiologics
- ❑ Contraindications and precautions
- ❑ Preventing and managing adverse reactions
- ❑ Reporting adverse events after vaccination
- ❑ Vaccine administration
- ❑ Storage and handling of immunobiologics
- ❑ Altered immunocompetence
- ❑ Special situations
- ❑ Vaccination records
- ❑ Vaccination programs
- ❑ Vaccine information sources

The topics addressed during this session included *Preventing and Managing Adverse Reactions* and *Reporting Adverse Events after Vaccination*, which will be combined in one section in the new document. The combined section will address a variety of topics, including the following:

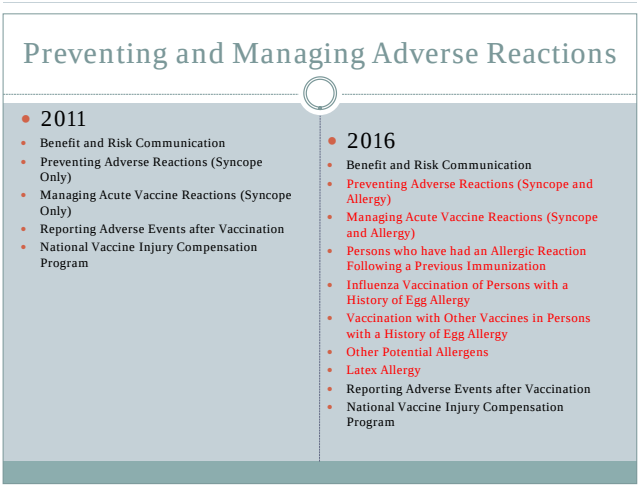
- ❑ Benefit and Risk Communication
- ❑ Preventing Adverse Reactions
- ❑ Managing Acute Vaccine Reactions
- ❑ Persons who have had an Allergic Reaction Following a Previous Immunization
- ❑ Influenza Vaccination of Persons with a History of Egg Allergy
- ❑ Vaccination with other Vaccines in Persons with a History of Egg Allergy
- ❑ Other Potential Allergens
- ❑ Latex Allergy
- ❑ Reporting Adverse Events After Vaccination
- ❑ National Vaccine Injury Compensation Program

The underlined topics were addressed during this session. The remaining sections to be addressed during the October 2013, February 2014, and June 2014 meetings include Vaccine Administration, Storage and Handling of Immunobiologics, Vaccination Records, and Vaccination Programs. Tentatively, a vote is anticipated on the entire document during the June 2014 meeting.

Preventing and Managing Adverse Reactions

Dr. Andrew Kroger
General Recommendations Working Group

During this session, Dr. Kroger provided an update on the proposed revisions for the *Preventing and Managing Adverse Reactions* section of the general recommendations. He reminded everyone that the definition of an "adverse reaction" is "a clinical outcome that is recognized and known to be caused by a vaccine." ACIP members were provided with two draft documents, one version with tracked changes and one clean version. During this session, Dr. Kroger referred to page and line references that corresponded to the clean copy when discussing major changes to this section. The differences in the 2011 versus the 2016 versions of this section are reflected in the following table:



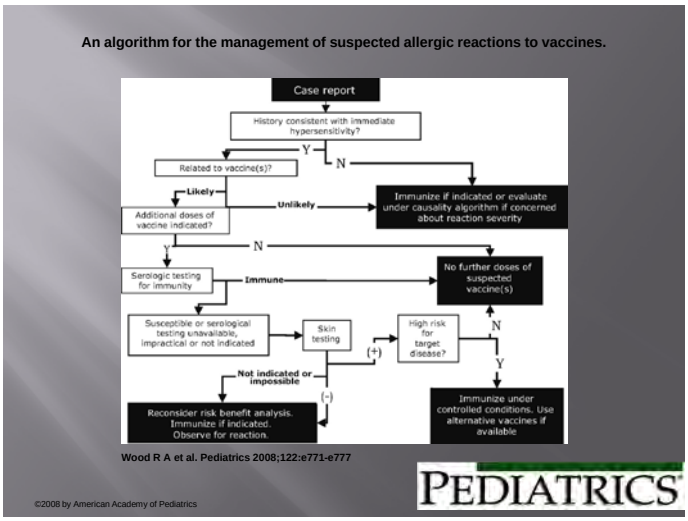
The *Preventing and Managing Adverse Reactions* section from 2011 focused on syncope only. The 2016 version will keep the syncope content, but will transfer the entire discussion on allergy from the *Special Situations* section of the document to this section. This is not new policy. Instead, it is the movement of content from one section to another. The WG made minimal changes to the *Benefit and Risk Communication*, *Reporting Adverse Events After Vaccination*, and the *National Vaccine Injury Compensation Program* sections. No changes were made to the syncope discussion at all.

An entirely new direction was not taken on allergy. Instead, the WG made explicit in the document some of the guidance that CDC and the General Recommendations have previously taken for granted. For example, previous versions of the General Recommendations have always presumed that providers have the capability to take an effective history for allergy, determine if that allergy was anaphylactic in nature, and determine what components may have been responsible. The revised document makes all of steps more explicit (Page 4, Line 14 and Page 5, Line 4). The WG was very careful to not explicitly state that allergy referral will always occur because this is not feasible for every provider.

Regarding the section on managing acute vaccine reactions, language was added that reads, "Vaccine providers should be familiar with identifying immediate-type allergic reactions, including anaphylaxis, and be competent in treating these events at the time of vaccine administration. Providers should also have a plan in place to contact emergency services, as circumstances often require help from outside the office" (Page 5, Lines 6-9). In addition to presuming that providers know what they are doing when someone reports an allergy, the WG also wanted to offer an option for providers to refer to an allergist or seek help from outside the office. Part of this involved a discussion about being able to contact emergency services when reactions occur. Some providers may be quick to refer to an allergist and may never need to manage such reactions, but a description of symptoms is included in the revised document. Page 5, Lines 10-11 contains specific symptoms and signs, including local or generalized urticaria or angioedema, respiratory compromise due to wheezing or swelling of the throat, hypotension, and shock.

This section was developed after consultation with allergists who reviewed the document and made some changes. They were very helpful, especially with regard to the need to reiterate that, "For respiratory or cardiovascular symptoms or other signs or symptoms of anaphylaxis, immediate intramuscular epinephrine is the management of choice" (Page 5, Line 20-22). The allergists revealed that there have been cases in which providers have withheld epinephrine because they felt that a patient's underlying condition contraindicated the administration of epinephrine, with the understandable complications that have occurred from anaphylaxis. While the WG thought it was important to strengthen that language, separate tables will be included for adults and children with additional diagnostic criteria and additional treatment options beyond epinephrine [Lieberman P, J Allergy Clin Immunol 2010; Kelso JM, J Allergy Clin Immunol 2012].

With regard to screening, there are specific discussions regarding people who have had an allergic reaction following a previous dose of vaccine. The essence of this section is a carryover from the 2011 version of the document, with the inclusion of a referral to Robert Wood's article in *Pediatrics* in 2008 regarding what to do if a patient reports allergy following a prior dose of vaccine—not a component to a vaccine. A specific algorithm is to be applied to identify whether symptoms are anaphylaxis; ascertain risk of disease; apply skin tests (skin prick, intradermal vaccine dose); and vaccinate under a control protocol, based on results of skin test. The algorithm from the Wood article is pictured as follows:



While not discussed in great detail in the WG, there has been an ongoing programmatic discussion about skin testing when applied generally to the issue of allergy and whether vaccine should be used as a diagnostic tool in this manner. When skin prick and intradermal tests are combined, the amount of vaccine used in this process suggests that one whole dose of vaccine is being used to carry out all of these processes according to the allergists (e.g., diagnosis and controlled vaccination/immunization if the decision is made to protect the patient). This is not really extra vaccine, which has been a concern. All of the doses are subdivided to administer smaller than the recommended dose amount, which is an acceptable practice. It is all being given on the same clinic day, so there is no concern about repeating doses that might be deemed invalid in this circumstance. This algorithm, which appeared in the 2011 document, will remain in the new document.

There is also a discussion in the new document regarding patients who report an allergic reaction following various components. The guidance is specific to each vaccine and is not generalizable. For example, skin prick testing is not recommended for influenza vaccination following a history of allergy to egg, but is recommended for yellow fever vaccine following a history of allergy to egg consumption. This discussion in the new document will closely follow the discussion in the influenza vaccine statement. There is a large section in the document beginning on Page 7, Line 6 through Page 9, Line 5 in which this is addressed. There was discussion within the WG regarding whether to focus on this in the revised document, or if it should be left to the influenza vaccine statement. This section will remain for several reasons. First, when discussing general vaccination, influenza vaccine is now one of the most broadly administered vaccines in various age groups. While pediatric influenza recommendations were first issued in 2004, by 2010 there were recommendations for everyone 6 months of age and older. Over time, there has been increasing attention to allergy in the screening process for influenza vaccine because there will be a lot of attention to first-time recognition of allergy on the part of providers generally. This first-time recognition will likely occur among infants and children with respect to influenza vaccine. Therefore, it is logical to ensure that this discussion is included in the General Recommendations document when it is published. Since this will not be published until sometime between 2014 to 2016, it will be made congruous with the current influenza recommendations at the time of publications.

There is also discussion regarding egg allergy vaccines other than influenza vaccine, including yellow fever, varicella, and MMR vaccines (Page 9, Line 6 through Page 10, Line 10). Dr. Kroger acknowledged that he needed to do some additional work on the document, and that he had not separated this discussion out as much as he should from the discussion of influenza vaccine and egg allergy. Nevertheless, there will be a discussion with regard to these other vaccines. In terms of yellow fever, the history of egg allergy is relevant. A prick test (scratch test) is recommended prior to administration via desensitization. For varicella and MMR vaccine, the point is made that history of egg allergy is not relevant prior to using these vaccines.

Allergic reactions following receipt of other vaccine components (e.g., thimerosal, neomycin, latex) are also addressed. Dr. Kroger emphasized that he would ensure that these topics are clearly distinguished in the document. Latex has its own special section. This information is still valid, so it will remain in the new document. The message common to all three of these allergens is that contact allergy, known as a Type IV reaction, as opposed to immediate hypersensitivity allergy, is not considered a contraindication to administration of vaccines containing these components, unless the allergy is deemed severe. This is very important to address because generally, contact allergy is much more common than immediate hypersensitivity for these three components and will arise more often during the screening process. If allergy is deemed severe, there is language in the *Contraindication and Precautions* section of the document that was presented during the February 2013 ACIP meeting. The general contraindication "Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component" has not changed. It is very important to understand this because it does give some flexibility/discretion to providers and uses anaphylaxis as an example and not the only type of severe allergic reaction, and may give providers pause. Providers very well may construe other forms of allergy as contraindications, so this really offers discretion to a provider. This is good in the context of making general recommendations. Most contact allergy is usually not considered severe for the most part. There is one vaccine-specific circumstance with less flexibility, which is that any allergy that includes a respiratory component would be a contraindication to live attenuated influenza vaccine. For example, the influenza vaccine specific ACIP statement would probably contraindicate live attenuated influenza vaccine (LAIV) because history of wheeze within the past year is considered to be a contraindication. A specific preference for inactivated products is stated for that circumstance. That information is accounted for in the influenza-specific statement, and any changes in the General Recommendations will parallel the influenza-specific statement.

There are no appreciable changes from the 2011 General Recommendation statement regarding the reporting of adverse events after vaccination. The language in this section is based on policies and programs that are similar among various Department of Health and Human Services (HHS) agencies, and will match the official programmatic language for these programs and will receive appropriate vetting.

Discussion Points

Dr. Rubin said he had a general sense that an egg allergy was a much greater issue for yellow fever vaccine than for influenza vaccine. If so, he thought the language should be more clear that yellow fever vaccine not be given unless truly needed; whereas, for influenza this is much more nuanced and there is a lot more experience and there are more publications.

Since the General Recommendations are published only every 3 to 5 years, Dr. Sawyer inquired as to whether there is a statement to readers of the General Recommendations that they should also refer to vaccine-specific statements for the most current information.

Dr. Kroger replied that there would be citations and references. However, the question regards whether to include actual language in text that says "refer to the recommendations" versus just a citation that links to a specific reference in the End Notes. The General Recommendations WG has discussed this extensively, and this is done sometimes and sometimes not. Perhaps specific references should be made to specific ACIP statements in the text of the document.

Dr. Temte noted that many people access this electronically on the web, and wondered if hot links could be included that would take people to a statement on a specific vaccine for more detailed information.

Dr. Kroger replied that hot links do exist and that he will follow up to determine whether it would be possible to include these in the document.

Given that the sections are being revised one at a time, Dr. Keitel wondered whether interim recommendations would be published, such as is done for influenza.

Dr. Kroger responded that CDC used to have provisional recommendations that would allow them to put certain components of these major documents on line more quickly, but this is no longer done. One of the challenges with provisional recommendations from his perspective was that they went through an exhaustive clearance process that almost slowed down work on the primary document. Unless they made a radical decision to break this document up into completely separate documents, this could pose a similar challenge.

Dr. Keitel said it was her understanding that there was a difference in interim and provisional recommendations. If there is a major change in the allergy section, perhaps interim recommendations could be published from the General Recommendations document regarding allergy.

Dr. Pickering stated that if there were sections of the General Recommendations for which updates were needed, these updated recommendations could be presented to ACIP for approval and adopted by the CDC director. Notification of these updates could be placed in MMWR and a link to these updated recommendations could be provided in the electronic version of the most recently published General Recommendations and then incorporated into the next version of the General Recommendations. The status of electronic publication of the General Recommendations is under discussion.

Now that egg-free influenza vaccines are available, Dr. Hahn (CSTE) wondered whether consideration was given to adding specific language about that under the influenza egg-allergic section for either the mild or more severe allergic patients. It is not mentioned at all. In addition, a 30-minute observation period is a burden for a provider versus the 15-minute standard. It might be worth including as an option that if available, egg-free vaccine could be used.

Dr. Kroger thought this would be feasible , and they will want to ensure that it exactly mirrors the influenza vaccine-specific ACIP statement. It is challenging to define "egg-free" and that is still being worked out. The WG will follow exactly what the ACIP recommendations state.

Dr. Keitel indicated that technically, there is only one egg-free vaccine, which is the recombinant hemagglutinin vaccine. The issue is that most of the egg-allergies occur in children, and this vaccine is not recommended for children.

Dr. Fryhofer (AMA and ACP) noted that egg-allergy is a major topic since vaccines that could possibly contain egg are being administered to egg-allergic patients or subsets of them. She suggested making this stand out more beginning on Page 7, so that a busy practicing physician can find this information easily. On page 7, rather than saying "all but one of the influenza vaccines may have come into contact with egg protein" the actual product should be stated. While this information may seem repetitive to many people who do this all of the time, this is a big year for new vaccines in the influenza arena. On page 9, perhaps subtitles should be included for yellow fever, MMR, and varicella. As presented, this section appears to be all about influenza.

Dr. Kroger reiterated that he would fix the typesetting to separate those sections out.

Dr. Harriman said she liked the box with medical management of anaphylaxis, but in the boxes for infants, children, and adults there is nothing that states at what point the provider should call for emergency medical services (EMS). For example, how many shots of epinephrine should be given before calling? That would be very helpful, and a prompt referral to EMS would be preferable for a patient who is in trouble.

Dr. Kroger responded that the reference is to a very detailed table in the draft, which he sent an email to request permission to use. If granted permission to use it, adaptations may have to be made in terms of diagnosis and treatment. Part of the discussion in the WG regarded the inclusion of a sentence in the document to offer flexibility for providers to contact EMS if they did not feel they could fulfill all of the steps.

Dr. Harrison emphasized that they need to know when that is. It is not in the box for which permission is required either. It does not state, "At this point you've given 2 doses. Call EMS." It just goes on to discuss epinephrine infusion, which would probably never be done in an office.

Dr. Temte's impression was that when calling his nurse for the crash cart with the epinephrine, he would also have her call EMS. He requested that Dr. Brady or Dr. Loehr comment on the sensibilities of practitioners in usual care.

Dr. Brady (AAP) responded that as time has gone on, the interest in getting EMS involved is getting quicker and quicker. With the exception of the allergists, most pediatricians would call EMS.

Dr. Temte thought perhaps a comment could be made in the algorithm to state that in most clinical circumstances, the call for epinephrine is also an appropriate time to call for advanced services.

Pertussis Vaccines

Introduction

Mark Sawyer, MD
Chair, Pertussis Vaccine Working Group

Dr. Sawyer reminded everyone that the terms of reference under which the Pertussis WG is currently constituted are to:

- Review existing statements on infants and young children (1997), adolescents (2006), adults (2006), and pregnant and postpartum women and their infants (2008) and consolidate these into a single statement.

- Review new data on Tdap including:
  - Effectiveness of ACIP recommendations
  - Interval between Td booster and Tdap
  - Use of Tdap in adults ages 65 years and older
  - Pregnant and breastfeeding women
    - Use of Tdap
    - Cocooning strategies
  - Vaccinated HCP and need for post-exposure prophylaxis
  - Tdap revaccination
    - Pregnant Women

- Review updated epidemiology of tetanus and diphtheria

The WG has completed its work on the underlined items, and is finishing up the last two major terms of reference (e.g., Tdap revaccination and consolidation of four separate recommendations). The largest term of reference still to be addressed is to consolidate into a single statement the four separate recommendations that are in existence that relate to different pertussis vaccines. This is task is anticipated to be completed near the end of 2013.

There are currently two licensed Tdap products in the US (e.g., Adacel® by sanofi pasteur and Boostrix® by GSK). These are recommended and approved by FDA beginning at 10 or 11 years of age and up. One vaccine has no upper age limit (Boostrix®), while the other is currently licensed through age 64 (Adacel®). These are combined vaccines with diphtheria and tetanus toxoid, which to some extent limits the ability to use them repeatedly at short intervals. The current ACIP recommendations are for a single Tdap dose beginning routinely in adolescents aged 11 through 18 years, with particular emphasis on adolescents of 11 and 12 years of age. All adults should receive at least one dose of vaccine at age 19 years and older. Further guidance will be forthcoming on the timing of revaccination in persons who have received Tdap previously, which was the topic of this session. The only exception to this was the recent recommendation published in February 2013 that pregnant women should receive a repeat Tdap vaccination with each pregnancy. A decennial Td booster is recommended for those who have received 1 Tdap dose, with the exception of accelerated use of Tdap in wound management situations.

There are a number of ongoing safety activities that relate to the recent maternal vaccination. VAERS is engaged in ongoing monitoring of pregnant women who have received not only first, but also repeat doses of Tdap. The Vaccine Safety Datalink (VSD) is assessing available coverage data, and has initiated further safety studies to continue to evaluate this. The Clinical Immunization Safety Assessment (CISA) Project has some potential targeted prospective clinical studies under discussion.

Based on preliminary data from the VSD for the years 2007 through 2011, a relatively small percentage of pregnant women have received Tdap during pregnancy at 6.1% of all pregnancies and 7.2% of pregnancies ending in a live birth. Much of these data are driven by the California numbers, which beginning in 2010 in response to the very large pertussis outbreak at that time, the California State Department of Health recommended vaccination during pregnancy. This was initiated in a number of provider offices during 2010, such that the 2011 data for California reflected a Tdap coverage rate during pregnancy of 29.3%. If California data are removed from the VSD sites combined, the remainder of sites achieved only 1.6% coverage for 2011. None of these data reflect the updated ACIP recommendations that all pregnant women be vaccinated during pregnancy. It is expected that some of these data will be available by Fall 2013 and may begin to reflect how the new ACIP recommendations are taking hold.

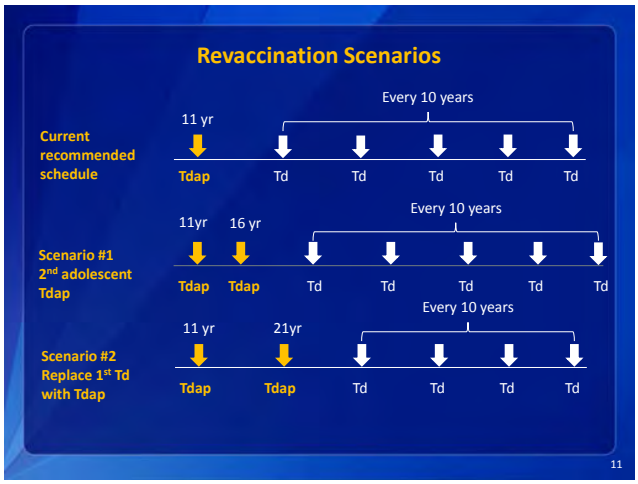
In terms of reasons to address Tdap revaccination, there has been an increasing burden of pertussis in US. Tdap vaccine was first recommended in 2005, with the decennial recommendation to follow. It has now been almost 10 years since Tdap was first recommended, making it timely to assess what role Tdap would play in revaccination setting. There are now growing data about the effectiveness and immunogenicity of first and second doses of Tdap.

As a reminder of the topics covered during the February 2013 ACIP meeting, there was a review of the resurgence of pertussis with an update on the national epidemiology. There was evidence of the effect of protection in adolescent populations, and the lack for a herd impact of that vaccination campaign, which has been underway for a number of years. In addition, the data were reviewed on Tdap effectiveness and waning immunity. The WG presented some options to ACIP at that time about what to consider for second doses of Tdap, and were guided to further investigate a second dose as opposed to multiple doses.

Presentation topics during this session included the following:

- ❑ Pertussis epidemiology in the US and Tdap vaccine effectiveness
- ❑ Tdap revaccination: antibody persistence, safety and immunogenicity
- ❑ Decision and cost-effectiveness analysis related to a second Tdap dose that the WG considered
- ❑ WG conclusions on a second Tdap dose
- ❑ The effectiveness of maternal Tdap programs in Australia and the United Kingdom

As a reminder, the following scenarios were presented during the February 2013 ACIP meeting for consideration of when and how a second dose of Tdap might be considered. The current recommendation, Scenario #1 that considers a repeat vaccination at 16 years of age followed by Td vaccinations thereafter, or Scenario #2 that considered a second Td vaccination 10 years after the first starting at age 21:



This has framed a lot of the WG's discussions since the February 2013 ACIP meeting, and was integral in the cost-effectiveness analysis related to a second Tdap dose.

Pertussis Epidemiology in the US and Tdap Vaccine Effectiveness

Anna Acosta, MD
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Dr. Acosta reported that although there has been a dramatic decrease in the number of reported pertussis cases with the advent of the vaccination program, pertussis remains endemic in the US. There have been substantial increases in the number of reported cases recently, especially in 2010 and 2012. More than 48,000 cases have been reported for 2012, with counts still coming in. This is the most number of cases since 1955. For 2013, there have been close to 7000 pertussis cases reported in the US. This is less than half the amount reported for the same time period in 2012 (16,344 in 2012). Despite the overall decrease in the number of pertussis cases thus far, some states are reporting increases over their 2012 numbers. For comparison, in 2012, every state except California had increases in pertussis cases over the previous year. In many states, the increase was greater than 3-fold.

As a reminder, the US pertussis vaccine program began in the 1940s with use of whole-cell vaccines. These were phased out in the 1990s and replaced with acellular vaccines. In 1992, acellular products were licensed and initially only recommended for the booster doses given at 15 to 18 months and 4 to 6 years. Subsequently, beginning in 1997, acellular vaccines were recommended for the entire childhood series. Tdap vaccines were licensed and recommended for adolescents and adults beginning in 2005. Pertussis vaccination coverage in the US is variable by age group. There has been sustained high coverage with pertussis vaccinations among children. With Tdap in adolescents, there have been substantial increases in coverage following the 2005 recommendation, with the most recent survey showing 78% coverage. However, the adult Tdap vaccination program has not been as successful, and coverage remains low.

The burden of pertussis disease changes with age. Regarding the average incidence of pertussis by age over a 10-year time period, infants less than 1 year of age are the group most affected by pertussis. However, there is increased risk of disease among 7 through 10 year olds and adolescents in comparison with adults. In terms of the reported US pertussis cases by age and year during the last three national peaks (e.g., 2004, 2010, and 2012), children born in 1998 or later would have received all acellular vaccines. In 2004, the acellular cohort included children 1 through 6 years of age. Adolescents, however, made up a large proportion of the reported cases at this time. In response to this adolescent disease burden, the Tdap booster was recommended for all adolescents and adults. Following the introduction of Tdap, there was a decline in adolescent cases, but also an unexpected increase in 7 to 10 year old children. During the 2010 peak, these 7 to 10 years olds were among the first birth cohorts to have received all acellular vaccines. Their high case counts could be explained by waning protection of the acellular childhood series. In 2012, there continued to be an increase in the number of cases among 7 through 10 year olds. However, cases were now also elevated among 13 through 14 year olds, an age group again representing the first birth cohorts to have received all acellular vaccines. This was the first time an increase among adolescents had been observed since the introduction of Tdap.

In summary, pertussis incidence has been increasing over the last decade. There is a resurgence of disease among older school-age children despite high vaccination coverage with the primary series, and there is now an increasing incidence of adolescent disease despite recent Tdap vaccination.

Moving to a description of the study of Tdap vaccine effectiveness in Washington State, like many states across the country, 2012 was a record year for pertussis in Washington, with close to 5000 cases reported. There was an increase in the number of cases among 13 through 14 year olds, reflecting the national trends just shared. In Washington, acellular pertussis vaccines fully replaced whole cell vaccines for the childhood series in 1997, and therefore anyone 14 or younger received all acellular vaccines. Adolescents 15 years or older received a mix of whole cell and acellular vaccines. Again, these 13 to 14 year-olds are the first birth cohort to have received all 6 pertussis doses as acellular vaccines.

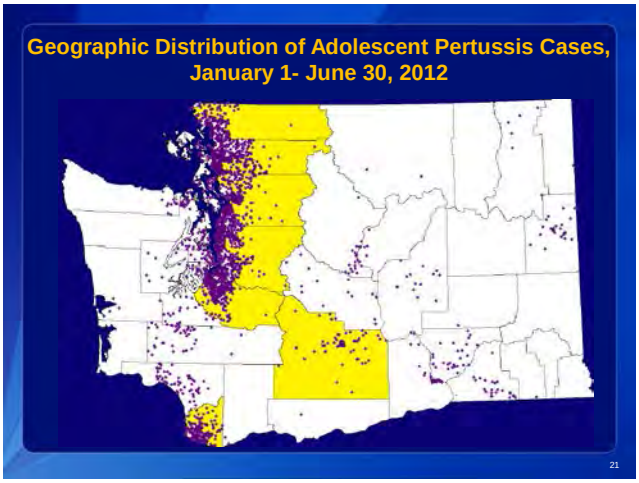
Previous estimates of Tdap vaccine effectiveness range between 66% to 78%. However, all of these studies involved adolescents who received some whole cell vaccines as part of their childhood series. At the time, the effectiveness of Tdap among adolescents who had received all acellular vaccines in childhood was unknown. The epidemic in Washington provided an opportunity to examine this question, so the CDC in collaboration with the Washington State Department of Health conducted a large-scale vaccine effectiveness study. The objectives of the study were to assess Tdap vaccine effectiveness among adolescents in Washington, and to estimate duration of protection among those adolescents who received all acellular vaccines.

Confirmed, probable, and suspect pertussis cases were included in the study. CSTE case definitions were used for confirmed and probable cases. Suspect cases were those with a positive polymerase chain reaction (PCR) test, and less than 2 weeks of cough or unknown duration of cough. The design was a matched case-control study. The study population was 11 through 19 year old residents of Washington born between 1993 and 2000. The study focused on the 7 counties with the highest case counts. All reported cases with cough onset from January 1 through June 30, 2012 were included. For each case, 3 controls were selected who were matched on birth year and provider. Potential controls were excluded while in the field if provider records noted suspicion of pertussis, the patient had been discharged from the clinic, or the last clinic visit was prior to 2005. Vaccination history was initially verified through chart

abstraction at provider offices and, if necessary, was supplemented by the state immunization registry, followed by parent phone interviews.

For a participant to be considered vaccinated, a Tdap vaccination date was confirmed in the provider records, or supplemented by the registry or parent interview. A participant was considered unvaccinated if no record of vaccination was found in the provider records or the registry, and Tdap non-receipt was confirmed by a parent. Additionally, a participant was considered unvaccinated if Tdap receipt was confirmed, but the vaccination occurred within 2 weeks of enrollment or after enrollment. Finally, a participant's vaccination status was considered unknown if Tdap vaccination was not documented in the provider records or the registry, and parent interview was inconclusive. It is important to note that these results are preliminary pending a final validation process. However, substantial changes are not expected to occur.

The following map shows all adolescent cases in Washington during the study timeframe. The 7 counties that participated are in yellow:



The study included 85% (945/1131) of all Washington adolescent cases and 74% of all Washington providers reporting adolescent cases (230/302). Data were collected for 94% of all adolescent cases reported during the study timeframe. Of the participants, 168 were excluded from the study population for reasons including being a prior pertussis case, having an out-of-state home zip code, receiving a misadministration of DTaP instead of Tdap, receiving a Tdap prior to 10 years of age, or receiving more 2 or more Tdap doses. Ultimately, 861 cases and 2485 controls were included in the study population. Of the 861 cases, 78% were confirmed.

With regard to the demographics of the study population, there was no significant difference in sex between cases and controls. However, 55% to 65% of ethnicity and race data were missing in provider records, and therefore is non-informative. Tdap vaccination status was verified in 94% of the study population. Of these, 83% were vaccinated and 11% were unvaccinated. Provider records contributed vaccine history for 76% of these participants, and the registry supplemented an additional 16%. Parent interviews only supplied Tdap vaccine history for 8%. Vaccination status could not be verified in 6% of study participants. These participants were excluded from the analysis. This left 826 cases and 2306 controls in the analytic population (3132 total). Among the 2761 participants who received Tdap, 73% were vaccinated at age 11, indicating adherence to current Tdap recommendations for vaccine receipt at 11 to 12 years of

age. In terms of the number of participants by age in the analytic population, the median age was 14 years. This is consistent with the elevated disease incidence in this age group.

Focusing the analysis specifically on the age groups that would have received all acellular pertussis vaccinations, this included participants 11 through 14 years of age who were born from 1998 through 2000. This was a total of 1682 participants. Of those in the acellular population who were vaccinated, nearly all received Tdap less than 3 years prior to study enrollment. The overall vaccine effectiveness for this acellular population was 65%, with 95% confidence intervals of 50% to 75%. This result was consistent with the previous studies Dr. Acosta showed. Regarding duration of protection, the initial effectiveness within 1 year of Tdap vaccination was 75%. Following this, vaccine effectiveness declined substantially. By 2 to 4 years post-vaccination, vaccine effectiveness was less than 40%. Supplemental analyses were performed to assess the stability of the estimates, which assessed the duration of protection. Duration of protection estimates when the acellular population is restricted to those with documentation of a complete childhood series were also assessed. The analysis was further restricted to those with a complete childhood series and confirmed case status. In all scenarios, results were comparable.

One question that remains unanswered is whether receipt of whole cell vaccine could influence the effectiveness of subsequent acellular booster doses. Although the chief objective of this study was to estimate vaccine effectiveness for adolescents who received all acellular vaccinations, the population currently at risk, the investigators were very interested in examining this issue. However there were limitations to the data that restricted the ability to perform this analysis. The population who would have received a mix of whole cell and acellular vaccines included adolescents 15 through 19 years of age born from 1993 through 1996. In this study, this was a total of 852 participants, a fairly small number. Secondly, among this mixed population, there was a greater proportion of participants with unknown Tdap vaccination status. Vaccination status could not be verified in this population, given that older study participants were less likely have vaccinations documented in provider records or the registry, and they were less likely to have visited a provider recently. This increasing trend of unknowns by age could lead to misclassification bias.

Finally, of those in the mixed population who were vaccinated, most received Tdap 4 to 5 years prior to study enrollment, which is a much different timeframe than that of the acellular population who were mostly vaccinated at less than 3 years prior to enrollment. For these reasons, vaccine effectiveness could not be reliably quantified by year since Tdap vaccination among this population. However, an overall vaccine effectiveness estimate was calculated for this population. The overall vaccine effectiveness for the mixed population was 41%. Again, this population was heavily weighted toward participants who received Tdap at least 4 years prior to enrollment, resulting in lower vaccine effectiveness. These findings suggest that there is Tdap waning among participants who received some whole-cell vaccines; however, the degree of waning could not be quantified. Additionally, no direct comparison of Tdap vaccine effectiveness or duration of protection could be made between the acellular and mixed populations, given the differences in the time since Tdap vaccination.

In summary, among adolescents who received all acellular vaccines, Tdap demonstrates modest effectiveness but has substantial waning with time. This waning is consistent with the observed epidemiology. These data on vaccine effectiveness helped inform the decision analysis for Tdap revaccination.

Discussion Points

Dr. Harrison inquired as to whether Dr. Acosta knew the frequency of pertactin mutants in the population and whether there was any impact on vaccine effectiveness.

Dr. Acosta responded that this study did not evaluate this.

Tdap Revaccination: Safety and Immunogenicity

Jennifer L. Liang, DVM, MPVM
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

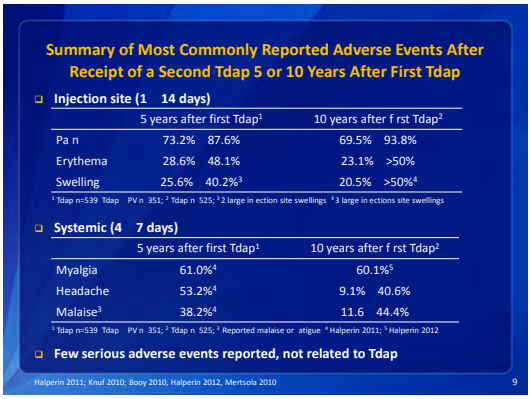
Dr. Liang reported that for over a year, the working reviewed the following as they discussed considerations for Tdap revaccination of the general population:

- ❑ Epidemiology of pertussis and state of vaccination program
- ❑ Current Tdap policy and objectives
- ❑ Tdap vaccine attributes
    - Effectiveness/duration of protection
    - Antibody persistence
    - Revaccination
        - Safety
        - Immunogenicity
- ❑ Programmatic feasibility and acceptability
- ❑ Decision and cost-effectiveness analysis for a second dose of Tdap

During the February ACIP meeting, Dr. Tom Clark presented a summary of these data with the WG's conclusions and began the dialogue on Tdap revaccination. During the February session, the committee guided the WG to consider a second dose of Tdap instead of multiple doses. During this session, Dr. Liang presented a brief summary of safety data after receipt of a second Tdap, and data on the immune response to the vaccine including antibody persistence after the first Tdap and immune response to a second dose. These were previously presented to the committee in February.

Before presenting a summary of these data, Dr. Liang reviewed the sum total of published studies assessed by the WG. Studies from several countries have measured antibody levels after receipt of one dose of Tdap, either Adacel® or Boostrix®. Antibody levels for diphtheria, tetanus, and pertussis were measured at several intervals through 10 years after vaccination. Also reviewed by the WG were studies from other countries that evaluated the safety and immunogenicity of a second dose of Adacel® or Boostrix® at a 5- or 10-year interval after first Tdap. As a reminder, both pharmaceutical companies are conducting clinical trials of a second Tdap 10 years after the first dose. Sanofi pasteur's study for Adacel® is complete and was presented to the WG and summarized to the committee in February. GlaxoSmithKline (GSK) began a clinical trial for Boostrix® in the first quarter of 2013 and anticipates a report in 2014.

Safety data after receipt of a second Tdap at 5- and 10-year intervals were reviewed by the WG. The sum total of the most commonly reported adverse events after receipt of a second Tdap dose at a 5 or 10 year interval are listed in the following table:



Summary of Most Commonly Reported Adverse Events After Receipt of a Second Tdap 5 or 10 Years After First Tdap

- **Injection site (1 14 days)**

	5 years after first Tdap[1]	10 years after f rst Tdap[2]
Pa n	73.2% 87.6%	69.5% 93.8%
Erythema	28.6% 48.1%	23.1% >50%
Swelling	25.6% 40.2%[3]	20.5% >50%[4]

[1] Tdap n=539 Tdap PV n 351; [2] Tdap n 525; [3] 2 large in ection site swellings [4] 3 large in ections site swellings

- **Systemic (4 7 days)**

	5 years after first Tdap[1]	10 years after f rst Tdap[2]
Myalgia	61.0%[4]	60.1%[5]
Headache	53.2%[4]	9.1% 40.6%
Malaise[3]	38.2%[4]	11.6 44.4%

[1] Tdap n=539 Tdap PV n 351; [2] Tdap n 525; [3] Reported malaise or atigue [4] Halperin 2011; [5] Halperin 2012

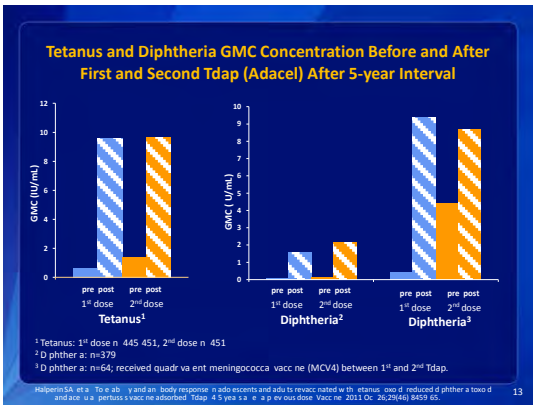
- **Few serious adverse events reported, not related to Tdap**

Halperin 2011; Knuf 2010; Booy 2010, Halperin 2012, Mertsola 2010 9

At the site of injection, the most commonly reported adverse events were pain, erythema, and swelling. For systemic adverse events, the most commonly reported were myalgia, headache, and malaise. Reporting rates were comparable at the 5- and 10-year interval, as well as generally comparable after receipt of a first Tdap. For both local and systemic adverse events, the majority were mild to moderate and self-limited. Of the few serious adverse events reported, none were related to the receipt of a second Tdap.

Dr. Liang summarized Tdap antibody persistence over time and response to a second dose, reviewing the geometric mean concentration (GMC) curves for diphtheria and tetanus antitoxin antibodies before and after receipt of Tdap in two populations or Td, and followed through 10 years. The Tdap product was Adacel®. Seroprotection for tetanus and diphtheria are defined as greater than 0.1 IU/mL. For diphtheria and tetanus, there are generally comparable curves for Tdap and Td. There is a boost at 1 month, with gradual decline above baseline at 5 years to near baseline at 10 years. By 10 years, the great majority were above seroprotective levels. For Boostrix®, the GMC curves through 10 years are similar, with the great majority above seroprotective levels out to 10 years at ≥0.10 IU/mL. Also included is the robust response to a second Tdap at a 10-year interval which is similar to the response after the first dose. Response to a second dose of Adacel 10 years after first Tdap is comparable to the first dose.

The following shows the GMC concentrations of pre- and post-vaccination for the first and second Tdap after a 5-year interval. The measured response is robust and similar to after a 10-year interval:



Note the differences between the two diphtheria graphs. For the group on the right, pre-first Tdap baseline was higher. The study authors note that this group was younger and had likely received a childhood diphtheria-toxoid containing vaccine more recently. The pre-second Tdap baseline was also higher. Before receipt of the second Tdap, this group received a quadrivalent meningococcal vaccine which is conjugated to diphtheria-toxoid [Halperin SA, et al. Tolerability and antibody response in adolescents and adults revaccinated with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed (Tdap) 4-5 years after a previous dose. Vaccine. 2011 Oct 26;29(46):8459-65].

In summary, the robust antibody response and persistence of diphtheria and tetanus antibodies are comparable to receipt of Td. Although antibodies wane, levels are protective out to 10 years. After receipt of a second Tdap, immune response to tetanus and diphtheria were robust at 5- and 10-year intervals. For acellular pertussis vaccine antigens, after a single dose of Adacel®, pertussis antibody levels peak after 1 month and then rapidly decline within the first year, with slower decline through 10 years. Similar curves are seen with adolescents who received Adacel®.

Unlike diphtheria and tetanus, for pertussis, there are no defined antibody levels which correlate to protection. After a single dose of Boostrix®, similar curves are observed though 10 years. Response to a second Boostrix® dose was similar to the response after the first at a 10-year interval. A second dose of Adacel® at a 10-year interval also showed similar response after a first dose. For Adacel®, after a 5-year interval, response to a second Tdap was robust, but was lower compared to the response after the first dose. But at 5 years, baseline for pertussis antibodies before a second Tdap was higher. For pertussis antibodies, there is a rapid decline during the first year with a gradual decline afterwards. After 10 years, the concentration of pertussis antibodies remained higher than pre-vaccination levels. It is know that antibody contributes to protection, but there are no defined antibody levels which correlate to protection. For a second Tdap, the immune response is similar to the first dose in cohorts boosted after 5 or 10 years, and in naïve groups receiving a first Tdap.

From the data presented thus far, the WG concluded that a second Tdap is safe and immunogenic at 5- or 10-year interval. However, Tdap vaccine effectiveness is 75% within the first year, but substantially wanes in 2 to 4 years. These vaccine attributes informed the decision and cost-effectiveness analysis.

Decision and Cost-Effectiveness Analysis: A Second Dose of Tdap

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Given that the process had not been described to ACIP in some time, Dr. Messonnier reviewed the procedures for reviewing presentations of economic studies. ACIP asked CDC economists to develop a process by which studies could be reviewed. In 2005 and 2006, an ad hoc committee of two CDC economists and one ACIP member did so. The procedure was formally adopted by ACIP in 2007, and since that time, over 20 studies have been reviewed. In the mid-2000s, economic studies of vaccines and vaccination were becoming more common and were more commonly presented to ACIP. The ACIP charter calls for inclusion of economic evaluations in committee deliberations, and prominent journals had already provided guidance related to economic studies.

The procedure that is used applies to studies presented to the full committee, its subcommittees, and its WGs. Researchers who wish to present results of economic evaluations to ACIP are required to submit two sets of materials. One is a manuscript describing the methods and results of the study, with more emphasis on methods and results and less emphasis on introduction and discussion. They must also submit the slides that they wish to use in their presentation. This process includes studies that are conducted by CDC economists, as well as non-CDC economics researchers. The materials must be submitted to the relevant ACIP WG chair, and to the CDC WG designated federal officer (DFO) at least 8 weeks before the ACIP meeting during which the researchers desire to present the study. Exceptions may be allowed for the 8-week rule under extraordinary circumstances. The studies undergo an anonymous peer-review that is managed by the NCIRD lead economist. The reviewers may consult with CDC subject matter experts (SMEs) to complete the review no less than 4 weeks before the meeting. The review results are then returned to the submitting researchers, with time for responses and revisions. For those interested, the following is a link to the *Guidance for Health Economics Studies* document that describes the procedures in detail: www.cdc.gov/vaccines/recs/acip/economic-studies.htm.

Dr. Kamiya then presented the results from the decision and cost-effectiveness analysis for a second Tdap for adolescent and adults. The framework for this analysis was presented to ACIP in February 2013. This analysis was done with CDC health economist Dr. Bo-Hyun Cho. This decision and cost-effectiveness analysis was performed because the incidence of pertussis among adolescents and adults is increasing, the ACIP Tdap recommendation is approaching 10 years since first being recommended, and available data show that Tdap duration of protection seems short. The objective of the analysis was to evaluate the cost-effectiveness of different scenarios of revaccination of Tdap for healthy adolescents and adults in preventing pertussis in this population.

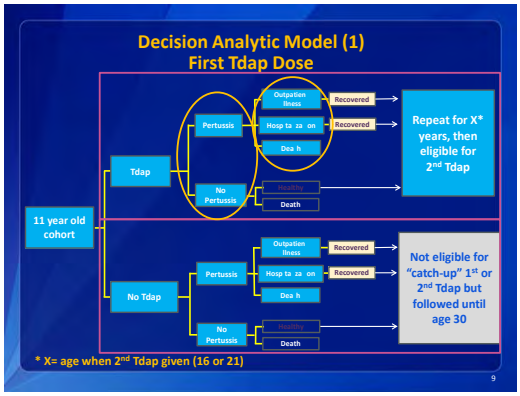
This model compares a Tdap revaccination strategy to no revaccination. "No revaccination" is defined as receiving one dose of Tdap at age 11, which is the current adolescent recommendation. The cohort population is healthy 11 year-olds followed over time for 20 years. Outcomes include number of cases, outpatient illnesses, hospitalizations, and deaths. Direct and indirect costs were examined from the societal perspective and quality adjusted life years (QALYs) were calculated.

In terms of the average incidence of pertussis by age from 2002 through 2011, there was higher incidence among adolescents compared to adults. This model used the weighted sum of reported pertussis incidence among vaccinated and non-vaccinated with the weight of Tdap coverage rate. Thus, the epidemiology of pertussis among different ages is an important consideration. Across all age groups in this analysis, the majority of cases (97%) are outpatient. Pertussis-related hospitalizations and deaths are rare [National Notifiable Diseases Surveillance System (NNDSS) and Supplemental Pertussis Surveillance System, 2011].

This model focuses on persons aged 11 to 30 years. The incidence for this age group in NNDSS is approximately 7 cases per 100,000 population. However, since NNDSS is passive surveillance, it is important to take into account the underreporting of pertussis cases. Several published studies have calculated the incidence of pertussis. Although the age range, inclusion criteria and diagnostic testing varied across these studies, the calculated incidence ranged from 66 to 507 cases per 100,000 person-years, which is much higher than the incidence from NNDSS. Another important consideration was to model realistic and feasible scenarios, and utilize the current immunization platform and practices for adolescents and adults. Based on these background considerations, two scenarios were chosen to evaluate the cost-effectiveness

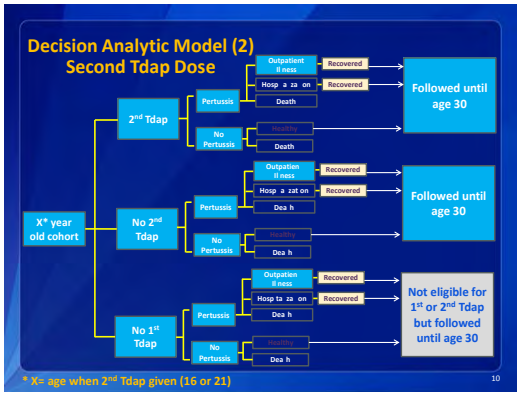
of a second dose of Tdap for healthy adolescents and adults. The first scenario is to add an additional Tdap dose for adolescents at age 16. This is based on the current epidemiology of pertussis, and also utilizes the current adolescent immunization platform, where a second dose of meningococcal conjugate vaccine (MCV4) is recommended. The second scenario is to replace the first decennial dose of Td with Tdap at age 21.

The following is the first half of the decision analysis model, with the 11-year old cohort either receiving or not receiving the first Tdap dose:



Only those who received the first Tdap are included in the revaccination group. In this analysis, persons who did not receive the first Tdap at age of 11 were not eligible for revaccination, but were followed until age 30. They were also not given a catch-up first dose when others received their second dose. Individuals from each group experienced either pertussis or no pertussis. The outcomes of outpatient illness, hospitalization, and death were assessed in those who experienced pertussis. Those who recovered from the illness or did not have pertussis were then evaluated for receiving a second Tdap dose.

The following is the second half of the decision analysis model, reflecting the second Tdap dose:



Depending on the scenario, either receiving a second Tdap at age 16 or 21, the revaccination eligible group was sorted based on the vaccine coverage rate for a second dose. As with the first dose, individuals from each group experienced either pertussis or no pertussis, and the same outcomes were assessed. This decision tree was repeated as the cohort population was followed over time.

The general parameters of the model incorporated disease incidence, population, disease outcomes, and discount rate. For the baseline estimate, disease incidence was based on the 10-year average incidence from 2002 through 2011. Population size was based on the 2010 US Census and incorporated the current age-specific natural death rate obtained from the 2008 Life Table from the National Vital Statistics System (NVSS). The outcome probabilities were based on the mean percentage of cases, with these outcomes also based on NNDSS data. The discount rate in the base-case was 3%. Discount rate is applied to express future outcomes in terms of present value.

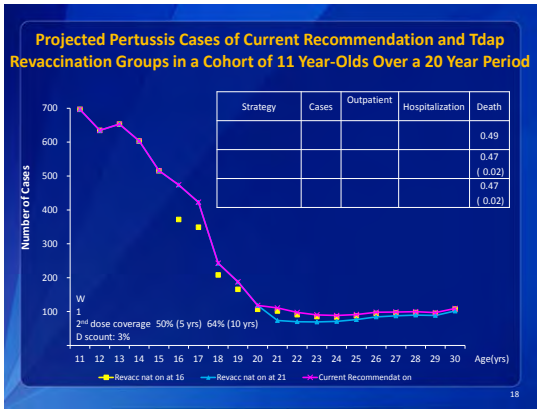
Parameters of the model related to the vaccine include vaccine effectiveness, waning of vaccine effectiveness, and vaccine coverage rate. Vaccine effectiveness and waning were based on the data from the Washington State investigation as presented by Dr. Acosta earlier. Waning of vaccine effectiveness was decreased by 15 percentage points each year post-vaccination. Vaccine coverage for the first Tdap was 78%, which is the 2011 Tdap coverage in adolescents 13 through 17 years of age from the National Immunization Survey-Teen (NIS-Teen). For the second dose at 16, coverage was 50%. This number was based on the assumptions. For a second dose at 21, coverage at 64% was based on current Td coverage in 19 through 49 year olds.

Cost parameters for this model are disease and vaccine costs. The average number of visits to a health care provider prior to diagnosis of pertussis and duration of cough was calculated from Enhanced Pertussis Surveillance (EPS) data. Length of hospitalization and disease costs were based on the MarketScan database used in a cost-benefit analysis of pertussis vaccination in adolescents and adults. Outpatient costs included treatment cost and prescription drug costs, such as antibiotics and cough suppressants. Hospitalization cost includes both hospitalization costs and any associated outpatient services. Productivity loss, or indirect costs, is the productivity lost because of death and is calculated based on economic productivity by age, so its value varied with the age of the cohort. Program costs included vaccination. A cost of $55.14 was used for the first Tdap dose and the second Tdap dose given at age 16. For the second Tdap dose given at age 21, a vaccine cost of $15.31 was used. This is the cost increase of Tdap relative to Td. The hourly median wage used for this analysis was $16.57.

To calculate QALYs, appropriate Health Utilities Index® (HUI®) had to be applied. HUI measures a person's preferences for specific outcomes on a scale of 0 to 1, on which 0 typically represents a state equivalent to death, while 1 represents the best imaginable health. From the study by Grace Lee, a mean HUI for mild coughing and severe coughing was calculated. In this model, the mild cough HUI from Grace Lee's paper was applied as outpatient HUI and severe cough HUI as hospitalization HUI.

There are several assumptions for this analysis. Although considered, acquired immunity after infection or vaccine herd immunity were not included because there are varying data on how long acquired immunity lasts and there are no data on the effects of Tdap vaccination on herd immunity. Also, adverse events following Tdap immunization were not included due to the low incidence of severe adverse events following immunization. Persons were not included who got pertussis but died from a different cause, given that the number of pertussis-related deaths in this age group is rare. As several clinical trials have shown, the immune response from a second Tdap is similar to the first dose. A higher response or booster effect is not seen. Finally, although the hospitalization rate among vaccinated and unvaccinated persons would likely be different, the number of hospitalized cases is so small in this study population, it was assumed that these two groups have the same hospitalization rate.

Turning to the results, the following line graph shows the projected number of pertussis cases calculated by the model for the current recommendation and two Tdap revaccination scenarios in a cohort of 11 year-olds over a 20-year period:



The pink line is the number of cases following the current recommendation. The yellow line shows the projected number of pertussis cases calculated by the model for revaccination at age 16. It falls behind the pink line until before receiving the second Tdap. The area between the pink and yellow lines indicates the decreased number of cases due to second Tdap. Likewise, the light blue line shows projected cases for revaccination at age 21. The light blue line falls behind the pink line until being revaccinated and the area between two lines indicates the decreased cases by revaccination. The number of cases calculated by the model is shown in the table. If the 11 year old cohort is followed for 20 years, revaccination at age 16 prevents 284 more cases compared to the current recommendation and 168 more cases are prevented by revaccination at age 21. The majority of cases are outpatient illnesses.

Regarding the cost associated with Tdap revaccination, because revaccination at age 16 is adding a new dose to the current program, the program cost is higher compared to the scenario of giving a second Tdap at age 21. The total costs, or the sum of vaccine program cost, direct cost, and indirect costs, are the highest when revaccinated at age 16. The total cost is approximately $260 million, and the difference between the cost for current recommendation is approximately $77 million. For the age 21 revaccination scenario, total cost is about $205 million, which is about $23.5 million more than the current recommendation.

In terms of the number of cases prevented for different outcomes in two scenarios compared to the current recommendation, as a reminder, Tdap at age 16 will prevent 284 cases compared to the current recommendation. This is about 5% of cases prevented by the current recommendation. Of prevented case, 98.6% are outpatient illnesses and very few severe cases that would require hospitalization or result in death are prevented. This trend is similar for a second Tdap at 21 years of age. An additional 3% of cases are prevented compared to the current recommendation, and the majority of the cases were mild.

Based on these numbers, the cost per cases prevented and cost per QALY saved were calculated for each revaccination scenario compared to the current recommendation. Net costs are the difference of total cost between current recommendation and each scenario. The cost per case saved for revaccination at 16 years old was about $270,000. For revaccination at 21 years old, it was approximately $140,000. The cost per QALY saved was $16.7 million and $14.7 million for each scenario, respectively.

One-way sensitivity analyses were also conducted for several variables with a variety of ranges (e.g., vaccine coverage rate, waning of vaccine effectiveness, under-reporting). For vaccine coverage rate, because uptake of a second dose at age 16 is unknown, a range from 25% to 100% coverage was assumed. Also used was 40% to 90% coverage for revaccination at 21 years old. For waning of vaccine effectiveness, a 10% to 25% range was assumed. For under-reporting, 100 times under-reporting was applied based on comparison between NNDSS data and literature review. However, it is believed that severe cases are well-captured by NNDSS compared to the mild cases. Thus, NNDSS and the National Impatient Surveillance data were compared for pertussis-related hospitalization and death cases. From this comparison, 2 times under-reporting was applied for the severe cases calculation.

With regard to the results of the one-way sensitivity analysis, for each parameter, the number of cases prevented by each scenario was compared to the current recommendation under the same condition. As a reminder, under the baseline analysis condition, revaccinating Tdap at age 16 prevents an additional 284 cases and 168 additional cases are prevented with a second Tdap at age 21. The number of prevented cases changes subtly under different vaccine coverage rate and waning of vaccine effectiveness scenarios. However, if under-reporting is taken into consideration, the number of prevented cases changes greatly. Because under-reporting of cases has a strong impact on the analysis, Dr. Kamiya presented the summary of the one-way sensitivity cost-effectiveness analysis with the under-reporting factor being applied. In terms of the results of calculated cost per cases prevented and cost per QALY saved applying under reporting factor, even though the number of cases prevented is large the cost per QALY saved still remains high.

Finally, several multivariable sensitivity analyses were performed. Dr. Kamiya presented the results from the most favorable conditions which include high coverage rate for second Tdap dose, less waning of vaccine effectiveness, and applying the under-reporting factor. For the multivariate sensitivity analysis under favorable conditions, the number of cases prevented became larger compared to the current recommendation scenario under the same condition, but due to a higher vaccine coverage rate for the second Tdap dose, the net costs remains high. Thus, the cost per QALY saved is still $200,000 for revaccination at age 16 and $240,000 for age 21 revaccination. Results from this model raised the question about the need for the first Tdap at age 11. Using the same model under baseline conditions, without the first Tdap at age 11, the number of cases is more than two times the number of cases when Tdap is given at age 11 and declines as the cohort gets older. By age 20, the number of cases becomes similar to the rest of the scenarios.

The main conclusions that can be drawn from this analysis are that a second Tdap results in a modest decrease in the number of cases. The majority of the cases are outpatient illnesses. A second dose at age 16 will prevent more cases than the current Tdap program or a second dose at age 21. However, adding an extra dose to the immunization program will result in higher program costs. A second dose at age 21 is at less costly, but less disease is prevented. Both revaccination scenarios had high costs per QALY saved. Based on one-way sensitivity analyses, incidence is the main driver of cost-effectiveness in this model. As incidence increases, the cost-effectiveness of a second Tdap increases. Even under the most favorable conditions for multivariate sensitive analysis, a high cost per QALY saved is still observed. Finally, the current Tdap program does have an impact on preventing pertussis cases.

Work Group Conclusions for on a Second Dose of Tdap

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Dr. Liang indicated that after review of the data on Tdap revaccination, the WG was not in favor of recommending a second Tdap. She presented the working considerations and rationale for not recommending a second Tdap for the general population.

The WG recognizes the increasing burden of pertussis in the US and the need for an effective strategy to reduce this burden, but the epidemiology shows that the burden of pertussis disease changes with age. The highest morbidity and mortality of pertussis is in infants. There is a strategy in place, which is to vaccinate pregnant women during each pregnancy to decrease pertussis morbidity and mortality in this age group. There are encouraging data from Australia and the UK which support this strategy. For adolescents and adults, the majority of cases are outpatient illness. Pertussis related hospitalizations and deaths are rare.

As a reminder, Tdap is FDA-approved for single use only. Therefore, a recommendation for additional doses would be "off label." Clinical trials support that a second Tdap would be safe and immunogenic at a 5- or 10-year interval, yet the WG recognizes the limitations of this vaccine. The initial immune response to a second Tdap is similar, but not greater than the response to the first Tdap. Diphtheria and tetanus protection would persist for 5 to 10 years post-Tdap, but pertussis antibodies decline rapidly after the first year, suggesting that protection wanes, which would likely limit the impact of a second Tdap on disease burden.

As the Washington Tdap evaluation shows, Tdap protects against pertussis, but this protection wanes in a few years after receipt of Tdap. Waning after a second Tdap would likely be the same. The decision and cost-effectiveness model suggests that with a second Tdap, the reduction of disease burden would be limited. As a reminder, this model followed persons from 11 through 30 years of age. In this age group, the model showed that the majority of cases are outpatient illness, hospitalizations are few, and deaths are rare. Although cost-effectiveness improves if under-reporting is assumed, the proportion of cases prevented is small. Under baseline conditions, by adding a second Tdap at either 16 or 21 years of age, the preventable burden compared to the current recommendation ranges from 3% to 5%. If the most favorable conditions in the model are considered, the preventable burden does not greatly improve and ranges from 4% to 10%.

The WG concluded that the data do not favor a general recommendation for a second Tdap and therefore does not favor a universal recommendation. The WG supports letting stand the current recommendation for a single dose of Tdap in adolescents and adults. The WG also strongly supports focusing efforts on preventing pertussis in infants through the existing ACIP recommendation to vaccinate pregnant women during each pregnancy. Though a universal recommendation for a second Tdap is not favored, the WG is willing to consider revaccination of "at risk" populations, but anticipates similar limited impact on overall disease burden. In closing, the WG requested ACIP members' to offer feedback regarding not recommending a universal second Tdap, and whether additional Tdap should be considered for "at risk" populations and, if so, who should be included.

Discussion Points

Dr. Duchin noted that the response to pertussis toxin seemed to be much lower than to the other antigens, but his understanding was that this might be the most important toxin. The conclusion was that the antibody response is similar for the first and second doses, but with such a diminished response to pertussis toxin, perhaps this really is not equivalent because the pertussis toxin is so diminished. This led him to wonder whether the boost would be even less effective than the primary, which is only modest.

Dr. Liang responded that the statement was in terms of the overall group of pertussis antibodies, but that the response to pertussis toxin was lower at a 5- and 10-year interval.

Dr. Clark (SME) added that the boost certainly would not be higher than the primary dose. There is some suggestion and belief that pertussis toxin is a critical antibody in protection, and there is a general concern that because there is not a response to very high levels, pretty low levels would occur fairly quickly.

Dr. Duchin pointed out that with this modestly effective vaccine and the resurgence of pertussis being observed in fully immunized younger children, more older people will be exposed to naturally occurring wild type pertussis. He wondered about the implications of that on the modeling when more people have preexisting natural type immunity subsequent to large outbreaks, whether that was accounted for in the model, and if a booster dose would be expected to be even less effective.

Dr. Liang replied that the model was limited to assessing the 11-year old dose, so the epidemiology that followed was from 11 through 30 years of age. The incidence data included some of the influences from that, but the model specifically targeted the younger age group receiving it. There are very few data regarding the impact of Tdap in the older population.

Dr. Clark (SME) added that there was some debate about this. Seroprevalence studies show that people seroconvert over the course of a year. Given that even 6% seroconversion is much lower than vaccinating 90% of people, the decision was made to exclude it from the model because it makes it easier. Odd things occur in terms of a transmission model. The experience of people acquiring disease currently, their boosting response, and to what degree that protects against infection are unknown.

Dr. Plotkin said that while they had heard some very interesting data, essentially the conclusion had been a very pessimistic one. In effect, the conclusion was that nothing could be done about adolescent and adult pertussis. That does not take into account the impact on confidence in vaccination. There are a number of possibilities regarding how the current pertussis vaccine can be improved upon. While there may be studies underway, he had not heard attempts to better define the correlates of protection against pertussis. That is essential, because it is probably going to be impossible to conduct a controlled efficacy study on a future vaccine for ethical and practical reasons. Therefore, licensure will depend upon the establishment of correlates of protection as was the case in licensing the current Tdap based on the antibody results from the 1990s European trials. He expressed his hope that prospective studies are in course to define those correlates, including estimation of cellular immune response, cytokines, et cetera. In addition, an issue has arisen based on baboon studies, which is the possibility that is shown in the baboon model that the acellular vaccines do not prevent nasal pharyngeal infection and that therefore, the circulation of the organism continues unabated. That could be relatively easily established in the current epidemic situations, and is extremely important to do.

He agreed that the current vaccine would not do the job, but it is essential to establish how to improve those vaccines.

Dr. Warshawsky (NACI) noted that the cost of vaccination at 16 versus the cost at 21 years of age differs substantially because it adds on to the Td. She wondered whether consideration was given to the fact that if vaccination is administered at 16, the next Td would be deferred to 26 instead of 21 years of age and that this could eventually result in some savings because there would ultimately be less Td.

Dr. Kamiya responded that they did not.

Dr. Warshawsky (NACI) requested clarity regarding why consideration was not given to the fact that there may be decreased transmission.

Dr. Kamiya replied that there were no good data to apply.

Dr. Bennett requested further information regarding the decision not to include the impact on adolescent and adult populations as directly due to the lack of data. It could be that naturally occurring disease would make more people immune and decrease the efficacy. But it also could be that because adolescent and adult disease are so underestimated, it would have an impact of improving the cost-benefit. In addition, it also appeared that the only productivity costs considered in the model were those due to premature death. She wondered whether any other costs had been considered, such as public health costs, parental costs, employee costs, and so forth.

Dr. Kamiya responded that only costs associated with premature death were included.

Dr. Bennett stressed that the public health costs are enormous and perhaps should be taken into consideration in the model.

Dr. Temte added that the costs for home quarantine for a child or an adult and the loss of work for an adult if he or she has to stay home for the obligatory five days are also worthwhile considerations.

Dr. Turner (ACHA) thought the cost per QALY represented the absolute worst case scenario. Factors such as transmission to others, the impact the disease has on others and other families, and the economic impact on families represent a pretty overwhelming burden on society. He was having difficulty reconciling the fact that at the beginning of the presentations there was discussion about 50,000 cases in 2012 scattered predominantly among adolescents, while the cost-effectiveness analysis indicated that 284 cases would be saved. However, each cohort in 2012 had between 2000 to 3000 cases and it seems that giving those adolescents a second dose would have prevented this. It seemed to him fairly primitive data were used for the cost-effective analysis. He suspected if it were possible to collect all of the other data, the costs would decrease substantially.

Dr. Liang responded that the WG struggled with trying to incorporate indirect protection, but they are no data to suggest at this time what the actual prevention would be with indirect protection with vaccination.

Dr. Clark (SME) stressed that there are no data for indirect protection, and there are some data for absence of indirect protection. In the surveillance data, no impact was observed of adolescent coverage on infant or younger disease. Presumably over time, there is just more and more disease and no suggestion yet that that is protecting cohorts of children. If incidence was increased by 100-fold, the cost-effectiveness would still be inching toward favorable.

Dr. Turner (ACHA) wondered whether this meant a willingness to tolerate 50,000 to 100,000 cases per year forever.

Dr. Clark (SME) responded that the conclusion from the model is the limited impact in reducing that burden by another dose.

Dr. Sawyer emphasized that not everything was worst case. Among the assumptions was 100% vaccine coverage, which is a long way from current coverage, and only 10% waning per year in antibody effectiveness, which is much less than currently observed.

While beyond the scope of what the WG was considering, given the short duration of protection for the vaccine, Dr. Jaffe (CDC) wondered whether there was still really a rationale for the use of a first dose of Tdap in adults other than pregnant women.

Dr. Clark (SME) replied that there is a much greater impact of dropping the 11-year old dose than one might expect based on the benefits of an additional dose. Coverage with the adult dose is minimal, and the WG did not reconsider the adult recommendation.

Dr. Schuchat pointed out that the highest priority for the program currently is pregnancy vaccination, a subset of the adult doses that are not at the level preferred yet. The issue of what effect raising adult coverage would have on morbidity is difficult to determine, given that the surveillance is not as complete for that population.

Dr. Salisbury (DOH, UK) wondered whether the WG considered that either of these strategies might push the age of infection to the right, and then cause more infant infections, because it is the wrong population who will then be getting pertussis.

Dr. Kamiya responded that consideration was given to vaccinating at age 13 when there was higher incidence at age 16, but it was believed that this would push infection to the right as Dr. Salisbury noted. The scenario must be realistic, so given the platform at age 16, this was utilized to determine what the numbers would be. That is, vaccinating might result in the graph shifting to the right.

Dr. Salisbury (DOH, UK) emphasized that this was exactly his worry. If the cases are shifted to the right, most infections may be caused in infants.

Tom Clark (SME) replied that protection wanes and may reduce the burden temporarily, but it will continue to increase. The phenomenon seems to be what happens early, so children who did not receive acellular vaccination seem less protected and are already at higher risk. The strategy to prevent disease in the most vulnerable group is the pregnancy vaccination. That is the only scenario that is going to reduce the risk in the youngest groups.

Dr. Hosbach (sanofi pasteur) clarified that sanofi pasteur is the manufacturer of Adacel®. A benefit of 65% over two to four years of the bacterial vaccine is a real value to the individual for protection, which should be kept in mind. Consideration must also be given to whether laboratories have changed, so the WG should question the groups doing those tests to ensure that they are apples-to-apples. He inquired as to whether the modelers included the cost of PCR testing, and if that could be reduced in an adolescent cohort over two to four years if that would add to a cost-benefit for this immunization. PCR tests cost approximately $100 each, and it would be interesting to know how much that has increased over the years.

Dr. Kamiya responded that this was not included.

Regarding the comments about public health and the cases that will continue to be observed until there are better vaccines, Dr. Harrison pointed out that some public health approaches to pertussis might change. For example, California does not necessarily recommend post-exposure prophylaxis for all contacts. Instead, they try to prioritize this to high risk contacts. Local health departments are told that they do not need to call everyone back in two weeks to find out if they are still coughing. Efforts such as these can save some on public health. Even with the issue of PCR, more clinicians may treat and diagnose clinically in the setting of a lot of cases, and perhaps PCR testing is not always necessary other than to confirm a case for public health or whatever other reasons might be necessary. She thought many other issues needed to be considered in this era of increasing pertussis.

Building on what Drs. Jaffe and Salisbury said about the issue of the routine adult dose of Tdap, Dr. Karron wondered whether it might be worthwhile for the WG to consider the standing recommendation. The US does not do a particularly good job of getting this dose to all adults. Perhaps efforts could be better targeted on particular groups such as pregnant women, cocooning strategies, and healthcare workers versus focusing on universal immunization.

Dr. Temte pointed out that little is known about how much pertussis there is based on regular population surveillance. A piece that is missing is the effect of vaccine in terms of modification of a course of pertussis in an individual who has been immunized and infected, and whether that alters the course even if someone does become ill with pertussis, and the ramifications of that. ACIP was also asked to consider additional Tdap for at risk populations, and how the at risk population should be defined.

Dr. Schuchat cautioned about generalizing what is being learned about performance of Tdap in teenager to adults at this point, because most adults who received a vaccine as children received a whole cell vaccine . The performance of Tdap and its duration of protection may not be what is being observed in the Washington teenagers who were primed with acellular vaccine. Because of low coverage and the lack of consistent diagnostics, she did not believe the data were very good yet in terms of performance of Tdap in the adult population, including data regarding duration, which might help to reconcile which subsets should receive a focus beyond pregnant women.

Dr. Pickering pointed out that one thing about populations is that when assessing vaccines, patients with primary and secondary immune deficiencies are considered at high risk. He did not believe there to be any specific primary immune deficiency for which pertussis is an organism of concern. However, people who have pulmonary fibrosis, pulmonary hypertension, cystic fibrosis, or chronic obstructive pulmonary disease (COPD) will not do well if they acquire pertussis. He wondered whether consideration had been given to specific high risk groups with

pulmonary or cardiovascular conditions that may predispose them to significant morbidity or death if they are infected with pertussis.

Dr. Loehr (AAFP) noted that the data showed a decrease of disease, but it was not clear whether it decreased the incidence of infectiousness. That is, could someone have the disease and still be infectious?

Dr. Clark (SME) responded that only the effectiveness of vaccine against preventing disease that meets the case definition was being measured, and not whether someone is affected but mildly symptomatic, infected but asymptomatic, or infected but more or less likely to transmit.

Representing the high risk children for whom she cares, Dr. Englund (PIDS) indicated that children with underlying heart and lung disease are already covered by the pediatric recommendations. Children with cancer, immunodeficiency, or transplantation are already covered by many of the transplant guidelines by the American Society of Transplantation (AST) and the Blood and Marrow Transplantation (BMT) societies in terms of family vaccinations, which is often one dose of Tdap vaccines. She did not believe much needed to be added, but perhaps the recommendations should be more explicit that immunizing family members of children or of patients who cannot respond to vaccine is recommended. In most pediatric centers, this is routine for children with cancer, immunodeficiency, or transplantation. These are actually highly compliant people.

Maternal Tdap and Cocooning: The Australian Experience

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Dr. McIntyre reported on the Australian experience with cocooning, beginning with a background epidemiology of pertussis to put the Australian situation in perspective. He also discussed cocoon programs in Australia, and a case control study in New South Wales that has the same population as the State of Washington.

In terms pertussis cases counts back to the early 1980s, as reported to WHO for Canada, the UK, Northern Ireland, US, and Australia, the situation in 1981 was very different from what has occurred over the last decade. Australia has been ahead of the US in case counts for the last decade. In fact, something that gave them a small amount of cheer was that Australia's case counts went below the US for the first time in 2012.

For the purpose of the discussion during this session, Dr. McIntyre focused on cases in very young infants based on data assembled for the last 10 years from Australia, California, and England and Wales. In terms of the individual number of deaths reported by year in these locations, the numbers are small. In trying to turning that into some kind of incidence summary, the total number of deaths reported from 2004 through 2012 was 12 in Australia, 31 in California, and 43 in England and Wales. If those deaths are calculated as a rate to a million live births, the differences observed in case counts and other parameters were much less. In fact, all of these estimates are really compatible with each other.

The rationale for the cocooning strategy in Australia and the US has been based on this sort of meta analysis. Australia recently published the "Australian Immunisation Handbook: Recommendation Since 2003," which assessed all of the studies that examined source of infection. It shows that parents were responsible for 50% to 60% of transmissions. It was on that basis that since 2003, similar to the US, Australia has recommended cocooning [Wiley et al, Vaccine 2013;31:618-25]. While cocooning has been recommended, it has not been funded. Also important is the uncertainty about the contribution of siblings to transmission to young infants. In this meta-analysis, that was the most uncertain parameter, with a very wide range. That is very important because if sibling contribution to transmission is significant, that cocooning does not really have anything to offer.

In the State of New South Wales in 2009, which is a long time in recent pertussis history, the only option available in the context of the outbreak at that time was to supplement cocooning. The New South Wales government provided one of the more generous subsidized schemes of any place. Effectively, any adult who was in contact with any child under 12 months of age could qualify for free vaccine and could obtain that from their family practitioner.

A case controlled study was conducted to evaluate the first two years of this experience between 2009 and 2011. The investigators were richly endowed with cases, with almost 400 cases of infants under 4 months of age in the State of New South Wales. Of those, just over half of those were interviewed. Full data were available for just under 200 with full timing information. There were about 200 matched controls, who were matched from the birth registry. There were 3 controls per case, and all control children were born on the same day as a case child. The cases for which contact could not be made were more likely to have had disease onset earlier in the 2-year period and were more likely to have resided in a metropolitan area, but otherwise were very similar to the cases the investigators were able to contact.

In terms of a snapshot of the characteristics of the cases in the study, in the context of the enormous amount of pertussis testing that is done in Australia, only about 70% of children under 5 weeks of age were hospitalized. The others were either seen in emergency departments or were only seen by their family doctor. That declined to just under 60% of cases over 6 weeks of age who were hospitalized and represented about two-thirds of cases. That reflects how much access to testing and how much focus on testing there is in Australia.

With regard to timing of vaccine in this program, which was delivered by family doctors, the proportion of mothers who were never vaccinated was similar in cases and controls at just over 20%. That is close to 80% coverage during this period in a funded program. What stands out is the higher proportion of control mothers who reported having received the vaccine prior to pregnancy. There was no vaccination in pregnancy during this period. What stands out in the periods following birth is that cases were more likely to be vaccinated late. What is observed overall us that there was a clear excess of controls who received dTpa at least 4 weeks before the onset of illness in the cases. The receipt of dTpa was matched in control mothers or parents to the data of onset of pertussis in the case child. Looking at cases within 4 weeks of onset, there was a bias toward cases. After onset, there were some individuals who were vaccinated as well.

In terms of the question regarding whether the mother was vaccinated at any time, the univariate analysis found no effect. In fact, the odds ratio for pertussis development in the infant was 0.82 with a confidence interval of 0.57–1.19. When the focus was place only on the mother having been vaccinated at least 4 weeks before onset in the case child, including before birth, the odds ratio was 0.56 with a confidence interval of 0.36–0.87. A high risk of pertussis was also associated with a number of socioeconomic factors, such as not having a father living in the household, being eligible for a healthcare card, having a low education level, larger households, and particularly households containing older children. If a household contained any children 6 years of age or older, there was a 3-fold increase in risk based on these data. The investigators were not able to demonstrate any independent effects of vaccinating fathers, but vaccination of fathers aligned very closely with vaccination of mothers. This offers a flavour of how many confounders there are in this analysis, and how many factors are playing out in terms of development of pertussis in an individual case. The investigators did their best to control for these factors.

Regarding the multivariate model that was developed, the eligibility for supplemented healthcare, low education level, absence of breastfeeding, not having a father living in the household, and the age of children living in the household all remained in the model as significant contributors. When all of those are controlled for, as in the unadjusted data, any vaccination was completely non-significant. However, if the specific situation of being vaccinated at least 4 weeks before onset was assessed, a reduction was observed. That was significant only amongst mothers who reported having received the vaccine prior to the current pregnancy, although there were similar estimates for the whole group of those who received the vaccine at least 4 weeks before onset, whether it was after birth or before pregnancy. In terms of the adjusted data focused on the impact of risk of pertussis associated with the age of children in household, it was very striking and unexpected to find that having 4 to 5 year old children in the household was not associated with an increase in risk. There was some increase in risk associated with 2 to 3 year old children, but the impact of having children in a household who were 6 years of age and older was evident.

The investigators were able to obtain validated data for the self-reported immunization status for only about 25% of cases and controls. That is because they were required to obtain written consent and have it returned to them before they could contact providers. While that resulted in incomplete provider data, the data that were acquired suggested that there was a high degree of correlation between report of receiving vaccine anytime, or receiving vaccine after birth in both cases and controls. However, in relation to the report of having received vaccine before birth, that was somewhat unreliable in the data that were identified. The report of receiving the vaccine at least 2 weeks or 4 weeks before onset was fairly reliable amongst the controls. If anything, the cases tended to over-report that, which would have been a bias in the data toward detecting no effect.

With regard to strengths and limitations, this is the largest study that is available to evaluate the impact of cocooning. In addition, very high coverage was achieved in the target population of approximately 80%. One of the limitations was the reliance on self-report of timing of a cocoon vaccine dose, so there were some misclassifications. However, this appears to be non-differential and by and large would have led to more difficulty in detecting an effect rather than a bias toward detecting an effect that was not present. While a number of cases could not be contacted, no difference was detected between the cases that were and were not in the study. There was limited power to evaluate the now critical question pertaining to whether vaccination in a previous pregnancy might provide any ongoing protection, particularly given the lack of complete data on timing.

In conclusion, this is the first evidence that in fact a cocoon vaccination strategy can decrease the risk of early onset pertussis. However, the timing of that dose is crucial and needs to be given at an adequate period of time before disease in the infant. Clearly, transmission from siblings is important and even the most successful cocoon strategies cannot impact that. Some evidence from this study supports the notion that there may be some continued protection of infants born in later pregnancies despite the very much lower antibody levels observed a year after vaccination. More data, particularly more detailed data on timing, are needed to confirm this impression. Given the fact that cocoon strategies like this were funded in a number of other Australian states, and there are evaluations ongoing, there may well be capacity to obtain additional data to inform this question over the next couple of years.

Maternal Tdap and Cocooning: The United Kingdom Experience

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Dr. Salisbury reminded everyone that during the October 2012 ACIP meeting, he alerted everyone that the UK had just made a recommendation to introduce pertussis vaccination for all pregnant women. During this June 2013 ACIP session, he shared some of the preliminary results of this program that started during the last week of September 2012.

With regard to the incidence of laboratory-confirmed pertussis, by total case-patients and age group in England & Wales from 1998 through 2013, the rates were very low compared to others. Notable, a switch was made to acellular pertussis in 2004. Therefore, it may be that the UK is late catching up with phenomena that others observed earlier. Two groups had the highest rates, one of which was those 10 to 14 years of age with a rate of 25/100,000. The other group was those less than 3 months of age with a rate of 250/100,000. Thus, the rate in those less than 6 months of age is 10 times higher than the rate in the nearest other high rate. This suggested that all efforts needed to be focused on the youngest children, while longer and harder consideration needed to be given to what to do with some of the other age groups.

In terms of total laboratory confirmed pertussis cases by month for all ages for England & Wales from January 2012 through April 2013, a seasonal variation of pertussis is observed. England & Wales are used to seeing cases increase over the summer and early autumn, followed by a natural decline through the winter. While Dr. Salisbury said he would like to persuade everyone that the implementation the pertussis vaccination program for all pregnant women had some impact on the overall number of cases, that would be entirely misleading. Clearly, it had no impact on the overall number of laboratory-confirmed cases. However, he said he would like to try to persuade everyone that there had been impact based on laboratory-confirmed cases showing that the proportionate fall in those who are the youngest had been greater than the proportion who fall within any of the other age groups.

Turning to the introduction of the emergency vaccination program for pregnant women, the program was launched in the last week of September 2012. The first step was to recommend the vaccination of all pregnancy women using TdaP/IPV since a very large reserve stock was already available. The recommendation was to vaccinate all women between 28 and 38 weeks of pregnancy, and to vaccinate during every pregnancy. To go along with the recommendation, a series of materials were produced aimed essentially at mothers. This includes leaflets, Q & A materials, posters, materials for healthcare professionals, and the department of health

websites. Pregnant women can sign up to receive weekly emails, text messages, or other forms of electronic messaging throughout their pregnancy and subsequent to the birth of their child. The mother and the father are able to sign up to receive this material. At 26 weeks, everyone who signs up for this information service receives information about the availability pertussis vaccine and the recommendation that they should receive it from 28 weeks onwards. A further reminder is sent out at 34 weeks about the need for whooping cough vaccination. Thus, fairly high awareness of this program has been achieved.

In terms of TdaP/IPV vaccine uptake, during the month of October 2012 over 200,000 doses were distributed. The amount of vaccine thereafter stabilized at between 40,000 to 50,000 doses per month. At 50,000 doses per month being used, that would relate to something on the order of about 80% coverage. During the 6 weeks it took to assemble this program, a scheme was put in place for national data collection for vaccination of pregnant women. Coverage based on this system was running close to 60% by March 2013, which is likely to be an underestimate because these data are provided essentially by midwives, who may not necessarily be well-connected with the data collection system because they may not be vaccinating in exactly the same places where normal primary care data are being collected. That would fit with the utilization data as potentially being an underestimate. They then went to the Clinical Practice Research Database (CPRD), which is a sentinel system that assesses all clinical contacts for 6% of the England population. Every contact is documented with all of the details. This showed that the coverage achieved through this system was between 70% to 80%, which comes quite close to what was observed through the other data collection system. Therefore, it is reasonable to assume that coverage is in excess of 60% and probably below 80%.

Obtaining these data allowed for making some estimates of the effectiveness. Using the screening method and starting with all of the cases that were being collected through the CPRD, a Welsh case was discarded because Wales is not included in the CPRD dataset. Nevertheless, this analysis reflected a vaccine efficacy for all cases of 89%. If the Welsh case and cases in which onset was after 2 months of age are discarded, efficacy is 91%. If coverage in the CPRD is reduced by 10% and it is assumed that the national system was more accurate than this, there is relatively little impact on efficacy, bringing it down to 87%. These are the first data for vaccine efficacy of vaccination of pregnant women. Analyzing the data a little deeper, assessing the efficacy according to the interval between vaccination and onset of disease, vaccine efficacy 28 days before birth is 90%. Efficacy between 7 to 27 days before birth is 75%. At a very narrow window of vaccine of 0 to 6 days before or 1 to 13 days after birth and the onset of disease after birth, efficacy is much lower at 29%. Clearly, if the mother is vaccinated at the recommended time between 28 to 38 weeks of pregnancy, there is a much higher prospect of achieving high efficacy with the vaccine of preventing disease in the infant.

Safety of pertussis vaccination in pregnant women has also been assessed through a prospective study using the CPRD dataset to examine a range of pre-defined pregnancy-related adverse events. Background data on the known rates of events were used to examine the short-term risk following vaccination using observed versus expected analyses. The conditions that were studied using observed versus expected rates included intrauterine death/stillbirth, pre-eclampsia/eclampsia, ante-/post-partum hemorrhage, uterine rupture, placenta praevia, vasa praevia, fetal distress, and pre-term birth. There was no increase in the rates of specific events in 17,000 vaccinated women, particularly stillbirths. For stillbirths, a further matched cohort study was undertaken using the CPRD with three historic controls matched to each vaccinated woman (6,000 vaccinated women matched to 18,000 controls). This resulted in

confirmation that there was no increase in the rate of stillbirths following pertussis vaccination in pregnant women, nor were there any increases in any of the other studied outcomes.

In conclusion, the pertussis vaccination program for pregnant women in the UK was put in place in approximately 6 weeks. High coverage has been achieved from the outset. Vaccine efficacy up to two months of age has been shown to be high. Studies on approximately 18,000 women offer assurance of safety in pregnancy. There is an ongoing study to assess the immune responses of infants whose mothers were vaccinated during pregnancy to examine the impact of antenatal immunization on infant responses to primary immunizations.

Discussion Points

Dr. Vazquez inquired as to whether previous vaccination of the pregnant women with Tdap was counted as vaccinated in the vaccine effectiveness study.

Dr. Salisbury responded that none of these women could have been vaccinated, because they would not have received any vaccination with pertussis vaccine since they were 3 years of age. There is no adult vaccination.

Dr. Campos-Outcalt thought it was important to put this into the context of the UK's immunization recommendations for other age groups. These women were vaccinated as children, but were not vaccinated as adolescents or as adults.

Dr. McIntyre indicated that Australia has had adolescent pertussis vaccination since about 2004. A small number would have been eligible for that, but it was not significant.

Dr. Campos-Outcalt wondered how they would assess the added value of a second vaccine in a second pregnancy.

Dr. Salisbury replied that the second recommendation made to have further vaccination in subsequent pregnancies was based on the very rapid decline in antibodies that was known. Therefore, it was assumed that if antibodies decrease as quickly as they do, it cannot be presumed that women will still be protected in subsequent pregnancies. It may turn out that they do have a degree of protection in subsequent pregnancies, but the UK opted for the safer choice. He may have to answer the question regarding how the value of vaccine in subsequent pregnancies will be assessed during another meeting, given that he did not know the answer at this stage in terms of how they will tease out the effect of vaccination in the first pregnancy having a protective effect in subsequent pregnancies. If there is high coverage during subsequent pregnancies, this will be difficult.

Dr. Baker congratulated Drs. Salisbury and McIntyre. An NIH-funded study was presented during the October 2012 ACIP meeting, which was a Phase I placebo-controlled study. This study assessed safety in the infant and mother, as well as immune interference with the routine immunization schedule. The bottom line is that the infant was assessed before the first dose at 2 months of age, and not surprisingly, the offspring of the vaccinated women had significantly higher antibodies to all of the pertussis antigens. This was antenatal Adacel® versus placebo, and then a crossover if a mother was not immunized antenatally with Tdap, but received postpartum. The infants were also assessed at 7 months of age after their 3 doses at 2, 4, and 6 months of age and no statistically significant interference was observed with any of the vaccines. However, the numbers are very small and the confidence intervals are very wide in these studies. There was one "statistically lower" for FHA that was fine for the other antigens.

At 13 months, after a 12-month fourth booster, there were no differences at all. Dr. Baker also emphasized that she had no doubt cocooning would work if it could be done. She asked Dr. McIntyre whether he knew how much it cost in New South Wales to prevent one case of pertussis in terms of free vaccine, free administration, et cetera.

Dr. McIntyre replied that they do know how many vaccine doses were purchased, but he did not have a figure. While he thought it was a very relevant question, they were making this decision in 2009 and it really did not seem like vaccination during pregnancy was an option at that point. That just indicates how quickly things have moved. In terms of maternal vaccination internationally, he asked Dr. Salisbury to comment on whether it is an outbreak response that should be stopped once the outbreak subsides, or if it would effectively become the first part of the infant schedule (e.g., dose one is the one received by the mother). This raises many other follow-on questions. Particularly given the UK's successful accelerated 2-, 3-, and 4-month schedule for pertussis in infants, that would be more of a concern in relation to interference. He wondered if this was being considered in the UK.

Dr. Salisbury responded that the program was put in place as a temporary program in response to an outbreak. There were a number of policy and political reasons why the UK did this. The quickest and easiest way to get the new program in was because there was an outbreak. The background data that would be necessary for putting in place a permanent program would have been very much greater. They thought that the length of time it would take to do complex modeling to support a formal policy change to the program would have resulted in increasing numbers of cases of pertussis. They were responding to what they saw as a national level outbreak, which is why it was implemented as such. It is a temporary program that has been reviewed twice, and the recommendations have been to continue until there is a much more certain idea of the direction of the epidemiology. For exactly the reasons stated, they are carefully assessing the possibility of the immune responses being blunted by the maternal immunization. The first vaccinated cohorts are being followed carefully.

Dr. Schaffner (NFID) joined in the chorus of admiration for what the UK and Australia have been able to do so efficiently. He inquired as to whether they could identify the practitioners who are and are not immunizing pregnancy women and if so, whether there are any plans to provide them with continuing education and motivation to do even better.

Dr. Salisbury said it depended upon which scheme. For the 6% within the clinical practice research database, compliance is very high with coverage between 70% and 80%. The whole country database can be analyzed down to the local level. There is more experience with influenza in terms of drilling down to individual practitioners and performance managing. With the recent program for catch-up for measles, they have been able to look at who has not ordered extra supplies of vaccine and they receive a visit.

Dr. McIntyre said they know what is happening to the children, but not the adults. They are actively exploring the notion of having midwives collect data on all births to get receipt of influenza and pertussis vaccine.

Dr. Temte appreciated the comments on the rapid assessment of safety being done in the UK. That is very helpful for ACIP making a recommendation on very thin evidence last time. That being said, he also appreciated that Dr. Sawyer mentioned ongoing safety evaluation for which data are anticipated as early as the fall. That being said, at the crude rate of use in the US and the coverage of the VSD, he did not think more than about 4000 cases would be accumulated compared to 18,000 in the UK. He requested that Drs. Ornstein and Gellin comment on the

NVAC discussion the previous week regarding some of the issues that have arisen within NVAC's maternal WG.

Dr. Gellin (NVPO) responded that it was the discussion of pertussis at NVAC a year ago that led not to a pertussis-specific WG, but a Maternal Immunization WG that would have broader implications. That group has been in place for some time, and the twin goals were to assess current barriers to pertussis vaccination of pregnancy women and barriers to development of other vaccines that are designed for maternal immunization, specifically those that are designed for the benefit more of the newborn than the mother. A vote on recommendation for the first goal is anticipated in September 2013. At the same time, the ACCV advises on the compensation program and also had a group that was focused on maternal immunizations that was considering a similar set of issues through the lens of the ACCV. The message is that from the advisory committee perspective, there are two federal advisory committees on vaccines that are seriously trying to assess how to improve maternal immunization now and the opportunities for the development of vaccines for maternal immunization in the future.

Dr. Ornstein (NVAC) added that the initial focus has been on how to improve, including issues on how pregnancy vaccination can be used in performance quality measures, how people are trained to adopt pregnancy vaccination, et cetera. ACOG has been engaged in quite a bit of work to improve immunization practices among obstetricians.

Dr. Riley (ACOG) pointed out that the US method of healthcare delivery is completely different from the UK. She was happy to see that much of the campaigning was directly to pregnant women. In the toolkit presented earlier in the morning, there is a section for Texts for Baby which pushes out messages about getting influenza vaccination, asking about pertussis vaccination, et cetera. She feels that obstetricians get much more pushback from patients, and as much as they want to educate providers, the other half of that equation regards what patients will accept. Anecdotally, pregnant women seem to be willing to get the pertussis vaccine during the first pregnancy. But she is getting pushback from women who were vaccinated previously, who now want more assurance that this is safe. This has become a much more extensive discussion. The UK data will make it easier to make the argument, but the way the US and the UK practice is significantly different. She wondered how much of that impacts how poorly the US is doing.

Dr. Schuchat commented that the perception of risk of disease changes attitudes during pregnancy. In the UK, this program was launched in the context of an emergency response. The VSD data showed that in California there was significantly higher coverage in 2011 following the epidemic disease in that state in 2010. Because 49 of the states had a lot of disease this past year, or at the time of ACIP's recommendation, perhaps the US will be doing better in the first year. The question remains of whether this will be sustained for second pregnancies in the UK, and whether there will be continued interest after the perception that this is new and concerning goes away. Conversely, CDC was very heartened that influenza vaccination coverage in pregnancy increased in the wake of the pandemic and has sustained at a higher level since then. It did not go right back to 15% after that. While there needs to be consistent work on this, Dr. Schuchat said she would not be too pessimistic yet.

Dr. Temte said he still observes a lot of pushback from clinicians who are providing obstetric care, not only from obstetricians but also family practitioners. There needs to be a lot of education. He recalled that when ACIP made the recommendation for Tdap in pregnancy the first time, it was a major paradigm shift for this committee because it was the first time ACIP had a recommendation for reduction of illness not in the vaccine recipient, but a secondary party (i.e., the fetus/newborn).

Dr. Baker emphasized that because the diagnosis of pertussis is not made in adults, nothing is known about the burden of disease in pregnant women. Until there is active surveillance, she would debate that a pregnant woman who has bad pertussis in the first trimester, there may be increased risk. This is an area that requires much more research, but surveys of actively pregnant women show that the greatest single influence on them is the recommendation of their obstetrical care provider. She works in a primarily Hispanic, very socioeconomically deprived population. If somebody speaks with these women about having pertussis immunization during pregnancy, they achieve 96% compliance. Those data are in press. She thinks the greatest barrier is in providers, not patients. It is known from pediatric studies that the more educated and intelligent people are, the more likely they are to be vaccine-refusing. While this may not be true in every circumstance, she thinks people sell pregnant women short. They need the encouragement to hear the data and get the education, but if their healthcare provider does not recommended influenza or pertussis immunization, they are not going to get these.

Dr. Paradiso (Paradiso Biologics Consulting) said he was surprised by 90% efficacy with passive transfer of pertussis antibodies to babies, which is better than the efficacy observed in immunization in almost all age groups. If he calculated correctly, he thought the UK should observe a 50% to 70% reduction in disease in children under 6 months of age during this summer season. That would clearly verify the efficacy rates stated for the UK. Being able to claim 90% efficacy or anything near that will help a lot in convincing providers that this vaccine is worth administering in the US. He asked whether the UK intends to evaluate how much antibody was passively transferred to try to get some correlation between the efficacy values and how much antibody to try to understand what constitutes protection.

Dr. Salisbury respond that the study is basically drawing blood from the children when they present for their first immunization at 2 months of age, so it will not correlate with antibodies that are transplacentally acquired at the time of birth. He agreed that the efficacy was extremely high.

Dr. Hayes (ANA) indicated that she is a nurse midwife who practices in the metropolitan Atlanta area in a high risk perinatology practice. When she asks pregnant women if their obstetricians have offered them a vaccine, 100% of them say they have not.

Dr. Temte pointed out that this was additional testimony to Dr. Baker's comments about the importance of education for clinicians.

Dr. Bennett commented that like every other vaccine, this really needs to be built into the system versus depending on providers offering it. When a woman presents for prenatal care, this should be a routine part of what she receives regardless of whether the provider remembers.

Human Papillomavirus (HPV) Vaccines

Introduction

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

Dr. Bocchini reported that over the last few months on teleconferences, the ACIP HPV Vaccine WG reviewed the more recent data on quadrivalent HPV vaccine in the pregnancy registry; long-term follow-up data becoming available on quadrivalent vaccine; HPV infection risk for research HPV laboratory workers; and HPV infection risk for selected health care workers.

The WG has also been planning for updating the ACIP HPV vaccine statement. The plan is to develop the ACIP statement to consolidate and update the 2007 quadrivalent HPV vaccine ACIP statement for females, the 2009 bivalent HPV vaccine Policy Note for females, and the 2011 quadrivalent HPV vaccine Policy Note for males. The updated statement will include female and male recommendations in one document, and wording differences will be reconciled. The statement will include updates on the burden of infection and cancers, cervical cancer screening, HPV vaccine trial data, and HPV vaccine safety data. Issues will also be addressed relating to research laboratory workers and certain health care workers.

Additional future WG plans are to review data on alternative vaccine schedules. Data were presented to ACIP in June 2012 on the study by Dr. Dobson and associates, and is now published [*JAMA* 2013]. The WG will also review data on other ongoing studies regarding alternative schedules for potential future presentations to ACIP. The WG also plans to review new data when it becomes available from ongoing trials of current and second generation vaccines.

Merck Pregnancy Registry for Quadrivalent HPV Vaccine

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Dr. Lievano reported data from the Merck Pregnancy Registry for qHPV Vaccine (Gardasil®) from June 1, 2006 through May 31, 2012. Gardasil® is not recommended for use during pregnancy. There are no adequate and well-controlled studies in pregnant women. However, inadvertent exposures may occur. All reports of exposure to vaccine during pregnancy are monitored closely by Merck, and provide the most robust data. The Pregnancy Registry for Gardasil® was part of a multifaceted plan to monitor the safety in pregnancy from approval in 2006. The registry was part of regulatory commitments with the US FDA, the European Medicines Agency (EMA), and Health Canada at the time of approval. The main goals of the registry were to acquire information on pregnancy exposures and outcomes; help identify safety signals; and provide information to providers, regulators, and patients. The data source for the registry is pregnancy exposures spontaneously reported to Merck. Patients were considered for enrollment in the registry if exposure was reported from the US, Canada, or France; there was a unique patient identifier; a healthcare provider was identified; and exposure occurred within 1 month prior to the onset of the last menstrual period or anytime during pregnancy.

Instructions about how to make a report into the pregnancy registry were described in the label and website: www.merckpregnancyregistry.com. The label and website also described the criteria for enrollment. In summary, the data source for the registry consisted of pregnancy exposures reported to Merck that were spontaneous and voluntary, and were submitted by healthcare practitioners and vaccinees. These reports were monitored as they were received.

The reports were classified as prospective or retrospective. The prospective reports comprised the primary cohort for rate calculations, and were received before the outcome of the pregnancy was known. Retrospective reports were those received after the outcome was known. A report was classified as retrospective if an initial report was received after fetal testing identified an abnormality. Because of the bias toward important and normal outcomes, retrospective reports were analyzed separately from prospective reports. The primary outcomes of interest were birth defects pregnancy outcomes, including elective and spontaneous abortions prior to week 20, fetal deaths after week 20, and live births. Infant outcomes included congenital anomalies. Medical records were requested for up to 2 years after birth from all newborns who had a signed consent on file. Birth defect frequencies were calculated on prospective reports using the Metropolitan Atlanta Congenital Defects Program (MACDP) methodology and included the number of affected cases that resulted in live born infants, fetal deaths, or terminations after 20 weeks per 100 live born infants. Appropriate experts were consulted as needed for selected cases.

From market introduction through May 31, 2012, 4740 reports of exposure to HPV vaccine were received by the company. Of these, 1865 cases did not meet the enrollment criteria and were not enrolled, and 2802 patients who reported exposure the HPV vaccine during pregnancy were enrolled in the pregnancy registry. However, 73 were not included in the analysis because the estimated data of delivery was after the cutoff date of May 31, 2012. Of the 2802 reports included in the analysis, 96% were received from the US, 12% were received from Canada, and 3% were received from France. There were 2440 prospective reports and 362 retrospective reports, of which 30% (n=725) were lost to follow-up; 69% (n=1675) had outcomes available; and less than 2% are pending. Of the 1573 pregnancy outcomes, 5 were ectopic pregnancies; 1452 were live births for a total of 1460 newborns because there were 8 sets of twins; 105 were spontaneous abortions; and 12 were fetal deaths. Of the 362 prospective reports, there were 29 elective abortions; 319 had pregnancy outcomes; and 14 were lost to follow-up. Of the 319 pregnancy outcomes, 8 were ectopic; 242 were live births; 61 were spontaneous abortions; and 8 were fetal deaths.

In terms of the prospective reports for the primary analysis population, as noted, of the 2440 reports, 30% were lost to follow-up despite multiple attempts; less than 2% have a pending follow-up; and 69% had outcomes available. The patient age ranged from 11 to 42 years, with a mean of 20 years. Approximately 91% of exposures were prior to the end of the first trimester. There were 102 elective abortions and 105 spontaneous abortions. In terms of infant outcomes, there were 1460 newborns. Of these, 1381 were normal infants (95%); 34 infants had major congenital anomalies as defined by MACDP; and 45 had minor congenital anomalies. The rate of spontaneous abortions was calculated to be 6.7 per 100 outcomes with a 95% confidence interval of 5.5 to 8.2. The background rate among clinically recognized pregnancies is 15%[1]. The rate of fetal deaths was calculated to be 0.8 per 100 outcomes with a 95% confidence interval of 0.4 to 1.4. In the general population, studies have indicated that the fetal mortality rate is about 0.62 to 1 per 100[2-3]. The overall rate of major congenital anomalies was 2.5 per 100 live born infants with a 95% confidence interval of 1.7 to 3.4. The background rate is 2.67 per 100 live born infants[4] [[1]Scott JR. *Danforth's Obstetrics and Gynecology*. Lippincott Williams

& Wilkins. 1999: 143-53; [2]Fox R et al. *Br J Obstet Gynaecol*; 104:4-10, 1997; [3]MMWR 56(49);1293, Dec 14, 2007; [4]Correa et al, Birth Defects Research, Part A: Clinical and Molecular Teratology. 79(2): February, 2007].

The most commonly reported anomalies included talipes (2 reports), atrial septal defect (2 reports), hypospadias (3 reports), gastroschisis (2 reports), and cleft lip and palate (2 reports). All other anomalies were reported just once. There were 362 retrospective registry reports. Of these, 25 infants had major congenital anomalies; 13 had isolated congenital anomalies; 4 had 2 anomalies each; 3 had multiple anomalies; and 2 had multiple anomalies as part of chromosomal abnormalities.

The registry has fulfilled its regulatory obligation of collecting information for at least 5 years and has now been discontinued. This is the largest vaccine pregnancy registry to date, with nearly 5000 reports and 2802 subjects as of May 31, 2012. The data do not show clustering of malformations in a specific SOC. In addition, there was no identified pattern in terms of birth defects. The overall rates of spontaneous abortions, fetal deaths, and congenital anomalies were at or below background rates. Continuation of the registry will not significantly increase the power to detect adverse pregnancy outcomes.

In terms of ongoing and future activities, routine pharmacovigilance activities will continue for all exposures during pregnancy including cases reviewed in real time; follow-up attempts on all cases; periodic aggregate analyses; and case reports and analysis routinely submitted to agencies. Merck has updated the website with text noting the discontinuation of the registry, and the company's continued interest in receiving reports of exposure during pregnancy. A summary of the overall results of the pregnancy registry will be added to the label. Merck will prepare a final registry report with all of the data and will publish the final data in a peer-reviewed journal.

In summary, data from the registry are reassuring with respect to safety after pregnancy exposures. Rates of spontaneous abortions, fetal deaths, and overall congenital anomalies compare favorably to background rates. The rate of congenital anomalies appears consistent with background rates. Reported anomalies are varied in type, etiology, and gestational age. This review does not support a causal relationship between qHPV vaccine and the birth defects reported to the pregnancy registry. Merck has monitored the safety of Gardasil® for over 6 years, including reports of exposure during pregnancy. The FDA, EMA, and Health Canada considered Merck's regulatory commitment for the pregnancy registry fulfilled as of April 2013.

Discussion Points

Dr. Keitel requested that Dr. Lievano explain the difference between the registry and future plans in terms of whether Merck is still going to submit each case and do aggregate analyses.

Dr. Lievano replied that when the registry was underway, several attempts were made to call physicians for two years to track down information for the prospective reports. Also for two years, the medical charts were requested to ensure that all of the data were collected. In terms of future activities, letters will still be sent to providers to request more information and Merck will continue writing periodic safety updates on the reports received to regulatory agencies.

Dr. Temte inquired as to whether Dr. Lievano had the background rate for elective abortion in the general population.

Dr. Lievano responded that he did not have that rate with him.

Ms. Hayes (ANA) indicated that the background rate of women in the US who terminate a pregnancy in general is about a third.

Dr. Temte pointed out that based on that, the number of elective abortions was lower than expected.

In terms of congenital anomalies, Dr. Vazquez asked whether consideration was given to whether most of them were first or second dose of vaccine.

Dr. Lievano responded that 91% of exposures were prior to the end of the first trimester, of which 76% were first dose recipients.

Plans for an Updated ACIP Statement

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Dr. Dunne discussed issues for consideration in the updated ACIP HPV vaccine statement. She highlighted some of the updated information for the ACIP HPV vaccine statement, which includes updates to the background information, HPV vaccine data, HPV vaccine safety data, and impact and cost-effectiveness. There have been many changes since the 2007 statement that need to be incorporated. Also in the updated ACIP statement, there will be no wording changes for vaccine recommendations in pregnancy. However, a change will be made in the information about the pregnancy registry reporting. As reported earlier, the quadrivalent HPV vaccine registry is no longer in existence; however, providers and patients are encouraged to continue to report to VAERS and a Merck 800 number. The GSK pregnancy registry reporting remains the same. Also for evaluations of child sexual abuse, the recommendation will be to start the vaccination series at age 9 years.

During this session, Dr. Dunne addressed several issues for ACIP to consider for the updated ACIP statement, including updated information on immunocompromised persons; consideration of vaccination for males through 26 years of age for the medical indication of end stage renal disease; and inclusion of information about select health care workers and research HPV laboratory workers.

New data on HPV vaccine in HIV-infected persons have been published, and there are now 1 clinical trial in men, 2 in women, and 2 in children. These studies have demonstrated an acceptable safety profile and good immune response to vaccine. Some studies have found differences in GMTs of antibody to HPV compared to historic controls; however, it is unclear if this finding has clinical significance. For other immunocompromised populations such as persons post-transplant and autoimmune disorders, there are ongoing evaluations. The WG proposed including these updates in the revised statement and ensuring harmonization of male and female recommendations [Wilkin T, et al. JID 2010; Levin MJ, et al. JAIDS 2010; Kahn J, et al. CID 2013.;Weinberg A, et al. JID 2012; Money, et al. CAHR 2013 Abstract].

Regarding the proposed changes in the medical indications for the current adult schedule for HPV vaccine, Dr. Dunne highlighted the current schedule for various medical indications and focused attention on HPV vaccine recommendations for males and females—the fourth and fifth

vaccines listed on the schedule. For males, vaccine is recommended through age 26 years for those with HIV infection, those with other immunocompromising conditions, and men who have sex with men (MSM). For the medical indications, including heart disease, asplenia, chronic liver disease, kidney failure, diabetes, and healthcare personnel, the recommendations are the same as per the general recommendations for males through age 21 years. A review of the literature was conducted on these specific medical indications and HPV-associated disease and cancer, which found there were data showing a higher burden of HPV-associated diseases and cancer for only one of these medical indications, kidney failure. The WG proposed to extend vaccination for males through age 26 years for this medical indication. This would mean inclusion of this information in the updated statement, as well as a change in the medical indications schedule [http://www.cdc.gov/vaccines/schedules/hcp/adult.html].

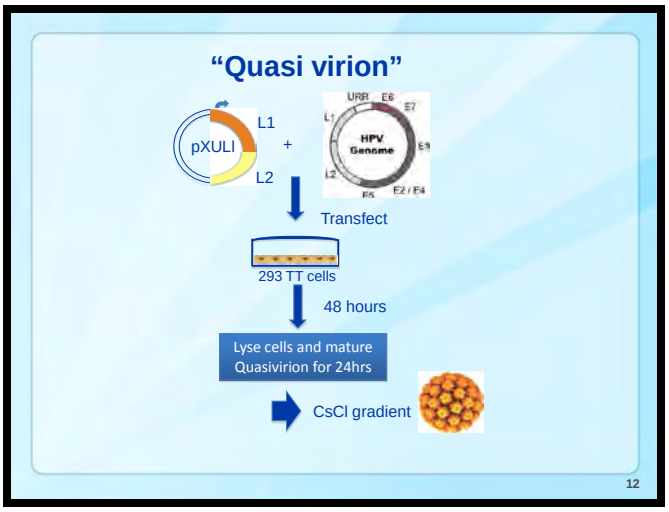
The reasons to extend to age 26 year old males for this specific indication are that data show a higher burden of HPV-associated lesions, including anogenital warts and cervical dysplasia in both end stage renal disease patients and post-renal transplant. Although these are primarily descriptive data, and there are no data on vaccine efficacy specific to this age group as yet, quadrivalent vaccine is licensed and safe through this age. There is likely to be a benefit to early vaccination, especially since many young persons with end stage renal disease will eventually receive renal transplants. As a note, ACIP already recommends vaccination for persons post-transplant through age 26 years [Banerjee S, et al. Indian J Dermatol Venereol Leprol. 2007; Leight IM, et al. Rec Reslts Cancer Res. 1995; Euvard S, et al. Cancer. 1993; Fairley CK, et al. Nephrol Dial Transplant 1994; Haberal AN, et al. Diagn Cytopathol. 2008].

Regarding the question of HPV laboratory workers and selected healthcare workers, the WG posed the following questions:

- Is there a risk to research HPV laboratory workers of acquiring HPV from work with wild type virions and newer synthesized virions?

- Is there a risk to select healthcare workers of acquiring HPV secondary to surgical smoke? This issue was also considered in the STD Treatment Guidelines Meeting in April, 2013.

For the first question about laboratory workers, it is important to note that HPV is difficult to culture, and PCR for DNA is often used to evaluate for infection. Some research laboratories are working with wild type HPV as well as newer synthesized virions to characterize the natural history and immunity to HPV. There are over 6 US laboratories and other global laboratories in which these laboratory-generated virions are being produced. There are two types of virions used in the lab. Wild type HPV virions are generated in the lab by infected xenographs grown in immunocompromised animals or transfected keratinocytes in organotypic raft cultures. The generations of these virions is time-consuming and produces very low virus yields. Some newer techniques recently introduced allow development of lab-generated virions called quasi virions or pseudo virions. Pseudovirions simply have capsid proteins encapsulating a reporting gene. These synthesized virions have no oncogenes and are not believed to be infectious. For the purposes of this discussion, Dr. Dunne did not discuss these pseudovirions further. However, another type of synthesized virions called quasi virions are lab-generated and are synthesized in the 293TT cell system. They consist of the capsid proteins L1 and L2, which encapsulate the complete 8 kb papillomavirus genome. They are generally indistinguishable from tissue derived papillomavirus genome [McCance Proc.Natl Acad Sci.1988; Meyers C J Virol. 1997;Pyeon et al. Proc Natl Acad Sci. 2005; Culp TD J Virol. 2006]. The following is a simple illustration of how quasi virions are created:



Quasi virions are created through transfection of the HPV genome with the L1 and L2 proteins in the 293TT cell system, which allows for mature quasi virions within 72 hours, and the virions are then purified. Synthesis of quasi virions produces 1000 times more infectious virus per cell culture than organotypic culture systems.

Wild type and quasi virions are infectious, which has been demonstrated using animal models in which rabbit papillomas were produced when these virions were injected in the skin. These virions contain whole HPV genomes, including oncogenes and other elements associated with disease and cancer development. For quasi virions, the cell system produces very high titers of virions, as highlighted earlier, over 1000 times more than the wild type systems and up to 10^9 transuding units from a single flask. However, it is important to note the minimal infectious dose is not known.

Some of the potential exposures that could occur in the laboratory include exposure to these virions through mucosal, cutaneous, or respiratory exposure. Although there are high virion titers of quasi virions in the lab, the potential risk to laboratory workers has not been characterized. There is no evidence of previous exposure, infection, or disease in the laboratory, although this is somewhat difficult to assess. There has been inoculation in rabbits using these virions, which did demonstrate disease as noted earlier.

In summary, there is a potential risk of HPV acquisition to research HPV lab workers working with quasi virions and wild type virions. However, there are limited data on risk and no data on transmission or vaccine efficacy for these potential exposures in this setting. The WG proposed that language be added in the updated ACIP statement.

For the second question regarding risk to health care workers of acquiring HPV during treatment of anogenital lesions, seven studies that collected smoke plumes after therapy for warts or cervical intraepithelial neoplasia (CIN) demonstrated intact HPV DNA in thee plumes. One study assessed specimens from Loop Electrocautery Excision Procedure (LEEP). There is evidence from an animal model that these virions from the smoke plume are infectious. Finally, there are two case reports of laryngeal papillmas reported in healthcare workers who treated persons with anogenital warts. Although the timing of disease development is consistent with this being the primary exposure, it is unclear whether RRP was a result of this potential exposure [Garden. Arch Dermatol.2002; Garden JAMA. 1988; Andre J,et al. Am Acad

Dermatol. 1990; Hallmo, et al. Eur Arch Otorhinolaryngol 1991; Calero, et al. Laryngorhinootologie. 2003; Kashima, et al. Otolaryngol Head Neck Surg. 1991; Ferenczy, et al. Obstet Gynecol. 1990; Sawchuk J Am Acad Dermatol. 1989; Sood,et al. Infect Dis Obstet Gynecol. 1994; Weyandt , et al. Arch Dermatol Res. 2011]. One study evaluated smoke plumes generated from laser carbon dioxide (CO_2) of papillomas in cows. The smoke plume was suctioned, collected, and reinoculated into the skin of calves. All smoke plume samples were positive for bovine papillomavirus, and all calves developed fibropapillomas at the site of inoculation [Garden. Arch Dermatol. 2002].

It is important to note that there are current infection control practice recommendations. The National Institute for Occupational Safety and Health (NIOSH) has issued guidance on using local exhaust ventilation or a smoke evacuator when these methods are utilized. The exact language reads, "Local exhaust ventilation (e.g., smoke evacuator) is recommended when CO_2 laser or electrosurgical procedures are performed on patients with anogenital warts or anogenital tract intraepithelial neoplasia [CDC-National Institute for Occupational Safety and Health. Control of Smoke form Laser/Electric Surgical Procedures. NIOSH Publication Number 96-128, available at http://www.cdc.gov/niosh/docs/hazardcontrol/hc11.html, Accessed 4/17/2013].

In summary, smoke plumes generated by electrocautery and laser CO_2 can contain papillomavirus. Current recommendations include use of a smoke evacuator for these procedures. Although there are two case reports in the literature, it unclear if the potential exposure led to the disease. There are limited data on risk and vaccine efficacy in this setting.

The WG proposed the following draft language for inclusion in the body of the updated ACIP HPV statement:

- Research HPV laboratory and select healthcare workers might have an increased risk of acquiring HPV from occupational exposures. These persons include those working in laboratories and handling wild type virus or "quasi virions" and healthcare workers treating anogenital intraepithelial neoplasias or anogenital warts with laser CO_2 or electrocautery.
- In the laboratory setting, proper infection control should be instituted including at minimum BSL2.
- Healthcare workers treating anogenital intraepithelial neoplasias or anogenital warts with laser CO_2 or electrocautery should have vacuum ventilation as recommended by NIOSH.
- The need for any additional infection control steps in these settings is being investigated. It is unclear if there would be a benefit of HPV vaccination in these settings as there are no data on transmission risk or vaccine efficacy.

Discussion Points

Regarding surgical smoke, Dr. Harriman said she would like language to be included about respiratory protection for healthcare workers conducting those procedures. She inquired as to whether the WG had considered this.

Dr. Dunne replied that there are active conversations about other potential infection control practices, such as personal protective equipment (PPE) that may be needed.

Dr. Sawyer inquired as to whether any age restriction would be proposed for the healthcare worker recommendation, and he wondered about the recommendation that only healthcare workers engaged in these specific types of surgery would be included. It is possible that people could be asymptomatically infected or infected without an obvious lesion. People doing cautery in the anogenital region in general might be at risk.

Dr. Dunne responded that most of the cases she described primarily occurred with anogenital warts and CIN, but there could be other areas of the anogenital mucosa for which those techniques are also used. In terms of any age restrictions, she explained that the draft language was primarily for information purposes and would be included in the draft statement. There would be no specific vaccine recommendations.

Dr. Keyserling (SHEA) asked whether consideration would be given to extending this to oral or other cancers that are probably HPV-related in terms of healthcare worker exposures, particularly for ablation of laryngeal lesions, which causes smoke.

Dr. Dunne responded that she would have to know whether these kinds of procedures are being used for oral cancers, and indicated that she would follow up on this issue.

Dr. Campos-Outcalt asked what was being proposed for males with kidney failure and end stage renal disease, given that he did not see any wording for those.

Dr. Dunne replied that the proposal is to extend the medical indications for kidney failure through 26 years of age for males.

Dr. Campos-Outcalt inquired as to whether a decision had been made to insert that information, or if a vote would be planned for the future.

Dr. Dunne responded that the purpose of this session was primarily to present information about what the WG was proposing. It would be up to others to consider whether a formal vote would be needed for that communication.

Dr. Temte added that the question regarded whether this represented an expansion at the level which would require a vote for a recommendation.

Dr. Coyne-Beasley, who serves on both WGs, assured everyone that this would be something the Adult Immunization WG would discuss in conjunction with the evidence presented by the HPV WG.

Dr. Bocchini added that this would come before the committee for its consideration as the statement was updated.

Dr. Campos-Outcalt indicated that procedurally he was confused.

Dr. Pickering clarified that the purpose of this session was information and to acquire feedback from the committee members regarding any specific areas that should be further investigated.

Dr. Temte added that technically, if it became a recommendation of the committee, there should be a formal vote.

Dr. Schuchat said her understanding was that during this session, the WG was trying to catch the committee up on all of the issues they have been considering. While this would be a good time to propose any thoughts or questions about what the WG should consider in terms of end stage renal disease. However, decisions about any substantive would be voted on in a future meeting. The purpose of this session was not to say there would never be a vote. It was simply to update the committee on a lot of issues on which the WG is still deliberating.

Dr. Temte viewed this as being very similar to the MMR WG that assessed new data regarding, for example, HIV-infected individuals, people on highly active antiretroviral therapy (HAART), and so on. It was presented once or twice prior to the time that it was all combined into a package and each of the components was voted upon. He thought this was probably headed in the same direction.

Dr. Keitel inquired as to whether before this came to a vote the committee would be briefed on how high the risk is, whether there are certain subgroups of end stage renal disease, if there are other risk factors that predispose them to these diseases, et cetera.

Dr. Bocchini replied that the WG would certainly bring forward the evidence, and present specific recommendations at the appropriate time.

Regarding not changing the pregnancy language and the positive information presented about Gardasil, Dr. Riley (ACOG) wondered whether consideration would be given to a statement that if there is an inadvertent pregnancy in the course of vaccination to not perform an elective pregnancy termination along the language of the MMR.

Dr. Dunne indicated that this is already included.

Dr. Temte wondered whether there was an estimated number of laboratory personnel actually involved or potentially exposed to smoke from vaporization. His guess would be that the number of people who would work in the 6 laboratories could probably be counted on a couple of hands.

Dr. Dunne responded that this was correct. Synthesis of quasi virions is a new technique, so Biosafety in Microbiological and Biomedical Laboratories (BMBL) is also going to be evaluating this in the future.

Dr. Rubin inquired as to whether the burden of end stage renal disease was primarily anogenital warts or if it was more cervical dysplasia. This would have implications about which vaccine is likely to be more effective for prevention of those.

Dr. Dunne replied that most of the data for end stage renal disease is primarily descriptive of anogenital lesions such as anogenital warts, but there is one description that is cervical dysplasia. There is no information on rates or incidence calculations. There are no data on vaccine efficacy in this particular group, although there are ongoing studies being conducted in this population.

Dr. Pickering reminded everyone that they have heard data about the durability of meningococcal conjugate vaccine (MCV4) and Tdap not being what it was originally thought to be. He requested the latest information on the durability of HPV antibody.

Dr. Dunne responded that the WG had heard data through about 6 to 10 years depending upon the vaccine that show immune response to vaccination.

HPV Vaccine Program and Impact Monitoring

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To close this session, Dr. Markowitz reviewed the HPV vaccination program and impact monitoring, and presented an update on vaccine safety. As a reminder, ACIP recommended quadrivalent vaccine for females 11 or 12 years of age in 2006 and through age 26 for those who were not previously vaccinated. In October 2009 after the bivalent vaccine was licensed, ACIP revised the recommendations to state that either vaccine could be used. Also in 2009, the quadrivalent vaccine was licensed for use in males. At that time, a routine recommendation was not made. However, in 2011, ACIP recommended quadrivalent vaccine routinely for males at 11 or 12 years and through age 21.

Based on data from the NIS-Teen from 2006 through 2011 for all vaccines, as of 2011, 78% of adolescents had received Tdap and 70% had received meningococcal conjugate vaccine. In contrast, only 53% of girls had received one or more doses of HPV vaccine and 35% had received all three doses. Each year, there was about a 10 percentage point increase in coverage for Tdap and meningococcal conjugate vaccine. However, for the past three years there has been very little increase in coverage for HPV vaccine [National Immunization Survey (NIS)-Teen. MMWR 2012; 61].

Vaccination status and intent to receive vaccine among parents of unvaccinated girls are also available from the NIS-Teen surveys. Based on data regarding the total population of girls for the survey years 2008 through 2011, each year the proportion of vaccinated girls has increased. The proportion who report they are somewhat or very likely to have their daughter vaccinated subsequently decreased. The proportion of parents who report that they are not likely to have their daughter receive vaccine in the next 12 months has remained relatively constant at about 25%. It is unknown whether this means that they never intend to vaccinate their daughter, or they are waiting for some time in the future. In 2011, the top 5 reasons for not vaccinating their daughter among parents who said they had no intention to vaccinate in the next 12 months were: feeling the vaccine is not needed or necessary, their daughter is not sexually active, they had safety concerns, lack of knowledge about the vaccine, and no recommendation by a provider [http://www.cdc.gov/vaccines/stats-surv/nis/nis-2011-released.htm#nisteen].

While NIS-Teen collects data on 13 through 17 year olds, the National Health Interview Survey (NHIS) collects data on older individuals. In contrast to the National Immunization Survey (NIS), NHIS vaccination histories are from self-report; whereas, NIS data are from provider-verified records. In terms of coverage from 2010 through 2011, at least 1 dose coverage in women aged 19 through 26 increased from 20.7% to 29.5%. The largest increase was in 19 through 21 year olds where coverage increased from 28.2% to 43.1%. Age at vaccination is actually not collected in the survey, so it is unclear whether vaccination occurred as an adult or whether they were part of the adolescent program and then just aged into this cohort [National Health Interview Survey: http://www.cdc.gov/vaccines/stats-surv/nhis/default.htm].

As a reminder, updates on vaccine safety have been provided periodically to ACIP. As for other vaccines, the Immunization Safety Office (ISO) safety monitoring infrastructure has three components, including: 1) VAERS, which is a spontaneous reporting system to detect potential vaccine safety problems; 2) VSD, which is a large linked database system used for active surveillance and research with approximately 9.2 million members representing about 3% of the US population, which conducts monitoring and evaluation. Rates and risk estimates can be calculated; and 3) CISA, which is an expert collaboration that conducts individual clinical vaccine safety assessments and clinical research.

About 56 million doses of quadrivalent vaccine were distributed in the US between June 2006 and March 2013. No new safety concerns have been identified in recent analyses of the post-licensure vaccine safety surveillance among males or females. Among the 7.9% of reports to VAERS were coded as "serious." The most frequently cited adverse events are headache, nausea, vomiting, fatigue, dizziness, syncope, and generalized weakness. The pattern of these reports, both serious and non-serious, are consistent with those reported in the summary published after the first two and a half years of VAERS data. Syncope continues to be a frequently reported event in adolescents. The adverse events reporting to VAERS following quadrivalent vaccine administered to females steadily decreased over time after 2008. The proportion of all events that were serious events also declined from the peak in 2009 where they accounted for 12.8% of all events to only 7.4% in 2013 [CDC, unpublished data].
In terms of the VSD, to date more than 1.8 million doses of quadrivalent HPV vaccine have been administered to patients within the VSD network. About 270,000 of those doses were administered to males. ISO was waiting until a large enough number had been administered to males to start their Rapid Cycle Analysis (RCA), which will begin this year. As previously published in a RCA study carried out in 7 MCOs among over 600,000 doses administered to females 9 through 26 years of age, there was no statistically significant increased risk for any of the pre-specified adverse events, including GBS, seizures, stroke, venous thromboembolism (VTE), appendicitis, anaphylaxis, and other allergic reactions[1]. The longer term surveillance of GBS and stroke among females 9 through 26 years of age following quadrivalent vaccine was evaluated after 1.5 million doses. No increased risk was observed for GBS or stroke. These data are in the process of being written and will be available in a publication [[1]Gee, et al. Vaccine. 2011; 29(46): 8279-84].

As reported earlier in the day, there were no safety concerns raised by the vaccine in pregnancy registry for the quadrivalent vaccine. CDC and FDA will continue to monitor the safety of HPV vaccines, including reports in pregnant women through VAERS. Merck will continue to collect this information as well. A retrospective analysis of pregnancy-associated VAERS reports is in progress. Since about 85% of reports were submitted to VAERS are submitted through the Merck Pregnancy Registry, it is anticipated that a very similar safety profile will be found as was reported by the Merck Pregnancy Registry. For VSD, there is a descriptive data of adverse

events following inadvertent exposure to quadrivalent vaccine during pregnancy. Those data will be available by 2015.

Turning to HPV vaccine impact monitoring, it is very helpful to consider early, mid, and late outcomes based on when outcomes would be expected according to the natural history of HPV vaccine. Early outcomes would include HPV prevalence and genital warts in teens and young adults. Mid outcomes would be pre-cancer lesions, and late outcomes would be HIV-associated cancer. Impact monitoring is occurring in a variety of countries, and data are available from countries that were early adopters of HPV vaccine. Before showing data from the US, Dr. Markowitz showed data from a few other countries. While she specifically focused on Australia and Denmark, there are data from a variety of other countries, some of which have been published.

Australia introduced their vaccination program in 2007 as a school-based program. This was publicly funded using quadrivalent vaccine. The target age group was 12 through 13 year old girls. They also had two catch-up programs that lasted for a 2-year period. One was in 14 through 17 year-olds in schools, and the other was for 18 through 26 year-olds in the community that was administered by primary care providers. They achieved over 70% 3-dose coverage in the school-based program, and about 51% 1-dose coverage among those 20 through 26 years of age. This was somewhat lower than some of the other catch-up age groups [Gertig, et al. Sex Health 2011].

Australia was the first country to publish data showing an impact of the vaccination program looking at genital warts in 6 sexual health centers across the country, which was previously presented to ACIP. The data Dr. Markowitz showed during this session were from a more recent publication from 2013. In terms of the proportion of Australian-born females diagnosed as having genital warts at first visit, by age group for the years 2004 through 2011, there was a dramatic and early decrease in genital warts in those under the age of 21. Through 2011, there has been a 93% decrease compared to the pre-vaccine era. Among those 21 through 30 years of age, there was a 73% decrease. No decrease was seen in those over age 30. Data from Australia also demonstrated a decline among males, although males were not included in the vaccination program. Again, the most dramatic decrease was in those under 21 years of age. This was a strong demonstration of herd immunity from their vaccination program [Ali, et al. BMJ 2013]. Australia has also demonstrated declines in vaccine type prevalence among 18 through 24 year old women. There was about an 80% decline in the prevalence of vaccine types within 3 to 4 years of introdcution of the vaccination program [Tabrizi, et al. JID 2012].

With regard to the data coming out of Denmark, HPV vaccine was introduced in 2009. Vaccine was delivered by general practitioners. This was also publicly funded using quadrivalent vaccine. The target age group was 12 year-old girls. They had a more limited catch-up program of 13 to 15 year-old girls, which began before Denmark's routine in late 2008. Through this general practitioner organized program, greater than 80% 3-dose coverage was achieved in the target and catch-up age groups. Danish National Patient Registry data from 2006 through 2011 on genital warts among 12 through 21 year-old girls and boys showed an incidence low for those 12 through 15 years of age. Among those 16 through 17 years of age, incidence peaked in the second half of 2008. That was followed by a sharp decline from 381 per 100,000 to 40 per 100,000 in the first 6 months of 2011. There were also more gradual but significant declines among women in the older age groups. Among men, there was no significant decline in genital warts, but there was a tendency for a decline in some men in the older age groups. The average annual percentage change was 45% among those 16 through 17 years of age among women [Baandrup, et al. STD 2013].

Turning to the US, a variety of efforts are ongoing to monitor the impact of HPV vaccination. This includes type-specific prevalence, genital warts, cervical pre-cancers, and HPV-associated cancers. The first data are from National Health and Nutrition Examination Surveys (NHANES). This is a representative survey of the US population. There are both home interviews and examination in a mobile exam center. The HPV component of this includes women and men 14 through 59 years of age. HPV DNA testing in self-collected cervicovaginal swabs for females was added to the survey in 2002. Demographic and sexual behavior data is collected as well. HPV vaccine questions were added in 2007, and HPV DNA testing in genital swabs for males was added in 2013. Those data will not be available until 2015.

With regard to the prevalence of vaccine-type HPV type in females by age group in the pre-vaccine and vaccine eras, a significant decline was found in 14 through 19 year-olds. This is the age group in which a change would be expected to be observed first. There were no significant differences in HPV vaccine type prevalence in the other age groups. Among 14 through 19 year-olds, there were no changes in the population characteristics that could have contributed to this decline, such as the percent sexually active, the number of lifetime sex partners, or race/ethnicity. The point estimate decline of 56% is greater than would have been expected based on 3-dose vaccine coverage in the US. This decline could be due to some changes in behavior that the investigators were unable to measure, but the data likely demonstrate early impact of vaccination and suggests impact from herd immunity or efficacy from less than a complete 3-dose schedule [Markowitz, et al. JID 2103].

Early impact of the vaccination is also suggested by some data available on genital warts. A variety of projects are assessing genital warts. During this session, Dr. Markowitz presented the administrative data from the MarketScan® data. The analysis results she shared were from the MarketScan® Commercial Claims and Encounters Database from 2003 through 2010. The objective of this analysis was to estimate the annual prevalence of anogenital wart diagnoses from 2003 to 2010. This analysis included persons aged 10 through 39 years of age who were continuously enrolled within a given year and includes over 64 million person-years of data. Cases were defined using International Classification of Diseases (ICD)-9 codes or medication codes combined with diagnosis or procedure specific codes, excluding the cervix. If the record did not have the ICD-9-CM diagnosis specific for condyloma acuminata, additional criteria such as a procedure specific to the anogenital region was not required. Of the cases, 88% had a code for condyloma acuminata. In terms of the data for females, the lowest prevalence was in 10 through 14 year-olds and the highest was in 20 through 24 year-olds. This is consistent with many other studies evaluating genital wart prevalence. In females 15 through 19 years of age, there was a significant decline in prevalence from 2.9 per thousand in 2006 to 1.8 per thousand in 2010. For women aged 20 to 24, prevalence increased from 4 to 4.5 in 2007 and then remained level through 2009. There started to be a decrease in 2010, and there is also maybe a suggestion of a decrease in 25 to 29 year-olds. In contrast to females, prevalence increased or was stable during this time in males. There was certainly no decrease in the 15 through 19 year-olds. Among 20 through 24 year-old males, prevalence increased through 2009 and there was a small decrease. These data will be further evaluated, but the early decrease in 15 through 19 year-old females, as well as trends in some of the other age groups do suggest an early impact of vaccination [Flagg, et al. AJPH 2013].

Several evaluations are ongoing to evaluate mid outcomes or cervical pre-cancers. During this session, Dr. Markowitz shared some data from a population-based assessment in the sentinel sites in the Emerging Infections Program (EIP). Since pre-cancer lesions are detected by cervical cancer screening, changes in cervical cancer screening recommendations will impact the ability to interpret these findings. This is particularly an issue for the youngest age group, since recommendations have changed such that screening is not recommended before age 21.

The HPV-IMPACT project being conducted in the EIP program is monitoring vaccine impact on high grade cervical lesions. This study is being conducted in five sites and data are collected on CIN2, CIN3, and AIS directly from histopathology labs. HPV typing is being conducted at CDC, and vaccination history is actively being collected from a variety of sources. Data are still being analyzed on race, because information must be collected on cervical cancer screening to adequately interpret these. Dr. Markowitz shared previously published data assessing the early impact of vaccination and the percent of CIN2 lesions due to HPV 16/18 among those who are unvaccinated and those who are vaccinated, analyzed by time since pap that led to the biopsy for that diagnosis. Time between pap and vaccination reflects the likelihood of being vaccinated before exposure to the type that was responsible for the pre-cancer lesion. As expected, those who were vaccinated in the recent past were not less likely to have HPV 16/18-related CIN compared to those who were unvaccinated. However, those vaccinated more than 24 months before their pap were significantly less likely to have HPV 16/18-related lesions compared to those unvaccinated [Powell, et al. Vaccine 2012].

In terms of late impact, it will be possible to assess cancer. There are cancer registries in all states that cover virtually 100% of the population. Regular updates on HPV-associated cancer overall and by state will be reported, and the first report was published in the *MMWR* in 2012. Typing of these cancers has been done in select registries as a baseline. These will also be reported to assess type-specific cancers.

In summary, vaccination coverage has increased since 2007, but very limited increase has been observed in recent years. Post-licensure monitoring data continue to show a good vaccine safety profile. A variety of early, mid, and late HPV-associated outcomes are being monitored. Data suggest impact on early and mid-outcomes in the US despite low coverage.

CDC's plans include publication of an HPV-specific *MMWR* scheduled to be released in July 2013. This will have data from the 2007-2012 NIS-Teen data and will summarize vaccine safety data. The annual NIS-Teen *MMWR* will be published at the end of August 2013, which will have 2012 data on coverage. There is work going on to utilize the Immunization Information Systems (IIS) to conduct reminder/recall and vaccination coverage assessment of providers reporting to the IIS. A variety of tools are being developed for providers, including a tip-sheet for talking with patients about HPV vaccine and development of a speakers bureau to present at meetings. There are continued efforts to evaluate barriers to vaccination and understanding what "safety concerns" truly means since this has been reported as one of the reasons for non-intent to be vaccinated. Further communication of safety data to providers and parents is also planned.

Discussion Points

In terms of the increase in oropharyngeal cancer in men, Ms. Hayes (ANA) wondered what the discussion was in the WG with regard to vaccinating men over age 26.

Dr. Markowitz replied that the WG has not had any discussions about vaccinating men over age 26.

Dr. Salisbury wondered if the impact on genital warts being greater than the coverage might have predicted had been analyzed by 1- and 2-dose coverage. Perhaps only 2 doses are needed.

Dr. Markowitz responded that the data she showed were from the MarketScan® data. Right now, there are no vaccine data associated with that. It is an ecological analysis. For the NHANES data for which prevalence is being assessed, there are self-report histories of vaccination, but the numbers are too small to break down by individual number of doses. That will be evaluated.

Dr. Schuchat noted that a lot of the day was spent discussing teenage vaccine, which has disappointing performance at this point. However, there has been very good uptake and achievement of Healthy People 2020 objective for vaccination of teenagers. This vaccine has greater than expected performance, even with pathetic coverage. She expressed her hope that this audience of highly motivated immunization experts, clinicians, and program staff saw this as a wake-up call to do much better. Every time she looks at coverage data, she is struck by the fact that in 2008, the first three vaccines were neck-and-neck in terms of first dose coverage. There was a really good initial program for HPV, with an expectation of good results. Since 2008, they have diverged in a major way. This is a point where these vaccines are working better than expected. They are safe and appear to be extremely effective. As clinicians, parents, and community members, she thought they really needed to do better in getting them administered to prevent the cancers that will be occurring if not.

Dr. Sawyer wondered if the coverage rates show by Dr. Markowitz might be a slight underestimate. California has a new law that allows minors to consent for prevention services for STDs, which includes HPV vaccine. That may lead them to get the vaccine from someone other than their primary care provider, which may result in it not being reported or not being as easily reported. He asked whether she had any idea of the impact of such practices. He assumed there must be states other than California that have similar laws.

Dr. Shannon Stokley responded that if she recalled correctly, that law was just recently passed or was within the past year. Very few states have that specific law. The word “prevent STD” has to be included in the law, which is usually the key. The NIS-Teen survey is with the parent, so the parent has to indicate where the child got the vaccine in order to be able to validate vaccine history. If teens are obtaining vaccines outside of their routine medical provider and not letting their parents know, then there would be under-estimating. It is not clear how frequently that is occurring, but she did not think the rates would be dramatically higher with this information.

Dr. Hahn (CSTE) emphasized that part of them problem is probably hesitancy of vaccinating too soon at age 11 to 12. Some data were presented during a previous meeting that younger adolescents respond better to this vaccine, at least serologically, than the older adolescent. She wondered whether there was a way to turn that information into a message of why it is better to vaccinate younger adolescents.

Dr. Markowitz indicated that CDC has been discussing this. Many of the communication messages include information stating that the immune response to vaccination is better at younger ages. Perhaps they need to evaluate whether providers understand that, and if it is well-communicated.

Dr. Bennett requested further information about how the decreasing rates of screening and the impact on assessing intermediate outcomes would be dealt with.

Dr. Markowitz replied that in monitoring pre-cancer estimates, an attempt is being made to obtain estimates of screening rates. This is difficult in the US because there is not a national Pap registry, and there is only one state Pap registry. Data are being collected from a variety of sources, but this is as challenging as acquiring vaccination history since there are not complete vaccine registries. This is incorporated into some of the analyses, and an attempt will be made to estimate this. That is why having some of the HPV type-specific data is going to be helpful.

In answer to Dr. Sawyer's question, Dr. Turner (ACHA) reported that in 2011, three schools representing the states of Wisconsin, Pennsylvania, and Virginia assessed immunization rates among females who had matriculated ACHA schools. They were at 46% uptake for three doses among females who were in college in obviously different socioeconomic climates. Each state has different rules, but Virginia has a permissive recommendation for 6th graders to get the vaccine, and minors can sign for and receive the vaccine if they have a way of paying for it. Cost remains a major issue for many people. Hopefully, with the ACA that will become less of a burden. A network of colleges is contributing data to the ACHA. Among 20,000 vaccines given in this network of 22 schools, about a quarter of the vaccines are still being given to males. Of the males receiving the vaccine, 60% are over the age of 21. This is with no marketing and no recommendations, so there remains a fairly robust demand among men to receive the vaccine over the age of the recommendation.

Dr. Loehr (AAFP) asked Dr. Markowitz for a reminder about how much more effective the vaccine is when given to 11 to 12 year olds versus older adolescents so that he could pass that on to AAFP members.

Dr. Markowitz responded that the efficacy trials were conducted only in recipients 15 to 26 years of age, so the efficacy data come from that age group. The bridging immunogenicity studies were done in the younger age groups, the 9 through 15 year-olds. What was referred to earlier were the data showing that the antibody titers are higher in the younger age group compared to the antibody titers in women in the efficacy trial. Efficacy was close to 100% in the older women, so the efficacy was very good and it is not believed that the efficacy will be different. The immune response to vaccination is higher in the younger age group.

Dr. Bennett inquired as to whether there had been any consideration of school-based strategies for delivering this vaccine.

Dr. Schuchat responded that there are some programs offering school-associated vaccination for a variety of vaccines. One thing that has been striking in assessing the data over the last few years is that the very high coverage with Tdap and meningococcal conjugate has not been delivered through schools. Those have been delivered primarily through the medical home. When the data for missed opportunities are analyzed, if every time a teen was receiving a Tdap or meningococcal vaccine they were offered and accepted and HPV vaccine, the first dose coverage could be 90%. In terms of whether school strategies are needed or are even cost-effective in the US, now that there is a pretty strong adolescent platform upon which to build, it is believed this can be done through the medical home if clinicians will make strong recommendations. There have also been some disappointing results in some of the school programs for influenza and other vaccines, so the medical home is probably the best location for this vaccine.

Dr. Temte reported that his state has one school nurse per every 1950 students, who spend all of their time administering stimulant medication and going on field trips with diabetics. There is simply no time for anything else at this point.

Dr. Bocchini recognized Dr. Markowitz, who has been the Designated Federal Official (DFO) for the HPV WG since its inception, for all of her contribution to the work of the committee. He also thanked the committee members who have worked hard over the years to bring them to this point.

Ms. Hayes (ANA) indicated that she shared an erroneous statistic earlier. The abortion rate in the US has dropped to 22%.

Day 1: Public Comment

No public comments were offered during this session.

Unfinished Business: Farewell to Dr. Turner

Dr. Temte announced that this would be Dr. Jim Turner's last meeting as the liaison from the American College Health Association (ACHA). Dr. Turner has served in this role for the last 12 consecutive years, missing only one meeting during that timeframe. That is a very long run of participation, and often quite passionate participation representing the views of post-adolescents. Dr. Turner is the Executive Director of the Department of Student Health at the University of Virginia. He is a professor of internal medicine, and a kindred spirit as a fellow graduate of the University of Wisconsin Medical School, and an avid Badger fan. He has served as the President of ACHA, and was the Chair of the Vaccine Preventable Disease Section of ACHA from 1999 through 2008. He has participated in numerous ACIP WGs. ACIP will sorely miss Dr. Turner's enthusiasm, wisdom, and wonderful representation of the college health population.

Dr. Turner responded that he had chosen to step down from his position to spend a couple of years conducting research on health trends in college students. Having been a director for 20 years, he said it was time to get up in the morning and do something he really wanted to do other than administrative activities. In his 40 years of work, serving on ACIP has been absolutely the most gratifying and important work he has done. He first began attending in the late 1990s to advocate for meningitis vaccine for students. He remembered Nancy Rosenstein asking him, "What makes you think you can give meningitis vaccine to college students?" This was prior to any policy, and now two-thirds to 70% of students are vaccinated. They rarely, if ever, see vaccine-preventable diseases on their campuses. This is because of the work of this body. It has been terrific. He thanked everyone for the friendships and the collegiality.

Rotavirus Vaccines

Introduction: Intussusception Following RV5 and RV1

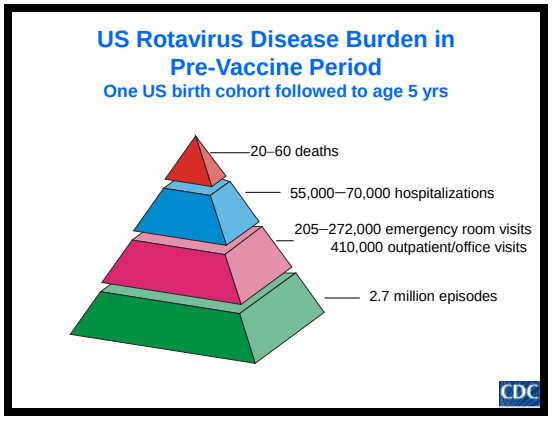
Marietta Vázquez, MD
Chair, ACIP Rotavirus Vaccines Work Group

Dr. Vázquez reminded everyone that the Rotavirus Vaccine WG was reconvened in February 2013, and updated data on intussusception and rotavirus vaccines would be presented during this session. These new data were presented to the WG and come from both US monitoring systems and Australia. This was the seventh presentation to the ACIP on results of intussusception monitoring in the US since introduction of rotavirus vaccines in 2006.

Given experience with RotaShield® vaccine, the rotavirus vaccines now used routinely in the US were licensed after large Phase III trials were conducted to permit evaluation of intussusception. The trials showed that these vaccines, RV1 (Rotarix®) and RV5 (RotaTeq®), were not only efficacious but also that their rates of intussusception were similar in the vaccinated and placebo arms. Post-marketing surveillance for intussusception became and continues to be an important focus.

Shortly after each vaccine was licensed by the FDA, ACIP recommended these vaccines to be used for all US age-eligible children. RV5 is a 3-dose series administered at 2, 4, and 6 months of age and RV1 is 2 doses administered at 2 and 4 months of age. The minimum age for Dose 1 is 6 weeks and the maximum age is 14 weeks 6 days. The minimum interval between doses is 4 weeks, and the maximum age for the last dose is 8 months 0 days.

The following graphic illustrates the US rotavirus disease burden during the pre-vaccine period for one US birth cohort followed to age 5 years:



Rotavirus vaccines have had a marked impact on disease burden in the US. Hospitalization data from the large MarketScan database on diarrhea and rotavirus-coded hospitalizations for children under five years of age from 2001 through 2009 show that from 30,000 to 40,000 hospitalizations for rotavirus disease were prevented nationally in 2008 and 2009 [Cortes J, Curns A, Tate, J et al N Engl J Med 2011]. Similarly to what was observed in the US, rotavirus vaccines have also had a positive impact outside of the US. RV1 was introduced in Mexico in

2007. Based on the data, there has been a decrease in deaths due to diarrhea in the infant population targeted by the rotavirus vaccination program since its inception there [Richardson V J et al N Engl J Med 2010; Richardson V, Parashar U, Patel M N Engl J Med 2011].

In terms of the background rate of intussusception hospitalizations in the pre-vaccine era in US infants from 1993 through 2004, the baseline incidence begins rising around 7 weeks of age, at which time rotavirus vaccines are given, and peaks around 32 weeks of age. The change in baseline rate needs to be accounted for in intussusception evaluations [Tate et al. Pediatrics 2008; 121;e1125-e1132]. Most studies that evaluate intussusception risk following rotavirus vaccines use the Brighton Collaboration criteria, with Level 1 being the highest level of diagnostic certainty, and based on surgical, radiographic, or autopsy findings.

The post-marketing study results available on intussusception and rotavirus vaccines were presented during the October 2010 ACIP meeting. A few of the results were not quite finalized during that meeting. For RV5, data from the VSD did not detect an increased risk. A post-marketing study by Merck examined the 3 doses combined and did not detect a risk. A study conducted in Australia using historical rates of intussusception suggested a risk following Dose 1 of RV5 in their population.

Regarding the main previously available post-marketing studies on RV1 and intussusception, due to its later introduction into the US market, data were not available for the US at the time of the ACIP meeting in 2010. In Mexico, a risk was detected following RV1 after the first dose in studies that were conducted by PAHO and CDC, and subsequently in a study conducted by GSK. In Brazil, a smaller risk was detected after the second dose of the vaccine, but not with the first dose. In Australia, a risk was suggested following the first dose, but was not statistically significant. The Rotavirus WG reviewed earlier data and the newly available data presented during this session.

A number of actions were taken by CDC and the partner agencies after the post-marketing studies from outside of the US showed a risk of intussusception with the newer rotavirus vaccines. During the October 2010 meeting, the results of a risk-benefit analysis were presented. Although a risk had not been detected in the US at that time, a lower risk could not be ruled out. The analysis estimated the risks and benefits of the vaccine program for the US if an intussusceptions risk existed at the level of that detected in Mexico. Communication materials were developed or updated, including the vaccine information statement to inform providers and parents of the possible risk. The FDA approved revised labeling for RV1, and a process was initiated for adding intussusception to the Vaccine Injury Table of the Vaccine Injury Compensation Program. Monitoring for intussusception continued through established US safety monitoring systems.

There are now new and updated safety data from the US and Australia on both FDA licensed rotavirus vaccines, which were presented to the WG and were presented to ACIP during this session.

Vaccine Safety Datalink Data

Eric Weintraub, MPH
Chair, ACIP Rotavirus Vaccines Work Group
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Mr. Weintraub presented an update on the rotavirus vaccines and intussusception within the VSD. As a reminder, the VSD was established in 1990. It is a collaborative project among CDC and 9 medical care organizations. It allows for planned immunization safety studies as well as timely investigations arising from hypotheses from medical literature and pre-licensure, reports to VAERS, changes in immunization schedules, and most importantly, the introduction of new vaccines. In 2013, the VSD sites include Group Health Cooperative, Northwest Kaiser Permanente, Northern California Kaiser Permanente, Southern California Kaiser Permanente, Health Partners, Kaiser Permanente Colorado, Marshfield Clinic, Harvard Pilgrim, and Kaiser Permanente Georgia. The VSD collects medical care and vaccination data on more than 9.2 million members annually, which is about 3% of the US population. The average yearly birth cohort is approximately 96,000.

The VSD has previously published manuscripts on rotavirus vaccine safety, which showed that no increased risk of intussusception has been found for pentavalent rotavirus vaccine (RV5) in the VSD. In a publication from 2010, which was the Rapid Cycle Analysis (RCA) surveillance manuscript, in a study of 207,621 doses, no evidence was found that RV5 was associated with intussusception during days 1 to 30 after vaccine administration[1]. That manuscript was later updated in 2012 after 786,725 doses of RV5 vaccine were administered, including more than 300,000 first doses, showing no increased risk of intussusception following RV5 in 1 to 30 day or 1 to 7 day risk windows[2]. An excess risk of 1 event per 65,287 RV5 vaccines following dose 1 can be reliably excluded from the study, but the possibility of a lower-level risk could not be ruled out [[1]Belongia EA et al. Pediatr Infect Dis J 29: 1-5, 2010; [2]Shui IM et al. JAMA 307: 598-604, 2012].

Mr. Weintraub then presented three analyses that were conducted, which were previously presented to the WG. The first analysis was RV1 RCA real-time surveillance using historical background rates. The case definition for intussusception was an ICD-9 coded medical visit, not chart-confirmed. The second was an RV5 cohort update, again using historical background rate and an ICD-9 coded medical visit. In thinking about conducting RV1 surveillance, consideration was given to what would be done for confirmatory analysis if there was a signal. For this, the next step was an RV1 compared to an RV5 analysis with a concurrent vaccinated cohort. That analysis was restricted to Brighton definition chart-confirmed cases.

The objective of Analysis 1, the RV1 RCA surveillance for intussusception, was to monitor for an increased risk of intussusception during 1 through 7 days after receipt of RV1. This is the same type of RCA that has been done for other vaccines as they have entered the market. Following licensure and the ACIP recommendation of the vaccine, there was not sufficient uptake of RV1 to monitor within the VSD until about mid-2012. The population was restricted to 6 VSD sites, including Northern and Southern California Kaiser, Group Health Cooperative, Northwest Kaiser, Kaiser Colorado, and the Marshfield Clinic. Important to note is that the large Northern and Southern California Kaiser sites were two of these. The analysis was among infants 4 through 34 weeks of age who were vaccinated between April 2008 and March 2013. The intussusception case definition was based upon the ICD 9 codes 543.9 (other and unspecified disease of the appendix including intussusceptions) and 560.0 (intussusceptions). For the

purpose of surveillance, the analysis was limited to first diagnosis from the emergency department and inpatient settings.

In terms of the methods for Analysis 1, a prospective cohort design was used to assess the risk of intussusception among children receiving RV1 compared to expected numbers of intussusception based on historical background rates. The historical background rates were stratified by age in weeks and VSD site, and were restricted to recent years prior to RV1 or RV5 on the market 2001 through 2005. Sequential analysis methods were utilized to monitor the risk on a weekly basis, and maximized sequential probability ratio test (maxSPRT) was used to adjust for the repeated weekly testing. One of the differences incorporated for this analysis is that a minimum of 3 cases was required to have a signal.

With regard to the results, for the purpose of the sequential analysis, the statistical test is the log likelihood ratio (LLR) compared to the critical value. Analyses included All Dose, Dose 1, and Dose 2. For All Doses, 6 cases were observed. The expected number of cases was 0.716. The resulting ratio for observed versus expected was 8.376. The LLR was 7.469, which was above the critical value of 2.565. For the purpose of the VSD, this would be called a signal because it is an elevation. For Dose 1, only two cases have been observed. A minimum of 3 were needed, so technically the LLR was not applicable and could not exceed the critical value. The observed of 2 was above expected of 0.227, and the observed versus expected of 8.818 was consistent with the All Doses. The same was true with Dose 2, with 4 cases observed, 0.489 cases expected, and observed versus expected of 8.172. The LLR of 4.892 for Dose 2 exceeded the critical value of 2.151. These are automated data, which were not chart-confirmed at this point.

The next step in this analysis was to calculate an attributable risk per 100,000 doses. For Dose 1, there was an attributable risk of 1.53, which is one additional case per 65,374 infants. For Dose 2, the attributable risk was 3.81, which is one additional case per 26,217 infants. Compared to Mexico and Brazil, there appears to be an increase following Dose 1 and Dose 2. When those doses are combined, the resulting attributable risk is approximately 5.34 per 100,000 infants or 1 additional case of intussusception for every 18,713 infants vaccinated with the RV1 series.

One of the major questions that always arises with historical comparisons regards temporal trends or increasing diagnoses over time. To assess this, Days 8 through 30 were also evaluated. The observed versus expected ratios were all between 1 and 2 and were much more attenuated than the previous figures. If this were being driven by any increase in trend in the diagnosis over time, it would be expected to be observed in Days 8 through 30. However, this has not been observed within the VSD. When signals are observed in the VSD, the next step is typically to perform a cluster scan to determine whether there is a clustering of cases. The cases were collected for Days 1 through 30. The cluster analysis detected a significant cluster in Days 3 through 6. There were only 10 total cases during the entire time period.

The next phase was to provide an RV5 cohort update to the WG. Analysis 2 was an update to the VSD RV5 findings published by Shui et al in the *Journal of the American Medical Association* (*JAMA*) in February 2012. The methods for the second analysis were the same as Analysis 1 except that this analysis is of RV5 vaccination, the study period was May 2006 through March 2013, and a one-time analysis was conducted versus weekly prospective surveillance. Therefore, there were confidence intervals around these estimates whereas previously there were not.

To date, 1.3 million doses were observed. There were 8 cases observed within the 7 days, expected was 7.11, observed versus expected was 1.13, and the 95% confidence interval was 0.49 - 2.22. A dose-specific analysis was conducted for Analysis 2 as well. For Dose 1, 4 cases were observed, expected cases were 1.52, observed versus expected was slightly elevated at 2.63, but the 95% confidence intervals were still not significant at 0.72 - 6.74. It is known that 2 of the cases for Dose 1 were not chart-confirmed. For Dose 2, zero cases were observed, expected was 2.37, so there is no observed versus expected. For Dose 3, at the peak of intussusception, 4 cases were observed, expected were 3.2, observed versus expected was 1.25, and the 95% confidence interval was 0.34 - 3.20. Thus, the same type of increase is not being observed with RV5 as with RV1 using the same methods.

An RV5 cluster analysis was conducted to assess the number of intussusception cases by days. With RV5 a significant cluster was not detected, so no timeframe stood out as a significant timeframe that clustered. It is important to note that there have been cases of intussusception following Dose 2, but they have not occurred within Days 1 through 7. They occurred from Days 10 through 30.

Analysis 3 was a comparison of RV1 to RV5. Medical charts were reviewed for all cases of intussusception regardless of setting, and outpatient visits were reviewed for this piece as well, within 1 through 7 days of any RV1 or RV5 vaccination. Cases were classified according to the Brighton Collaboration case definition and were reviewed by 2 independent adjudicators. A third review was conducted if the independent adjudicators disagreed. An analysis was conducted on chart-confirmed intussusception cases within 1 through 7 days following RV1 compared to RV5 vaccination. This analysis was restricted to Brighton Collaboration Level 1 cases only. The risk of intussusception following RV1 was compared to the risk following RV5 during the time period April 2008 to March 2013. An exact logistic regression was performed.

In terms of the chart confirmed intussusception case findings for Days 1 through 7 following vaccination, 7 cases were reviewed following RV1 and 9 following RV5. For RV1, 5 cases (71%) met Brighton Level 1 criteria, 2 of whom met the surgical criteria and 3 of whom met the radiologic criteria. Given that 1 was Brighton Level 2 and 1 was not a case, the result was 6 confirmed cases. For the 9 RV5 charts reviewed, 6 (67%) were Brighton Level 1. Of these, 1 met the surgical criteria and 5 met the radiologic criteria. None were Brighton Level 2 and 3 were not cases, resulting in 6 total confirmed cases. For age in weeks the mean was 15 for RV1 and 22 for RV5, which is slightly different because of the 3-dose schedule. A somewhat odd finding for RV1 was that none of the cases were male, which is probably a chance finding. For RV5, 50% were male. Of the cases for RV1 and RV5, 100% were hospitalized. The length of stay was very consistent at 1.6 days for RV1 and 1.5 days for RV5. Very importantly within VSD, none of these cases had died. Moving forward, it was important to assess whether these vaccines were being administered at the same timeframe in an infant's age. In terms of the total number of doses of RV1 and RV5 in the VSD, there was consistency between the doses in terms of the age in weeks when the vaccines were delivered. Assessing this by dose, it was found that Dose 1s and Dose 2s were given at the same time.

With regard to the results comparing RV1 to RV5 Brighton Level 1 intussusception cases, there were 5 total confirmed Brighton Level 1 cases following 207,955 doses of RV1. There were 6 total confirmed Brighton Level 1 cases following 999,123 doses of RV5. As a reminder, this is from 2008 forward, about 400,000 doses were not included in this analysis for RV5. For Dose 1, there were 2 confirmed cases following 115,908 doses of RV1 and 2 confirmed cases following 355,944 doses of RV5. For Dose 2, there were 3 confirmed cases following 92,047

doses of RV1 and no confirmed cases following 345,025 doses of RV5. For Dose 3, there were 4 confirmed cases following 298,104 doses. There is no Dose 3 for RV1.

For the purposes of the next analysis, relative and attributable risks were calculated. Based upon the similarities of the vaccine administration, the logistic models were focused only on Doses 1 and 2. In terms of the exact logistic regression for RV1 compared to RV5 restricted to Brighton Level 1 intussusception cases, for Dose 1 there was a resulting relative risk of 3.07, and the 95% confidence intervals were 0.22 - 42.37. It was underpowered, so the p-value was 0.509. Because there were zero cases following Dose 2 of RV5, the relative risk and upper confidence bounder were undefined. However, there was a significant p-value of 0.0187. In addition, crude relative risk was calculated for Doses 1 and 2 combined. The result was a relative risk of 8.43, with a 95% confidence interval of 1.38 - 88.50 and a significant p-value of 0.0173. Adjusting for age and site for Doses 1 and 2, the relative risk was 9.37 with a very wide 95% confidence interval of 1.42 - 103.84 and a significant p-value of 0.0163. Another model was done that included Dose 3. Adjusting for dose resulted in a nearly identical relative risk of approximately 9.1. Some precision was gained, but it was felt that validity in the model was lost by including Dose 3 in the analysis.

The next step was to calculate risk differences for RV1 compared to RV5, again restricted to Brighton Level 1 intussusception cases. For Dose 1, the risk per 100,000 was 1.73 for RV1 and 0.56 for RV5. The risk difference per 100,000 was 1.16, which is one additional case per 95,933 infants. For Dose 2, the risk per 100,000 was 3.26 for RV1 and 0 for Dose 2 of RV5. The risk difference per 100,000 was 3.26, which is 1 additional case per 30,682 infants. When combining the two, the risk difference was 4.42 per 100,000. The 95% confidence interval for that attributable risk was 0 - 8.89. The result is 1 additional case per 22,610 infants vaccinated with the RV1 series compared to RV5 when restricted to Doses 1 and 2, with a 95% confidence interval of undefined - 11,250.

In summary, the VSD study found a statistically significant elevated risk of intussusception following RV1 within 1 through 7 days of vaccination. The risk was increased following both doses of RV1. After analyzing over 1.3 million doses, no significant increased risk was identified following RV5. The increased risk for RV1 and intussusception was similar when historical and concurrent chart-confirmed studies were conducted. For the historical comparison, the attributable risk was 5.34 per 100,000 infants, which is approximately 1 additional case for every 18,713 infants vaccinated with the RV1 series. For the concurrent RV5 comparison restricted to Brighton Level 1, the risk difference was 4.42 per 100,000 infants, which is 1 additional case for every 22,610 infants vaccinated with RV1 series versus an RV5 series and restricted to Doses 1 and 2.

Vaccine Adverse Event Reporting System Data

Ms. Penina Haber, MPH
Immunization Safety Office
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention

Ms. Haber summarized the reports for intussusception after rotavirus vaccines for both vaccines from 2005 through 2012. She reminded everyone that VAERS is a national surveillance system that receives adverse event reports following vaccination. This system is co-managed by CDC and FDA. The primary strengths of VAERS include rapid signal detection, the ability to detect rare adverse events, generation of hypothesis, encourages reports from healthcare providers

and accepts reports from patients and others. Data are available to the public. The main limitations of the system include reporting bias (e.g., underreporting, stimulated reporting), inconsistent data quality and completeness, inability to assess whether a vaccine caused an adverse event, and the lack of unvaccinated comparison group.

A 2008 analysis from VAERS suggested clustering of intussusception reports during 3 to 6 days after the first dose of RotaTeq® (RV5) and after approximately 9 million doses of RV5 were distributed in the US. The study objectives were to update evaluation of temporal clustering of intussusception reports to VAERS after RotaTeq® (RV5); and to present descriptive data of VAERS intussusception reports after Rotarix® (RV1). All intussusception reports were assessed among infants less than 1 year of age reported to VAERS during February 2006 through April 2012 for RV5 and February 2008 through December 2012 for RV1. All intussusception reports were verified using the Brighton Collaboration Level 1 case definition for intussusceptions. Vaccine history and dose number were ascertained via immunization records [Brighton case definition Level 1: Documented on autopsy, surgery or radiologically; Tapiainen T, Vaccine 2006 24(9); 1483-7].

A self-controlled risk interval (SCRI) analysis[1] was conducted using conditional Poisson regression to estimate the daily reporting ratio (DRR) of intussusception comparing average daily reports 3 to 6 versus 0 to 2 days after vaccination. Reporting rate differences were calculated based on DRRs and background rates of intussusception[2] from VSD data during 2005 when there was no vaccine in the US. The excess number of events in the US was estimated based on number of births per year and vaccine coverage similar to that of a mature vaccination coverage of diphtheria tetanus acellular pertussis (DTaP) vaccine. Few reports were submitted after Rotarix® (RV1), allowing only a descriptive analysis [[1]Weldeselassie YG, et al. Use of the self-controlled cases-series methods in vaccine safety studies. Epidemiol Infect 2011;139 (12):1805-17; [2]Background rates from VSD hospital discharge data and ER visits for intussusception during 2000-2006, when no rotavirus vaccine was in use in the US].

From 2006 through 2012, approximately 47 million doses of RotaTeq® (RV5) were distributed in the US. VAERS received a total of 6989 RV5 reports. Of these, 657 (9.4%) were intussusception reports, 584 (89%) were confirmed intussusceptions, 182 (31%) were after Dose 1, and 60 (33%) occurred within 0 through 6 days. Approximately 7.4 million doses of Rotarix® (RV1) were distributed in the US. VAERS received a total of 678 total RV1 reports. Of these, 71 (21%) were intussusception reports, 66 (93%) were confirmed intussusceptions, 31 (47%) occurred after Dose 1, and 13 (42%) were within 0 through 6 days. Of the 584 RotaTeq® (RV5) cases, 544 (93%) were hospitalized. Of those, 266 (45.5%) had surgery. Of the 266 who had surgery, 73 (28.6%) had bowel resections and there were 2 death reports. Of the 66 Rotarix® (RV1) reports, 64 were hospitalized. Of those, 37 (56%) had surgery. Of the 37 who had surgery, 3 (8%) had bowel resections and there were no death reports.

In terms of the reporting pattern following Dose 1 of RotaTeq® (RV5), the peak for non-intussusception was 0 to 1 day and the peak for intussusception was 3 to 6 days post-vaccination. Of the confirmed reports, 182 (31%) occurred after Dose 1. After Dose 2, there were 233 (40%) reports and a similar pattern after about 3 to 6 days, but this was not significant. This was also not significant after Dose 3 for which there were 169 (29%) reports. For Rotarix® (RV1), there were 66 reports and there was clustering between Day 4 and Day 7. It is important to note that for Dose 1, there are no reports prior to Day 4. After Dose 2, there were 29 reports and an increase in Day 4.

Regarding the daily reporting ratios and excess risk of intussusception after RotaTeq® (RV5) using the self-controlled risk interval analysis for VAERS data, there were 50 reports at 3 to 6 days and 10 reports at 0 to 2 days. The daily reporting ratio was 3.75 with a confidence interval of 1.90 to 7.39. The excess risk per 100,000 infants was 0.74 and the excess cases in the US per year related to rotavirus vaccine was 30.1 with a confidence interval of 9.8 to 69.9. For Doses 2 and 3, there was no significant difference when the same comparison was made. When all three doses were compared, the excess rate was 0.79 per 100,000 vaccinations. This translates to 33 additional events per year in the US under a fully mature rotavirus vaccination program.

In terms of limitations, applying the SCRI method to VAERS generally violates a key criterion of self-control designs that ascertainment of cases should not be influenced by exposure history; however, the analysis was limited to a narrow time window of 0 to 6 days and 0 to 2 day interval as the comparison time period. Since reporting efficiency is likely to be greatest in the first few days after vaccination, using the 0- to 2-day window as the comparison period should result in conservative relative risk estimates. Lower reporting of cases in days 0 to 2 after Dose 1 could occur due to a possible healthy vaccinee bias; however, the presence of a significant signal after the first dose but not the second or third dose argues against this bias.

In summary, a persistent clustering of reported intussusception events 3 to 6 days after the first dose of RV5 vaccination was observed. This clustering could potentially translate to 33 additional events per year in the US, which is outweighed by the benefits of rotavirus vaccination of about 40,000 diarrhea hospitalizations prevented annually in the US since rotavirus vaccine introduction. It was not possible to quantify the risk after RV1 due to the small number of reports in the US.

Discussion

With respect to the comparison of RV1 versus RV5 versus 2-dose, Dr. Duchin said that to him it would make more sense to compare one series to the other (e.g., the risk of intussusceptions associated with being vaccinated with the complete series of one product versus the other). He also request clarification regarding the 7-day cutoff for the detection of intussusception in the analysis and whether it would be useful to extend that time period out to determine whether the risk changed 10 or 14 days post-dose.

Mr. Weintraub responded that when the model strategies were being developed, the original comparison was both doses of RV1 compared to all three doses of RV1. When that analysis was performed, the resulting relative risk was nearly identical to what he presented of 9.1. The confidence intervals were somewhat tighter. It is known that there really is not an attributable risk for Dose 3, so an additional analysis combining Dose 3 with Dose 2 for RV5 and the attributable risk slightly decreased from 1 in every 26,000 versus 22,000. The selection of the 7-day cutoff had to do with biologic plausibility and was based upon the literature from VAERS and the previous studies that have been conducted. From a VSD perspective, if the statistical scan picked up a different timeframe that was clustering, they probably would have focused on that as a secondary analysis. Because it did not, the 7-day cutoff was utilized. Days 8 through 30 were also analyzed as a comparison to the 7-day analyses.

Dr. Sawyer requested information about how intussusceptions cases are verified in the VAERS system. He was surprised at how many of the initial reports were actually verified as true cases of intussusception in contrast to the VSD data where about a third turned out not to be cases when chart confirmations were done.

Ms. Haber replied that every time there is a report of intussusception and all similar codes, the medical records are obtained, such as hospital discharge. They try to do this as the cases are identified. They were able to obtain all of the medical records necessary to verify them. Only Brighton Level 1 cases were included in the analyses. Immunization records were also obtained to ensure that the vaccine was given and what dose it was.

Dr. Temte asked whether the two deaths were also verified. Ms. Haber replied that they were.

Dr. Brady (AAP) thought one thing this suggested was that live virus vaccine has the potential to cause intussusception. The data only assess a very short period of time. He wondered whether a VSD assessment out to 2 years of age would show that the reduction in intussusception that occurs by reducing rotavirus would significantly outweigh the increased number of cases. This would be very valuable to understand from a public health perspective because it may be that if rotavirus is attenuated it results in some cases, but the actual natural disease results in a lot more.

Dr. Parashar responded that Dr. Cortese would be presenting some information on population level trends and intussusception from the Healthcare Cost and Utilization Project (HCUP) database, which is a national hospitalization database. An analysis is planned in the VSD to assess long-term rates after vaccination compared to unvaccinated infants. One of the challenges is the statistical power needed to evaluate this issue. Even if there is a small decrease in a later time period, because the time period is so much longer than the one week increase, it could very well offset the one-week increase. Those findings will be presented during a later meeting.

Postlicensure Rapid Immunization Safety Monitoring System

W. Katherine Yih, PhD, MPH
Harvard Pilgrim Health Care Institute

Dr. Yih explained that the Postlicensure Rapid Immunization Safety Monitoring System (PRISM) is part of the FDA-sponsored Mini-Sentinel pilot program to conduct surveillance for medical product safety. PRISM data partners are national health insurance companies, so data in this system are claims data. The various data partners contribute data for slightly different time periods, but the maximum period in this study is from 2004 through mid-2011. Thus, some years of data are available from before rotavirus vaccine was available. This unexposed period was used in one of the analyses.

In the claims data, the way doses of rotavirus vaccine are identified is through Current Procedural Terminology (CPT) codes, which are specific for the two vaccine brands: CPT-4 codes 90680 (RotaTeq®) and 90681 (Rotarix®). In some PRISM projects, state immunization registry data are used to ascertain exposure to certain vaccines, but this was not done in this rotavirus vaccine safety study. For intussusceptions, an algorithm was used of scanning the claims data for first-ever of any of three codes in the emergency department or inpatient setting: ICD-9 code 560.0 (intussusception), ICD-9 code 543.9 (unspecified diseases of appendix, including intussusception), and CPT-4 code 74283 (therapeutic enema, contrast or air, for reduction of intussusception or other intraluminal obstruction). Chart review was done to confirm intussusception diagnoses and to confirm the rotavirus vaccination status (specific vaccine, dose number, age) of intussusception cases. To keep the chart review process somewhat manageable, the group for whom the chart reviews were conducted was restricted to 5 to 36 weeks of age. This covered the recommended vaccination ages (2, 4, 6 months) plus

follow-up time to look for intussusception cases. Charts were reviewed for unvaccinated cases as well, because those were included in one of the analyses. The adjudicators of the intussusception cases were blinded to the vaccination status to avoid any unconscious bias that knowledge might have introduced. The adjudicators used the Brighton Collaboration criteria. Only Brighton Level 1 cases, the ones of highest diagnostic certainty, were included in the analyses [J Bines et al. *Vaccine* 2004;22:569-574]. A sensitivity analysis was performed that included the Level 2 cases, but Dr. Yih did not present the results of sensitivity analyses during this session.

The algorithm identified 343 potential cases. Charts were obtained for 267 (78%). Of that number, 124 (46%) were confirmed as intussusceptions at Brighton Level 1. That resulted in a positive predictive value of 46%. There were 20 (7%) cases classified as Brighton Level 2 for the secondary analyses. There were approximately 1.3 million total doses of RotaTeq®, similar to VSD. Of these, just over half a million were first doses. There was fully an order of magnitude fewer doses of Rotarix®, which affected the statistical power to study that particular vaccine. Age had to be adjusted for to avoid bias in the analyses, because it is associated with both the outcome and the exposure, given the recommended ages for vaccination.

Two designs were used. The primary design was the self-controlled risk interval design, which is also commonly used by the VSD for influenza vaccine safety surveillance, for example. This includes vaccinated infants only. The secondary design was the cohort design, including all infant-time in the 5-36-week age range, regardless of rotavirus vaccination. The self-controlled risk interval design using the vaccinated cases, specifically included the cases that had intussusception either in a pre-specified risk window or a pre-specified control window. The risk windows used were 1 to 7 days and 1 to 21 days. For both of those, the comparison window used was 22 to 42 days after vaccination. Only vaccinated children who had had a case of intussusception in a risk or comparison window would have been included in these self-controlled analyses. Each of the children is contributing person time in the risk as well as the control window, which controls very nicely for risk factors that do not vary with age (e.g., sex, race, ethnicity, underlying chronic conditions that last for a while that might influence the probability of getting intussusception and the probability of being vaccinated on time, et cetera). Logistic regression was used for the analysis, with an offset term to adjust for the differential risk of intussusception at the ages in the risk versus the comparison windows. With the cohort design, person time from exposed and unexposed infants in the age range for which chart review was done was incorporated. Analysis was by Poisson regression for the cohort design, adjusting for age using a polynomial function in the model. The function that fit the data best was a quadratic function.

These designs are somewhat complementary. The major advantage of the SCRI design is that it controls well for fixed risk factors such as race/ethnicity. A possible downside is that it requires accurate age-specific incidence for the age-adjustment. Based on descriptive statistics, there was not a nice precise risk function of the risk of intussusceptions with age but rather there was a lot of scatter in the data. However, it was known from the paper by Tate and colleagues that there was a good deal of precision around the curve from the HCUP hospital discharge data, given the inclusion of 11 years worth of data from dozens of states and more than 3400 intussusception cases [Tate et al. 2008]. Also, although the case ascertainment methods were somewhat different for HCUP and PRISM, there was no concern about possible differences in the *absolute* incidence in the HCUP population versus the PRISM population, because for the offset term, only the *shape* of the curve matters, and there was no reason to think that the shape of the curve would differ between the two populations. The great strength of the cohort design is its higher statistical power from the fairly large amount of historical and

concurrent unexposed person time that gets used in the generation of the expected counts. A downside is that it could be affected by residual confounding and does not have the nice self-controlled character of the other design. Both designs were used, pre-specifying that the self-controlled design would be primary.

As a reminder, there were two risk windows, 1 to 7 days and 1 to 21 days, and the various doses were analyzed as well. The original intent was to use both designs with both risk windows; however, resource constraints for programming within the PRISM program as a whole led to a decision to make do with just the 1 to 21 day window for the cohort design, since it was a secondary design. (Data already available for descriptive purposes used the 1- to 21-day window, and these data could be (and were) used to create a Poisson regression dataset for the cohort design. It would have taken too much programmer time to create the corresponding dataset with the 1 to 7 day window, given other demands. Furthermore, creation of such a dataset would have entailed using data from a source that had been refreshed several times since the original data had been obtained, which would have led to discrepancies in case counts.) The fact that the cohort analyses used only the 1-21-day risk window is a limitation.

In terms of the results for RotaTeq® attributable risks by dose number, study design, and risk window, for Dose 1 the point estimates for these attributable risks varied between about 1.1 to 1.5 per 100,000 first dose vaccinees. This was for the two designs and the two risk windows, and all of the results were statistically significant. Doses 2 and 3 did not appear to confer an increased risk of intussusception. The 1 to 7 day risk window for Doses 2 and 3 had point estimates that appeared to be somewhat higher than 0, but these were not statistically significant. Thus, Dose 1 seems to be the dose of concern for RotaTeq®.

For Rotarix®, only about a tenth as many doses of that vaccine were administered in this population, and there were many fewer cases. Given that for Dose 1 there was only one case in the risk window (true for both the 1 to 7 and the 1 to 21 day windows) and zero in the control window, it was not possible to calculate a confidence interval. With the cohort analysis, there was not a statistically significant elevated risk either. In terms of Dose 2, for the self-controlled design with the two different risk windows, there was not a statistically significant elevated attributable risk. For the cohort design, which was the secondary design, the risk estimate was approximately 7.3 cases per 100,000 second-dose vaccinees, which was, in fact, statistically significant. However, since this result was not clearly supported by the primary design, Dr. Yih concluded that the picture was less clear with Rotarix® than with RotaTeq, related to the lower numbers of doses and cases for Rotarix®.

To evaluate clustering of onset timing after vaccination, temporal scan statistics were used that evaluated all potential risk windows starting 1 to 14 days after vaccination and ending 1 to 21 days after vaccination. Due to the multiple potential cluster periods that were evaluated, adjustment had to be made for multiple testing. Age was also adjusted for using the age-specific incidence curve from Tate et al. and a randomization method, because otherwise, after Dose 1, there would tend to be more doses later after vaccination due purely to the increasing natural background incidence at this age. Analyses were conducted using SaTScan™, which is freely available software. Highly statistically significant clusters were found in Days 3 to 7 after RotaTeq® vaccination for both the Dose 1 and All Doses analyses. For Rotarix®, there was just one case in the 42 days following Dose 1. There were a few more cases in the All Doses analysis, where a statistically significant cluster was found on Day 4 after vaccination.

In conclusion, for RotaTeq®, Dose 1 was found to be associated with an increased risk of intussusception in both the risk windows of 1 to 7 and 1 to 21 days after vaccination. Statistically significant clustering was found on Days 3 to 7 after vaccination, for both Dose 1 and all doses combined. The point estimates for all Dose 1 attributable risks ranged from 1.1 to 1.5 per 100,000 first doses. With the 3 estimates (from the self-controlled design with each of the two risk windows and from the cohort design), the lowest of the lowest bounds of the 95% confidence intervals was 0.2 excess cases per 100,000 first-dose vaccinees and the highest of the highest bounds was 3.2 excess cases per 100,000 first-dose vaccinees. Those correspond to about 1 case per 520,000 first doses at the low end and about 1 case per 30,000 first doses at the high end. There was lower statistical power for Rotarix®, and the results were not as clear. There were 103,098 total doses, of which 53,638 were first doses. Nonetheless, a statistically significant cluster was found on Day 4 after vaccination. The attributable risk results for Rotarix® were also suggestive of an increased risk.

Discussion Points

Dr. Temte said he thought it was wonderful to have all of these systems in place for vaccine safety, all of which were showing relatively consistent findings.

Dr. Harrison asked Dr. Yih to help put these data in perspective relative to the data from RotaShield®.

Dr. Yih responded that the data from RotaShield® came from several different studies, and the attributable risk was estimated to be between about 1 and 2 excess cases per 10,000 (so in terms of the denominator used in the PRISM presentation, 10 to 20 per 100,000). The PRISM estimates for RotaTeq® were only about a tenth of that, varying between about 1.1 and 1.5 excess cases per 100,000. Thus, the RotaTeq® findings are quite reassuring relative to RotaShield®. Regarding Rotarix®, she said she would not stand by any specific magnitude of risk from the PRISM data. Perhaps the VSD data would be more appropriate to consider. The one point estimate in the PRISM data for Rotarix that was statistically significant was 7.3 excess cases per 100,000 second-dose vaccinees—somewhat less than the 10 per 100,000 that was found for RotaShield®. But she reiterated that she did not have much confidence in that specific number from PRISM.

Intussusception and Rotavirus Vaccines in Australia

Peter McIntyre MBBS, PhD
National Center for Immunisation Research and Surveillance

Dr. McIntyre reminded everyone that Australia had a certain ownership feeling about rotavirus, because in 1973, rotavirus was discovered in Melbourne by the team of Professor Ruth Bishop and colleagues. The next significant event in relation to rotavirus was following the introduction of the RotaShield® vaccine, and a long time has passed while waiting for the new generation vaccines RotaTeq® and Rotarix®, which were adopted in 2006 in Vaccines for children. It was only one year later that they were included on the National Immunisation Program in Australia. Thus, Australia has quite a long experience even though the population size is much smaller than the US. Also unique is that Australia is using both vaccines simultaneously.

The first Australia data that suggested issues with the first dose were published in 2010 [First published study of association between both rotavirus vaccines and IS (dose 1) from Australian PAEDS network: Buttery et al, *Vaccine* 2011 (February)]. The Mexico study data were published that same year [Association between Rotarix and IS, predominantly post dose 1 in Mexico: Patel et al, *NEJM* 2011 (June). Statements were made by a variety of groups in 2010, including ACIP, related to the overwhelming benefits. In early 2011, a statement based on the data from the expanded Australia study required extensive consideration by their advisory committees about whether to release this early, whether to wait, and how much should be said. It was quite surprising that when this report was published, there was little or no public reaction. This was probably because while issues with the first dose were acknowledged, the statement was made that the benefits overwhelmingly exceeded the risks in the Australian context. In 2013, the work which was the basis of the statement in 2011 was accepted for publication [Carlin et al, Clin Inf Dis 2013 in press, July].

In terms of the background, the annual birth cohort for Australia is approximately 300,000 and the total population is about 23 million. The National Immunisation Program (NIP) delivers all of the included vaccines free of charge. RotaTeq® and Rotarix® have been funded by NIP since July 2007. There was a very rapid increase in vaccine coverage to 85% for either 2 or 3 doses within the first year of introduction, and the timeliness was overall very good with only about 2% to 3% given later than the upper age limits in the analysis[1]. The background rate of intussusception, based on ICD coded hospitalisation data, in Australia has historically always been about double that in the US, with an incidence pre-vaccine of approximately 80 per 100,000 in the first year of life[2], so cases accumulated more rapidly [[1]Hull et al, Vaccine 2013; [2]Justice et al J Pediatr Child Health 2005].

RotaTeq® and Rotarix® were distributed fairly evenly around the country, and both were implicated in the study published in 2011 that only had 92 cases. This prompted the Australian regulator, the Therapeutic Goods Administration (TGA), to commission a large national study. TGA asked John Carlin, Professor of Biostatistics, University of Melbourne, to take the lead on the analysis of these data because it was known that this would be complicated. It was also important to assess trends in age-specific incidence, due to a concern that there might be an increase in very young cases, and perhaps those young cases would have a worse outcome. Morbidity in vaccine-proximate versus other cases has also been assessed in more detail, but data are available only from New South Wales for that currently. Importantly, the same very favourable impacts have been observed on the disease impact as have been seen in the US.

Initial descriptive analysis examined age-specific trends in ICD-coded hospitalizations without chart confirmation from 1998-2009, which included the pre-vaccine period and 2-years of post-vaccine data. This suggested some increased incidence in children under 3 months of age. When evaluated more formally with incidence rate ratios, there was a significant increase in the incidence rate ratio in this age group but not in any of the other age groups assessed. Considering the curve of the pre- and post-vaccine time periods, there appeared to be a leftward shift in the onset of intussusception around the time that the vaccines were first used [Unpublished data derived from the National Hospital Morbidity Database – Australian Institute of Health and Welfare].

The two sources of cases for the national study evaluating ICD-coded cases were hospital discharge databases from most of the Australian states and territories, and cases ascertained by an active hospital-based surveillance network, which captured some emergency department cases who were not actually hospitalized. Only infants under 12 months of age were assessed using 3 years of data. All of the cases were chart-reviewed and only the Brighton Level 1 cases

contributed to the analysis. The national childhood immunization register was used to ascertain immunisation status, (the Australian Childhood Immunisation Register (ACIR), which includes data through 7 years of age and is believed to have very complete data at the national level for timing and nature of vaccines. Two methods were used, a self-controlled case-series (SCCS) and a case-control method. The case-control method used the immunization register to identify controls who were born within 1 day of the date of birth of each case, randomly selected from children who resided in the same state and, therefore, should have been receiving the same rotavirus vaccine as the case. The case-control study was only able to match for gender and state of residence, because there are no other variables on the register. Date of disease onset in the case was assessed, and relevant to that index data, the date of vaccination was looked for in controls. Risk was defined for pre-specified periods post-vaccination of 1 to 7 days and 8 to 21 days separately as opposed to more than 21 days. Vaccine-attributable risk was compared with estimated reductions in gastroenteritis hospitalisations using national hospitalisation data for gastroenteritis.

In terms of case ascertainment, 282 cases were identified from ICD-coded chart-confirmed data. When the active surveillance sites were added in, and additional 38 cases were identified for a total of 320 cases of intussusception, of which 14 could not be included in the SCCS analysis because an immunization register record could not be identified for them or the record was incomplete. More cases had to be excluded from the case-control analysis because cases were not included who had received both vaccines or had received a vaccine that was not the standard vaccine in that state.

In terms of the number of cases by day of onset, the unadjusted data suggested some evidence of clustering with at least the first dose for both Rotarix® and RotaTeq®. By the SCCS method, both Rotarix® (RV1) and RotaTeq® (RV5) had a significantly increased relative incidence, which is the SCCS equivalent of relative risk. Given the small number of cases, there has to be a focus on the 95% confidence interval as well as the point estimate. For Dose 1, particularly in the first 7 days after vaccination, the lower bound of the confidence interval for both vaccines was more than a 2-fold increase in risk. There was also a statistically significant increase for both vaccines for Dose 2, but the lower bound of the confidence was close to 1. This was important to keep in mind in terms of the risk evaluation, because clearly by adding risk windows for both doses, the result was a lot more vaccine attributable cases. The case-control analysis yielded higher point estimates for dose 1, but the confidence interval was entirely compatible with that identified from the SCCS. The Dose 2 estimate was not significantly elevated for either vaccine in the case-control data.

Mindful of the foibles of rare events and statistical analysis of these, multiple sensitivity analyses were performed to evaluate the robustness of both the SCCS and case-control analysis. Smooth curve (fractional polynomial) was used for age adjustment using monthly and weekly age categorization. In addition to the age adjustment evaluation, various other ways of analyzing each vaccine were utilized. Also included was a phenomenon that is often mentioned in self-controlled case series analyses, which pertains to whether there is a "healthy vaccine effect." In an effort to try to account for that possibility, the incidence estimate was lowered in the immediate post-vaccination risk interval to take into account the possibility that children were not vaccinated for various reasons. However, this had a minimal impact on relative incidence. Also interesting was that for both the self-controlled case series and the case-control analyses, if cases were removed who received their first dose of vaccine outside of the recommended age range for that vaccine dose, the association substantially weakened for both Rotarix® (RV1) and RotaTeq® (RV5), although it remained significant. While these data on age of administration were not believed to be definitive, age of administration seemed a potentially important issue in

settings like Australia and the US where there are not typically deaths from rotavirus, making the imperative to maximize vaccine coverage by expanding age groups for eligibility less strong.

Regarding strengths and limitations of the study, there was near complete case ascertainment, although not all cases were included. However, there is no reason to suspect that the cases who were not included would have been likely to bias the estimates. Although a lot of unmeasured confounding should be accounted for by the SCCS analysis, there was a lack of ability to control for confounders in the case-control analysis due to the limited data available from ACIR. Despite the best efforts to include as many cases as possible, case numbers were still limited.

Turning to the sub-study, a small amount of data were available from New South Wales to try to address the question regarding whether there is any difference in case severity between the vaccine-proximate cases and others. New South Wales has a birth cohort (n=95,000) similar to the VSD cohort, but only uses Rotarix®. Interestingly, of the 183 episodes that were coded as intussusceptions in infants under 12 months of age, only about 60% could be confirmed through chart review using Brighton Level 1 criteria. Most cases who could not be confirmed were transfers from small hospitals who had initial clinical features that were suggestive. Some cases may have spontaneously resolved, but some may have been misdiagnosed. This suggested that case confirmation is an important issue. However, applying the same methods to the New South Wales data gave results consistent with the results of national study. Amongst the 113 Brighton-confirmed cases, comparing the 19 that occurred in the 21 days after vaccination with those that occurred later, there was little difference in age between the two groups, so there was a suggestion that the vaccine proximate cases were younger. Length of stay, the proportion with an unsuccessful reduction by enema, the proportion who had surgery, and the proportion who had resection were all similar. There were no deaths, but one child was admitted to intensive care. Based on limited data, so far there does not seem to be any compelling evidence of different severity in vaccine-proximate cases.

In terms of the overall impact of rotavirus vaccines on morbidity, there has been a very dramatic effect on all gastroenteritis and rotavirus coded admissions. It is estimated that approximately 7000 (71%) admissions are averted annually in the Australian birth cohort, a reduction from an estimated 11,000 cases with rotavirus attributable gastroenteritis to 4545 with the vaccination program. Applying the longer risk period and increased risk from Dose 2 resulted in 18 attributable cases, compared with 6 vaccine-attributable cases when only Dose 1 data were included in the original Australian analysis. Clearly, there is uncertainty about the Dose 2 issue. However, it is important because it makes quite a substantial difference in the overall estimates. No deaths from intussusception in the last decade have been identified in Australia. Although deaths were rare from rotavirus, it was estimated that there were probably 10 childhood deaths over a decade in the pre-vaccination period and it was estimated that approximately 7000 rotavirus-attributable hospitalisations were prevented compared with a maximum of 18 additional cases of intussusception.

With respect to the policy and practice implications, the initial risk estimate of 6 excess cases annually was widely publicized and appeared to be highly acceptable to providers and parents. The ongoing risk-benefit has been reviewed by a number of advisory committees and was published in Australia's most recent immunisation handbook March 2013. The advice to parents and providers is in the process of being updated. The TGA has requested changes to the product information and has obtained those from both manufacturers.

In summary, the risk estimates were found to be similar for Rotarix® and RotaTeq® by 2 methods. The Australian investigators believe that there is evidence of a significant vaccine attributable risk of intussusceptions for both doses and vaccines, although the evidence is much more robust for Dose 1 than Dose 2. It does not appear to be possible to distinguish the two vaccines based on the Australian data. No difference has been identified in case severity. The policy-making bodies in Australia still consider the risk-benefit to be very favorable in terms of the vaccine.

Discussion Points

In addition to the possibility that the vaccine may avert later cases of rotavirus because it protects children, Dr. Keitel inquired as to whether Dr. McIntyre had any information on the rates of nosocomial complications among the 7700 children who are admitted for sepsis, urinary tract infections, and other complications to add into the equation.

Dr. McIntyre responded that this was a fairly crude assessment of risk-benefit. More detailed studies have been conducted using pre-vaccine data in Australia, so those data are available. It is not just nosocomial infections, but it is also infections of parents, grandparents, and others that have also demonstrated impacts. This has been demonstrated in the US as well.

Summary and Review of Risk-Benefit in the US

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During this session, Dr. Cortese discussed trends in intussusception hospitalizations, a summary of attributable risk estimates, rotavirus vaccine impact in the US, estimates of benefits and intussusception risk of rotavirus vaccination in the US, and recommendations.

To assess trends in intussusception hospitalizations among US infants, investigators used the State Inpatient Databases (SID), which includes hospital discharge data provided by 26 states for 2000 through 2011, remarkably covers 75% of the US birth cohort, and is very representative of the national picture. As would be expected, this is an examination of the discharge diagnosis based on the ICD-9 code for intussusception (560.0). Population data were used from the Census to generate the rates of hospitalization.

Based on the trends among all infants combined under 12 months of age from 2000-2011, the number of intussusception hospitalizations was approximately 1100 to 1200 in the 26 states combined. The overall picture did not show a dramatic change in hospitalization rates amongst infants overall aged <12 months, comparing the pre- to the post-vaccine periods. There appeared to be a small increase in 2007, followed by a lower rate and a small increase in 2010, which was followed by a somewhat lower rate overall in 2011. Examining this by the age groups receiving rotavirus vaccine doses, infants ages 6 through 14 weeks receive virtually all of the Dose 1 doses while infants ages 15 through 24 weeks receive Dose 2, and infants ages 25 through 34 weeks receive Dose 3. It is important to remember that these data cover through 2011, so for the post-vaccine period this was a time when most of the doses administered were RV5. No consistent change was noted comparing the post-vaccine to the pre-vaccine periods, and there was some variation by age group. Looking closer at the trend for the age group receiving the first dose, it is important to keep in mind that there were a total of 40 to 90 hospitalizations annually across the 26 states, so there could be variability based on just those

small numbers. The Yen paper included data through 2009, and there was a statistically significant increase in the rate during 2007 through in 2009 for the very tight age group of 8 through 11 weeks. For 2010 and 2011, there was not a consistent finding in infants 6 through 14 weeks of age or in the preliminary look at the tighter age group [Yen C, Tate J, Steiner C et al J Inf Dis 2012; Tate J, Steiner C et al, Preliminary].

It is important to keep in mind that the analyses of the most recent data from 2010 and 2011 are preliminary. Also important to remember is that it is known that some intussusceptions cases are managed in the emergency department setting, and it is believed would not be captured in these databases because these are hospitalization discharge databases. Of course, it would be of great interest to evaluate the categories of inpatient combined with emergency department intussusception cases and examine those for a long pre-vaccine period and a long post-vaccine period. Unfortunately, looking at the data as Dr. Tate has, combining the emergency department data and inpatient hospitalizations, the data are much less robust because those combined data only cover approximately 22% of the US birth cohort. Less than one-third of the children who are covered with the inpatient hospitalization data can also be covered with emergency department data in for a pre- and post-vaccine period. Moreover, the pre-vaccine period for emergency department databases began in 2003. Therefore, very limited data are available to try to combine emergency department with inpatient data. The inpatient picture offers some reassurance that there was not a dramatic change in intussusception hospitalization rates in the age group receiving most of the doses, during the time when RotaTeq® was predominantly used. Again remembering that these are preliminary results, in general, a trend has not been identified with these ecological data when evaluating whether the incidence changed during the usual rotavirus season, from January to June. In 2008 and 2010 in the US, there was very little rotavirus disease. Looking crudely at those time periods, no real change was observed in the inpatient intussusception rates.

To summarize attributable risk estimates for the US population, based on the VSD data for RV5, a significant risk was not detected despite over 1.3 million doses and about 500,000 first doses having been administered. The point estimate was not statistically significant; 0.5 excess intussusceptions cases per 100,000 vaccinated infants. These data can basically be interpreted as per 100,000 infants who received the full series since the risks that have been identified were with the first dose for RV5. The confidence interval for the RV5 VSD estimate included zero; the risk estimate was not statistically significant. In comparison, the PRISM data included 1.3 million doses administered to the population being investigated with almost the same number of first doses as in VSD. The PRISM investigators performed analyses with the periods Days 1 through 7 or 1 through 21. Their point estimates with the self-controlled case series and the cohort study were in the range of 1.1 to 1.5 excess intussusception cases per 100,000 vaccinated infants (first-dose recipients). The VAERS study was a slightly different way of assessing the data, but it provided useful information to consider, with an estimate of the possible attributable risk of 0.74 cases per 100,000 vaccinated infants. In this method of analysis, that was statistically significant for Dose 1. The VSD RV1 data detected a risk with both Doses 1 and 2 in the first week following those doses, with an overall attributable risk of 5.3 cases per 100,000 infants receiving that series. A confidence interval could not be calculated from the method of analyses used for this study.

In Australia, the self-control case series provided similar results as their case-control study. For RV5, a risk was detected for Doses 1 and 2. The summary overall attributable risk estimate for this non-US population was 6.9 cases per 100,000 vaccinated infants. A similar analysis was performed for RV1, which detected a risk with Doses 1 and 2 in the same time periods as with RV5. The attributable risk was about 5 cases per 100,000 vaccinated infants who received that

series. In October 2010, the ACIP heard about the two studies from Mexico by PAHO and CDC, and by GSK. These studies identified a risk of 1.9 cases per 100,000 infants, and 3.7 cases per 100,000, roughly in the first week following the first dose. The PAHO/CDC study also identified a risk in Brazil. This was a lower relative risk and was with Dose 2, with an attributable risk estimate of 1.4 cases per 100,000 infants vaccinated.

It is important to keep in mind the tremendous impact that the rotavirus vaccine has had in the US. Several methods have been used to monitor impact, and ACIP has seen updates of these in the past. A very simple and very timely system that is used is from national laboratory surveillance for rotavirus testing across the country. On a weekly basis, laboratories provide their results to CDC for the number of rotavirus tests performed and the number testing positive. These are just tests ordered as part of routine patient management. Since 1991, 22 labs have reported continuously. The estimate overall for the post-vaccine seasons compared to the pre-vaccine seasons was a mean annual reduction in the number of rotavirus-positive tests of 73%[1]. A similar picture was observed for hospitalizations based on the MarketScan data, with approximately 30,000 to 40,000 hospitalizations estimated to have been prevented nationally in both 2008 and 2009,[2] based on the reductions detected in this database. Recall that the among the reductions described in this and other papers, in 2008 there was an approximately 75% reduction in rotavirus hospitalizations, including notable reductions amongst the cohorts who were too old to have received vaccine. Thus, there is y evidence from the US and other countries of the indirect benefits to unvaccinated children [[1]Tate, J, Haynes A, Payne D et al PIDJ 2013; Tate J et al, Preliminary; [2]Cortes J, Curns A, Tate, J et al N Engl J Med 2011].

Extrapolating the MarketScan data to the national burden, an estimated $278 million was saved in hospital costs. As could be expected with the figure depicting the trend in laboratory tests, the reduction in rotavirus hospitalizations has also continued. The number of hospitalizations from large nationally representative discharge databases, for which the estimate of reduction for the whole US can be extrapolated, are shown in the following table:

	Reduction in 2008	Reduction in 2009	Reduction in 2010
Study 1	36,890	27,965	
Study 2	37,697	39,099	
Study 3	50,665	49,381	69,753

Study 1:Cortes J, Curns AT, Tate, JE et al N Engl J Med 2011
Study 2: Desai R, Curns AT, Steiner CA et al, CID 2012: 55
Study 3: Gastanaduy PA, Curns, AT, Parashar UD, Lopman BL (submitted)

Without a doubt, the rotavirus vaccination program has quickly had a remarkable and sustained impact on the burden of rotavirus disease in the US. This is readily visible in the National Vaccine Surveillance Network (NVSN), which is a “Cadillac” active rotavirus surveillance monitoring system, and originally involved 3 children’s hospitals. Since 2006, children less than 3 years of age who present with acute gastroenteritis who are hospitalized or receive emergency department care are consented and enrolled in this prospective surveillance system. Stool specimens are collected from these children and are tested for rotavirus. Epidemiologic and clinical data are collected. The three original sites (University of Rochester, Cincinnati Children’s Hospital Medical Center, and Vanderbilt) are particularly useful because they can provide the longitudinal data, including before rotavirus vaccine was introduced. Although monitoring has expanded to additional sites and additional ages, Dr. Cortese presented the data for children less than 3 years of age. The rotavirus burden at the three original hospitals dramatically declined during the January through June period between 2006 when 107 of 211

children tested were positive and 2012 when 3 of 100 children tested were positive [Payne D et al Clin Infect Dis 2011:53:245 and unpublished].

This network and additional networks have then been able to perform case-control studies with these same enrolled children to quantitate the vaccine effectiveness. This network contributed three studies (A, B, and D) for RV5 effectiveness, while the Emerging Infections Program (EIP) contributed two studies (C and E) shown in the following table:

	RV5 Study A	RV5 Study B	RV5 Study C	RV5 Study D	RV5 Study E
3 Doses	**89%** (70, 96)	**87%** (71, 94)	**90%** (84, 94)	**84%** (78,98)	**92%** (75, 97)
2 Doses	**82%** (15, 96)	**88%** (66, 96)	**90%** (75, 96)	**78%** (65, 86)	**84%** (1, 99)
1 Dose	**65%** (-11, 89)	**74%** (37, 90)	**66%** (16, 86)	**70%** (50, 82)	N/A

Study 1: Boom J et al. Pediatrics 2010;155:e199.
Study 2: Staat M et al; Pediatrics 2011:128:e267
Study 3: Cortese M et al, Pediatrics 2011:128:e1474.
Study 4: Payne P et al. Clin Inf Dis 2013.
Study 5: Cortese M et al; Pediatrics 2013. Control group = Rotavirus-test negative children. Point estimate and 95% CI

Other investigators have conducted similar robust work, but Dr. Cortese presented only the data from these two networks during this session. As illustrated in the above table, with these different evaluations covering different time periods, RV5 was found to be very highly effective in preventing the combined outcome of rotavirus hospitalizations or emergency department care. The dose-specific vaccine effectiveness is also shown in this table.

For RV1, which was more recently introduced in the US in 2008, there have been two published studies, one from the NVSN network and one from the EIP network. The first study had a smaller number of cases, so the confidence intervals are wide, but again demonstrating good protection against the severe outcome of rotavirus hospitalizations or emergency department care as shown in the following table:

	RV1 Study D	RV1 Study E
2 Doses	**70%** (39, 86)	**91%** (80, 95)
1 Dose	**57%** (-45, 87)	**53%** (-41, 84)

Study 1: Payne et al. Clin Inf Dis 2013.
Study 2: Cortese et al; Pediatrics 2013
Control group = Rotavirus-test negative children. Point estimate and 95% CI

To try to quantitate the benefits and risks of the rotavirus vaccination program in the US, a risk-benefit analysis was presented to ACIP in October 2010. At that point, a risk had not been detected in the safety monitoring systems in the US. However, a low level risk could not be ruled out. Therefore, this analysis was presented to ACIP and was then published in 2012. This analysis evaluated health outcomes, not costs. In terms of the inputs that went into the analysis, this model used the 2009 birth cohort of 4.26 million infants and followed them to 5 years of age. The rotavirus burden, if that cohort remained unvaccinated, was estimated to be 33 deaths; 71,175 hospitalizations; and 226,126 emergency department visits. The confidence intervals around many of these estimates are in the paper, but for simplicity Dr. Cortese did not include them here. To estimate the full impact and the possible full risk of a program, a fully vaccinated cohort was evaluated. If rotavirus vaccine uptake was similar to that of DTaP, but taking into account the age restrictions that would keep the rotavirus vaccine coverage somewhat lower than DTaP, the rotavirus vaccine coverage that could be reached was estimated to be 96% for 1 dose, 93% for 2 doses, and 82% for 3 doses. The input for the model

for rotavirus vaccine effectiveness was based on the initial studies of the effectiveness measured in the US for RV5. The disease burden reduction would be quite similar with this model if the model were redone using just the two point estimates that are currently available for RV1, a 2-dose vaccine. The fact that both vaccines are highly effective and this model incorporates high vaccine coverage, the benefits would be very similar with any combination of the vaccines. For a birth cohort followed to age 5 years with a fully implemented vaccine program, a 42% reduction in rotavirus deaths, 75% reduction in rotavirus hospitalizations, and a 75% reduction in emergency department visits for rotavirus would be expected. As illustrated by the previous data presented, the observed results in the US are very close to or exceed the predicted 75% reduction in hospitalizations [Desai R, Cortese M, Meltzer M et al. Pediatr Inf Dis J 2012].

In the original analysis that was published in PIDJ, we assumed that a risk with Dose 1 existed in the US at the level of that found in Mexico. At the time of that evaluation, a risk had not been identified in the US. For this updated US risk-benefit analysis, because there are some statistically significant attributable risk point estimates, or point estimates that were suggested to be statistically significant, the risk estimates used were the low and high ranges of the attributable risk point estimates shown earlier, from VSD and PRISM.. A correction factor was included in the model for the proportion of intussusception cases that were managed as short-stay or emergency department patients (22%). Additional inputs were the proportion of hospitalized cases that required surgery (53%, or 37% of total intussusception cases), and the proportion of hospitalized intussusception cases who died. For the estimate of excess intussusception cases and sequelae, Dr. Cortese showed the previously published results and the updated results based on data presented during this session. Of note, the results presented during the October 2010 ACIP meeting had not been t finalized at that time, so the results presented at that meeting were slightly different from the published results. With a fully vaccinated cohort, a baseline of 1856 intussusception cases would still be expected to occur. An additional 45 to 213 excess intussusception cases would be expected, including 35 to 166 hospitalized cases, 18 to 88 intussusception cases with surgery, and 0.1 to 0.5 intussusception cases resulting in death. Based on the updated information, it was estimated that 251 to 1191 rotavirus hospitalizations would be prevented for every excess intussusception case caused, and 322 to 1530 rotavirus hospitalizations prevented for every excess hospitalized intussusception case.

Taking into consideration the totality of the data available at this time and the benefits and risks, CDC continues to recommend that all US infants receive rotavirus vaccine, following the age and precaution/contraindication criteria. The benefits of RV5 and RV1 outweigh the small excess risk of intussusception. Importantly, parents and providers need to be aware of the small risk of intussusception, the signs and symptoms of intussusception, and the need for prompt care if these develop. Important next steps include continued monitoring through the established safety monitoring systems to further quantitate the intussusception risk following each vaccine. When additional results become available, they will be presented to ACIP. CDC communication materials, including VIS, are being updated. The FDA approved the revised labeling for RV5, which describes the intussusception risk. A formal GRADE review of the available safety data will be performed through the WG and will be presented during a future ACIP meeting.

Discussion Points

Dr. Temte pointed out that this was a wonderful opportunity for the use of the GRADE methodology in the context of a safety signal. He suggested to the WG that when the GRADE evaluation is done, that consideration be given to some comparisons of RotaShield® to the new vaccines. Regarding the rotavirus tests at reporting laboratories, the Wisconsin State Laboratory of Hygiene has noticed a similar trend as shown during this session of an increase every two years. The possibility has been considered that accumulation of enough unvaccinated children triggers a small outbreak every two years.

Dr. Cortese replied that in some modeling studies, a shift to biennial peaks could occur after vaccine introduction. A strong possibility is that unvaccinated children accumulate, and every two years there are enough of them to sustain a small outbreak, at a level which is still dramatically lower than the seasons during the pre-vaccine timeframe. Using vaccine coverage data from the sentinel site information systems (8 sites throughout the US), the median coverage with at least 1 dose of rotavirus vaccine among infants aged 5 month was 79%, at the end of December 2012. There was variability between the sites, with a low value of 55% and a high value of 89%.

Dr. Duchin inquired as to whether children who were vaccinated outside the recommended age range were included or excluded from the risk estimates, and whether many of the intussusception cases used in the calculations were vaccinated outside of the recommended age range.

Dr. Cortese responded that, in the risk-benefit analysis, estimates are for the fully vaccinated cohort and include the small percent of children who would receive the vaccine outside the recommended window. The proportion anticipated to receive vaccine outside that window was estimated earlier from the National Immunization System and the Sentinel Site Immunization Information System (IIS) in which approximately 2% to 5% of first doses were given beyond the 15-week age window. The great majority of any intussusception cases caused would occur among the children who received most of the doses. The majority would have received doses at the recommended ages. These analyses used the attributable risks estimates from VSD and PRISM. In those evaluations, while a change in risk may not have been detected with increasing age,, there is very limited power to assess that question. Dr. McIntyre was able to evaluate that, so his results are very notable and worthy to keep in mind.

Based on the overall data and biologic plausibility, Dr. Rubin wondered how the 21-day window affected the analysis of the VSD. The comparison group included the 8 through 30 days, so perhaps relative risk may be underestimated.

Dr. Cortese replied that based on the data from Dr. Yih, the analyses were performed using the 1 to 7 day period for the self-controlled case series and the 1 to 21 day period for the cohort analysis, and the attributable risk estimates were very similar at 1.1 to 1.5 cases per 100,000. That suggests that the risk is concentrated in the first week. The attributable risk estimates can be considered as encompassing whatever risk period was identified in that analysis. As Mr. Weintraub mentioned, the VSD results were focused on the 1 to 7 days because this was suggested by the temporal scan. In Australia, as Dr. McIntyre described, there seemed to be a risk extending beyond the first week for both vaccines after the first dose. However, as he mentioned, the data were more robust for the first week.

Regarding the fairly dramatic drop in the rate of testing and the rate of positivity of tests, Dr. Bennett said she thought the NVSN data answered this question fairly well by showing a true reduction in rotavirus. She requested that Dr. Cortese comment on what is known about testing patterns. There is always a struggle in evaluating the impact of vaccines, given that people sometimes stop testing for whatever the particular agent because of vaccination. She also wondered whether anything had been done to model the impact of testing, or to investigate practices among physicians.

Dr. Cortese responded that this very important question is why multiple systems are in place to measure impact. Evaluating testing is most useful as a quick, timely assessment of what is occurring during the season. If everyone just stops testing, of course rotavirus will not be detected. That is why it is very important to have "Cadillac" systems in place like the NVSN, which now encompasses 8 children's hospitals around the country that are very geographically dispersed, where every child who presents is approached for enrollment and, if enrolled, is tested for rotavirus. She was not aware of testing practices among physicians being investigated.

Dr. Schuchat emphasized that the ACIP often has to make very difficult decisions that are important to the public and clinicians, and it is much easier to make decisions when there are good data to review. While it is frustrating that the US does not have the really high immunization uptake of neighbor countries or partners from around the world, she remained proud of the investment in the evidence base for the committee to review so that the best policies could be made. This session reflected the placement of priority on safety, effectiveness, surveillance, and quality evaluation so that when concerns or problems arise, ACIP can make the best decisions possible. The resources for this are not minimal. In addition to buying vaccines and supporting public health programs, this evidence base is a very important part of the system.

Having worked in diarrheal disease for a very long period of time, Dr. Pickering observed that since withdrawal of the ACIP recommendations for the first rotavirus vaccine, RotaShield®, and removal of that vaccine from the market until licensure of the two current vaccines and the ACIP recommendations for use of those vaccines, there have been tens of thousands of children worldwide who have died from rotavirus diarrhea dehydration. Hundreds of thousands, if not millions, have been hospitalized with many suffering sequelae from the disease and the treatment that is given. For people worried about vaccine safety, he thought the display of the data presented, the systems used to monitor data, and the quality of the people who are monitoring those data should be very reassuring.

Dr. Zahn (NACCHO) observed that in terms of making the case to providers and the general community about the utility of rotavirus vaccine, the number of deaths due to rotavirus have not been emphasized in the past because they are not tremendously high. The numbers are also not very high for the sequelae of intussusception. The case was being made of overall estimates of the number of deaths being prevented as being X as opposed to the actual number of significant cases of intussusception. Better data are needed regarding the actual number of deaths that occur in the US due to rotavirus, so that the argument can be made that while admittedly small, the numbers are still significant.

Thinking about the background rate of intussusception in Australia being 2-fold that of the US, Dr. Temte wondered if there was any demographic characterization (e.g., race, ethnicity) of intussusception that would make one more susceptible.

Dr. Cortese replied that except for male sex, other risk factors are difficult to come by. At least in the national datasets, it is not possible to find a statistically significant difference in rates, or if they are there, they are based on small numbers [Clarification by M. Cortese August 25, 2013: Based on data from a pre-vaccine period, statistically significant differences in intussusception hospitalizations rates were observed among US infants 4 months of age and older, with rates among non-Hispanic black infants and Hispanic infants higher than those among non-Hispanic white infants. These differences were not detected in infants less than 4 months of age (Tate J et al, Pediatrics 2008). A US case-control evaluation also found infants in these race/ethnicity groups to have higher odds of intussuception compared to non-Hispanic white infants (Johnson B et al, JPGN 2010)]. Other case-control studies and case series reports have tried to identify risk factors for intussusception, but findings are not conclusive. It does appear, however, that different populations could have different baseline rates of intussusception.

Dr. Vázquez said that she thought everyone would agree that more data are needed for further quantification; however, very little is known about intussusceptions, its causes, and its risk factors. It would be beneficial for researchers to study intussusception so that more is known about not only association with the vaccine, but also intussusception itself and whether it is the host, other viruses, et cetera.

The Role of Retail Pharmacists/Pharmacies in Vaccine Delivery in the US

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Member of the National Vaccine Advisory Committee

Dr. Rothholz presented an overview of the role of pharmacists/pharmacies in immunizations in terms of the history and focus of pharmacy-based immunizations, “Immunization Neighborhood,” training of immunizing pharmacists, the process of care, legal and regulatory considerations, the scope of immunization activities, documentation and communication, and what is on the horizon.

The American Pharmacists Association (APhA) is focused on improving medication use, advancing patient care, and meeting the public health needs of the nation. Through the last 20 plus years of activities, the APhA has been able to support pharmacists in the areas of advocacy and policy, education, periodicals, publications, practice guidelines, research, community, and networking.

In 1993 in a meeting of APhA’s then CEO with HHS Secretary Donna Shalala, the Secretary asked how APhA could help increase the immunization rates for children. Based on that challenge, APhA began to develop an active program that has been in existence for 20 plus years. Pharmacists were involved in immunization and working with public health in different ways even before that meeting. This program was incorporated within APhA’s strategic focus as a profession and organization. In 1995, HCFA then, now CMS, recognized pharmacists as providers. That addressed one of the barriers APhA faced in trying to put these services in place. In 1996, APhA’s piloted its first national training program that has now trained more than 200,000 pharmacists in immunizations. This is a 20-hour certificate training program that is based on the existing guidelines, as well as best practices that have been gathered over the years. This program has become the gold standard for the profession. It has been reviewed by

CDC and others in public health, medicine, nursing, other professions, and other stakeholders. All have recognized its quality and content. Early on, APhA committed to educating pharmacists across the lifespan. It was APhA's belief that pharmacists needed to be a knowledgeable resource for the public. In doing so, they needed to understand that even if they were not going to administer pediatric vaccinations, they needed to understand the nuances of the pediatric schedule so that they could help a caregiver sort through the schedule, answer questions, and be a resource for public health. In the face of myths and misinformation, pharmacists are an extension of the public health department and the immunization community in terms of disseminating those messages. In 1999, APhA began licensing the program to schools of pharmacy, state associations, and pharmacy corporations to expand the reach.

In 1996, about 9 states authorized pharmacists to administer vaccines, but none of them were doing it. Therefore, APhA began concerted efforts in this area in 1996. By 2012, all states and territories were authorized to administer vaccines. The number of pharmacists trained grew from about 40,000 in 2007 to approximately 200,000 by 2012. In 1996, the APhA House of Delegates adopted a policy that called on pharmacists to take on all or at least one of three roles as 1) Advocators for immunization, which entails educating the public and motivating patients about the importance of immunizations; 2) Facilitators to use their practices as an extension of the public health and immunization communities to host other healthcare practitioners to increase access and information to the public; and 3) Immunizers in the states that allow pharmacists to immunize, to obtain the training and begin to offer those services in their practices.

Pharmacy has a unique contribution to make to the immunization initiative. Access, proximity, and extended hours are assets that pharmacies offer, especially when other practices are closed. Where this really came to light was during the 2009 H1N1 pandemic when clinics, other practices, and public health departments were beginning to close for the holidays. CDC reached out to the pharmacy community and requested their help in continuing to maintain access to the public during that time. Pharmacies stepped up and worked with CDC to continue to provide access to vaccinations. Studies have shown over the years that the equivalent of the US population enters a pharmacy each week [Doucette W, McDonough R. Beyond the 4 P's: using relationship marketing to build value and demand for pharmacy services. Journal of the American Pharmacists Association. 2002;42:183-189]. While this is multiple patients versus the same patient, pharmacies are an access point to reach the public. Pharmacies have an ability to identify high-risk patients easily based upon their medications. They also have the public's trust and can disseminate information and messages. APhA follows nationally adopted guidelines and advocates that in all of its efforts, trains pharmacists to do this, and constantly reminds pharmacists of what the guidelines say. Pharmacists can also support completion of multi-dose vaccines (HPV, et cetera), are knowledgeable of vaccine resources through education and training, and have an ability to handle storage issues.

All 50 states, DC, and Puerto Rico authorize pharmacists to administer vaccines at some level. However, one challenge for APhA is that there are many state nuances in terms of the vaccines pharmacists are permitted to provide, what age limit can be served, et cetera. The public health community has begun to recognize and tap into the reach to the community that pharmacies have in terms of educating the public about the importance of vaccinations. Based on a snapshot of what its members were doing in this area, APhA estimated that approximately $40 million was spent in the 2010-2011 influenza season to educate and market to the public about the importance of influenza vaccination. APhA can also target patients who are in need of vaccinations based on age and medications. Systems are currently in place to do this. Almost

all pharmacies are computerized, so those systems can be tapped into. Pharmacy also experiences challenges in terms of linking to electronic health systems.

During the 2009 H1N1 pandemic, APhA worked with the public health community, ASTHO, NACCHO, and CDC to evaluate whether the relationship had been improved between public health and the pharmacy community, and how that resource could be utilized again to increase access to important vaccinations. This resulted in the publication of the "Operational Framework for Partnering with Pharmacies for Administration of 2009 H1N1" about how to build that relationship. This publication is available for download from the Pharmacist Immunization Center at www.pharmacist.com. This report recognized the uniqueness of pharmacies in terms of offering convenience, accessibility, and extended hours of operation.

Ultimately, the goal has been to build an "Immunization Neighborhood." The way that this has been couched is that the "Immunization Neighborhood" is a collaboration, coordination, and communication among immunization stakeholders dedicated to meeting the immunization needs of the patient and protecting the community from vaccine-preventable diseases. APhA has embraced the achievement of this vision as a profession. In order to meet the "Immunization Neighborhood" goal, several issues must be addressed as healthcare providers. This is not just limited to the pharmacy profession. This includes everyone who has that same common goal. It is important to increase access points. Consistent communication and education efforts with providers and patients must be enhanced. Everyone can support documentation and quality measures (outcomes) and the interface between primary care, public health, and pharmacists. Does it really matter who administers the vaccination, or is the goal to ensure that the patient is vaccinated. Slowness in building technology or innovations should not be permitted to hamper progression. Work is being done on some electronic solutions to overcome some of the documentation barriers. Collaboration is important, and some of the barriers and battles occurring at the state level that are keeping vaccines from being administered into patients' arms need to be addressed. There are payment challenges as well.

Pharmacy brings a unique perspective in the touch points that it has to the public. The general public sees the marketing, communication, and the messages on the billboards of pharmacies advocating the importance of immunizations. Individuals who actually enter the pharmacy as customers offer another opportunity to educate about the importance of immunizations. Those who obtain care from pharmacies, such as prescriptions or other services, offer another touch point at which pharmacies can work with patients to coach them about the importance of immunizations. The following advertisement from the 1950s illustrates the current dilemma that good vaccines are available and there are good access points, but vaccines are only effective when used:

In terms of the education and training pharmacists receive, APhA has a nationally recognized 20-hour certificate training program, which is only one part of the education provided to pharmacists. The APhA also provides year round continuing education programs and has embraced the philosophy that it is not just the practitioner who is being educated. APhA begins early in the careers of pharmacists. When they are students, they are trained on the importance of immunizations. APhA also provides a biweekly immunizing pharmacist listserv and an e-community for immunizing pharmacists to network, ask questions, and discuss cases.. In addition, APhA provides a webinar after each ACIP meeting to update pharmacists on changes in recommendations. The webinar is hosted by Dr. Stephan Foster, the APhA liaison to ACIP.

The 20-hour certificate training program is comprised of 12 hours of self-study and 8 hours of live programming, and covers the gamut of issues. The self-study component focuses on pharmacists as vaccine advocates, immunology, vaccine-preventable diseases, establishing a pharmacy-based immunization program, administering vaccines, appendices, and self-study assessment. The live program component focuses on the importance of vaccines, shortfalls in vaccine delivery and opportunities for pharmacists, how vaccines prevent disease, vaccine-preventable diseases, identifying vaccination needs, establishing a pharmacy-based immunization program, practice implementation, adverse events following vaccination and emergency preparedness, and vaccine administration technique. The education program was developed around a set of guidelines that APhA adopted for pharmacy-based immunizations that was created in 1996. In 2012, the guidelines were reviewed again to ensure they continued to be appropriate and timely. The five areas of the guidelines are as follows:

- Guideline 1 - Prevention
  Pharmacists should protect their patients' health by being vaccine advocates.

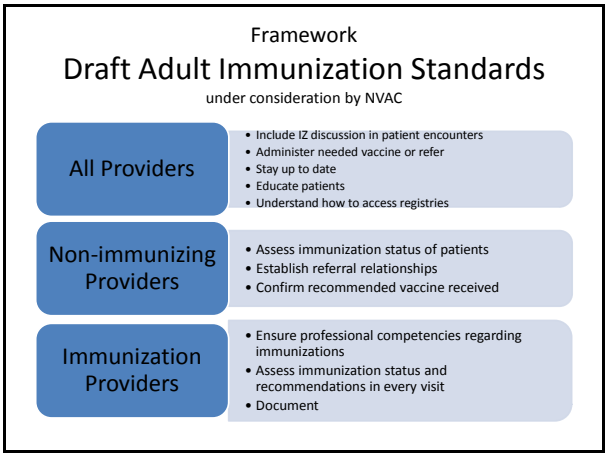
- Guideline 2 - Partnership
  Pharmacists who administer immunizations do so in partnership with their community.

- Guideline 3 - Quality
  Pharmacists must achieve and maintain competence to administer immunizations.

- Guideline 4 - Documentation
  Pharmacists should document immunizations fully and report clinically significant events appropriately.

- Guideline 5 - Empowerment
  Pharmacists should educate patients about immunizations and respect patients' rights.

NVAC is currently working on the Draft Adult Immunization Standards, which they will be considering for a vote in September 2013, which follow:



APhA has reviewed this in comparison to the standards for pharmacy and feels very comfortable that with the APhA guidelines, pharmacists will more than meet these proposed new standards. The uniqueness of these standards is that not only do they address practitioners who actually administer vaccines, but also those who do not. There is a role and responsibility for practitioners who do not administer vaccinations themselves to refer that patient to someone who does.

Pharmacists who administer vaccinations do so using the same procedures that nurses and physician assistants utilize currently either through protocol or prescription, depending upon the state requirement. Protocols identify the individual who has delegated activity; identify the pharmacist authorized to administer vaccine; the types of vaccines the pharmacist is authorized to administer; the procedures, decision criteria, or plan pharmacist should follow, including when to refer patient; the procedure for emergency situations; and state record keeping and documentation procedures. When APhA surveys its pharmacists to ask them where they are obtaining their protocols and who is signing them, it is across the gamut in terms of the type of physician or situations in which pharmacies are engaged in this activity (e.g., corporate physicians, family physicians, internal medicine physicians, by prescription, public health department, not required by state law, state law requires prescription, emergency department physician, pediatric medicine physician). Pharmacists also can identify patients who need vaccinations through their medication records. The auxiliary labels on prescription vials are a way to disseminate a message to the patient based upon a pharmacy's records on that patient.

With respect to state laws and regulations, state law governs health care practice. State-specific regulations may require written or verbal prescriptions and protocols similar to nurses and physician assistants. The protocol could be with individual physicians, a health department medical officer, or the authority could come from the statute. Authority varies in regard to which antigens a pharmacist can give, the patient age, and the process the pharmacist may need to follow. There is also a caveat that in an emergency or pandemic situation, a Governor may sign a declaration that may expand authority. APhA tries to track authority across states, which is a never-ending battle because it changes continuously. At the time of this presentation, 44 states allowed pharmacists to administer any vaccine, except some situations require a protocol, a prescription, or some other process to be put in place. That varies as well depending upon the state, age of the patient, and type of antigen. In some states, authority is derived from the state

law, public health department, or statute. In 21 states, pharmacists may administer vaccinations to persons of any age. In terms of antigens, 51 states currently allow pharmacists to administer pneumococcal vaccine. All states allows pharmacists to administer zoster vaccine, but some states have some type of nuance that require pharmacists to obtain a prescription or some type of patient-specific protocol.

The percentage of influenza vaccine administered by pharmacists to adults is 18% to 20% depending upon the age group. The majority of the patients to whom pharmacists are administering vaccination are adults. The primary referrers of patients to pharmacists are physicians, and it varies across the board in terms of nurses, public health departments, and others. APhA also wanted to ensure that the pharmacist profession was "walking the walk." Therefore, the House of Delegates passed a resolution in 2007 in terms of calling on pharmacists to be immunized themselves to serve as an example to patients. In 2011 that policy was strengthened by making it a condition of employment training, or volunteering with an organization that provides pharmacy services.

The 2007 existing APhA policy stated:

1. APhA supports efforts to increase immunization rates of healthcare professionals, for the purpose of protecting patients, and urges all pharmacy personnel to receive all immunizations recommended by the CDC for healthcare workers.

2. APhA encourages employers to provide necessary immunizations to all pharmacy personnel.

3. APhA encourages federal, state and local public health officials to recognize pharmacists as first responders (like physicians, nurses, police, etc.) and prioritize pharmacists to receive medications and immunizations.

The 2011 statement adopted states:

> APhA supports an annual influenza vaccination as a condition of employment, training, or volunteering, within an organization that provides pharmacy services or operates a pharmacy or pharmacy department (unless a valid medical or religious reason precludes vaccination). Some preliminary results released at the Summit by CDC showed that 88.4% of pharmacists had received an immunization, which is very similar to the numbers shown in APhA surveys that ranged between 85% to 86%. Thus, APhA feels good about that number and continues to work to achieve as close to 100% as possible.

APhA also engages its student pharmacists in getting involved in immunizations early. In 1997, APhA launched the Operation Immunization Campaign, a competition between schools of pharmacy through which they go into their communities to collaborate with public health, other healthcare professionals, and other healthcare students to promote immunizations and facilitate clinics being set up in their communities. Since the launch, over 1 million individuals have received an immunization through the Operation Immunization campaign. Every program that participates is recognized, but 1 national and 8 regional winners are awarded. Again, this is to get students engaged in the importance of immunization early in their careers and to carry it forth when they become practitioners.

Another example of how pharmacists are integrating immunizations into their practice is a project through which pharmacists worked with patients with diabetes mellitus. This was called the Diabetes Ten City Challenge. This was comprised of practitioners in the community who were working with patients who were trying to manage their diabetes. One of the elements of that project was assessing their influenza vaccination rate. When this project began, the rate was approximately 30%. Three years later, the rate increased to 65%. That is due to coaching—the practitioner spending time [The Diabetes Ten City Challenge: Interim Clinical and Humanistic Outcomes of a Multisite Community Pharmacy Diabetes Care Program. J Am Pharm Assoc. 2008 Mar-Apr;48:181–90]. One challenge that all healthcare practitioners face is how to integrate immunizations into already busy practices. This is one example that shows that pharmacists are another advocate for immunizations who could help patients manage chronic disease. They are working with the diabetes care team, including the diabetes educator, endocrinologist, and nurse practitioner. Everyone is working together for that same cause.

Another example is the University of California San Diego Health System Tdap Cocooning Clinic, which was managed by pharmacists. The clinic was staffed by pharmacists and student pharmacists. While a physician in that system served as the supervising physician, all activities were done by pharmacists. This program was focused on vaccinating the household contacts and other close contacts of newborns. Approximately 1250 Tdap vaccines were provided at no cost, and nearly 15% of recipients were Hispanic. This was the only cocooning clinic in San Diego County, and the only clinic to use pharmacists as the sole providers. In terms of authority, 47 states allow pharmacists to administer Tdap, but administration depends upon the age of the patients and the state's current situation. While this varies, it represents 47 opportunities to focus on increasing Tdap immunization rates [http://www.pharmacist.com/AM/Template.cfm?Section=Pharmacist_Immunization_Center1&CONTENTID=25537&TEMPLATE=/CM/ContentDisplay.cfm].

In another example of how pharmacists are using their database to follow up the immunization message, a pharmacist worked on a TAMIFLU® outreach program in which he called every patient from a previous visit who received this medication and talked to them about avoiding influenza by getting vaccinated. He had a 75% success rate in converting those patients to getting immunized.

The challenges of HPV vaccination and completion of the 3-dose series are well-known. APhA believes that pharmacy has a solution to working with the health system on this issue. Pharmacists do not need to conduct the initial evaluation, although they could. The medical provider could do the initial evaluation and administer the first dose, and then the pharmacist could follow-up to ensure that the patient completes the other two doses in the series. HPV is just one example. There are other vaccines for which this could be done as well. The ultimate goal is to make it convenient for the patient to complete a series, and pharmacists can contribute to this goal. HPV authority is somewhat more complicated in terms of state laws. This varies by the age of the patient and whether a protocol or prescription is needed, and some regulations are changing. APhA does not count a state as having authority until the rule has been promulgated. The variation makes it challenging to educate the public about the vaccine, because campaigns have to be state-specific rather than nationwide due to the authority differences.

For a number of years, pharmacists have been addressing an unmet need in the travel vaccine arena. Travel by individuals increased from 457 million in 1990 to 880 million in 2009, and is estimated to reach 1.6 billion by 2020, with an increasing number of those individuals traveling

to developing countries. Pharmacists have been working with their public health departments in some situations or working with other providers in their communities to increase access to travel-related health activities. The pharmacists who are doing this are doing so under a protocol similar to those for other immunizations. They receive the required education and are following published guidelines. This is a practice in development, and as experience increases, new innovations will be put into place. Pharmacist-run pre-travel health clinics can provide consistent evidence-based care and improve patient compliance. This requires time, resources, and knowledge. The International Society of Travel Medicine (ISTM) officially recognizes pharmacists and established the Pharmacists Professional Group. Patients complete a travel health assessment and depending upon the state, the pharmacist operates under a protocol with a physician and could administer vaccines and dispense medication. Pharmacists use various tools just like other practitioners to assess personal risk for travel-related illnesses; recommend non-prescription products and travel-related equipment; counsel on behavioral measures (e.g., food, water, and insect precautions); fill prescription medications; administer vaccines; provide written educational materials; and counsel on personal safety and security. This has not been done in a vacuum. Pharmacists receive additional training for these activities in order to provide services to the patient who may have difficulty accessing these services elsewhere ["A Comparison of Pharmacist Travel-Health Specialists' versus Primary Care Providers' Recommendations for Travel-Related Medications, Vaccinations, and Patient Compliance in a College Health Setting", Journal of Travel Medicine 2010].

APhA has been working with ASTHO to try to identify some of the barriers that pharmacists and other healthcare practitioners are facing in terms of increasing their immunization activities and increasing access to the public. The ASTHO Pharmacy Taskforce identified the top three priorities that need to be addressed: communication and collaboration, minimum dataset and data exchange/registries, and payment and compensation. One thing APhA is encouraging its pharmacists to do when giving their patients their influenza vaccines is to determine whether there are other vaccines the patient needs. Walgreens has developed an effective program to find out what other vaccines a patient needs when working with them on other issues, by having patients complete different survey forms based on their age (60 years and older, 27-59 years and older, 18-26 years and older) while they are in the store. The patient then has the opportunity to obtain the vaccine from that pharmacy if it is allowed in that state, or to take this back to their physician to get the vaccine.

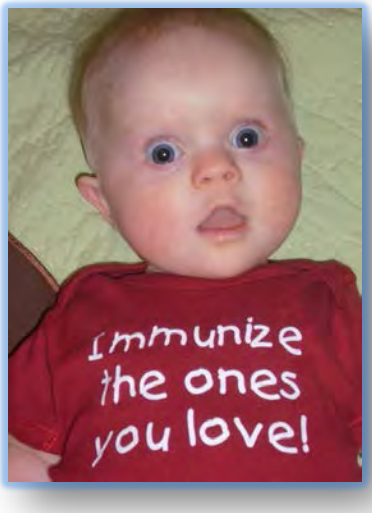
Currently, providers have immunization record cards and forms for minimum documentation. But electronic solutions are also being developed. A data exchange company called Surescripts has been working on technology to connect immunization records, which will allow the physician to receive the information electronically, through a secure fax, or via regular mail. The goal is to send documentation back to the medical home, physician's practice, clinic, or where ever the patient wishes to have that information sent. The future for this is really two-way, seamless access to the electronic health record so that the pharmacy or any other provider can have access to that electronic health record to enter the information and to look at what the patient has already received. That same type of seamless access is being sought with the immunization registry.

There are many complications involved with this, but solutions are being considered. Some of the challenges working with immunization registries is that agreements must be signed between the pharmacy and the registry. Each state has its own type of agreement, and in some situations the agreement cannot be signed as a corporation, it must be signed by the individual practice. While there are barriers, they can be overcome but it will take more time for these activities to be put in place. Some states require mandatory reporting to the immunization

registry while some allow voluntary reporting. Some states allow global corporate agreements, there is variability in data requirements in various states (e.g., mother's maiden name, et cetera), and patient consent requirements vary by state. Surescripts has been actively working with 45 of 61 immunization registries to develop electronic solutions to make this seamless for the practitioner, and they are having discussions with the remainder. Of 36 current registry partners, one-third have not moved to the current HL7 2.5.1 CDC/Meaningful Use-compliant data exchange standard. In addition, nearly a quarter of registry partners do not provide automated notice of errors, resulting in a need for support intervention.

In terms of ACA and the impact of compensation, one of the other challenges from a pharmacist perspective is that there is a caveat on first dollar coverage for vaccines that pertains to whether the provider from whom the patient is attempting to obtain services is "In Network." Public health departments are dealing with this issue as well, so this is a multi-profession, faceted issue. APhA believes that the newly adopted adult immunization standards will help facilitate this. Another challenge is the great recommendation ACIP made for patients with diabetes mellitus to obtain hepatitis B vaccination. Currently, the barrier is that pharmacy providers cannot bill Medicare for the provision of hepatitis B vaccination even if the state law allows them to do so because they are not a recognized provider. That is a nuance that APhA has been trying to work through with CMS. Another challenge in terms of payment is the variability in Part D plans that are causing frustration among pharmacy, medical, and other providers.

Evan Marcus Rothholz; Born November 8, 2010



Ultimately, APhA's goal is for every patient encounter to provide an opportunity to educate and advance immunization status. APhA is committed to this goal in order to protect the loved ones of everyone.

Public Comments

Dr. Temte read the following letter from Jeffrey T. Brand, MD of Oakland University William Beaumont School of Medicine into the record:

Beaumont®
William Beaumont Hospital
Royal Oak

Department of Medicine
Jeffrey D. Band, M.D.
Corporate Epidemiologist and
Director, Division of Infectious Diseases

May 16, 2013

Advisory Committee on Immunization Practices (ACIP)
Attn: Jonathan L. Temte, M.D., Ph.D.
ACIP Chair
Department of Health and Human Services
Centers for Disease Control and Prevention
1600 Clifton Rd., NE
Mailstop A27
Atlanta, GA 30333

Re: The Role of Retail Pharmacies/Pharmacists Providing Travel Medicine Counseling AND Specialized Travel Medicine Vaccines

Dear Advisory Council Committee Members on Immunization Practices:

It has recently come to my attention that pharmacy chains are entering the field of providing travel medicine counseling and highly specialized vaccines without a physician order. Such counseling is performed by a pharmacist or pharmacist aide (attachment).

I feel this practice is quite dangerous to patients and must be stopped. Travel medicine counseling should best be performed in a specialized travel clinic by a person who has both the education and training necessary to provide counseling and also has clinical experience in the field.

In the past, two basic models have existed for delivery of care to the international traveler. In the first, an educated and trained physician obtains the traveler's demographic and travel information, provides the health advice, and helps the traveler with decision-making. The nurse then reviews vaccine adverse effects, obtains informed consent, and administers the vaccine.

In the second model, the nurse, nurse practitioner or physician's assistant renders all pre-travel counseling and care under detailed protocols developed by an educated supervising physician. If questions exist, the supervising physician is always available. Protocols must exist not only for all vaccines and medications but also for the provision of health care to special patient populations. Likewise, a detailed protocol for managing acute allergic reactions or cardiopulmonary arrest must exist. Patient's records should then be reviewed by the supervising physician to ensure appropriate care and that all protocols are followed. Such guidelines have been established by the Infectious Diseases Society of America and have been endorsed by the International Society of Travel Medicine and the American Society of Tropical Medicine and Hygiene.

I am quite opposed to a pharmacist or pharmacist aide performing the necessary medical assessment in assessing traveler's needs and providing the detailed counseling required. Likewise, I am opposed to a pharmacist administering many specialized travel medicine vaccines without **first obtaining** a specific physician's order.

3601 West Thirteen Mile Road Royal Oak, Michigan 48073-6769
(248) 551-4041

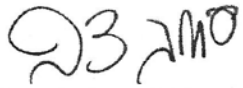
As the medical director of a travel medicine clinic, I know and understand the complexities of travel medicine. Each of our nurses must pass a 6-week orientation period before being permitted to counsel under guidance. It takes at least 6-12 months for a healthcare nurse (whose position involves the direct care of patients) to fully understand the practice of travel medicine. I do not feel that a pharmacist or pharmacy aide has the training and experience to "practice" travel medicine:

- provider knowledge, training, and experience in the field;
- ability to perform risk assessment of a traveler;
- provision of advice about prevention and management of travel-related diseases;
- ability to advise travelers of all ages and with diverse health conditions;
- administration of specialized, reactogenic vaccines and biologics in a setting without physician guidance or emergency support.

The practice of medicine must not be delegated to a pharmacist. A pharmacist is not trained or licensed to provide direct medical care to patients. I look forward to your comments, response and guidance.

It is in our patients' best interests to ensure care is provided by a licensed physician, nurse or physician assistant; persons with years of medical training and experience in direct patient care activities.

Sincerely yours,



Jeffrey D. Band, M.D.
Professor of Medicine,
Oakland University William Beaumont School of Medicine
Rochester, Michigan

Medical Director, InterHealth®:
Health Care for International Travelers,
Beaumont Hospital – Medical Office Building
Royal Oak, Michigan

Former Program Chair,
International Society of Travel Medicine

Former Committee Member, Clinical Practice Committee
and Public Practice Committee,
Infectious Diseases Society of America

Former Director, Special Pathogens Branch
Centers for Disease Control and Prevention

JDB:dk

Attach.

Discussion Points

Dr. Coyne-Beasley agreed that pharmacists have an incredibly important role in vaccines, and was glad to see the plans to address HPV. Often when she goes to pick up her prescriptions or obtain vaccines when she travels to other countries, the person who gives her the prescriptions is not necessarily the pharmacist. Particularly with travel vaccines, she has had some encounters during which the person could not give her advice because they did not know enough about the actual vaccines. She wondered whether there were plans to educate the individuals actually giving patients their prescriptions at the window or the cash register.

Dr. Foster (APhA) replied that this is a frustration in the field of pharmacy. Patients tend to go to pharmacies where they obtain $4.00 prescriptions, so they are shopping for price versus service and quality. There are pharmacies that have someone to talk to the patients, but in many cases the places that offer super prices, do not offer personal services. By law, pharmacists do not have to counsel patients on every prescription they pick up. While Dr. Foster thinks that is a mistake, it is also a fact of life. Pharmacy services have changed a lot over the years, and people sometimes question why pharmacies are expanding their practice. However, the pharmacy practice has been shrinking. When he was a child, the pharmacists could refill prescriptions without a physician's prescription. When he was in the Indian Health Service, he was a pharmacist practitioner and pulled prescriptive authority. But over time, pharmacists have lost some of their privileges. They never had an issue with administering vaccines years ago. To answer the original question, he would find another pharmacy.

Mr. Rothholz added that one of APhA's challenges and goals is to educate pharmacists and their support staff, just as in medical offices with medical technicians. Another answer would be to ask to speak with the pharmacist. The APhA is trying to educate the public to know their pharmacist and know their medicine. It is important to develop a relationship with the pharmacist. Pharmacists who are actually administering the vaccines have developed relationships with patients. In terms of travel, not every pharmacist is currently educated on travel vaccines. Those who are interested in this are obtaining the training.

Dr. Hahn (CSTE) requested that someone address the issue of pharmacists as VFC providers in terms of whether that is allowed, including the challenges. While she understood that this was being discussed at every level, she hoped they could discuss it in this setting.

Dr. Schuchat responded that pharmacists are allowed to be VFC providers. An agreement has to be signed, and they have to fulfill all of the functions of a VFC provider.

Mr. Rothholz added that APhA worked with CDC to get clarification to the states on that issue. One of the clarifications was that pharmacists who are in an area where there is a need for assistance with the adolescent population could administer adolescent vaccines, but would also have to administer childhood vaccinations. There was some trepidation about how to put that in place, given that one of the challenges pharmacies face is getting states to allow them to become VFC providers. Some states require them to be Medicaid providers, but Medicaid will not permit pharmacies to become Medicaid providers for immunizations. APhA is trying to address barriers all along the line.

Dr. Keitel requested comments on any issues faced with the record keeping requirements with regard to providing people who have received vaccines with information about what they have received if there is no link to the provider. In her experience, there has been no question about a provider and where to send the information.

Mr. Rothholz replied that record keeping requirements depend upon the state, but at a minimum the pharmacy should be giving the patient a consent form and documentation and encouraging them to take that to their physician. There are examples across the nation of pharmacists sending documentation to physicians. Some have automated systems that send the documentation to the provider, and some states require submission to registries. While this varies by states, there are systems and guidelines in place to give documentation at a minimum to the patient and then get it to the primary care provider.

In terms of retention of records at the pharmacy, Dr. Keitel wondered what the requirements were for maintaining records.

Mr. Rothholz responded that the legal requirements are state-based and are the same as for other medical records in each particular state.

Dr. Sawyer noted that both public health systems and professional organizations have worked for many years with physician providers on quality improvement in immunization delivery. He wondered whether systems were in place within the pharmacy organization to assess the quality of delivery, including communication and documentation and missed opportunities in proven practices such as reminder recall.

Mr. Rothholz responded that the APhA is encouraging its Science Academy to evaluate some of those issues, and are recommending topics for research to its members. Some studies have demonstrated pharmacies' capability to do that. Some studies have shown improvements in quality measures. Pharmacists can help medical providers meet their quality standards and work with them to get the documentation back into the record so that they receive credit for those vaccinations.

Ms. Haynes (ANA) commented that healthcare is a state-regulated industry, so the regulation of advance practice nurses and physician assistants varies from state to state. In many states, they are independent practitioners and are not supervised by physicians. They have collaborative agreements, but they are not supervised. The word "supervision" is highly contentious in many states.

Dr. Temte stressed that the letter probably pertained to Michigan where Dr. Band's site is located.

Dr. Foster (APhA) emphasized that the one thing that was not true in the letter was the statement that pharmacists administer vaccinations without physician supervision. Pharmacists are required to have prescriptions, protocols, or collaborative agreements in order to administer vaccines. Every state requires that. Pharmacists do not administer vaccines without physician approval or physician referral. Several travel vaccine pharmacists are on the APhA national advisory committee who are members and are certified through the International Society of Travel Medicine as certified travel specialists.

Dr. Grogg (AOA) said he had mixed emotions about this issue. He has a certificate in travel medicine by the International Society of Travel Medicine. When he first heard that pharmacists were conducting travel consultations, he was concerned. However, they are not doing that much in the way of travel consultations that cannot be obtained from the CDC travel website. In terms of health departments that administer travel vaccines, there are no consultations and they

do not even offer medications for malaria prophylaxis. Therefore, he suggested watching and waiting to see what occurs in the future.

Mr. Rothholz clarified that pharmacists' aids do not deliver the service as suggested in the letter. They may give the patient a form to complete, but all of the clinical interaction occurs with the pharmacist.

Dr. Fryhofer (AMA/ACP) indicated the AMA and ACP support many of the concerns expressed in the letter. She engages in travel consultations in her office, and as the patients' primary care physician she has knowledge of their diseases. It is not as easy as it may sound. It is fairly complicated and involves a lot of consultation and discussion with patients about their risks and activities. She thought it was concerning that others than those taking care of patients are providing this service. When they return from their trip, if they were not properly protected, she will have to "pick up the pieces" and would like to make sure they are protected when they travel internationally. It is one thing to administer a vaccine if given a prescription. It is another to engage in travel consultations. When patients return from a trip with problems, are they going to go to their pharmacists with their problems? She did not think so, and emphasized that this should be done under a physician's guidance.

Mr. Rothholz indicated that the tool pharmacies are using is the same tool that travel health clinics and practitioners are using, so those questions are being completed with patients and reviewed. Where appropriate, patients are referred either to their own practitioner if they have one or one who the pharmacy has identified as an expert to whom the patient should be referred.

Dr. Sawyer was not aware of any increase in errors in vaccine administration that are attributable to pharmacists administering routine vaccination. He expressed his hope that data systems are in place to track that to make it a clear scientific-based conclusion through the VAERS system or others. However, he thought the experience to date would support the role of pharmacists in administering all vaccines.

Dr. Grogg (AOA) clarified that CDC is responsible for the yellow fever sites, so CDC approval is required to administer yellow fever vaccine. Pharmacies are not administering yellow fever vaccine.

Mr. Rothholz clarified that in some states they are. They go through the same CDC training as any other healthcare provider who administers yellow fever vaccine. Some states allow pharmacists to obtain a yellow card.

Dr. Harrison inquired as to whether there were any existing successful models that illustrate that this is working well.

Mr. Rothholz replied that there are a number of practices, as well as a number of chains that are doing an excellent job. Some of the smaller practices are university-based, such as University of Southern California's clinic that is run by a pharmacist. Safeway has some practices. There is a regional small chain in Virginia that has been doing this for a number of years. This is all based on a community need that came to them, in that their communities had people who were traveling who needed that service but could not access it.

Dr. Loehr (AAFP) inquired as to how many student pharmacists were completing their training with this vaccine certification, and whether this was common or uncommon.

Mr. Rothholz responded that APhA graduates between 12,000 to 14,000 pharmacy students per year. Almost all of them have gone through the training.

Dr. Sun (FDA) requested clarification on pharmacists being trained to document adverse reactions.

Mr. Rothholz replied that they are trained like any other healthcare practitioner who has gone through the CDC program or their own program. A component of the program addresses VAERS reporting and managing situations. Part of the training and information that they receive regards how to use the system and its purpose.

Dr. Sun (FDA) asked who would be responsible for reporting if an adverse event occurs and the patient has a primary care doctor.

Mr. Rothholz responded that this would depend upon the situation. In the events he is aware of, there was a dialogue between the pharmacist and the physician regarding who will submit the VAERS report.

To locate state-specific information on the laws governing pharmacists and vaccines, Dr. Foster (APhA) directed everyone to the Immunization Center link on the APhA website, which can be accessed at www.pharmacist.com. There is a Top Resources area in the middle of the Immunization Center section.

Vaccine Supply

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

During this session, Dr. Santoli reported on the vaccine supply status for adult hepatitis A vaccine, Pentacel® and DTaP, and Boostrix®.

Merck's adult hepatitis A vaccine is currently available for order as vials as well as pre-filled syringes. Availability of sanofi pasteur's Pentacel® and DAPTACEL® vaccines is currently reduced. Increased availability of supply is expected in April 2013. However, sanofi pasteur's single antigen inactivated polio and Hib vaccines continue to be available in sufficient supply to address historic usage of Pentacel® as well as the single antigen vaccines. Regarding DTaP-containing vaccines, production and supply of GSK's single and combination vaccines is currently sufficient to address anticipated supply gaps for DTaP-containing vaccines.

The prefilled Boostrix® syringe presentation is currently out of stock and supply interruptions are anticipated to continue until mid-third quarter 2013. An ample supply of the single dose vial presentation is currently available for order. Supply is sufficient to meet historical demand for both presentations. GSK will continue to provide updates on the availability of the prefilled syringe presentation.

CDC's Vaccine Supply/Shortage Webpage can be found at:
http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm

Herpes Zoster Vaccine

Jeff Duchin, MD
Chair, ACIP Herpes Zoster Working Group

Dr. Duchin indicated that the purpose of this presentation was to provide ACIP with an update of the Herpes Zoster WG's activities and future plans. As a reminder, ACIP recommended herpes zoster vaccine for adults 60 years of age and older in 2006. Subsequently, the FDA approved herpes zoster vaccine for the 50 through 59 year old age group in 2011. However, ACIP declined to recommend the vaccine for adults in that age range and reaffirmed its current recommendation. At the time, there were issues regarding production shortfalls of the bulk product used to manufacture varicella zoster virus-based vaccines, and limited data were available on long-term protection of herpes zoster vaccine and the optimal timing at which to administer the vaccine.

Throughout the last year, the Herpes Zoster WG has convened 6 WG meetings to review various issues related to herpes zoster vaccine. The WG heard from Merck about its market research and media campaign; vaccine supply issues; and updates regarding the long-term persistence study about which information will be shared during the October 2013 ACIP meeting, which extends the vaccine effectiveness estimates 7 through 11 years post-vaccination. This is important information for determining whether ACIP needs to revisit the current recommendation. The WG has also heard about safety and immunogenicity studies, particularly in immunosuppressed adults; partial results for adults 60 years and older on low-dose chronic/maintenance corticosteroids; partial results for a booster dose of herpes zoster vaccine 10 years after first dose; an update from Merck on the inactivated vaccine development program for certain immunocompromised populations; and an update from GSK on the adjuvanted subunit vaccine development program for immunocompetent adults 50 years of age and older and certain immunocompromised populations.

The Herpes Zoster WG's plans for 2013 are to review recent data on vaccine supply and duration of protection, update the herpes zoster vaccine economic models, review current recommendations and determine if revisions are needed, and update ACIP in October 2013. Plans for 2014 and beyond include a review of the use of glycoprotein E subunit herpes zoster vaccine in immunocompetent adults 50 years of age and older, and use of inactivated herpes zoster vaccine and glycoprotein E subunit herpes zoster vaccine in immunocompromised adults (e.g., HIV positive, hematologic malignancies, solid tumors, autologous stem cell transplant).

Influenza

Introduction

Wendy Keitel, MD
Chair, Influenza Working Group

Dr. Keitel began the influenza session by making a few comments about her experience as a member of ACIP over the past four years. She said she followed along with everyone who had gone before her to say that it had been an incredible experience. She thanked the ACIP leadership; the people around the inner circle, including several who had rotated off the committee, particularly her ACIP mentor, Dr. Cody Meissner; all of the liaison and *ex officio* members; and the people who sit in the audience, especially the members of the public who come to share their stories and remind the committee about the faces of these diseases. She thanked everyone for an incredible experience, especially in giving her a totally different perspective from the public health standpoint.

During the 2009 pandemic, Dr. Keitel joined the Influenza WG when it was under the leadership of Dr. Kathy Neuzil. At the time Dr. Neuzil rotated off of the ACIP, she gave a very nice perspective on the introduction and use of influenza vaccines in the US beginning with licensure through 2010 when ACIP voted to recommend universal immunization of everyone 6 months of age and older who is a candidate to receive the vaccine. With such a sweeping recommendation, there clearly was a greater responsibility than in the past to ensure that ACIP issued recommendations to providers on how to use the vaccines as well as antivirals; ascertain vaccine effectiveness; ensure vaccine supply; and ensure vaccine safety.

The Influenza WG has a very broad scope of activities, which continue on an ongoing basis. Also during this time, ACIP endorsed the GRADE approach to establish recommendations. This process has been launched for influenza vaccines, and it is clear that this process is going to be very complex for influenza given the various age groups, risk groups, and vaccines available for prevention of influenza. Dr. Keitel expressed her certainty that with Dr. Karron at the helm, the WG will focus on recommendations so that they have more specificity with regard to use of particular vaccines and particular populations to maximize the effectiveness of their use. During Dr. Keitel's tenure, the WG has also entertained a number of presentations on certain safety issues, including febrile seizures; surveillance and emerging viruses, including the H3N2 variant and H7N9; and the five new vaccines that have been introduced into the armamentarium (e.g., High Dose IIV, Intradermal IIV, Quadrivalent IIVs and LAIV, Cell Culture-Grown IIV, and Recombinant HA), which greatly expands the ability to respond seasonally and in the setting of a pandemic. Dr. Keitel noted that the Influenza WG is quite large and the members are very dedicated, attending a call generally every other week to address these diverse issues. In passing the baton to Dr. Karron, she thanked the ACIP members, *ex officio* members, and liaison representatives who have served on the WG. She also thanked Dr. Grohskopf, who has done a phenomenal job supporting the WG.

Dr. Keitel reported that since the last presentation in February 2013, the *MMWR* Policy Note was successfully published based on what ACIP approved with regard to immunization for the 2013-2014 influenza season [*MMWR* 2013; 62(18):356]. She indicated that ACIP would vote during this session on a component of the draft 2013-2014 Influenza Statement addressing egg

allergy. Over the last several months, the Influenza WG's discussions have included quadrivalent influenza vaccine, 2012-2013 influenza vaccine effectiveness, and updates on influenza vaccine safety, and issues related to vaccination of persons with egg allergies.

Epidemiology and Surveillance Update

Lyn Finelli, DrPH, MS
Influenza Division
Epidemiology and Prevention Branch
Influenza Surveillance and Outbreak Response Team
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Finelli presented a brief update on the surveillance data. Regarding virologic surveillance, about 311,000 specimens were tested this year. Of those, 73,000 were positive. This resulted in an overall percent positive of 23%. That percent positive peaked at 38% during Week 52, the last week of the year. Overall there was a predominance of Influenza A, specifically H3N2. Overall, Influenza A was 71% and Influenza B was 29%. Even though there was a predominance of Influenza A (H3N2), Influenza B predominated from about Week 7 (February 23rd) through the rest of the season. That predominance continues, with an overall percent positive at the time of this meeting of about 3% to 4%.

In terms of antigenic characteristics, 2009 H1N1 was overall a small percentage (~4%) of the total viruses observed during this year. Of the 252 H1N1 viruses characterized, 249 (98.8%) were A/California/7/2009-like, the H1N1 component of the 2012-2013 Northern Hemisphere vaccine. Of the 1324 H3N2 viruses characterized, 1319 (99.6%) were characterized as A/Victoria/361/2011-like, the H3N2 component of the 2012-2013 Northern Hemisphere vaccine. Of the 879 Influenza B viruses characterized, 581 (66.3%) were from the Yamagata lineage and were characterized as B/Wisconsin/1/2010-like, the influenza B component of the 2012-2013 Northern Hemisphere vaccine. The remaining 295 (33.7%) were from the Victoria lineage of viruses. There was little antiviral resistance. No Influenza B viruses were resistant. Of the H3N2s, two viruses were resistant to Oseltamivir, one virus was resistant to both Oseltamivir and Zanamivir, and one virus was resistant to Zanamivir. Of the H1N1s, two viruses were resistant to Oseltamivir.

Regarding the percentage of visits for influenza-like illness (ILI) from the Influenza-like Illness Surveillance Network (ILINet) for 2012-2013 and selected previous seasons, the season peaked at a rate this year of 6.1%. The pandemic year peaked at 7.7%, and the 2003-2004 season peaked at 7.6%. These are two of the highest years recorded in this system since 1997. This was a bad influenza season, which was characterized at moderately severe at 6.1%. As of June 8, 2013, the rate was down to 0.9%. With respect to hospitalization surveillance, this was a particularly severe year for the elderly at 191 per 100,000. In 2012, the elderly rate was 40 per 100,000. The rate for the elderly for 2013 is 2.5 times the rate ever recorded in the history of this system. Surveillance has been conducted for adults in this system since 2005. The overall rate for hospitalization this year is 44 per 100,000. The next highest rate under the elderly rate for this year is in the 0 through 4 year old age group at 66 per 100,000. The rates for other age groups are much lower than that. This year, there have been many hospitalizations, especially for people over 65 years of age. Compared to last year, this was a severe year. Other than the pandemic year, the last highest rate in this system was in the 2007-2008 season.

With regard to the number of influenza-associated pediatric deaths by week of death for 2009-2010 to June 8, 2013, there was a particularly severe year during the pandemic with 348 total deaths. 2010-2011 was a fairly moderate influenza season, with 123 pediatric deaths reported. There were 34 pediatric deaths reported during the 2011-2012 season, which was characteristic of a very mild influenza season. For the 2012-2013 season, 152 pediatric deaths were reported. With exception of the pandemic, this is the highest rate since surveillance began. This system was launched in 2003-2004 after a particularly severe season in which H3N2 and Influenza B circulated, with 153 pediatric deaths reported during that timeframe.

Turning to the pneumonia and influenza mortality deaths reported for 122 US cities from 2008 to June 8, 2013, overall there was a particularly high proportion of deaths for pneumonia and influenza this season, with 9.9% of all deaths due to pneumonia and influenza. This seems particularly severe looking back to 2008; however, for 2003-2004 and in the early 1990s there was a much higher proportion than 2012-2013. Based on weekly influenza activity reported through Week 20 (May 18, 2013) by state and territorial epidemiologists, very little influenza was circulating.

In summary, influenza activity in the US during the 2012–2013 season began approximately 4 weeks earlier than usual, and occurred at moderately high levels. Activity peaked in late December. Influenza A (H3N2) viruses predominated overall and until late February. After late February, influenza B viruses predominated through the end of the season. There were high rates of influenza hospitalization, especially in the elderly. The peak percentage of outpatient visits for ILI (6.1%) was one of the highest reported since the system began in its current format in 1997. The number of pediatric deaths was the highest reported since surveillance began, excluding the pandemic year.

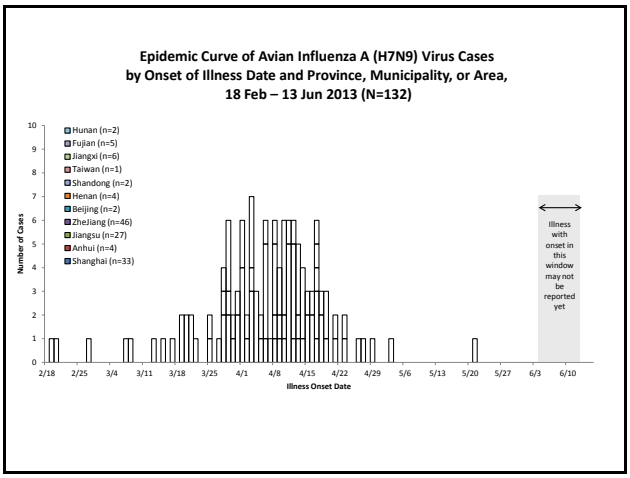
H7N9 Update

Daniel Jernigan, MD, MPH
Deputy Director, Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Jernigan reported on the investigations and epidemiology of Influenza A(H7N9) that occurred over the last few months, pointing out that this was a manifestation of a post-severe acute respiratory syndrome (SARS) and post-2009 H1 era in terms of how the response differed with the speed of technology and the benefits of transparency. On March 31, 2013, the China National Health and Family Planning Commission (NHFPC) notified WHO of three cases of human infection with influenza A(H7N9)[1,2]. Two cases were from the Shanghai Municipality and 1 case was from the Anhui Province. All three cases presented with respiratory tract infection with progression to severe pneumonia and breathing difficulties. There were two deaths, and one patient was in critical condition at the time. This is distinct from previously reported H7 cases, which were mostly mild. It is important to point out that the area in which the initial cases occurred have approximately 575 million people, which is about 45% of the population of China and 8% of the world population. This highlights that what occurs there can have a significant impact in terms of travel. Also important to note is the proximity of Korea, Vietnam, and other nearby areas [[1]MMWR / May 10, 2013 / Vol. 62 / No. 18; [2]WHO Global Alert and Response (www.who.int/csr/don/2013_04_01/en/index.html].

As of June 20, 2013 there were 132 lab-confirmed patients with Influenza A (H7N9) of whom 127 (96%) were hospitalized, 78 (59%) recovered, and 39 (30%) died. Of these, 77% had exposure to live animals, mostly chickens and ducks. It is important to note that in terms of speed of technology, the development of diagnostic kits was extremely rapid. In the US, the kits were cleared under Emergency Use Authorization (EUA) and were quickly disseminated to all 50 states, the DoD, and other places around the globe. Cases have been diagnosed in 8 provinces and 2 municipalities in China and in Taiwan. There have been 5 lab-confirmed clusters. While human-to-human transmission is possible; however, there have been a lot of exposures to animals as well in terms of these clusters, so it is difficult to discern whether there was human-to-human transmission alone. There was 1 lab-confirmed asymptomatic infection in a child in Beijing. Over 2000 contacts have been followed to date, and only two were lab-confirmed positive infections by PCR. US virologic and influenza surveillance were ramped up for people returning from China and the surrounding areas. Though there were 67 suspect US cases, all turned out to be negative. Dr. Jernigan shared a map to depict where the cases have been occurring and the number of individuals who have died or recovered, with a general explanation that this began in Shanghai and moved outward.

The following epidemic curve for Avian Influenza A (H7N9) virus cases showing the onset of illness date and province, municipality, or area. Important to note is that the colors are in waves, illustrating that the virus appeared in a location, cases occurred in that location, and then no more cases seemed to occur in that area. The reason for this is not entirely clear:

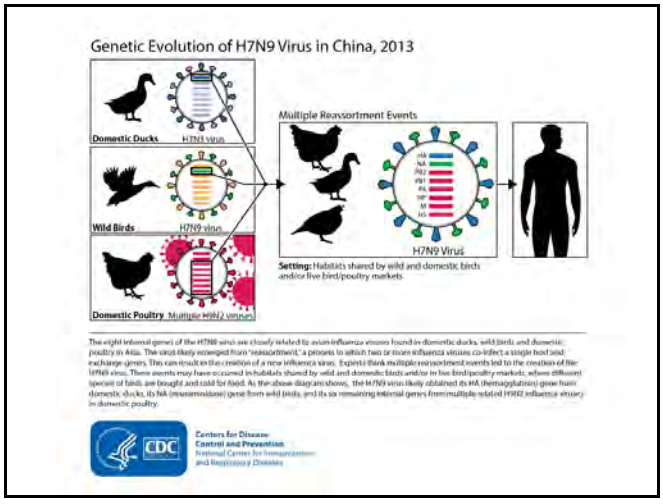


In terms of the demographic information for the cases thus far, an overall generalization that can be made is that it is a predominantly severe disease in older men with underlying conditions (95%). That is a different type of epidemiologic assessment from other novel influenza viruses. It is important to emphasize that prior human illness due to H7 has been mild, generally with conjunctivitis, when it causes disease in humans. Only 1 death has been reported previously, so there is something different about this virus, which is why there is great concern about it.

Regarding age and gender distribution, the median age for men is 69 years and for women 59 years. Comparing the age distribution for H5N1 to A (H7N9), for those cases that occurred in China there is a very different epidemiologic phenomenon. The median age for H5N1 is 26 years, while the median age for A (H7N9) is 61. While the exact reasons are unclear in terms of why A (H7N9) predominately affects older men, some of CDC's colleagues at FAO and OIE indicated that older men tend to do the buying in live bird markets in Shanghai, which may be different in other places. In addition, younger individuals tend to buy processed food and not

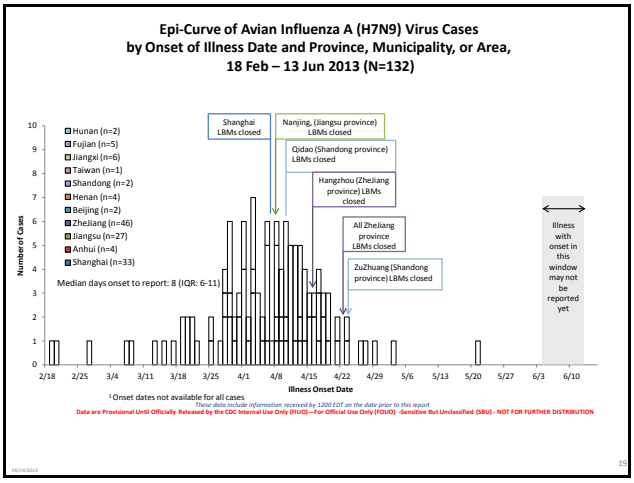
buy food from live markets. Older individuals, especially older men, also tend to smoke more than older women and have underlying conditions that may be associated with that.

With regard to the laboratory investigation, 43 human viruses representing 35 cases have partial or complete genetic sequences posted. All of the genes that have been sequenced so far are from avian origin. In terms of the genetic changes that have been identified from genetic sequences, three issues of concern have been pointed out. Adaptations have been identified that lead to enhanced virus binding to mammalian respiratory cells, enhanced replication in mammalian respiratory cells, and increased severity of infection. These mutations that have been identified have been associated in the past with those features in animal models. Regarding antiviral susceptibility, overall the virus is susceptible to oseltamivir and zanamivir. One virus shows resistance to oseltamivir and zanamivir; however, the clinical relevance of that virus is currently unknown. The following diagram depicts the origins of the different genetic sequences to show that all 8 genes are from poultry and wild birds:



Serologic studies using the hemagglutination inhibition (HAI) and micronuclei (MN) assays and serum from people vaccinated with the 2012-2013 seasonal trivalent inactivated influenza vaccine show no existing cross-reactive antibodies to H7N9, either before or after vaccination in young children, adults, or older adults. Basically, this demonstrated that there was no cross-reactive antibody. Preliminary results of the National Health and Nutrition Examination Survey (NHANES) sera collected from the general US population in 2010 suggest that there are very little to no pre-existing cross-reactive antibodies against H7N9 in all age groups tested. That is, across a wide age spectrum there does not appear to be any existing immunity in the population. Sera from individuals who have received 2 doses of a Eurasian lineage H7N7 LAIV and one dose of Eurasian H7N7 inactivated vaccine (LAIV prime and inactivated vaccine boost) showed good cross-reactivity for the H7N9 virus. Candidate H7N9 vaccine viruses have been developed and have been provided to vaccine manufacturers. A clinical trial of inactivated, non-adjuvanted, vaccine is planned. Decisions for stockpiling H7 vaccine are under discussion within the federal government.

In terms of the animal investigation, while humans have severe disease, testing indicates that chickens and quail show no signs of illness. However, birds are shedding virus. H7N9 has been confirmed in chickens, ducks, feral and captive pigeons, and environmental specimens primarily associated with live bird markets. Over 4000 swine have been tested in China, and are reported negative. In the US, ongoing surveillance has not identified H7N9 viruses in tested birds. Dr. Jernigan shared a map to show where animals which shed virus have been identified in China, which has primarily been in live bird markets. An important phenomena to note is that animals but not human cases have been identified in Guandong Sheng, which is close to Hong Kong. The following epidemic curve depicts what is occurring in the live bird markets. Information thus far indicates that Shanghai may have a more liberal process for animals coming in and out, and in how live bird markets are managed. Following the appearance of H7N9, there have been changes in terms of live bird market management and there is a likelihood that many of these may not open again:



In conclusion, recognition and response has been faster and more transparent than in the past. Public health concerns persist given the high severity of illness; genetic changes in H7N9 associated with mammalian adaptation and transmission; and the fact that birds may shed virus without symptoms, which may be a challenge for control efforts and demonstrates the need for ongoing surveillance in animals. There have been no new H7N9 cases with onset after May 21, 2013. However, it is unclear whether this is an effect of live bird market closures and/or seasonal and other factors. It is possible that cases may recur in the fall. There is no evidence of sustained human-to-human spread; however, ongoing surveillance in humans is needed. Vaccines are currently being developed and evaluated.

Discussion Points

Dr. Karron wondered whether there was any information about serologic surveillance in China either for contacts of cases, workers in bird markets, or the general population.

Dr. Shaw responded that the Chinese have conducted some preliminary studies, but are still getting their assays set up. They are basically not finding seroconversion to any high level, which indicates that there are not that many undetected cases thus far. However, they are still optimizing the serologic assays.

Dr. Vazquez said she was trying to understand what proportion of the animals are positive, and if positivity is high, why the rate of asymptomatic infection is very low. She also wondered how the one asymptomatic infection was assessed.

Dr. Jernigan responded that there was not a good denominator that could be used to determine the actual rate of positivity. All of the information CDC has is from the China Ministry of Agriculture, which is working on assays as well. They have a means for collecting specimens, testing them, and then using a culture as the gold standard for what they call a positive animal. That probably leads to less identification of cases. There is no ongoing surveillance for asymptomatic animals. Surveillance is in place, but it is not quite to the level that would be able to answer the first question posed by Dr. Vazquez.

Dr. Schuchat indicated that the asymptomatic infection identified was a contact of one of the confirmed symptomatic cases. China conducted very intensive monitoring of contacts to look for fever and so forth, and to look for asymptomatic infections. They have very good ILI surveillance, which has been strengthened greatly in the past few years. They found a total of 6 confirmed cases through the ILI system out of many thousands of specimens. It does not appear that this strain was causing a lot of ILI. People with bird exposures primarily experienced severe disease.

Dr. Sawyer noted that one of the potential advantages of the non-egg-based vaccine is rapid production as new strains arise. In this case, he wondered if there were any updated protections from the manufacturers regarding how quickly they could make a vaccine.

Dr. Gellin (NVPO) responded that the point that had been highlighted was that a lot of attention has been paid to the machinery of vaccine development. Optimizing seeds is a key piece of this in terms of making sure they yield as much hemagglutinin as possible, because that will directly impact how much vaccine can be produced. This is moving forward in terms of ensuring that vaccine could be available. There also must be a commitment to develop product for clinical trials. There is now a range of technologies other than eggs, but there is also varying capacity.

Dr. Schuchat added that the US is in a different place than in 2009, because beyond the inactivated egg-based and LAIV available in 2009, cell-based and recombinant vaccine development activities are underway. In addition, there has been potency and sterility and manufacturing dialogue is much better than in 2009. One lesson learned very well in 2009 was that predicting capacity and production is not a winning strategy. Based on the H7 influenza vaccine literature, there are reasons to believe that it may be more challenging to make an immunogenic H7 vaccine. In the studies conducted in the past, it was more like the H5 situations for which large doses or adjuvant were required to achieve a good response. There is a very active cross-HHS and cross-manufacturing dialogue underway. However, it would be inappropriate to anticipate what type of production might be achieved from the various strategies.

Dr. Keitel inquired as to whether post-infection sera had been obtained from the cases to determine whether the assays are able to detect a sera response.

Dr. Shaw replied that post-infection sera have been collected; however, the results have not yet been seen.

Preliminary Data on 2012-2013 Vaccine Effectiveness

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Dr. Thompson discussed the background of influenza vaccine effectiveness, updated adjusted vaccine effectiveness estimates for the 2012-2013 season, a comparison of the interim versus full season estimates, and updates on vaccine effectiveness against inpatient outcomes.

The answer to how effective influenza vaccine is varies by age and other host factors, vaccines, viruses, and seasons. Observational studies are conducted in the US, which compare the odds of vaccination among cases to the odds of vaccination among controls. The study designed used for the US Flu VE Network is a test-negative control design, which minimizes potential biases by using controls who are seeking care for acute respiratory illness (ARI), but who test negative for influenza. Dr. Mike Osterholm's group released a pooled estimate for adults for the time period of 2004-2008 of 59%. When that is compared to the other adult estimates from the US Flue VE Network, what was observed for the adult age group for the 2010-2011 and 2011-2012 seasons was consistent.

The US Flu VE Network consists of 5 sites across the US (Group Health Cooperative, Marshfield (Wisconsin) Clinic, Scott & White Healthcare in Texas, University of Michigan, and University of Pittsburgh), with a focus on estimating vaccine effectiveness for prevention of outpatient visits. The design is a prospective case-control study for which the cases are those with medically attended ARI and RT-PCR confirmed influenza and the controls are those with medically attended ARI who are negative for influenza. Dr. Thompson emphasized that the result he would be presenting during this session would be interim, given that the investigators were still awaiting medical records and were relying on self-report vaccination status for one of the sites. The data for vaccination would reflect fitting within the ACIP recommendations for days prior to illness onset, and the combination of doses recommended for children under 9 years of age. The adjusted estimates controlled for age, sex, site, days from illness onset to enrollment, and calendar time. Adjustment was also made for potential confounding by race/ethnicity and self-rated health that has been observed in the current season. As noted, this has been a very early and robust season. There have been approximately 2000 influenza cases and about 4000 influenza-negative controls. The enrolled cases are comprised of 1136 Influenza A (H3N2), 53 Influenza A subtype pending, 538 Influenza B (Yamagata), 283 Influenza B (Victoria), 50 Influenza B unsubtyped, and 47 Influenza A(H1N1) pandemic.

In terms the results for vaccine effectiveness for all ages, 33% of the cases were vaccinated compared to 50% of controls. Once the adjustments were made for the patient and illness characteristics mentioned earlier, vaccine efficacy was 52%. Against all circulating strains, vaccine effectiveness was 56% for those 6 months through 8 years of age, 42% for 9 through 17 year olds, 44% for 18 through 49 year olds, 66% for 50 to 64 year olds, and 32% for those 65 years of age and older. The numbers for vaccine effectiveness against B of any lineage were quite respectable, and there was significant vaccine effectiveness for all age groups against B. There have never been sufficient sample sizes in the past to be able to say definitively that there was significant vaccine effectiveness for all age groups against B. Of note, the results were disappointing for H3 among those 65 years of age and older this season. Once children were divided under age 18 into two age groups, vaccine effectiveness of 50% was observed for the full immunization of children under 9 years of age, but lower than expected

vaccine effectiveness against H3 in those 9 through 17 years of age. The lineages of the B viruses were also assessed. Vaccine effectiveness was very similar for all age groups against B Yamagata, which was the component in the vaccine, and B Victoria.

In summary, adjusted vaccine effectiveness against influenza A and B was determined to be 52% (46%-58%). This was similar to the early unadjusted vaccine effectiveness of 62% (51%-71%) and mid-season adjusted vaccine effectiveness of 56% (47%-63%) against A and B. This was also similar to international interim vaccine effectiveness estimates. Vaccination reduced the risk of outpatient medical visits due to influenza A (H3N2) by half (44%), except among children aged 9 through 17 years and adults aged 65 and older. Vaccination reduced the risk of outpatient medical visits due to influenza B by two-thirds (62%), which was consistent for all ages. Similar vaccine effectiveness was observed against both B lineages in circulation for the second year in a row. Further research is needed to confirm and understand age differences, chronic medical conditions, and vaccine type.

With regard to adjusted vaccine effectiveness against circulating strains by season in the US Flu VE Network, comparing the current season to the two prior seasons, the story is fairly consistent with older adults having a somewhat lower vaccine effectiveness. There were a couple of interim results, a crude unadjusted vaccine effectiveness that was released in January 2013 and then what turned out to be a mid-season adjusted vaccine effectiveness in February 2013. The good news is that this allowed CDC to address some early misconceptions about the vaccines' performance. Specifically, they were hearing from state health departments that they were seeing "unprecedented" numbers of vaccine failures, so it was reassuring to see that the vaccine efficacy being observed was similar to past seasons. In retrospect, it was realized that this was due to the volume of circulation and the predominance of H3. In the process, especially regarding older adults, CDC was able to disseminate the message about clinical management and the importance of antivirals as a second line of defense. In general, early and later estimates were largely consistent, with strata and precision limited by number of cases.

Against all circulating strains and for all ages, the three estimates CDC published included 61% for the period 12/03/12 through 01-02-13[1]; 56% for the period 12/03/12 through 01/19/13[2]; and 52% for the full season. The estimates decreased stepwise and the confidence intervals become smaller, but the story was not substantially different. For all ages, vaccine effectiveness against A (H3N3) and B at the three estimates also decreased stepwise and the confidence intervals become smaller, but again, the story is not substantially different [[1]*MMWR*: Jan. 11, 2013; [2]*MMWR*: Feb. 22, 2013]. In terms of the adjusted vaccine effectiveness against A(H3N2) at the mid- and full-season estimates by age, of interest is that for those 65 years of age and older the interim estimate was 9% and the full-season estimate increased to 19%. However, once the two age groups of children were broken out, the estimates were lower and different. With regard to the mid- and full-season estimates by age for B only, in some age groups the estimates seemed very stable while in other age groups there seemed to be a steady decrease.

A primary driver of CDC influenza program is to prevent inpatient outcomes. Three studies were conducted to assess recent seasons in terms of hospitalized influenza cases using a similar influenza-negative control design. The first study assessing the time period from 2006-2009 had 39 cases and 256 influenza-negative controls, all of whom were 65 years of age and older. This study showed vaccine effectiveness against hospitalization in this age group of 61%[1]. The second study assessing the time period from 2010-2011 had 61 cases and 208 influenza-negative controls comprised of all ages. This study showed vaccine effectiveness against hospitalization of 59%[2]. The third study assessing the time period from 2011-2012 had

17 cases and 152 influenza-negative controls comprised of those 18 years of age and older. This study showed vaccine effectiveness against hospitalization of 71%[3] [[1]Talbot et al. (2011) JID 203: 500-8; [2]Costilla (2013) BMC Public Health 13:191; [3]Talbot et al. (2013) CID 56:1774-7]. Each of those numbers is at or higher than CDC's numbers for the same age mix among outpatients.

Interestingly, to assess adjusted vaccine effectiveness against hospitalization, Castilla et al in Spain used age-matched controls instead of the test negative design. They found a vaccine effectiveness of 57% against inpatient influenza versus non-respiratory illness, and 72% vaccine effectiveness against ICU severe inpatient influenza versus non-respiratory illness. In terms of the prevention of complications, no difference was observed in vaccine effectiveness against inpatient influenza and outpatient influenza. However, they did notice a difference in those receiving ICU influenza patients versus those who were receiving care on the hospital ward. Vaccine effectiveness was 58% against severe inpatient influenza versus non-severe inpatient influenza. This suggested that among those who were infected with influenza, the vaccine may have reduced the likelihood of more severe illness [Castilla et al. (2013). CID: doi: 10.1093/cid/cit194].

In conclusion, vaccine effectiveness against influenza-associated inpatient care has been similar to or higher than estimates of outpatient vaccine effectiveness during the same season. The theme seems to be that influenza vaccines may potentially reduce the risk of hospitalizations due to influenza by about half. The US currently lacks a consistent platform to assess vaccine effectiveness against inpatient outcomes, so it is necessary to depend upon the kindness of academic strangers in other countries for the time being. Important questions remain about vaccine effectiveness against mild versus severe disease.

Vaccine Safety Update

Tom Shimabukuro, MD, MPH, MBA
Immunization Safety Office
Centers for Disease Control and Prevention

Dr. Shimabukuro presented an end-of-season update on the 2012-2013 influenza vaccine safety monitoring. He pointed out that the VAERS data for this particular review end on May 4, 2013; however, at this stage in the season it was not anticipated that there would be many additional reports. In terms of US reports to VAERS following trivalent inactivated influenza vaccines (TIV), the results are fairly comparable for the 2011-2012 and 2012-2013 seasons. For the 2012-2013 season, there were 7171 total US reports. Of these, 457 (6.4%) were serious and 6664 (93.6%) were non-serious. There were 72 (1.0%) reports of GBS and 31 (0.4%) reports of anaphylaxis. Approximately 121.9 million TIV doses were distributed in 2012-2013. There was no disproportional reporting in data mining for Guillain-Barré syndrome, *febrile seizures*, or *anaphylaxis* for 2012-2013. Dr. Shimabukuro noted that the FDA provided the data mining data for all of the data mining findings he would report during this session.

Regarding reports to VAERS following LAIV, for the current and previous seasons there was roughly the same number of reports. There was a slightly higher number of serious reports for the current season versus the previous season, but further review revealed no unusual or concerning patterns. For the 2012-2013 season, there were 494 total US reports. Of these, 41 (8.3%) were serious and 453 (91.7%) were non-serious. There were 2 (0.4%) reports of GBS and 5 (1.0) reports of anaphylaxis. There were a few more anaphylaxis reports than in the previous season, but it is important to note that these are small numbers. Of the 5 reports for

the current season, 4 of the 5 had multiple other vaccinations administered during the same visit, so it is difficult to draw any conclusions about those reports. Approximately 13 million LAIV doses were expected for 2012-2013. That information was provided by the manufacturer at the beginning of the season. There was no disproportional reporting in data mining for *Guillain-Barré syndrome*, *febrile seizures*, or *anaphylaxis* for 2012-2013.

With regard to Fluzone® High-Dose (TIV-HD) reports in VAERS for the first three seasons of Fluzone® High-Dose use in the US, the total number of reports were 642 in 2010-2011; 605 in 2011-2012; and 730 in 2012-2013. Of these, 58 (9.0%) were serious in 2010-2011; 69 (11.4%) in 2011-2012; and 64 (8.8%) in 2012-2013. Of the total reports, 412 (64.2%) were in females in 2010-2011; 407 (67.3%) in 2011-2012; and 511 (70.0%) in 2012-2013. The median age ranges was 71 (1-95) in 2010-2011; 71 (24-98) in 2011-2012; and 71 (2-98) in 2012-2013. The number receiving TIV-HD alone was 587 (91.4%) in 2010-2011; 540 (89.3%) in 2011-2012; and 590 (80.8%) in 2012-2013. The reports are fairly consistent across the first three seasons of Fluzone® High-Dose. Common signs and symptoms following TIV-HD include pyrexia, chills, nausea, vomiting, headache, and injection site reactions.

More specifically with regard to Fluzone® High-Dose reports in VAERS during the 2012-2013 influenza season, disproportional reporting in data mining was identified for *vomiting* and *drug administered to patient of inappropriate age*. The vomiting data mining finding has persisted since the 2010-2011, so this does not represent a new safety concern. Most reports of vomiting are non-serious and self-limiting. Vomiting is frequently accompanied by the coded outcomes of nausea (51%), chills (41%), diarrhea (36%), or pyrexia (30%). What this means is that for VAERS high dose reports where vomiting was a coded outcome, 51% of the time nausea was also a coded outcome in that report.

In terms of reports to VAERS following Fluzone® Intradermal (TIV-ID) vaccine during the first two years of Fluzone® use in the US, there were more reports in 2012-2013 (N=391) versus 2011-2012 (N=86). However, this could possibly represent increased use and uptake in the marketplace. The percent serious, percent female, and median age range for 2012-2013 are comparable to 2011-2012. Common signs and symptoms following TIV-ID were mild and self-limited injection site reactions. Disproportional reporting in data mining was identified for *injection site nodule*, *injection site pruritus*, and *drug administered to patient of inappropriate age*. Local reactions are in the package label and were expected. Thus, findings for injection site nodule and injection site pruritus do not represent new safety concerns.

There were 43 total reports to VAERS following TIV administration during pregnancy for the 2012-2013 influenza season. The reports were comprised of 14 spontaneous abortion (32.6%), 1 placenta previa, 1 excessive bleeding during labor, and 27 non-pregnancy specific reports or no adverse event indicated on the VAERS report. There were no reports of major birth defects. To put these numbers into context, approximately 2 million pregnant women received influenza vaccine during the 2012-2013 season. A review of these VAERS reports identified no unusual patterns.

Moving to influenza vaccine administration in patients with history of egg allergy, as a reminder the recommendation for patients with egg allergy was updated for the 2011-2012 season. Generally those recommendations were that persons with a history of egg allergy who have experienced only hives should receive TIV with some additional safety measures; and persons with more severe reactions to egg should be referred to a physician with allergy expertise for further risk assessment. CDC has conducted enhanced monitoring for allergy and anaphylaxis in VAERS since 2011-2012, the season that these new recommendations went into effect. A

search is done for the code *anaphylaxis* combined with text search for *egg*, and then all reports from that search and the medical records are manually reviewed to identify potential cases of anaphylaxis in suspected egg allergic patients reviewed through CDC's CISA Project.

The CISA assessment of VAERS anaphylaxis reports after influenza vaccine in people with suspected egg allergy for the time period 7/1/2010 through 5/3/2013 identified 4 reports. The CISA Project reviewed these 4 cases (3 TIV and 1 LAIV). Of the 4 cases, 3 cases did not meet the criteria of (1) existing egg allergy, (2) diagnosis of anaphylaxis, and (3) anaphylaxis consistent with reaction to egg protein in the vaccine. The 1 case that met the criteria was vaccinated in 2012-2013. This was a 12-month old male with history of atopic dermatitis and egg allergy, who was prick test positive for ovalbumin. He developed generalized urticaria, dyspnea, cough, wheezing, and angioedema of the uvula following TIV. The child had never ingested egg in the past. This case met Brighton Level 1 criteria [Rüggeberg et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25(31):5675-84]. The take home message for this review was not to get wrapped up in the details of this case or the 3 who were ruled out. Instead it was to illustrate that VAERS surveillance detected an individual who after expert review was determined to have an existing egg allergy, had a diagnosis of anaphylaxis after receiving a TIV, and the anaphylaxis was consistent with a reaction to egg protein in the vaccine.

Turning to VSD surveillance for the 2012-2013 influenza season, for RCA near real-time monitoring the pre-specified outcomes for TIV and LAIV were GSB, seizures, encephalitis, myelitis and encephalomyelitis, and anaphylaxis. RCA used automated data from approximately 9.2 million health plan members within the VSD sites. There were just over 3.6 million TIV Dose 1s. Of these, 31,257 doses were TIV-HD and 4,713 doses were TIV-ID. Although TIV-HD and TIV-ID were included in the 3.6 million total of TIV doses, they were dropped from the analysis for RCA. There were 264,262 LAIV Dose 1s. The bottom line is that no signals were detected in RCA during the 2012-2013 influenza season for any pre-specified outcomes.

In summary, no new safety concerns were detected for TIV or LAIV during the 2012-2013 influenza season. A review of pregnancy reports in VAERS identified no unusual patterns. A review of VAERS reports for the past 3 influenza seasons identified 1 case of anaphylaxis in an egg-allergic person following TIV that was consistent with a reaction to egg protein in the vaccine.

With regard to next steps, enhanced VAERS surveillance for 2013-2014 will include physician review of reports for pregnancy; anaphylaxis in egg-allergic people; and recently licensed vaccines (quadrivalent IIV4 and LAIV4, cell culture-based, and recombinant). For VSD RCA near real-time monitoring for 2013-2014, surveillance of new vaccines will depend upon the number of doses observed in VSD.

Discussion Points

Dr. Harriman noted that the efficacy of the H3N2 vaccines varied widely amongst people under 65 and in different age categories. She inquired as to whether data could be presented for the next season for vaccine effectiveness by various formulations of vaccines. That could explain different uptake in different age groups, et cetera.

Dr. Thompson responded that one of the goals is to try to incorporate vaccine type into the interim estimates as well. Thus far, there has only been enough LAIV administered to make estimates for the under age 9 group. There were a few dozen over age 9, but there is not even much across seasons to assess that. In terms of high dose or other formulations, there were perhaps a dozen this season. It is not clear that this is going to be the platform that can do that, although it is certainly an important question.

Given the disappointing data in the 65 and above age range and the importance of understanding whether efficacy is higher for the high dose vaccine, Dr. Harrison wondered how this issue could be addressed if this was not the right platform.

Dr. Thompson responded that all of these sites have a clearly defined source population, and their health plans are all open to enriching their membership with more high dose vaccine, for example. However, that might not be a practical option.

Dr. Keitel added that at least one study is underway comparing high dose to the standard dose.

Dr. Sawyer inquired as to whether Dr. Thompson could comment on how surprising the cross-protection for Influenza B Victoria was, and what the implications were for the utility of the new quadrivalent vaccine, which he thought were designed to address a lack of cross-reactivity.

Dr. Thompson responded that a couple of years prior, vaccine efficacy against B was not especially good. It is difficult to know how any year applies to policy. There are plans to assess prior year vaccination. There is some indication that some of this could be due to the fact that people receive repeated vaccinations. They would have received B Victoria lineage for the past several years.

Regarding B efficacy, Dr. Karron thought it was great that children were being stratified. She wondered if it was possible to stratify even more if there are the numbers to do that. Because 6 months to 8 years is a really wide range, many of those children have received multiple vaccines, including B vaccines from the other lineages; whereas, the very young children may not have received B from both lineages. Given the comments about the high number of hospitalizations in the elderly this year and relying on the kindness of strangers, she wondered if any institutions had plans to investigate efficacy against hospitalization in the elderly.

Dr. Thompson asked Dr. Karron what she thought a good cut point would be for children.

Dr. Karron said that if they have the numbers, she would suggest 6 through 24 months, 6 months through 3 years, and 3 to 8 years.

Dr. Thompson replied that this could be done and shared with the WG. The confidence intervals will be wide, but it is sometimes interesting to see. He was not aware of other plans to study efficacy against hospitalization in the elderly during the coming season in the US.

Dr. Keitel said she thought it was worth remembering that one should not stare to long and hard at a single variant in a single year, but rather should assess trends over many years. It is well known that different vaccine antigens may be more or less immunogenic. For example, it would be interesting to know how immunogenic the H3N2 component was for the 2012-2013 seasons. She has seen no data on this, and it would be nice to determine whether the elderly respond well to vaccination.

Dr. Brady (AAP) wondered whether it would be possible to compare people who have positive results for influenza versus those with ILI who are negative. It seems like there may be a lot of confounding there. His guess was that some of the people who have ILI during influenza season and were negative actually had influenza; whereas, it might be more valuable to try to identify just a cohort of people who are matched for age, gender, and potentially underlying illness who have no medical problems to determine whether there is a difference. While he did not know where those with ILI who were negative would fall in terms of vaccinated and unvaccinated, that may have implications for the comparison.

Dr. Thompson responded that one advantage is that this is limited to people who have been sick less than 7 days, so that given the highly sensitive test, there can be some confidence that the negatives for that illness do not have influenza. He agreed that there was a value in assessing at other control types. For a pregnancy study completed recently, they were able to use the test-negative controls and matched community controls as Dr. Brady described. The results were identical, which was reassuring.

Following up on Dr. Brady's comments, Dr. Temte said he had some fairly significant concerns about the methodology. There seems to be an assumption that PCR performs equally well across ages, but he does not believe it does. The interplay between age, time from onset of illness to the time of sample, and clinic-seeking behavior across the ages is so confounding that it makes the results almost unattributable. If a layer of multiplex PCR was added in, and a non-entity was pulled out, for example, testing people for human metapneumovirus (hMPV) and looking for influenza vaccine efficacy against something that it should not, would give the control regardless of whether the methodology is functional or if they are just seeing all of these other things coming into play.

Dr. Thomson responded that the test-negative design, about which he was initially skeptical, seems pretty effective at controlling for health-seeking behavior. There is no doubt that people in outpatient care have higher vaccination rates than people in the community, but these are definitely important questions. There are some studies comparing test-negative not only to influenza, but against other respiratory pathogens that are positive. Those are good studies, but the ones he has seen so far show similar results.

Dr. Bennett noted that it was somewhat difficult when looking at the VAERS data to track the implications of the data without some kind of denominator. She noticed that Dr. Shimabukuro showed some estimates of the distribution of vaccines in the US, but he wondered whether he thought about any methodology for essentially determining rates of adverse events.

Dr. Shimabukuro responded that when they display the distribution data, if they were going to calculate a rate, they would be calculating reporting rates, which are not ideal. In order to obtain true reporting rates, they would have to use coverage data and then calculate doses administered. However, they do not have any way to his knowledge to capture those data by product. The way product-specific monitoring is done is through FDA's data mining, because they are actually looking at a specific product compared to the other products that are captured in the VAERS database.

Dr. Greenberg (sanofi pasteur) reminded everyone that Fluzone® High-Dose vaccine was licensed by the FDA under an accelerated approval process based on its safety and superior immune response compared to the regular Fluzone® vaccine. As part of that process, sanofi pasteur conducted a post-licensure efficacy trial. This was a double-blind, randomized study among approximately 30,000 persons all 65 years of age and older. They anticipated providing

results from that study in 2015, which was substantiated by the fact that the study was started last season, which was one of the mildest seasons on record. However, this season was more severe. A recent analysis of the cases collected last season and this season showed that enough influenza cases have been collected to conclude this study. The laboratory work and safety follow-up will be collected for the remainder of 2013, and sanofi pasteur plans to supply the data and study report to the FDA in the first quarter of 2014.

Dr. Gellin (NVPO) remarked on the fact that 2 million pregnant women were vaccinated this year. While the birth cohort and percentages are known, to put that in hard terms of 2 million people now protected who years ago would not have been is really remarkable. That now is the maternal platform.

Dr. Keitel pointed out that actually, 4 million people (considering fetuses/newborns) were protected.

FluLaval: GSK's Inactivated Quadrivalent Seasonal Influenza Vaccine

Varsha K. Jain, MD, MPH
Director, Vaccine Discovery & Development
Seasonal Influenza Vaccines
GlaxoSmithKline

Dr. Jain presented information on FluLaval® Quadrivalent, GSK's inactivated quadrivalent influenza vaccine manufactured in Quebec, as well as information on FluLaval® trivalent (Q-TIV). FluLaval® TIV is licensed in the US for adults 18 years of age and older. In 2012, two supplemental Biologics License Applications (BLAs) were filed, one for Q-TIV to expand the age indication to 3 through 17 years of age because it is approved currently for only 18 years and above; and the other for Q-QIV for the initial indication of 3 years of age and older. The target indication for FluLaval® Quadrivalent (Q-QIV) would be active immunization for the prevention of disease caused by the 2 influenza A virus subtypes and the 2 influenza B virus types contained in the vaccine in adults and children from 3 years of age. The following studies were part of the licensing application:

Q-QIV & Q-TIV Pivotal Studies (for sBLAs)

Study	Key results	Groups	N
Q-TIV-008	Demonstration of Immunogenic NI to US licensed comparator (3-17 yrs)	- Q-TIV - Fluzone (TIV)	1055 1062
Q-QIV-003	Demonstration of Immunogenic NI & superiority of added B strain vs US licensed comparator (3-17 yrs)	- Q-QIV - Fluarix-VB - Fluarix-YB	932 929 932
Q-QIV-007	Demonstration of lot consistency, immunogenic NI & superiority of added B strain vs. US licensed comparator (18+ yrs)	- Q-QIV TF (lot 1) - Q-QIV TF (lot 2) - Q-QIV-TF (lot 3) - FluLaval-VB - FluLaval-YB	423 424 425 213 218
Q-QIV-006	Demonstration of Efficacy vs US licensed non-influenza vaccine (3-8 yrs)	- Q-QIV - Havrix	2584 2584
	Safety was assessed in all subjects	Total QIV exposed Children Adults	4788 3516 1272

Prepared for ACIP Meeting on 20 June 2013

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During this session, Dr. Jain described the study results for all of these studies except Q-TIV-008. She explained that Q-QIV-003 was a pediatric immunogenicity study among children 3 to 17 years of age in which immunologic non-inferiority and superiority of the added B strain in the quadrivalent versus a US licensed comparator. The comparators in this study were two trivalent vaccines, Fluarix® with Victoria B lineage and Fluarix® with Yamagata B lineage. This allowed for a comparison of Q-TIV, which contains both lineages, to individual TIVs. Q-QIV-007 was an adult immunogenicity study in adults 18 years of age and older to demonstrate lot consistency, immunogenic non-inferiority, and superiority of the added B strain versus a US licensed comparator. The comparator in this study was FluLaval® trivalent vaccine. Q-QIV-006 was a study among children 3 to 8 years of age to demonstrate the efficacy of Q-QIV versus a US licensed non-influenza vaccine, Havrix™. Overall in the quadrivalent studies, there was total exposure of more than 4500 subject, of whom 3000 were children. Therefore, there are safety data based on 4500 subjects.

In terms of the HI antibody response, the pediatric study (Q-QIV-003) demonstrated non-inferiority in terms of the common strain of QIV versus TIV. Superiority was also shown of the strain that was added to the QIV versus the TIV. Little cross-reactivity was observed. The adult study (Q-QIV-007) had a similar pattern of responses. Non-inferiority was shown in terms of common strains, and superiority was also shown. Regarding the increased immune response of Q-QIV over TIV for the added B strain, Q-QIV was compared to TIV-Victoria. There was a GMT ratio increase for B-Yamagata of 2.6 for the pediatric cohort and 2.4 for the adult cohort, and a seroconversion rate difference for children of 33.9% and adults of 21.5%. For the comparison of Q-QIV to TIV-Yam, there was a GMT ratio increase for B-Victoria of 3.8 in the pediatric cohort and 2.2 in the adult cohort, and a seroconversion rate difference for children of 44.6% and adults of 25.7%.

Regarding safety and reactogenicity in the pediatric study (Q-QIV-003), the quadrivalent showed that children experienced slightly more pain compared to TIV. In the pediatric study, children from 6 to 8 years of age were given 2 doses, depending upon their priming status. After the second dose, the pain difference was not observed. Other safety endpoints (e.g., adverse events, medically attended adverse events, or serious adverse events) were comparable between QIV and TIV vaccines. Similarly in the adult study (Q-QIV-007), there were slightly more reports of pain in those receiving QIV versus those receiving TIV. No other differences were observed in terms of adverse events.

The vaccine efficacy study in children, Q-QIV-006, is the largest efficacy study conducted for a quadrivalent inactivated vaccine which was submitted with a licensure application. This was a randomized controlled trial in which the Quebec-based quadrivalent vaccine was the test vaccine and the non-influenza vaccine was the hepatitis A vaccine. Over 5000 subjects were enrolled who were randomized 1:1 to receive QIV, with Havrix™ vaccine acting as the placebo. Subjects were further age-stratified into 3 through 4 and 5 through 8 years. Subjects were given 1 to 2 doses of vaccines based on CDC's definition of "primed" and "unprimed," with unprimed children receiving 2 doses. After administering the first dose, active and passive surveillance was conducted for approximately 180 days during the 2010-2011 influenza season. Active surveillance was conducted by telephone calls every week or every other week, and passive surveillance involved training the parents at the time of enrollment to report any ILI. Once an ILI was reported, nasal and throat swabs were obtained. For transportation, both swabs were combined.

The key confirmation objectives were to evaluate QIV efficacy for the prevention of any RT-PCR confirmed influenza A/B (success criterion: LL 95% CI >30%), and moderate to severe RT-PCR confirmed influenza A/B (success criterion: LL 97.5% CI >0%). Moderate to severe influenza detects the more clinically consequential outcomes of influenza. The case definitions for influenza confirmed by RT-PCR in a nasal/throat swab were as follows:

Any Influenza:

- Temperature ≥37.8°C, and
- One or more symptoms on the same day (cough, sore throat, runny nose or nasal congestion)

Moderate to Severe Influenza = Any Influenza Plus:

- Fever >39°C, or
- Physician-verified acute otitis media, or
- Physician-verified lower respiratory tract manifestations (shortness of breath, croup, wheezing, pulmonary congestion, bronchiolitis, bronchitis, pneumonia), or
- Physician-diagnosed serious extra-pulmonary complication of influenza (including myositis, myocarditis, seizure or encephalitis)

In terms of the results, study subjects were enrolled in 8 non-US countries in three regions of the world, including Central America, Asia, and the Middle East. A controlled study could not be conducted in the US, given that influenza vaccination is recommended in the US. Dominican Republic (N=1200), Philippines (N=1100), Thailand (N=1008), and Bangladesh (N=1000) contributed more than 80% of the subjects in the study. The demography was similar between the QIV and hepatitis groups, with a mean age of 5.4 years and approximately 48% females. The majority of children received 2 doses because they were vaccine unprimed. There were 206 RT-PCR positive cases. Notably, these were almost a third each in terms of H1N1 (N=58; 28%), H3N2 (N=70; 34%), and B Victoria (N=76; 37%). Two cases, which were from the Philippines, were B-Yamagata (1%). The study was conducted during the 2010-2011 season, so B Victoria was the strain that was recommended to be included in the trivalent vaccine. The circulation of viruses varied among different countries.

For any influenza, 55% efficacy was demonstrated and the primary endpoint was met. Interestingly, higher efficacy was observed against moderate to severe influenza, or more clinically consequential influenza. For moderate to severe influenza, 73% efficacy was demonstrated and the lower limit of the 97.5 confidence interval was 47. The majority of the moderate to severe cases had high fever. The efficacy in preventing high fever and lower respiratory tract infection was similar at 70% to 80%. There was only one case of otitis media, which was in the control group. All 3 pneumonia cases were also in the control group. Any breakthrough cases that occurred for H1N1 were mostly mild, so the vaccine prevented moderate to severe influenza at a higher efficacy. In other words, vaccine attenuated the disease. For H3N2 and B, the difference cannot be observed as clearly. There was a robust immune responses in terms of GMTs, which were high for all four strains in the study. No such increase was observed in the Havrix™ group. In terms of safety, hepatitis B is a fairly inert vaccine, but local reactions are known to be common with trivalent and quadrivalent vaccines. There were higher local adverse events mainly due to pain, at about 47% for the Q-QIV group

and about 34% for the Havrix™ group. No differences were observed throughout the study in serious adverse events, medically attended adverse, or Grade 3 medically attended events.

In summary, FluLaval (Q-TIV) has non-inferior immunogenicity versus a US licensed comparator in 3 through 17 year olds. The data for this study were not presented during this session, but the data are already published (PIDJ, 2012;31:605). FluLaval Quadrivalent (Q-QIV) met all objectives in all pediatric and adult studies. Efficacy was demonstrated against any influenza (55%) and moderate to severe influenza (73%) in children 3 through 8 years of age. A superior immune response was demonstrated to the additional B lineage versus the TIV. The additional B strain did not interfere with the response to TIV strains. The safety and reactogenicity profile was acceptable relative to licensed TIV or hepatitis vaccine for over 4500 individuals receiving Q-QIV. Q-QIV and Q-TIV licensure is anticipated for 3 years of age and older in mid-August 2013. Note: FDA licensed both products in August 2013.) Q-QIV and Q-TIV will have the same presentations: multi-dose vials containing 10-doses with the preservative thimerosal; and prefilled single-dose syringes that are preservative free. FluLaval® TIV will be available for the 2013-2014 influenza season pending FDA approval. GSK will make a limited supply (N=2 million doses) of FluLaval® Quadrivalent available as well, pending FDA approval.

Discussion Points

Dr. Keitel inquired as to whether sub-group analyses had been performed for the different age strata with regard to immunogenicity and efficacy. Regarding the pattern of spread of influenza in the various regions where the study was conducted, she wondered what the seasonal occurrence of influenza was in the different countries.

Dr. Jain responded that the season in countries where the study was conducted was throughout, but there were peaks. In some countries, there were two peaks. In most of the country, the first peak coincided with the Southern Hemisphere type of circulation. For example, the distribution from the previous year was assessed in order to estimate when the season would begin. For example, the 2009-2010 season began in the Dominican Republic. It is difficult to predict exactly when the season will start. In terms of age stratification, analyses were performed for moderate and severe influenza and any influenza. In children 3 to 4 years of age, the efficacy against any influenza was slightly lower. However, efficacy against moderate to severe influenza was preserved. In the exploratory analyses, any influenza was approximately 40% in children 3 to 4 years of age and approximately 67% in children 5 to 8 years of age. Moderate to severe influenza was approximately 68% in children 3 to 4 years of age and approximately 75% in children 5 to 8 years of age. The study was not powered to show definitive results, but the lower limit was above zero.

Dr. Pickering inquired as to whether the pediatric and adult submissions were linked, or if it was possible that one would be licensed before the other. He also asked what proportion of trivalent and quadrivalent vaccines would be available for the coming season.

Dr. Jain replied that the submissions were about a day or two apart, so the anticipated data is mid-August for both trivalent and quadrivalent from 3 years of age. GSK will make about 8 to 9 million doses of the Dresden-based quadrivalent, which is already licensed. About 2 million doses of FluLaval quadrivalent will be made since it is not yet licensed.

Dr. Friedland (GSK) added that GSK plans to distribute approximately 22 to 24 million doses of influenza vaccine across its portfolio in the coming season. About 8 million to upwards of 10 million doses will be quadrivalent, most of which will be the Dresden-based quadrivalent, which is currently approved. Should the new vaccine be approved in August, upwards of 2 million doses will be made available for in-season ordering.

2013-2014 Recommendations

Dr. Lisa Grohskopf
Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Personally and on behalf of the Influenza WG, Dr. Grohskopf thanked Dr. Keitel very much. She emphasized that it had been a very exciting couple of years, and that she had learned a lot.

Dr. Grohskopf presented a summary of the new items proposed for inclusion in the recommendations for influenza vaccination for the 2013-2014 season. She reminded everyone that a preliminary draft of the 2013-2014 ACIP Influenza vaccine recommendations was circulated to the ACIP members prior to the February 2013 meeting. The core recommendations for vaccination of persons 6 months of age and older, the recently approved vaccines that had been licensed up to that point, and the new abbreviations were discussed during that meeting. New material that was added since February 2013 included the influenza vaccine virus strains selected for the 2013-2014 season, which had not yet been confirmed as of the last meeting; the licensure of an additional new quadrivalent influenza vaccine, Fluzone® quadrivalent, which was licensed in June 2013; and two proposed minor modifications to the recommendations for persons with a history of egg allergy.

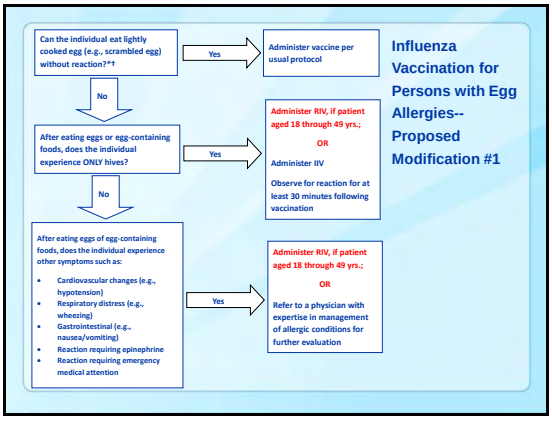
In terms of the influenza vaccine viruses selected for the 2013-2014, trivalent influenza vaccines will contain an A/California/7/2009 H1N1 virus, which is the same virus contained in the H1N1 vaccines for the last several seasons and is similar to the 2009 pandemic strain; an H3N2 virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011, specifically an A/Texas/50/2012-like virus (an A/Victoria/361/2011-like virus was also recommended in the 2012-2013 season; for this season, the specific candidate virus suggested is A/Texas/50/2012, which is an A Victoria 361/2011-like virus); and a B/Massachusetts/2/2012-like virus which is a Yamagata lineage virus. In addition to the above 3 viruses, quadrivalent vaccines will contain a B/Brisbane/60/2008-like virus, which is a Victoria lineage. The B viruses are divided into two different lineages, and as intended, quadrivalent vaccines will contain a representative virus from each lineage.

Regarding recently approved influenza vaccines anticipated to be available next season, those that had been licensed to date were discussed during the February 2013 ACIP meeting. Those include a quadrivalent live attenuated influenza vaccine (LAIV4), Flumist® Quadrivalent from MedImmune; a quadrivalent inactivated influenza vaccine (IIV4), Fluarix® Quadrivalent from GSK; a trivalent cell-culture based inactivated influenza vaccine (ccIIV3), Flucelvax® from Novartis; and a trivalent recombinant hemagglutinin vaccine (RIV3), FluBlok®, from Protein Sciences. These have all been added to the table of available vaccines, which is available on the CDC web pages. An *MMWR* Policy Note was published with a url link to that table in May.

An additional vaccine was licensed earlier in June, Fluzone® Quadrivalent from sanofi pasteur. The Influenza WG and the ACIP previously heard a presentation of data from sanofi pasteur.

Fluzone® Quadrivalent is approved for persons aged 6 months and older. To date, this is the first quadrivalent influenza vaccine that has an age indication below the age of two years. For the 2013-2014 season, it is anticipated that Fluzone® Quadrivalent will be available in 0.5mL and 0.5mL prefilled syringes and 0.6mL single use vials. Now that it is licensed, it will be included in the table of available vaccines in the 2013-2014 influenza statement as an acceptable alternative to other licensed products when used within indications and recommendations.

Regarding modifications to vaccination recommendations for persons with egg allergy, the following graphic depicts the current algorithm for egg allergy in determining whether and when referrals are needed to vaccinate:



This algorithm was originally developed for the 2011-2012 season, but this particular modification was proposed because there is now an egg-free influenza vaccine, FluBlok®, which was discussed during the February ACIP meeting. This is a recombinant influenza vaccine, abbreviated RIV in the new abbreviations scheme. Flucelvax® from Novartis was also licensed, which was discussed during the last ACIP meeting. This is a cell culture-based vaccine that does not involve cell propagation of virus in eggs during the manufacturing process. However, because the reference candidate strains used to start the manufacturing process are passaged in eggs by the manufacturer, that particular vaccine cannot be considered egg-free though it has a much lower quantity of egg protein than all of the other current influenza vaccines.

The text shown in blue in the algorithm represents the current recommendations, the additional text proposed for inclusion is shown in red. The current recommendations as they stand take a stratified approach to influenza vaccination in persons with egg allergy, in that the first consideration regards the history of symptoms experienced by the person with exposure to eggs. For persons who experience only hives following eating eggs or egg-containing foods, it is currently recommended that these people should receive an inactivated influenza vaccine, with some additional precautions, including observation for at least 30 minutes for a potential reaction following administration. It is proposed that recombinant influenza vaccine be an option for persons with only hives following egg exposure if they are within the indicated age group, which is currently licensed for people 18 through 49 years of age. For people with a history of any other symptoms following egg exposure, including but not limited to cardiovascular changes, respiratory distress, gastrointestinal tract reactions, reactions requiring epinephrine or emergency medical attention, it is currently recommended that these people be referred to a physician with expertise in the management of allergic conditions for further evaluation prior to vaccination. It is proposed that RIV also be added as an option of these people , provided that they are aged 18 through 49 years.

The second modification posed for the egg allergy recommendations is intended to address situations similar to the case that was described in Dr. Shimabukuro's safety presentation earlier, specifically instances where individuals who have no known previous exposure to egg are suspected of possibly being egg allergic on the basis of previously performed allergy testing. These testing results alone are generally not considered to be diagnostic without a clinical history. In general, the diagnosis of egg allergy is confirmed by a consistent medical history of adverse reactions to eggs and egg-containing foods, in addition to skin and/or blood testing for immunoglobulin E antibodies to egg proteins. However, tests can be difficult to interpret in isolation because there are not absolute cutoffs for what constitutes a normal versus abnormal result. Also, the further work-up of such individuals would involve tests that would normally be performed by an allergist. With these considerations in mind, the following language was proposed to be added to the egg allergy language:

> *For individuals who have no known history of exposure to egg, but who are suspected of being egg-allergic on the basis of previously performed allergy testing, consultation with a physician with expertise in the management of allergic conditions should be obtained prior to vaccination*.

In summary, Dr. Grohskopf recapped the following new items for discussion and vote:

- Addition of Fluzone® Quadrivalent to the table of available vaccines, which may not require a vote since ACIP has not generally been proposing inclusion within indications
- Modification of the egg allergy algorithm to include RIV
- Addition of language to address persons with no history of egg exposure, but questionable allergy testing

Discussion Points

Dr. Temte pointed out that because each of these modifications represented a fairly minor change, it seemed reasonable to address them with a single vote rather than three separate votes. However, he offered to entertain discussion on that suggestion.

Dr. Sawyer expressed concern about non-inclusion of Flucelvax® with all other egg-based vaccines as if they were all equivalent. He requested that Dr. Grohskopf share further information about what the allergy experts conveyed to the WG about the amount of egg albumin and whether that is really likely to cause allergic reaction. The practical implication is that if RIV is not available, they could suggest that the next best choice might be the cell culture-based vaccine.

Dr. Grohskopf responded that this question was the subject of a fair amount of discussion. She invited any Novartis representatives present to comment on potential levels of albumin and other egg proteins in the vaccine. There is no known safe threshold for egg protein in the vaccines. For regulatory reasons, CDC has been informed that Flucelvax® cannot be considered to be an egg-free vaccine. This makes it difficult to cite with some degree of concreteness how safe it would be. This was also discussed in 2011-2012 when egg allergy recommendations were initially revised. Many allergists would argue that, for the most part, the currently available inactivated vaccines produced by egg-based means are not likely to cause a

reaction. The difficulty is that there is not an absolute threshold, so a prediction cannot necessarily be made. Though probably not likely, it is known that anaphylaxis can occur. Given no threshold and the low content level, albeit higher versus lower content in other vaccines, and the fact that it cannot be considered egg-free makes it difficult to make a concrete recommendation.

Dr. Sawyer thought that in the previous recommendation, clinicians were at least guided to use vaccines with the lowest available content. It would seem consistent to highlight that the new cell culture vaccine has by far the lowest content compared to any other egg-containing vaccine.

Dr. Grohskopf confirmed that the current wording in the draft statement discusses this so that clinicians have the information and are able to utilize it.

For the second modification, Dr. Bennett wondered whether there was a reason why RIV could not be considered. The new statement indicates "refer." In the situation of giving vaccines, referral to a physician with expertise and management of allergic conditions can be cumbersome and difficult.

Dr. Keitel responded that RIV is included as an alternative in the appropriate age group in the algorithm. She suggested proposing to add "or if age-appropriate, RIV."

Dr. Pickering noted that the abbreviations had RIV3, while the algorithm had RIV. Unless people read another table or the text, they may not know from the algorithm that this is trivalent rather than quadrivalent.

Dr. Grohskopf replied that this could be further specified, if desired. At present, that is all that is available, as least as far as a recombinant vaccine. At this time, the recombinant vaccine for the 2013-2014 season was anticipated to be trivalent. She indicated that the algorithm could be revised to specify administration of RIV3."

Dr. Fryhofer (AMA/ACP) inquired as to whether there were any updates regarding the jet injector.

Dr. Grohskopf indicated that the WG would be discussing this within the coming months, but that she did not have any further information at this time.

Dr. Lewin (Novartis) reiterated that the manufacturing process does not contain any eggs. It is cell culture. Where the egg starts is in the seed that is used to start producing the vaccine. There is a large series of dilution steps, and no egg protein is detectable in the product. The 50 femtogram calculation comes from assuming the minimum dilution, not the maximum and assuming that the protein stays there. However, that might not be the case because trypsin in the vaccine has shown a very high clearance factor. What can be said is that the residual protein is no higher than 50 femtogram of egg protein, of which ovalbumin would only comprise a portion. Essentially, that is probably the maximum theoretical amount. As Dr. Sawyer noted, it is very difficult to calculate because there is not very much there.

Dr. Temte recapped that there was a suggestion to make a modification to indicate RIV3 in the algorithm, and to add RIV3 to the proposed modification to the text.

Vote: Influenza Vaccine

Dr. Coyne-Beasley made a motion that ACIP approve the recommendations, with the proposed revisions to indicate RIV3 in the algorithm and to add RIV3 to the proposed modification of the text. Dr. Bocchini seconded the motion. The motion carried with 13 affirmative votes, 0 negative votes, and 0 abstentions. The disposition of the vote was as follows:

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

Day 2: Public Comment

No public comments were offered during this session.

Certification

Upon reviewing the foregoing version of the June 19-20, 2013 ACIP meeting minutes, Dr. Jonathan Temte, ACIP Chair, certified that to the best of his knowledge, they are accurate and complete. His original, signed certification is on file with the Management Analysis and Services Office (MASO) of CDC.

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