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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
June 25-26, 2008
Atlanta, Georgia

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Acronyms

ACIP	Advisory Committee on Immunization Practices
AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
AI / AN	American Indian / Alaskan Native children (AI / AN)
BLA	Biologics License Application
BOI	Burden of Illness
CAIS	Childhood / Adolescent Immunization Schedule
CAIV-T	Cold-Adapted Influenza Vaccine
CCID	Coordinating Center for Infectious Diseases
CDC	Centers for Disease Control and Prevention
CIN	Cervical Intraephithelial Neoplasia
C. jejuni	*Campylobacter jejuni*
CMS	Centers for Medicare and Medicaid Services
DBD	Division of Bacterial Diseases (of NCIRD)
DoD	Department of Defense
DSMBs	Data Safety Monitoring Boards
DVA	Department of Veterans Affairs
DVBID	Division of Vector-Borne Infectious Diseases
DVD	Division of Viral Diseases (of NCIRD)
DVH	Division of Viral Hepatitis (of NCIRD)
DVRD	Division of Viral and Rickettsial Diseases
FDA	Food and Drug Administration
GBS	Guillain Barré Syndrome
GSK	GlaxoSmithKline
HepA	Hepatitis A
HepB	Hepatitis B
HHS	Department of Health and Human Services
Hib	*Haemophilus influenzae B*
HMO	Health Maintenance Organization
HPV	Human Papillomavirus
HRIG	Human Rabies Immune Globulin
HRSA	Health Resources and Services Administration
IC	Immunocompromised
ID	Influenza Division (of NCIRD)
IDSA	Infectious Disease Society of America
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHS	Indian Health Services
ILI	Influenza-Like Illness
IND	Investigational New Drug
IOM	Institute of Medicine
IPD	Invasive pneumococcal disease
ISD	Immunization Services Division (of NCIRD)
ISO	Immunization Safety Office (of CDC/OD/Office of the Chief Science Officer)
MCO	Managed Care Organization
MCV4	Meningococcal Conjugate Vaccine
MMRV	Measles, Mumps, Rubella, Varicella
MMWR	*Morbidity and Mortality Weekly Report*
NCHHSTP	National Center for HIV, Hepatitis, STD, and TB Prevention (of CDC/CCID)
NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
NCPDCID	National Center for Preparedness, Detection, and Control of Infectious

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	Diseases
NCVIA	National Childhood Vaccine Injury Act
NCZVED	National Center for Zoonotic, Vector-Borne, and Enteric Diseases (of CDC/CCID)
NIH	National Institutes of Health
NIS	National Immunization Survey
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
OD	Office of the Director (of CDC)
OMB	Office of Management and Budget
P&I	Pneumonia and Influenza
PCECV	Purified Chick Embryo Cell Vaccine
PCV	Pneumococcal Conjugate Vaccine
PEP	Postexposure Prophylaxis
PhRMA	Pharmaceutical Research Manufacturers of America
PSC	Protein Sciences Corporation
QALMs	Quality-Adjusted Life Months
QALYs	Quality-Adjusted Life Years
RCA	Rapid Cycle Analysis
sBLA	Supplemental Biologics License Application
SMEs	Subject Matter Experts
VAERS	Vaccine Adverse Event Reporting System
VFC	Vaccines for Children
VICP	National Vaccine Injury Compensation Program
VSD	Vaccine Safety Datalink
VZV	Varicella-Zoster Virus
WHA	World Health Assembly
WHO	World Health Organization

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Centers for Disease Control and Prevention
1600 Clifton Road, NE, Tom Harkin Global Communications Center (Building 19), Atlanta, Georgia
June 25-26, 2008

	AGENDA ITEM	PURPOSE	PRESIDER/PRESENTER(s)
Wednesday June 25			
8:00	**Welcome & Introductions**		Dr. Dale Morse (Chair, ACIP) Dr. Larry Pickering (Executive Secretary, ACIP; CDC)
8:30	**Pneumococcal Vaccines**		
	• Pneumococcal Vaccines Workgroup: update	Information	Dr. Julie Morita (ACIP, WG Chair)
	• Use of pneumococcal polysaccharide vaccine in adults	Information Discussion	Dr. Pekka Nuorti (CDC/CCID/NCIRD/DBD)
	• Considerations regarding new risk factor information	Information Discussion Vote	Dr. Jennifer Rosen, Dr. Pekka Nuorti (CDC/CCID/NCIRD/DBD)
	• Use of pneumococcal polysaccharide vaccine in children previously vaccinated with pneumococcal conjugate vaccine	Information Discussion Vote	Dr. Pekka Nuorti (CDC/CCID/NCIRD/DBD)
10:30	*Break*		

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11:00	**Combination Vaccines**		
	• Combination Workgroup activities & information	Information	Ms. Patricia Stinchfield, RN, MS, CPNP (ACIP, WG Chair)
	• Pentacel®	Information	Dr. David Greenberg (sanofi pasteur)
	• Pentacel® safety, immunogenicity, indications and use	Information	Dr. M. Patricia Joyce (CDC/CCID/NCIRD/DBD)
	• KINRIX™	Information	Dr. Leonard Friedland (GSK)
	• KINRIX™ safety, immunogenicity, indications and use	Information Discussion	Dr. Angela Calugar (CDC/CCID/NCIRD/ISD)
	• VFC vote for Pentacel® & KINRIX™	VFC Vote	Dr. Greg Wallace (CDC/CCID/NCIRD/ISD)
11:55	**Measles, Mumps, Rubella and Varicella (MMRV) Vaccine**		
	• MMRV Vaccine Safety Workgroup: update	Information	Dr. Jonathan Temte (ACIP, WG Chair)
12:00	*Lunch*		
1:00	**Rotavirus Vaccines**		
	• Rotavirus Vaccines Workgroup: update	Information	Dr. Lance Chilton (ACIP, WG Chair)
	• Update on safety monitoring of RotaTeq®	Information	Ms. Penina Haber (CDC/OCSO/ISO), Dr. James Baggs (CDC/OCSO/ISO)
	• Update on 2007/08 rotavirus season	Information	Ms. Cathy Panozzo (CDC/CCID/NCIRD/DVD)
	• Rotarix® vaccine: summary of efficacy and safety data, and GSK post-licensure monitoring plans	Information	Dr. Leonard Friedland (GSK)
	• Update on cost-effectiveness of rotavirus vaccination	Information	Dr. Marc-Alain Widdowson (CDC/CCID/NCIRD/DVD)
	• Plans for post-marketing safety monitoring of Rotarix®	Information	Ms. Penina Haber (CDC/OCSO/ISO)
	• Proposed Rotarix® vaccine recommendations and updated RotaTeq® vaccine recommendations	Information Discussion Vote	Dr. Margaret Cortese (CDC/CCID/NCIRD/DVD)
	• VFC vote	VFC Vote	Dr. Greg Wallace (CDC/CCID/NCIRD/ISD)
3:35	*Break*		
3:50	**Human Papillomavirus (HPV) Vaccines**		
	• HPV Vaccines Workgroup update and session overview	Information	Dr. Janet Englund (ACIP, WG Chair) Dr. Lauri Markowitz (CDC/CCID/NCHHSTP/DSTDP)
	• Cost effectiveness of HPV vaccination in the US	Information	Dr. Jane Kim (Harvard University)
	• Review of HPV vaccine economic analyses in the US	Information	Dr. Harrell Chesson (CDC/CCID/NCHHSTP/DSTDP)
	• Recommendations for women age 26-45 years: issues and options for quadrivalent HPV vaccine	Information Discussion	Dr. Eileen Dunne (CDC/CCID/NCHHSTP/DSTDP)
	• Quadrivalent HPV vaccine dose intervals – VFC vote	VFC Vote	Dr. Greg Wallace (CDC/CCID/NCIRD/ISD)
5:10	**Public Comment**		
5:30	**Adjourn**		

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Thursday June 26

8:00	**Unfinished Business**		Dr. Dale Morse (Chair, ACIP)
8:30	**Agency Updates (CDC/CCID/NCIRD, CMS, DOD, DVA, FDA, HRSA, IHS, NIH, NVPO); NVAC (Dr. Gus Birkhead)**	Information	
8:45	**Anthrax Vaccine**		
	• Anthrax Vaccine Workgroup Activities	Information	Dr. Dale Morse (ACIP, WG Chair)
	• Draft recommendations for the pre-event use of anthrax vaccine in first responders	Discussion	Dr Jennifer Wright (CDC/CCID/NCIRD/DBD)
9:30	**Update: Measles Outbreaks, United States - 2008**	Information Discussion	Ms. Amy Parker (CDC/CCID/NCIRD/DVD)
9:40	*Break*		
10:10	**Vaccine Safety**		
	• Update: Immunization Safety Office, CDC	Information	Dr. John Iskander (CDC/OCSO/ISO)
	• Update: CDC's Immunization Office Scientific Agenda	Information	Dr. Karen Broder (CDC/OCSO/ISO)
	• Rapid Cycle Analysis in the Vaccine Safety Datalink for adverse events after Tdap vaccination	Information Discussion	Dr. James Nordin (HealthPartners Research Foundation, Minneapolis, Minnesota)
	• Update on CDC Vaccine Safety Activities	Information Discussion	Dr. Tanja Popovic (Chief Science Officer, CDC)
10:45	**Rabies Vaccines and Biologicals**	Information Discussion	Dr. Charles Rupprecht (CDC/CCID/NCZVED/DVRD)
11:15	**Vaccine Supply**	Information Discussion	Dr. Greg Wallace (CDC/CCID/NCIRD/ISD)
11:45	**Influenza**		
	• Update on influenza surveillance	Information	Dr. Anthony Fiore (CDC/CCID/NCIRD/ID)
	• Update on antiviral resistance among Influenza A H1N1 viruses	Information	Dr. Anthony Fiore
	• Influenza vaccines workgroup report	Information	Dr. Anthony Fiore
	• Interim vaccine effectiveness estimate, 2007-2008 season	Information	Dr. David Shay (CDC/CCID/NCIRD/ID)
12:35	**Public Comment**		
12:50	**Adjourn**		

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

June 25-26, 2008
Atlanta, Georgia

Summary Report

The Department of Health and Human Services (HHS), Centers for Disease Control and Prevention (CDC), National Center for Immunization and Respiratory Diseases (NCIRD) convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on June 25-26, 2008 at CDC's Global Communications Center in Atlanta, Georgia. The following represents a summary of the proceedings.

Wednesday, June 25

Welcome & Introductions

Dr. Dale Morse (Chair, ACIP)
Dr. Larry Pickering (Executive Secretary, ACIP; CDC)

Dr. Dale Morse, ACIP Chair, welcomed those present and called the meeting to order at 8:00 a.m.

Dr. Larry Pickering, ACIP Executive Secretary pointed out several individuals who were to be present throughout the meeting to assist with meeting functions, and he reviewed housekeeping issues. In addition, he referred participants to the ACIP website (www.cdc.gov/vaccines/recs/acip), noting that copies of the handouts distributed to ACIP members were available on the table outside the meeting room for members of the public, that slides used during the meeting would be posted on this site where they would be available approximately one week following the meeting, and that the minutes of the meeting would be posted within approximately 90 days following the meeting. ACIP recommendations and other information related to immunization and ACIP activities also can be found on this site. Members of the press interested in conducting interviews with ACIP members were instructed to contact Curtis Allen to arrange those interviews.

Those unable to attend the June 2008 ACIP meeting included: Dr. James Cheek, Indian Health Services (IHS), with Ms. Amy Groom was attending on his behalf; Lieutenant Wayne Hachey, Department of Defense (DOD); Dr. Kristin Nichol, Department of Veterans Affairs (DVA). Liaison representatives who were unable to attend included: Dr. Ken Schmader, American Geriatrics Society; Dr. Damian Braga, Pharmaceutical Research Manufacturers of America (PhRMA), with Dr. David Johnson

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attending on his behalf; Dr. Greg Poland, American College of Physicians (ACP), with Dr. Sandra Fryhofer attending on his behalf.

To avoid interruptions during the meeting, Dr. Pickering requested that all business not directly related to discussions of the ACIP be conducted in the hallway outside of the meeting room and that all electronic devices placed on vibrate or turned off.

Dr. Pickering shared the ACIP url address (www.cdc.gov/vaccines/recs/acip), noting that the website is updated at frequent intervals with the current version of the meeting agenda, meeting minutes, presentations, and ACIP recommendations and other related information. CDC has also implemented a vaccine safety website, which is updated regularly (www.cdc.gov/vaccinesafety/).

He then shared the ACIP Recommendations Notice to Readers published since the February 2008 ACIP Meeting, which illustrated the vast amount of work the ACIP conducts. Copies of the slide were made available outside the meeting room for those interested in the exact wording, and Dr. Pickering pointed out that the information could also be downloaded from the CDC website in the *MMWR* section as well.

Dr. Pickering stressed the importance of all members remaining throughout the meeting in order to maintain a quorum. He explained that the ACIP charter gives the Executive Secretary, or his or her designee, the authority to temporarily designate ex officio members as voting members. This would occur only if there were fewer than eight appointed members available or qualified because of conflicts of interest. The ex officio members, if needed, would be formally requested to vote when necessary, and would also be required to declare any conflicts of interest.

Topics presented at ACIP meetings include open discussion with time reserved for public comments. In certain circumstances, a formal comment period may be scheduled during the deliberation of a specific topic. Comments from the public may be received during open discussions depending on available time. Individuals planning to make public comments were instructed to sign-in at the registration table at the rear of the auditorium. Those who registered prior to the meeting were instructed to check the sign-in roster to ensure that they were included. Microphones were located at either end of the committee tables for comments from the audience. Those making comments were instructed to identify themselves and their organizations prior to making their comments. Both CDC and members of the public believe in a transparent process for information gathering and decision making. To ensure such transparency during the public comment session, CDC believes that it is important to understand the context of an individual's comments. With that in mind, CDC encourages people at the beginning of their comments to advise the committee of any financial relationship that they may have with any company or organization that is likely to be impacted by the topic discussed. For example, such financial information may include the company's or organization's payment of travel, lodging, or other expenses in connection with attending this specific meeting. Although encouraged, choosing not to address the

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issue of financial relationships prior to making comments would not preclude individuals from speaking.

As in previous ACIP meetings, a review of vaccine safety issues and a discussion of the vaccine supply of recently approved vaccines were included in the agenda.

With respect to disclosures, Dr. Pickering explained that the goal in appointing members to the ACIP was to achieve the greatest level of expertise while minimizing the potential for actual or perceived conflicts of interest. To summarize conflict of interest provisions applicable to the ACIP as noted in the *ACIP Policies and Procedures Manual*, members of the ACIP agree to forgo 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 granted limited conflict of interest waivers. Members who conduct vaccine clinical trials or serve on data safety monitoring boards may serve as consultants to present to the committee on matters that relate to those specific vaccines. However, they are prohibited from participating in deliberations or votes of the committee on issues related to those specific vaccines. Regarding other vaccines of the affected company, a member may participate in discussions with the proviso that he or she abstains on all votes related to vaccines of that company. ACIP members who may have a potential financial conflict of interest should make this conflict known by disclosing all of their vaccine-related financial interests and related activities.

Regarding applicants for membership, Dr. Morse indicated that the ACIP Secretariat solicits applications throughout year for candidates to serve as ACIP members. Detailed instructions for submission of names of candidates may be found on the ACIP website. Applications may be submitted at any time during the year; materials in support of the next cycle, which begins in July 2009, are due no later than November 16, 2008.

Dr. Pickering then turned the meeting over to Dr. Morse to announce the appointment of new ACIP members. Dr. Morse first offered the following quote from Anne Frank, "How wonderful it is that nobody need wait a single moment before starting to improve the world." ACIP certainly provides such an opportunity, especially when its two new members have such distinguished careers and have already been assisting with ACIP. The new members included Dr. Mark Sawyer, Professor of Clinical Pediatrics in the Department of Pediatrics at the University of California in San Diego. He serves as an immunization practice consultant for numerous San Diego medical institution programs and research projects, and collaborates with the county immunization branch to promote the improvement of immunization practices. Dr. Sawyer's work with representatives of managed care health plans, and county, state, and national public health leaders will be of tremendous benefit to the committee. Dr. Sawyer thanked the committee, and added that his background was that of a practicing pediatric infectious disease physician, that he spends a lot of time working with his local county health department on immunizations, and that he is a member of the Board of the Immunization Registry Association.

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Dr. Morse introduced the second new member, Dr. Jonathan Temte, an Associate Professor of Family Medicine at the University of Wisconsin in Madison, Wisconsin. He is an experienced researcher in the area of infectious diseases and immunizations, and has been involved in the interface between public health and primary care medicine, centering much of his activity on surveillance of influenza and other respiratory tract viruses. He is an active member of the Immunization Collaborative Advisory Group. Dr. Temte previously served as one of the two liaison representatives from the American Academy of Family Physicians (AAFP). Dr. Temte thanked the committee, acknowledged that it was a great honor to serve on the ACIP. He spent the last four years as one of two liaisons for the American Academy of Family Physicians. It struck him that his colleagues on the committee and in the room had very true and honest concerns about preventative healthcare and care for safety for both for children and adults. He expressed his appreciation for the nomination and being able to work with this wonderful group of people.

Dr. Morse then thanked the three members who were cycling off the committee, saying what a privilege and honor it had been to work with and recognize Doctors Tracy Lieu and Julie Morita and Ms. Patricia Stinchfield, who were completing their tenures with ACIP. During their tenure, ACIP reviewed, discussed, and approved more new vaccines than in its entire history. This experience included vaccines for rotavirus, HPV, zoster, pertussis boosters, second-dose varicella, modifications of schedules for multiple other vaccines and expansion of the flu vaccine to cover a universal childhood recommendation, among others. Throughout, they have worked tirelessly, unselfishly, and with little or no remuneration, which Dr. Morse likened to the following quote from Xenophon, “As there are persons who mend torn garments, so there are physicians who heal the sick; but your duty is far nobler, and one befitting a just person—namely, to keep people in good health” (from Cryopaedia, 400 BC).

Dr. Morse recognized each of these members for their particular contributions to the ACIP during the past four years. While serving on the ACIP, Dr. Lieu contributed uniquely with her expertise on the cost-effectiveness of vaccines. Her expertise in health economics was useful when the committee weighed trade-offs between the potential costs and logistical burdens of new vaccination programs. Dr. Lieu was one of the authors of “Guidance for Health Economics Studies,” presented to ACIP. The procedures in this document were to be initiated during this ACIP meeting. During her term with ACIP, she served as Chair of both Hepatitis and Economic Standards Working Groups. In addition, she participated actively in the Varicella Zoster and Evidence-Based Working Groups. Dr. Julie Morita’s experience in childhood immunization greatly assisted the committee on issues of immunization policies and practices. While serving on the ACIP, Dr. Morita led the Harmonized Childhood and Adolescent Immunization Schedules and the Pneumococcal Working Groups as Chair, and contributed significantly to the Hepatitis, Pertussis, and Rotavirus Working Groups. Her experience as a pediatrician, CSTE member, and health department representative added a vital public health practice perspective to the deliberations. Ms. Patricia Stinchfield is a pediatric nurse practitioner at the Children’s Hospitals and Clinics in

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Minnesota, where she specializes in infectious disease and immunology. During her tenure on ACIP, Ms. Stinchfield served as Chair of the Combination Vaccines and Japanese Encephalitis Working Groups. She also served as a member of the Harmonized Childhood and Adolescent Immunization Schedules and Influenza Vaccines Working Groups. The ACIP is pleased to continue to work with Ms. Stinchfield as she transitions to her new role as Liaison Representative from the National Association of Pediatric Nurse Practitioners (NAPNAP). Dr. Morse presented each of these individuals with an award for her service, asking them to open these as they each offered their own comments.

Dr. Lieu said that as she joined the committee four years ago, Orin Levine, a colleague who studies pneumococcal vaccines at Hawkins said that ACIP is the best committee. It has the best process—they deliberate, then take action. He was entirely right. This has been one of her favorite committees to serve on, and she appreciated being a part of it in thinking deliberatively and carefully about the public health issues and the benefits and tradeoffs for the decisions the committee has made. The past four years have been a golden time on the committee, with the broad impact of ACIP on the public health of children and adults. She thanked Dr. Pickering and Dr. Jean Smith for making it a great process for all, as well as CDC's leadership for inviting her to serve.

Dr. Julie Morita said she could remember as a resident and as a practicing pediatrician coming out of residency looking forward to the ACIP recommendations for the guidance she needed. When she was asked to be on the committee, she was excited, hopeful, and anxious about the responsibility. Her experience there fulfilled all of her expectations. The process had been unbelievable and it gives her full confidence in the ACIP recommendations that came out while she served, and those that will come out in the future. For her, it had been an honor and a privilege to serve. She expressed her gratitude to Drs. Pickering and Smith for having greatly improved the process during the time that she had served.

Ms. Patricia Stinchfield thanked those members of NAPP who nominated her and who believed nurses belonged at this table as an integral part of the vaccine delivery system. She was pleased that Kris Ehresmann would be another nurse at this table in the future. It has been a privilege and an honor to serve. Coming in from the outside, she immediately observed the dedication, hard work, and integrity of the process. She stressed that she had full confidence in what this committee does and how it is run. She too recognized the dramatic change in how the committee is organized and run, and she appreciated Drs. Pickering's and Smith's efforts toward that goal. This is truly a community, which she learned personally when the 35W bridge collapsed last year in Minnesota and so many of them sent her concerned emails. Everyone is here with the same goal: To do good work, protect children and adults, provide safe vaccines, and prevent disease. There are challenges ahead, and they will need to make their voices strong and clear regarding vaccines and preventable diseases. She thanked everyone for the opportunity to participate.

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Dr. Morse pointed out that as the father of two daughters, he was very cognizant of the glass ceiling. However, based on their merits, contributions, and accomplishments alone, these three women had completely shattered that barrier. It was ironically fitting, therefore, that the awards commemorating their accomplishments were made of glass so that they would be able to take these fragments home as symbols of success and to eliminate other obstacles.

Prior to beginning the first session, Dr. Morse requested that ACIP state any conflicts of interest. Dr. Janet Englund indicated that she has research support from sanofi pasteur and MedImmune. All other ACIP members present declared no conflicts.

Pneumococcal Vaccines

Pneumococcal Vaccines Workgroup Update

Dr. Julie Morita, MD
Medical Director
Immunization Program
Chicago Department of Public Health

Dr. Morita provided an update and a general overview of what the Pneumococcal Vaccines Working Group has been doing for the past couple of years. She acknowledged the working group membership, noting that they had a wide array of organizations represented and this diversity contributed a lot to their work. In particular, she acknowledged Pekka Nuorti for his work in leading them through a large amount of complex material, as well as for his leadership abilities.

To set the stage for discussions, Dr. Morita reminded everyone of the status of the current ACIP statements. The adult polysaccharide vaccine recommendations were included in the *Prevention of Pneumococcal Disease MMWR* that was issued in1997. The childhood or conjugate vaccine recommendations were included in the *Preventing Pneumococcal Disease among Infants and Young Children MMWR* issued in 2000.

This working group was established in October, 2006. Terms of reference included reviewing the need and optimal timing for updated statements on the use of pneumococcal conjugate (PCV7) and polysaccharide vaccines (PPSV23). They were also asked to work on developing a revised statement on the use of pneumococcal vaccines for ACIP review and approval. The working group reviewed the 1997 and 2000 recommendations to identify areas that were in need of clarification. They also reviewed new data that had become available since the issuance of the 1997 and 2000 recommendations. The list was long and the topics were complicated. Regarding adult recommendations, they reviewed the epidemiology of invasive pneumococcal disease among adults after implementation of the conjugate vaccine. That included the direct and indirect PCV7 population effects, non-vaccine serotype replacement, trends in antimicrobial resistance, and previously identified and new risk factors. In addition, they considered alternative PPSV23 schedules and also cost-effectiveness studies that examined the alternative schedules. They also reviewed revaccination recommendations, new and existing data regarding the duration of protection, safety and immunogenicity, and optimal

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timing and frequency of vaccination. Lastly, they reviewed the PPSV23 use and effects among Alaskan Native/American Indian (AN / AI) adults.

With respect to childhood recommendations, this group reviewed a long list of topics. These included the epidemiology of disease among children after implementation of PCV7 and alternative PCV7 schedules, which included reduced risk schedules. They looked at existing information from the US as well as other countries that had implemented schedules. The group reviewed PCV7 use among incompletely vaccinated children 24-59 months of age. These recommendations were modified in the October 2007 meeting. Additionally, the group discussed PPSV23 use among high risk children who had already received PCV7; PCV7 / PPSV23 use and effects among AN / AI children; and PCV7 use among HIV infected children five years of age and older. The list of topics was vast. In many cases, limited data were available. Nonetheless, the process used included a careful of new and relevant data. They also solicited expert opinion when data were not available. This expert opinion came from within as well as outside of the working group. Because of the complexity of the topics, working group members completed a survey that included topics for which there was little or no consensus. The results were then used to facilitate discussion among the group. On the conference calls, controversial topics were discussed again.

During this session, Drs. Nuorti and Rosen presented a summary of key topics the group had most seriously considered for revision. For the adult recommendations, these included the age for universal PPSV23 vaccination; considerations about PPSV23 revaccination; and new risk factor information, particularly as it relates to persons aged 18-64 years who have asthma and persons who smoke cigarettes. For the childhood recommendations, the topics included use of PPSV23 following PCV7, in particular among children who have asthma without high dose corticosteroid therapy; the use of PPSV23 among AN / AI children; clarification of the use of PPSV23 revaccination recommendation for high risk children; and the use of PCV7 among HIV infected children five years of age and older.

Although the working group anticipated having completed a formal statement by October 2008, on-going activities continue. They include reviewing new data regarding PPSV23 long-term immunogenicity, as well as review new vaccines that will be available in the near future. In particular, the FDA has granted a 13-valent PCV a fast track review for their clinical development plan for pediatric use.

Use of Pneumococcal Polysaccharide Vaccine (PPV23) in Adults Ages 50 Years and Older

Dr. Pekka Nuorti
CDC / CCID / NCIRD / DBD

Dr. Nuorti briefly reviewed his agenda for discussing adult recommendations regarding PPV23. He then discussed the current recommendations for PPV23 that date back to1997. These recommendations have aged reasonably well, but a lot of data have become available since 1997 and the working group has spent much of the past year reviewing it. Most discussion and debate has centered on the age 50 years and revaccination recommendations, both of which are areas where less than compelling and often inconsistent data are available. This has been a major challenge for the working group. Dr. Nuorti presented the recommendations table for use of the pneumococcal vaccine. It is recommended for all persons 65 and older, and for those 2 to 64 years of age who have chronic diseases or live in certain settings. They offer different labels for the strength of the recommendation reflecting the quality of evidence

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available at the time of the recommendation. Also, the vaccine is recommended for immunocompromised groups.

Among those adults 65 and older who reported ever receiving PPV23 in the US between 1997 and 2007, vaccine uptake increased until about 2002. Since 2002, the uptake among this group has not changed much. Based on data from the National Health Interview Survey, among the age 50 to 64 categories, in 2006, coverage was 32.5%. In total, in 2006, an estimated 71 million persons had an indication for the PPPV23, including those 65 and older. Naturally, these are rough estimates and some persons may have more than one condition (CDC / NCHS, Sample Adult Core component of the 1997-2007 NHIS). Dr. Nuorti emphasized that among the group he was discussing, ages 50-64, 16.7 million persons have a current indication for the PPV23, or about 30% of the total population, leaving about 38.5 million persons who do not have indications for the PPV23 (US Census Interim Population Projections, 2008).

When the working group was discussing the need to change the recommendation to include all adults age 50 years and older, they considered several key factors. These included the remaining disease burden after the introduction of the childhood conjugate vaccine; vaccine effectiveness estimates; the achievable public health impact compared with the current policy of vaccinating all 65-year-olds and those younger with high-risk conditions. They discussed issues of vaccine safety in terms of adverse events as well as potential immunological consequences. Programmatic issues included feasibility of implementation, and acceptability and demand of the vaccine. Although cost was an important consideration, and the group did review relevant studies and unpublished information, they decided not to present that information in this meeting, as it was only one component of the deliberation process.

Regarding the epidemiology of invasive pneumococcal disease (IPD) in adults after routine childhood PCV7 use, all data presented were from CDC's Active Bacterial Core surveillance (ABCs), which is an active laboratory-based surveillance system for IPD, with a total population of 18.5 million. These data showed the percent decline in 2006 compared with the 1998-99 baseline. After introduction of the conjugate vaccine, rates in all adult age groups, particularly 65 and up, declined between 16% and 38%. With respect to PCV7 serotypes contained in the conjugate vaccine, there have been dramatic changes in the rates of these serotypes, ranging from the decline of 84% among ages 50-64 to 89% among ages 65 and above. The rates of the conjugate vaccine type disease are extremely low. PPV23 serotypes have also decreased from 31% to 51%. However, it is apparent that this decline has been exclusively due to the serotypes that are common to both PCV and PPV. The rates of the 16 serotypes that are included only in the PPV23have increased substantially in the adult age groups, ranging from an 18% to 50% increase. In summary, with respect to the indirect effects of childhood PCV7 on adult IPD, after the conjugate vaccine introduction, rates in all adult age groups have decreased in all serotypes and for the conjugate vaccine types as well as the PPV23 types. The decline in the PPV23types is due to the conjugate type decrease and the rates of the 16 serotypes only in the polysaccharide vaccine have actually increased from 18% to 50%.

In adults age 50 to 64, the overall rate, although it has decreased from 24 to 20 per 100,000 per year, compared with the baseline, this group has had one of the smallest decline rates and the largest increase in non-PCV serotypes. They had focused on this age group to try to determine what is occurring. Some hypotheses they considered included possible differences in serotype distribution and the possible influence of the underlying medical conditions on risk of disease. To do that, investigators at the CDC evaluated trends in the incidence of IPD among adults with and without the underlying medical conditions that are current ACIP indications for PPV23. The proportion of IPD cases among adults ages 50 to 64 with ACIP indications for the PPV23

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increased from 65% to 74% in 2006. In other words, ¾ of existing cases already had a current indication for the PPV23. In analyzing this, the numerators were age and race-adjusted standardized pneumococcal case projections from ABCs surveillance to the US population. The denominators were national estimates of individuals with and without the co-morbid illnesses that are PPV indications from National Health Interview Survey.

When looking at the rates stratified by PPV indications, those with current ACIP indications had about four-fold higher rates of IPD compared with those without indications, and the difference has persisted following PCV7 introduction. There has been no decrease in disease since introduction of the conjugate vaccine among those with current PPV indications. In 2006, respective rates of these two groups were about 40 cases per 100,000 among those with underlying conditions and about 10 cases per 100,000 without underlying conditions. Among the group without the current ACIP indications for PPV23 by serotype groupings, all serotypes have decreased about 39%. PCV7 serotypes have decreased about 87% since conjugate vaccine licensure. This reflects the overall rates. At the same time, the non-PCV7 serotypes increased by 24%. These rates are very low. Among 50 to 64 year olds with any ACIP indication, there was a 4% increase in incidence of all serotypes. This was a result of an 81% decline in PCV7 serotypes and a 90% increase in non-PCV7 serotypes. No other group showed a similar pattern. Essentially, the increase in non-conjugate types cancelled out decrease in conjugate types. This was the only adult age group where this type of pattern was seen. In terms of the proportion of cases caused by serotypes in different vaccine formulations, there are small differences between those with and without indications, but those were not substantial. Overall, in 2006, 11% of the remaining cases were caused by PCV7; 51% by investigational PCV13; and 73% by PPV23 (Muhammad et al; CDC Active Bacterial Core Surveillance, unpublished, 2008).

In a summary of indirect PCV7 effects in adults aged 50-64 with and without PPV23 indications, there have been substantial decreases in IPD rates among persons aged 50-64 years without current PPV23 indications, and current rates are relatively low. Among persons with current PPV23 indications, the IPD rates are about four-fold higher. There has been no decrease in overall rates because of a substantial increase in non-PCV7 type disease. The proportion of persons with chronic illnesses that are current indications has increased. In 2006, about ¾ of cases had a current indication. This suggested to the working group that vaccinating adults in these high-risk groups is increasingly important.

The current epidemiologic trends are consistent with an earlier study conducted in 2002, also using the ABCs data. This study estimated those cases that could have been prevented if the indications for vaccination were expanded to include new indications. In this study, although many cases had co-morbidities that were not among the current indications, most cases also had a current indication. They concluded that current PPV23 indications identified most persons at greatest risk of IPD. Expanding indications to include all persons aged 50-64 years would have prevented an additional 5% of cases. They concluded that increasing PPV23 coverage among persons with current indications may prevent more cases than expanding existing indications (Greene et al. CID 2006; 43:141-50).

Regarding considerations related to revaccination with PPV23, there are three groups for whom PPV23 revaccinations are currently recommended: Those age 65 and older should receive a second dose if they received the first before age 65 and it has been more than five years since; persons two to 64 years with functional or anatomic asplenia; and immunocompromised persons. It is important to note that the current revaccination recommendations were based on expert opinion, and they were given the lowest quality of evidence and strength of

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recommendation rating, or "C" for all revaccination recommendations. There is no documented vaccine effectiveness in immunocompromised persons for the first or second dose, but the potential benefits and the safety of the vaccine justify vaccination (CDC. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1997; 46 (No. RR-8)). One key issue of the working group's discussion was that the change in the age of the first PPV23 vaccination would necessitate changing the revaccination regimen. Considerations of possible revaccination strategies required evaluating the safety of revaccination; the immunologic response to a second PPV23 dose; and the potential clinical benefits of revaccination. With time since first vaccination, risk of disease and mortality increase; antibody levels in older adults decline; and vaccine effectiveness estimates decrease. Studies regarding decline of antibody levels in older adults are somewhat inconsistent. As to whether this involves the prevaccination baseline, studies also vary in their conclusions. The few data from observational studies regarding duration of protection after first vaccination are also limited and inconsistent. Several studies in older adults indicate that a second PPV23 vaccination given five or more years after the first dose is well-tolerated, with local reactions more frequent but self-limited and systemic reactions rare. However, there are few data on the clinical effectiveness of revaccination, and it is basically unknown.

It is very challenging to summarize the immunologic response to a second dose of PPV23. Immunologic correlates of protection for PPV23 in adults have not been established. That said, several studies have shown a significant increase in anticapsular antibody levels from pre- to post- revaccination in older adults. In most studies, however, the magnitude of antibody response to revaccination has been lower than with the first vaccination. There is a concern that administration of the first dose of plain polysaccharide may blunt the immune response to subsequent doses of PPV or PCV. Two recent studies have evaluated this potential hyporesponsiveness issue. The clinical relevance of the lower antibody response is not known. A current longitudinal study of 1008 older adults aged 65 years and older with chronic diseases found that primary vaccination and PPV23 revaccination induced increased IgG antibody and opsonic activity. These IgG and OPK antibody levels persisted above unvaccinated base-line levels for at least five years. Additionally, the revaccination antibody levels at Day 30 were somewhat lower than the primary vaccination antibody levels, but there was no difference in antibody levels at five years. This study is sponsored by Merck and yet to be published. Results of the 10 year follow-up of subjects are expected in fall, 2008. Data were provided by John Grabenstein of Merck. The working group will take these data into account when re-evaluating the question of revaccination.

Concerning new conjugate vaccines, a 13-valent PCV is currently in phase three for infants and adults. Details were provided by of Peter Paradiso of Wyeth Vaccines Research. The 13v PCV contains the seven conjugate serotypes in PCV7 (Prevenar) plus conjugates for serotypes 1, 3, 5, 7F, 6A, and 19A. They are currently completing phase three studies, including evaluation of safety and immunogenicity; compatibility with co-administered vaccines; lot consistency; transition from 7v to 13v; and catch-up immunization schedules. The infant program was granted fast-track status by the FDA in May 2008. The manufacturer anticipates a rolling submission completed in the first quarter of 2009. Licensure will be based on non-inferiority to PCV7 for the seven common types and a comparable response to six new types. This information will be provided to the committee in the October 2008 ACIP meeting. In the adult program, licensure is based on functional antibody response compared to the polysaccharide vaccine. It is currently in phase three studies, including adults over 50 years of age; adults over 65 who have previously received polysaccharide vaccine; booster dose responses; and

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overcoming hyporesponsiveness. The manufacturer plans to file in the US as a supplement after the infant indication is approved.

The working group's considerations related to lowering the age of universal PPV23 included consideration of programmatic simplicity and logistical considerations. Age-based strategies may reach more groups with increased rates of IPD including those who are currently not recommended for PPV23. Lowering the age would also make for harmonization with the influenza vaccine recommendation (age 50 years since 2000).

That said, the working group felt there were a number of disadvantages related to lowering the age of universal PPV23. Due to the indirect effects of childhood PCV7, rates of IPD in the majority of persons aged 50-64 years without current ACIP indications are very low. It is possible that future childhood immunization with PCV13 may further reduce disease rates in these adults due to additional indirect effects, although the epidemiology of those serotypes is somewhat different from the seven in the current vaccine, so this is speculative. Most persons aged 50-64 years who develop invasive pneumococcal disease already have a current PPV23 indication. Finally, and perhaps most importantly, the working group felt that available data do not allow determining the optimal timing and frequency of PPV23 revaccination because of concerns about potential immunologic hyporesponsiveness after PPV23 doses, inconsistent data on duration of antibodies, and the lack of evidence for clinical effectiveness of revaccination.

Another area of uncertainty is the feasibility of program implementation. Although most published studies have showed PPV23 effectiveness against invasive disease, there have been inconsistent results in different populations. The lack of a documented population impact may limit the ability to expand recommendations to new target groups. As the PPV23 target population would increase by 38.5 million people, adequacy of the vaccine supply would be another consideration. The program would also target many healthy persons at low risk of IPD, potentially raising issues about acceptability of vaccination. Based on the experience with the influenza vaccination recommendations in this age group, the coverage for influenza has been sub-optimal after the universal recommendations.

The working group concluded that the available evidence as a whole does not favor recommending PPV23 vaccination to all adults aged 50 years and older. Compared with the current policy of vaccinating all adults aged 65 years and older and younger adults with high-risk conditions, the potentially achievable incremental public health impact of changing the recommendation appears to be small . A program targeting all adults aged 50 years and older would substantially increase the vaccine target population. Most of these persons are relatively healthy and at low risk of pneumococcal disease, potentially leading to reduced acceptability of the vaccine. The working group highlighted the fact that targeting adults aged <65 years who have current ACIP indications for PPV23 is a high priority. As already recommended by the ACIP, "Persons aged 50 years should have their overall vaccination status reviewed to determine whether they have risk factors that indicate a need for pneumococcal vaccination."

With regard to PPV23 revaccination, the working group concluded that available data are insufficient to determine the appropriate target groups, optimal timing and frequency of PPV23 revaccination. Therefore, existing recommendation will not be modified. However, they did recommend that language be clarified. The group also concluded that further research is needed to guide the revaccination policy, particularly regarding its clinical effectiveness, potential adverse immunological consequences of repeated PPV23 doses, long-term persistence of antibodies and the optimal sequence of PCV and PPV in adults. They hope to be

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able to examine antibody persistence later this year, as long-term immunological follow-up data may become available to re-evaluate the PPV23 revaccination recommendation this fall.

Concerning persons with asplenia or immunocompromising conditions, some providers have found the current PPV23 revaccination recommendation confusing. The recommendations have been misinterpreted as suggesting revaccination every five years, although the ACIP clearly specifies only one revaccination. The content of the proposed clarification to the recommendation is the same as previously. It has merely been edited to read as follows:

> "The ACIP does not recommend routine revaccination for most people. A second dose of vaccine is recommended five years after the first dose for persons with functional or anatomic asplenia or for persons with immunocompromising conditions. The ACIP does not recommend multiple revaccinations because of insufficient data concerning the degree and duration of protection and safety of PPV23 when given three or more times."

The group also proposed clarification to revaccination recommendation language for persons aged 65 and older:

> "All persons should be vaccinated with PPV23 at age 65 years. Those who received PPV23 before age 65 years should be administered another dose of the vaccine if at least five years have passed since their previous dose."

Discussion

Regarding the upcoming Merck study, Dr. Temte asked if it was entirely immunologic, or contained clinical information on emergence of pneumococcal disease.

Dr. Nuorti responded that it was an entirely immunological study, looking at the persistence of the antibody 10 years after vaccination.

Dr. Neuzil commented that this was very difficult for the working group. There were many areas without very much strong evidence. This is a perfect example of where the group likes to highlight where recommendations are evidence-based and strong as compared with their expert opinion.

Dr. Duchin, NACCHO, remarked that he assumed there were some data that corroborated the self-reported rates of vaccine coverage. More information about the coverage rates in the average groups would be helpful, as would other data sources that would confirm or question that reliability. Additionally, he wondered about the impact of PPV23 coverage among persons in the 50–64 year old age group who have indications. Dr. Nuorti had shown the impact of those with no indications, and the amount of pneumococcal disease that would be prevented, but not those that could be prevented in individuals who do have indications.

Dr. Nuorti replied that the vaccine uptake data were based on the National Health Interview Survey and were provided to them by their Immunization Services Division. Those are the only data that allow for looking at trends over time in national vaccine uptake. He invited any others from the Immunization Services Division to comment on the reliability if they wished. Those are the best available. For comparison, there are data from the same survey regarding flu vaccine. In looking at the healthy 50-64 year olds, there has been about 10% increase in coverage from 2002-2006. There has not been a major increase in coverage and it is currently a little over 30% in that age group. If one looks at the high risk groups, the coverage was about 44% in

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2006. Among healthy adults the same age, it has been quite low. Again, these are the data in looking at trends of coverage. They did review the available cost-effectiveness data. There were two published studies. One study, published in 2003, included data from the pre-conjugate vaccine period and would not be relevant at this point. That study did conclude that vaccinating those high-risk 50-64 year olds was cost effective, but it did not make a strong recommendation to reducing the age, particularly because of the uncertainties related to revaccination regimens. The preventability study Dr. Nuorti had referred to briefly was conducted early in the conjugate era in 2002. It speaks to the cases that could potentially be prevented if current recommendations were perfectly implemented given the disease caused by the vaccine serotype. It concluded about one in five cases would be preventable by adhering to the current recommendations. They would discuss the risk-based indications in the next section. If indications were expanded to include all persons aged 50-64 years in this study, it would have prevented an additional five to seven percent of cases. There is also a more recent cost-effectiveness model that the working group reviewed. One of the working group members is a co-author on that model, and it was published earlier this year. Data are not in the format that is required for ACIP for presenting economic information. This was a very complex model, and the working group had a lot of discussion regarding the assumptions that went into model. They thought it was a very good attempt to model the current situation, since the conjugate vaccine introduction. The results were particularly sensitive to vaccine effectiveness estimates and coverage estimates. That study concluded that the current policy of vaccinating persons aged 65 years and older and younger individuals with high risk conditions is the most cost effective, with about $3,300 per QALY gained, compared to no vaccination. As an example, a policy of vaccinating at 50 and 60 years would have cost about $23,000 per quality gained compared to current policy. So, those were some of the data the working group had reviewed in terms of program impact on the overall population and of vaccinating individuals with current indications.

Regarding the cohort of 50 to 60 year olds who have no indications for vaccination, and considering disease incidence for vaccine serotype proportion, vaccine effectiveness and case fatality rates, Dr. Cieslak asked if Dr. Nuorti had any notion of the number needed to needed to prevent death.

Dr. Nuorti replied that the working group, when reviewing the new cost-effectiveness model, were trying to estimate the numbers needed to vaccinate for those without indications. Unfortunately, it was not possible to get that from the data available which looked at lifetime instead of annual risk. They could probably come up with estimates, because that is an important question . He pointed out that, given what they had looked at in the epidemiology, the working group's sense was that the number needed to vaccinate might be quite large.

Dr. Schaffner, NFID, thanked Dr. Nuorti for presenting a very large amount of varying quality data in a succinct fashion. He was quite convinced that the final recommendations were sound. He wondered whether the clarification on the reimmunization issue, which continues to plague a lot of practitioners, needs more tweaking. As an example, a 40-year old patient with an underlying condition is vaccinated. The patient then becomes 45 or 46 and is revaccinated. What happens when the patient reaches 65? That is the notion that still needs clarification.

Dr. Nuorti replied that this is always a very relevant consideration. The recommendation is probably less than satisfactory. The current recommendation is to vaccinate everyone at age 65 years if it has been more than 5 years since the previous dose. One of the things that may need addressing in the future is what to do after age 65. If one looks at the data which includes ages 80 and over, who have the highest rates of disease, given that vaccination is at age 65

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and antibody levels decline in four to seven years, there might be a consideration to be given for recommending revaccination after 10 years. He hoped the long-term antibody persistence data could guide them in whether they should make a recommendation for another vaccination for all who received a dose as 65 year olds.

Dr. Plotkin, sanofi pasteur, said that he agreed with the bottom line, but that he would stress that the major problem is the lack of immunologic data. Although Dr. Nuorti may be right, that they do not formally have a correlate of protection in the elderly, there is no need to invent new correlates. They are pretty satisfied with opsonophagocytic antibody to pneumococcus, certainly for children. An important point is that the response of adults with opsonophagocytic antibodies, unfortunately tails off at about 50. Additionally, they do not have the data, but it would be nice if they did because potentially, immunization of everyone at 50 might give a better long-term response and better protection in the older age group. They do not have the data to confirm that, but he wanted to stress the need for such a study comparing the immune responses and persistence in people age 50, particularly normal people age 50, who will eventually become 65 and therefore go into a high risk group.

Dr. Nuorti pointed out that an additional consideration relates to the lower antibody levels after revaccination compared with primary vaccination, and what is happening in the immunologic system with multiple plain polysaccharide doses. They would hear more about the new conjugate vaccine in the fall, and whether that might be a way overcome the hyporesponsiveness issue. He agreed that was need for immunologic data for ages 50 and over.

Sandy Fryhofer, ACP, commented that in revisiting Dr. Schaffner's comment, wherein a patient loses his spleen at age 40 in a car accident, for example, and they get revaccinated at 45, she believed it was reasonable under this set of recommendations to be vaccinated at age 65. If they could directly say that, it would be very helpful. It is a question they hear a lot.

Dr. Nuorti commented that the current recommendation is to vaccinate everyone aged 65 years and older if it has been more than 5 years since the previous dose.

Sandy Fryhofer, ACP, remarked that another real-life scenario is that immunization has become a quality measure in hospitals for patients age 65 and older. The good part is that immunization rates will be increased. However, what is happening is that patients are vaccinated without any questions asked until later. There is often no attempt to collect history, sometimes practitioners don't know if a patient has received vaccinations in the past. As the working group continues to look at these issues, the consideration of immunoresponse after revaccination is something they should consider. Practicing doctors and hospitals may need that guidance.

Dr. Nuorti replied that in a 1997 document, it states that if the vaccination history is unknown in persons age 65 and older, they should receive the polysaccharide vaccine.

Dr. Fryhofer replied that it is being zealously done because of those quality measures.

Dr. Langley, NACI, inquired as to whether the homeless were included.

Dr. Nuorti replied that homeless persons were not included. For all the current special setting recommendations that are included, the level of evidence is Category C (low).

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Use of Pneumococcal Polysaccharide Vaccine (PPV23) in High Risk Adults Aged 18-64 Years

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Dr. Rosen pointed out that the 1997 ACIP Recommendations for the Pneumococcal Polysaccharide Vaccine (PPV23) state that, "Persons aged 2-64 years with chronic pulmonary disease, including chronic obstructive pulmonary disease and emphysema, should receive PPV23." Asthma was not included in the chronic pulmonary disease category because no data on increased risk of pneumococcal disease among persons with asthma was available when the recommendation was made. Previously, asthma had not been associated with an increased risk for pneumococcal disease, unless it occurs with chronic bronchitis, emphysema, or long-term use of systemic corticosteroids.

The first objective of this session was to review new information regarding the association of asthma and smoking with increased risk for invasive pneumococcal disease (IPD). The second objective was to review considerations related to expanding PPV23 target groups to include persons aged 18-64 years who have asthma or who are cigarette smokers.

Asthma is a chronic inflammatory airway disorder of airway hyper-responsiveness, and it involves the activation of several cell types. Symptoms include recurrent wheezing, shortness of breath, cough, variable expiratory airflow obstruction, which is partially reversible. There are varied definitions of asthma. A widely accepted clinical case definition does not exist. This lack of standardization creates difficulty when applying public health interventions and recommendations to individuals with asthma. The case definition for public health surveillance is complicated, and is not practical for use in clinical practice. The diagnosis of asthma is made by a combination of history, physical exam, reversibility of symptoms with therapy and pulmonary function testing. In adults, the diagnosis of asthma versus COPD is often confused, leading to misclassification, particularly in midlife, when symptoms from COPD are most likely to begin. To further add to the confusion, there are individuals with co-existing asthma and COPD.

The accurate assessment of asthma prevalence is complicated by the varying definitions of asthma. During 2006, approximately 6.8 million (9.3%) US children and 16.1 million (7.3%) US adults were reported to have asthma. Diagnosis in children less than five years is similar to that of adults. However, pulmonary function testing is difficult and rarely available. The occurrence of three or more episodes of wheezing is typically considered a risk factor for the development of asthma. Other risk factors include a history of allergies, eczema, family history, and second-hand smoke exposure. Below the age of two years, there is a high incidence of wheezing with upper airway disease such as allergic rhinitis and sinusitis, as well as obstruction involving the small airways. It has been difficult to define a subset of these children who will have a more benign course and should not be labeled as having asthma, which typically implies a more chronic course. Nine million children have a lifetime asthma diagnosis, of which only 70% have current asthma.

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In 2005, a nested case-control study for asthma as a risk factor for IPD was published (Talbot et al. N Engl J Med 2005; 352(20): 2082-90). Cases with IPD were identified from CDC's active surveillance of IPD, Active Bacterial Core surveillance (ABCs), who were also enrolled in Tennessee's Medicaid program (TennCare). Asthma and other diagnoses were determined using ICD coding. 635 cases, aged two to 49 years, were included in the study. For every case with IPD, 10 age-matched controls without IPD were randomly selected from TennCare. IPD cases were included if they had one inpatient or emergency department diagnosis, two outpatient diagnoses (ICD-9-CM), or the use of asthma-related medications. Individuals were considered to have high-risk asthma if they had a hospitalization or ED visit; used rescue therapy or long-term oral corticosteroids; or if three or more *B*-agonists were prescribed within one year. For all age groups, asthma was significantly associated with IPD. For the two to four age group, the odds ratio was 2.3; for the five to 17 age group, the odds ratio was 4.0; and for the 18 to 49 age group, the odds ratio was 2.4. Of note, there was poor information to smoking for the control cases. Smoking was classified based on ICD-9CM coding, which likely underestimates the true number of smoking and may have led to residual confounding in the results.

A retrospective cohort study was conducted to evaluate the impact of PPV23 on pneumonia hospitalization rates in patients with COPD and asthma, as compared to age matched controls without respiratory disease (Lee et al. J Gen Intern Med 2007; 22(1): 62-7). Outcomes measured were both pre- and post-vaccination pneumonia hospitalization rates. Asthma diagnoses and outcomes were based on administrative data and ICD-9 codes. Individuals in this study were older than those in the previous study discussed, with an average age of greater than 50 years. The study included 2,746 individuals with asthma and 1,345 controls. The risk of pneumococcal pneumonia was not significantly increased in persons with asthma before the PPV23 vaccination. The relative risk was .76 before vaccination and .3 after vaccination. There was no significant difference in risk of pneumococcal pneumonia after vaccination either compared with controls.

In the Talbot et al study, the IPD incidence rate (cases / 100,000) for persons with low risk and high risk asthma was 23 and 42, respectively. This compares to an incidence ranging from 51 among diabetics to 503 in persons with hematological cancer in data from CDC's ABCs database using population estimates from National Health Interview Survey,

Cigarette smoking is not included in the 1997 ACIP recommendations for the use of PPV23. A 1995 evaluation of IPD surveillance in Texas, in which 432 cases Ages two months to 100 years were ascertained using active, laboratory, and population-based surveillance, and a review of medical records (Pastor et al. CID 1998 Mar;26:590-5). 47% of IPD cases were current smokers; smoking was significantly associated with IPD in the 24 to 64 year age group, and the 65 year and older age group with the respective odds ratio of 2.6 and 2.2 and attributable risks for smoking of 31% and 13%.

A population based case-control study using CDC ABCs data was performed that looked at the contribution of various factors to IPD risk (Nuorti et al. N Engl J Med 2000;342:681-9)). Cases were identified using active, population-based IPD surveillance (ABCs) and random digit dialing for control selection. Immunocompetent adults aged 18 to 64 years were included. There were a total of 297 cases and 301 controls.

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IPD was significantly associated with current cigarette smoking, with an odds ratio of 4.1. Passive smoking among non-smokers was 2.5, after adjusting for age and other independent risk factors. There were dose response relations for the current number of cigarettes smoked per day, pack-years of smoking, and time since quitting. The adjusted population attributable risk was 51% for current smoking and 17% for passive smoking.

Dr. Nuorti briefly reviewed the working group's considerations regarding asthma and smoking in adults 18-64 years. Whether or not asthma is an indication for PPV23 has been an area of confusion among health care providers since it is an indication for the influenza vaccine. Working group members felt that including asthma in the chronic pulmonary disease category might be consistent with the current clinical practice of many adult immunization providers. Most adult IPD cases with asthma also have another condition for which PPV23 is recommended. New information suggests that asthma is an independent risk factor for pneumococcal disease.

On the basis of the new information, the working group proposed including asthma among the chronic pulmonary diseases that are indications for PPV23 among persons aged 18-64 years. The pediatric recommendation will be addressed in a subsequent section. The proposed language is as follows:

> "Persons at increased risk for invasive pneumococcal disease include those with chronic pulmonary diseases (such as COPD, emphysema or asthma)."
>
> and
>
> "Persons aged 18-64 years with chronic pulmonary disease including chronic obstructive pulmonary disease, emphysema and asthma should receive PPV23."

Regarding cigarette smokers, the working group had these considerations: Currently, about one-fifth of US adults smoke cigarettes; defining the criteria for a significant smoking history is challenging and using indicators such as number of pack-years smoked may not be feasible in clinical practice. Among adults, most of the cases with invasive pneumococcal disease who are cigarette smokers already have another condition for which PPV23 is currently recommended. Furthermore, acceptability of vaccination among smokers may be low, particularly in younger age groups. For these reasons, the working group elected not to propose recommending PPV23 specifically to cigarette smokers, although information on the increased risk will be included in the new statement.

Discussion

Dr. Tanner expressed concern about the smoking recommendation. The data shows this is a significant risk factor. Despite the fact that the logic is understandable, it is important to look at that and say that the smokers should be a recommended population, logistics aside. He found it hard to buy into low acceptability as a reason not to put smokers in that risk group.

Dr. Nuorti replied that this was one of the considerations the working group had discussed. Other organizations, such as IDSA, have made recommendations for smokers. As an example, the IDSA guidelines for management of community acquired pneumonia (CAP) in adults states that smoking cessation should be the goal for those hospitalized with CAP and continue to

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smoke. Smokers who will not quit should be vaccinated for pneumococcus and influenza. Again, the working group considered this, but the weight of the evidence was on the other side.

Dr. Temte remarked that coming from primary care, one thing that plagues them with the risk-based recommendations is confusion. He sees many adults, and it is not always apparent who has COPD, chronic bronchitis, and so on. Oftentimes it is after the fact, for example when a person has pneumonia, that one starts to make those diagnoses. He wondered whether the pie was cut in terms of data regarding smoking and age. A 26-year-old smoker is very different than a 55-year-old smoker, especially if they are like most, who start at age 13. It is very clear from the data presented that pack years is a true risk factor. He wondered if they had considered making a recommendation for smokers aged 50 and older, or some other cut point. Those patients, if they have been smoking all along, almost by default have COPD or chronic bronchitis. His hope was that they would try to expand it and to make it easier for those in primary care. If he could tell smokers they were at higher risk for something, this could be very beneficial.

Dr. Nuorti responded that the working group did not discuss specific age-based recommendations for smokers. It is possible they could revisit that discussion. Regarding what the data shows by age in terms of risks from smoking, there was a trend that older smokers had somewhat higher risks than the younger smokers. The study looked at three age groups. Other working group members may want to comment on the age 50 recommendations.

Dr. Sumaya (AMA) commented that he was uncomfortable with the wording around low acceptability of vaccinations among smokers as a consideration for why vaccinations aren't recommended. Vaccination among many groups is low, including high-risk groups, and yet vaccinations are still recommended for them. This should be included as one of the considerations.

Dr. Cieslak wondered about the number needed to prevent the case of invasive disease, and number needed to prevent death, as well as smokers with no other indication. A *New England Journal of Medicine* paper in 2000 stated that only 13% of smokers have chronic lung disease, and 23% have at least one chronic illness, which suggests that most of them did not have another indication for vaccination. Nevertheless, the adjusted odds ratio was four, which suggested a pretty significant risk in that group.

Dr. Nuorti replied that one of the reasons fewer smokers have other conditions in that study population was that it was limited to the immunocompetent group, so cases with immunocompromised conditions were excluded. Most of the other information does show that many smokers do have other indications.

Getting at the acceptability issue, Dr. Schuchat pointed out that one of the pieces of data they did not go into this time was information about adverse events based on health status. She recalled that severe arm pain is greater the healthier one is. The adult population has more of that than the elderly population. She wondered if there was information about the frequency of severe arm pain or large, local reactions in healthy younger smokers versus older ones with chronic conditions. Acceptability is more than just a question of whether they want this. There are unintended consequences in giving a vaccine to a group that will have problems with it. She wondered if that was discussed among the working group.

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Dr. Nuorti replied that they had not looked at this issue by smoking status. There was another larger study that looked at adverse events , by Jackson and others in1999. It concluded that the prevalence of adverse reactions was related to preexisting antibodies. Other studies have not quite found the same thing. There was not information in that study regarding whether a person was healthy or not.

Dr. Judson commented that given the known pathophysiology of asthma and pneumococcal infection and disease, he was always surprised a direct association could not be shown. He supported adding that as a risk indication. As for smoking, given the enormous population morbidity and mortality from tobacco smoking, using pneumococcal vaccine in smokers is maybe a dangerous diversion. It could be seen as another reason not to deal with a fundamental public health problem. The overall benefit of telling smokers they have a small risk of pneumococcal disease, and it will be dealt with by a vaccine, does not get directly at smoking and thus is not helpful. Additionally, as asthma is being addressed here, environmental tobacco smoke from those smokers who might get immunized has been attributable to half of all asthma attacks in children, according to a couple of studies. That would also be a conflict.

Dr. Gall, ACOG, commented that in the patient population his membership sees, up to 37% of pregnant women are smokers and frequently have asthma, chronic hypertension, and obesity. Most practitioners are not routinely administering the pneumococcal vaccine. Smoking definitely exacerbates everything that happens in the lung, which is really the Achilles' Heel of pregnancy.

Dr. Fryhofer, ACP, disagreed that getting a pneumococcal vaccine would encourage smoking. As a practicing physician, she sees patients in the office every day. Getting people to quit smoking is difficult, but giving them a shot that would prevent them from getting very sick is not going to interfere with efforts to get them to stop smoking. She was very impressed with the *New England Journal of Medicine* (*NEJM*) article in the background material that links cigarette smoking and IPD.

Dr. Schuchat commented that regarding this article, for which Dr. Nuorti was lead author, it was important to recognize that it was written before the conjugate vaccine was in use. It included adults aged 18 to 64, and it excluded immunocompromising conditions. It did not incorporate the impact the conjugate vaccine was having on the population. This does not invalidate it, but it needs to be looked at with that in mind.

Dr. Sawyer said the relative risk for invasive disease is at least as high as or higher than asthmatics. The number of clinical infectious disease cases prevented in this country, at least based on the Greene et al paper in the information packet, would be higher. Related to a previous comment about the number of doses that would need to be administered to prevent a case, or cost-benefit data, he wondered whether that was that part of the deliberation that lead the Working Group to recommend it for asthmatics but not smokers.

Dr. Nuorti replied that they did discuss this issue. They did do not do a formal cost evaluation. Some of the considerations that weighed more heavily toward including asthma were that it was already an influenza vaccine indication. It was excluded before from the group of chronic lung diseases for which the vaccine is recommended. It seemed to be reasonable to now include it in that category because of the new data. With regard to smoking, the working group felt that the feasibility of programmatic issues might be too difficult, or more difficult than with asthma.

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Dr. Morse remarked that regarding the discussion on smoking, they would not vote on it that day, but could either refer it back to the working group to report on tomorrow. They would also be having discussions on IPD in the fall, and they could revisit it then.

Dr. Temte liked the inclusion of asthma with the other chronic lung diseases. It is often hard to separate those out with patients. Their goal is to get vaccines out to those who will benefit. Regarding smoking and the *NEJM* article, where those aged 50 to 64 represented 30% of the patients of there study, the indications for receiving PPV23 as 28%. There is not a breakdown by age. He guessed this was because a lot of people who have an indication are also the smokers under 50. This is such a good proxy what they are seeing in primary care. The see patients not only for lung disease, but also for heart disease and other things that might be good indications for the vaccine they may not be aware of.

Dr. Nuorti responded that he did not recall that they had looked at the data they way Dr. Temte was suggesting. The most relevant information on the proportion of smokers and asthmatics that have other indications is from the Greene et. al. study which is included in the background package. Current smokers constituted 39% of all cases in the study; 80% of current smokers already had other indications for PPV23. Asthmatics were about 11% of all cases; 86% already had another condition that would be a PPV23 indication. They also constituted a very small proportion of the total study population.

Dr. Judson remarked that the risk factor within the coronary artery disease spectrum for IPD would be heart failure and pulmonary edema. Anything that caused pulmonary edema would greatly increase the risk of pneumococcal pneumonia. He would not expect to see an association with undefined coronary artery disease unless there was heart failure.

Dr. Nuorti replied that this was why coronary artery disease was not included in the chronic heart disease category in the 1997 recommendation. He was unaware of any further studies showing an association.

Dr. Cieslak expressed his interest in incidence of IPD in smokers without other indications and incidence in asthmatics and whether the two differ. That is, is the risk in asthmatics much higher? Realizing that they also have to consider vaccine efficacy in different cohorts, it would be nice to have a general idea of the line above which vaccination would be indicated, for some level of consistency in recommendation.

Dr. Neuzil reported that she was a member of the working group, and as they had seen from this discussion, there was also a lot of discussion and controversy regarding this topic among the working group members. She indicated that her personal ideas on this perhaps did not reflect the group's. While they did not have the number needed to treat, they did consider the addition of individual risk groups at this point as being of small, incremental benefit. The issue with asthma was a completely separate issue. They have a current recommendation for chronic lung disease, which is perceived as excluding asthma. They know that the studies they are showing are based on ICD-9 codes. As an internist it is very difficult, especially the older the patient is, to differentiate between asthma and chronic bronchitis and asthmatic bronchitis, and many other different descriptions of chronic lung disease. So, while asthma looks incremental, too much emphasis is being placed on studies. The asthma was to be more inclusive within that chronic lung disease group, where they did not feel as though sitting in office one could make a differentiation that was accurately reflected in a database study. Regarding the other groups, there would be small, incremental benefits for adding each one. Many of the group looked at asthma differently. It is not clear what really the definition is of asthma, and how

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someone who treats adults is supposed to deal with that in the real world, differentiating chronic lung disease.

2008 PPV23 Vote

Pekka Nuorti, MD, DSc
Respiratory Diseases Branch
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

In preparation for a vote, Dr. Nuorti reviewed the current recommendations for including asthma among the chronic pulmonary diseases that are indications for PPV23 among persons aged 18-64 years and discussed the rationale that was the basis for these recommendations:

> "Persons at increased risk for invasive pneumococcal disease include those with chronic pulmonary diseases (such as COPD, emphysema or asthma)."
>
> and
>
> "Persons aged 18-64 years with chronic pulmonary disease including chronic obstructive pulmonary disease, emphysema and asthma should receive PPV23."

Discussion

Dr. Sawyer wondered whether this would cover the middle cohort of adolescents who would not fall into the category of receiving PPV23, but who do have asthma. That is, it was not clear whether this wording should somehow answer the question regarding a 14-year-old with asthma.

Dr. Nuorti replied that the next section would address the pediatric age groups.

Motion: Pneumococcal Vaccines in Adults

Dr. Morita motioned that the recommendation be approved as written. Dr. Temte seconded the motion. The motion carried with 15 affirmative votes, 0 abstentions, and 0 negative votes.

Use of Pneumococcal Polysaccharide Vaccine in Children Previously Vaccinated with Pneumococcal Conjugate Vaccine

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Respiratory Diseases Branch
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Dr. Nuorti reviewed the list of underlying medical conditions for which PPV23 is recommended after PCV7; current rates and serotypes of invasive pneumococcal disease (IPD) in children; the recommendation language for use of PPV23 after PCV7 in Alaska Native and American Indian

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(AN / AI) children; the recommended time interval for PPV23 revaccination in high risk children; and use of PCV7 in HIV-infected, school-aged children.

The ACIP previously added cochlear implant recipients to the list of pediatric high risk conditions in children aged 24-59 months. In October 2007, the ACIP recommended that all children aged <5 years should receive PCV7. Therefore, the complicated list of medical high risk conditions in Table 8 of the MMWR was simplified to a list of children who are recommended to receive PPV23 after their PCV7 series at age ≥2 years (ACIP. MMWR 2000;49(RR-9). Currently, PPV23 after PCV7 is recommended for children in three groups: asplenics, immunocompromised, and chronic illnesses. In addition, it can be considered for Alaska Native / American Indian children. Current ACIP recommendation for use of PPV23 in children who have received PCV7 are as follows:

> "Children who have completed PCV7 vaccination series before age 2 years and who are among risk groups for which PPV23 is already recommended should receive one dose of PPV23 at age 2 years."
> "These groups at high risk include children with SCD, children with functional or anatomic asplenia, children who are HIV-infected, and children who have immunocompromising or chronic diseases."
>
> "For children of Alaska Native or American Indian descent, addition of PPV23 after PCV7 can be considered."

The current ACIP recommendation for use of PPV23 in children who have received PCV7 is as follows:

> "Although data regarding safety of PPV23 administered after PCV7 are limited, the opportunity to provide additional serotype coverage among these children at very high risk justifies use of the vaccines sequentially."

With respect to rates of invasive pneumococcal disease among children aged 24-59 months, by serotype (1998 / 99-2006), Dr. Nuorti pointed out that by 2006, the overall rate had decreased from the baseline of 36 to 11/100.000. PPV16 types increased from 4 to 9/100.000 (Data source: CDC, Active Bacterial Core surveillance, unpublished, 2008). The proportion of invasive disease cases among children aged 2-4 years who have various underlying medical conditions has increased after PCV7 introduction. However, the total number of cases is very small. In 2006, out of 65 children with IPD, only 7 (11%) cases had any high risk condition. In 2006, there were no PCV7 type IPD cases among the 7 children with underlying medical conditions. Most of cases were caused by serotypes not in PCV7 or PPV23. Only 2 cases were caused by PPV types suggesting that in this age-group there may not be substantial increase in serotype coverage from PPV23 use (Table 8, MMWR 2000;49(No. RR-9):22; Data source: CDC, Active Bacterial Core surveillance, unpublished, 2008).

Pertaining to the recommendation concerning chronic pulmonary disease in children, there were several reasons why the working group decided to considered pediatric asthma differently from adult asthma. As mentioned before, the clinical practice implication of adding a condition to the pediatric high risk list would be that children would be recommended to receive PPV23 after they have completed PCV7 series. Adding asthma without high dose corticosteroid therapy to the high risk list would target a large group of children. The working group also consulted the AAP COID regarding the recommendation. The working group recommends that children aged 2-18 years who have "asthma without high dose corticosteroid therapy" should not be

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administered PPV23 after their PCV7 series. No changes are proposed to the list of children with underlying medical conditions who are recommended to receive PPV23 after their PCV7 series.

The current recommendation for use of PPV23 after PCV7 in Alaska Native / American Indian (AN / AI) children is as follows:

> "For children of Alaska Native or American Indian descent, addition of PPV23 after PCV7 can be considered."
>
> "Health care providers of Alaska Natives and American Indians should consider whether these children would benefit by the additional coverage provided by the expanded serotypes in PPV23."

Considerations for revising the PPV23 recommendation for AN / AI children were that data on increased risk of pneumococcal disease are limited to Alaska Native, White Mountain Apache, and Navajo populations. Current ACIP language lacks specificity. All Alaska Native and American Indian groups are not at equal risk. It is unclear how "American Indian descent" is defined. Burden of that decision seems to rest on individual practitioners. With respect to current clinical practice among children ≥2 years in Alaska Native, White Mountain Apache and Navajo populations, despite the recommendation to consider PPV23, it is not routinely given to all AN / AI children in these populations, except for those with high risk medical conditions. Current rates in Alaska Native children are about 5-fold higher compared with the general US population. The rate of non-PCV7 type disease has increased. Current rates in Navajo children are about 2-fold higher compared with the general US population. In summary regarding IPD among AN / AI children aged 2-4 years, rates of non-PCV7 disease increasing in AN but unchanged in Navajo and White Mountain Apache. There are small numbers of cases. Overall rates are 24-60 per 100,000 per year, which is 2-5 fold compared with the general US population, and 80-90% of IPD is due to PPV23 serotypes.

The workgroup's considerations with respect to AI / AN children were that in Alaska Native children, PPV23 is a potentially useful tool for preventing IPD in 2-4 year old Alaska Native children. Recent increases in non-PCV7 type disease have increased interest in PPV23. For Navajo and White Mountain Apache children, rates of PPV23 type disease, although higher (for some time-periods) than general US, reflect a small number of cases. PPV23 was not routinely implemented in these populations before PCV7 when rates were significantly higher. Two concerns are that PPV23 effectiveness after PCV7 is unknown, and there can be immunological hyporesponsiveness after PPV23.

The proposed recommendation for Alaska Native / American Indian Children is to keep the permissive recommendation and specifying risk group definitions as follows:

> "Currently, data on increased risk of pneumococcal disease are limited to Alaska Native, White Mountain Apache, and Navajo populations. On the basis of these data, routine use of PPV23 is not recommended for all AN/AI children aged ≥2 years."
>
> "For Alaska Native or American Indian children aged ≥2 years, living in areas with documented elevated rates of invasive pneumococcal disease, addition of PPV23 after PCV7 can be considered."

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The current recommendation for revaccination with PPV23 in children follows:

> "Immunocompromised children or children with SCD or functional or anatomic asplenia should be revaccinated with PPV23."
>
> "If the child is aged ≤10 years, one revaccination should be considered 3-5 years after the previous dose of PPV23."
>
> "Data are limited regarding adverse events related to second dose of PPV23 administered after PCV7. Health care providers should not administer a second dose of PPV23 any earlier than 3 years after the initial dose."

With regard to the summary of considerations for PPV23 revaccination in children, the workgroup felt that the "3-5 year interval" may be confusing. Recommendation to revaccinate high risk children three years after the first dose was based on immunologic data from the 1980s indicating rapid antibody decline after PPV vaccination in children at highest risk. Of the studies conducted in the 1970s and 1980s, 5 of 6 observed lower antibody concentrations for some serotypes with a second PPV dose. Clinical effectiveness of PPV23 revaccination is unknown.

The proposal from the working group is that the PPV23 revaccination interval in high risk children might be more practical if it was defined on the basis of the age at first PPV23 dose. If the child is aged 2-4 years at the first PPV23 dose, one revaccination should be administered after 3 years. If the child is aged ≥ 5 years at the first PPV23 dose, one revaccination should be administered after 5 years.

With respect to the use of the conjugate vaccine in children aged ≥5 years, data are limited regarding the efficacy of PCV7 in children aged ≥ 5 years. PCV5 is immunogenic in children 2-9 years, and some data suggest that PCV7 is immunogenic in children aged 2-13 years with recurrent respiratory infections. PCV7 is currently licensed for use up to age 9 years. The current recommendations state the following:

> "Administering PCV7 to older children with high-risk conditions is not contraindicated."
>
> "Current (in year 2000) data do not support replacing PPV23 with PCV7 among older children and adults."

The American Academy of Pediatrics (AAP) Report of the Committee on Infectious Diseases, "Redbook", 2006 states that PCV7 is safe and immunogenic up to 13 years old; that administration of a single dose of PCV7 to children of any age, particularly children who are at high risk of IPD, is not contraindicated; and that immunization with a single dose of PCV7 or PPV23 is acceptable.

Regarding the rates of invasive pneumococcal disease among children aged 5-9 years, by serotype (1998 / 99-2006), the overall rate is very low at 6 / 100.000. There has practically been no change after PCV7 introduction in this group because of increases in non-PCV7 types. The rates of all different serotype groupings are < 4cases / 100.000. With respect to the proportion of invasive pneumococcal disease cases caused by indicated serotypes among children 5-9 years-old, with ACIP indications for PPV23 (N=13), in 2006, 13 (23%) of 56 children aged 5-9 years had an underlying medical conditions that are indications for PPV23. Of the 13

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cases with underlying medical conditions, 10 (77%) were caused by PPV23 types. There were no cases with HIV infection. The overall rate in invasive pneumococcal disease among children aged 10-19 years, by serotype, in 2006 was 2 cases / 100.000. All rates for different serotype groups rates were <1 cases / 100.000. The proportion of invasive pneumococcal disease cases caused by indicated serotypes among children 10-19 years-old, with ACIP indications for PPV23, in 2006, 9 (27%) of 33 cases aged 10-19 years had a PPV23 indication. Of the 9 cases with underlying medical conditions, 8 (88%) were caused by PPV23 types. There were no cases with HIV infection. So, it appears that in children older than 5 years, there might be additional benefit from expanded serotype coverage of PPV23 (Data source: CDC, Active Bacterial Core surveillance, unpublished, 2008).

In terms of the evaluation of immunogenicity and safety of combined PCV7 / PPV23 schedule in HIV-infected children, 225 HIV-infected children aged 2-18 years (median 9.6 yr) were receiving HAART, did not receive PCV7 in infancy, and 75% had received PPV23. The study showed that the recommended schedule of 2 doses of PCV7 followed by PPV23 (interval 8 weeks) was immunogenic:76-96% and 62-88% had antibody concentrations ≥0.5ug/mL and ≥1.0 ug/mL), respectively, to 5 serotypes; and no increase in frequency of local or systemic reactions (Abzug et al. Pediatr Infect Dis J 2006;25:920-929). Thus, with respect to HIV-infected, school-aged children, the working group's considerations were that among children aged ≥5 years, the current rates of PCV7 serotype disease are very low. Most IPD cases among children with underlying medical conditions are due to PPV23 types. ACIP has not made a specific recommendation for PCV7 use in children aged ≥5 years for other high risk groups. PCV7 use in children aged ≥10 years would be off-label. It appears that the current ACIP and AAP recommendation seems appropriate:

> "Administering PCV7 to older children with high risk conditions is not contraindicated."
>
> "Current data do not support replacing PPV23 with PCV7 among older children and adults."

For HIV-infected children, on the basis of available new immunogenicity and safety data, the workgroup recommends the following permissive statement:

> "For HIV-infected children aged 5-17 years on HAART who have NOT been previously immunized with PCV7, practitioners may consider administering 2 doses of PCV7 followed by PPV23."

Vote #1: Alaska Native, White Mountain Apache, and Navajo Populations

For this vote, ACIP members were asked to consider the following:

> "Currently, data on increased risk of pneumococcal disease are limited to Alaska Native, White Mountain Apache and Navajo populations. On the basis of these data, routine use of PPV23 is not recommended for all AN / AI children aged ≥2 years."
>
> "For Alaska Native or American Indian children aged ≥2 years, living in areas with documented elevated rates of invasive pneumococcal disease, addition of PPV23 after PCV7 can be considered."

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Discussion

It appeared to Dr. Chilton that the working group had considered lack of data as a way of making a recommendation that the vaccine not be given. He thought much of the research had been conducted in Alaska on the Navajo and in the Western Mountain Apache. One would guess that other Native Americans have similar genetic susceptibility and also that other parts of the country, especially in the North Central area, have higher passive smoking rates than do the Navajo at least. Therefore, it seemed to him that the first statement was somewhat strong and should not be recommended in the absence of data.

Dr. Nuorti responded that the primary concern was that not all of these populations may be at high risk, and that it is very difficult to define who is of AN / AI descent, especially if these individuals live outside of the special settings or environments where high rates of disease have been documented.

Dr. Morse inquired as to whether Dr. Chilton was suggesting a more positive statement.

Dr. Chilton responded that he would want to make the statement less strongly against giving it to other groups of Native Americans. The other point is that the Indian Health Service along with CDC should consider studying other Native American groups for incidence of disease.

With respect to the second part of the recommendation, Dr. Sumaya inquired as to whether the working group defined “living in areas” (e.g., school district, city, county, state).

Dr. Nuorti responded that in this context it related to persons in these populations where the data are available, so it would be Alaska Natives living in Alaska and the White Mountain Apache and Navajo living in the Reservation area.

Ms. Stinchfield agreed that the second component was a localized, specific recommendation. Therefore, it would rely heavily upon state public health to communicate clearly with clinicians about what their local rates are.

Dr. Nuorti responded that in the American Indian and Alaskan Native populations for whom information is available, the previous recommendation really has not been implemented. It is likely that this is due to the unknown effectiveness of the vaccine and perhaps potential adverse consequences.

Dr. Englund pointed out that for the first statement, it was not just on the basis of data, it was on the basis of “limited” data on vaccine, antibody response, safety, et cetera for all populations—not just these populations. She agreed that the statement was too strong.

Amy Groom, Indian Health Service, thanked Dr. Chilton for making that very important point. It is of great concern that the absence of data gets interpreted as the absence of disease. The Indian Health Services are very concerned about some of their populations who may be very similar and suffer some of the same living conditions and socioeconomic status that may put them at increased risk as the Navajo and White Mountain Apache, such as in the Northern Plains. They have been fortunate to have excellent data on those populations, but each time there is a vaccine shortage, this issue comes back to haunt them. The important note is that in the case of a shortage, this will be interpreted as affecting only documented, elevated areas for

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these populations, yet these populations may be at increased risk and will not get prioritized to receive vaccine.

Dr. Nuorti indicated that this language was modeled after some of the shortage language used during the conjugate vaccine shortage a couple of years ago.

Col Ted Cieslak, DoD, pointed out that he began his career with the Indian Health Service and as someone who practiced in two Eskimo villages, he wanted to go on record as agreeing with the Indian Health Service representative and with Dr. Chilton. While the Native American population is certainly not genetically homogenous, but a lack of data does not equal a lack of risk. He said he would personally like to see the statement watered down considerably in that regard.

Dr. Judson added that the real problem was that they were dealing with poorly defined, non-genetically or socioeconomically homogenous populations. He suggested basing the recommendations on known prevalence, or incidence in this case, of invasive disease. He recognized that this information was not available when needed, but this statement was not a way out of that problem. At one point ACIP recommended routine use of Hepatitis A vaccination based on incidence rates per 100,000. That made sense because it would change from time to time in different populations. He said he would feel most comfortable if they could develop recommendations clearly based on incidence and who is at risk rather than populations they could not define. He also noted that they had morphed to the terminology “a vaccine can be considered.” Whether that was really helpful for a vaccine that is already licensed by the FDA for these populations was not clear. That is, were they providing useful guidance when they stated, “not recommended” but it “can be considered?”

Dr. Morse suggested that given the discussion, this motion be tabled in order for the working group to review and revise the language.

Motion #1: Pneumococcal Vaccine in Children (AI / AN / WMA)

This vote was tabled, given that a request was made for the working group to review and language to reflect the discussion.

Vote #2: Revaccination in High Risk Children

For this vote, ACIP members were asked to consider the following:

Determine the PPV23 revaccination interval in high risk children on the basis of their age at first PPV23 dose:

- If the child is aged 2-4 years at the time of first PPV23 dose, one revaccination after 3 years
- If the child is aged $\geq$ 5 years at the time of first PPV23 dose, one revaccination after 5 years

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Discussion

Amy Middleman, Society for Adolescent Medicine, said it appeared to her that revaccination or a booster dose is not required under the age of 18, but the implication of the previous vote was that at the pre-college visit, when someone turns 18, they will then receive the pneumococcal vaccine for those who have asthma. She also inquired as to whether it was expected that as children grew older and had all had Prevnar® up to age 18, that for those with increased risk the recommendation would hold.

Dr. Nuorti responded that she understood the recommendation correctly. With respect to Prevnar®, the overall picture is that the rates of disease are very low in older children. The data he showed were based on small numbers of children with the current high risk conditions. It seemed to be in line with what was voted in the previous session that everyone age 18 with asthma should receive the pneumococcal vaccine at their pre-college visit, although he pointed out that there was not specific discussion of the pre-college visit in the working group.

Dr. Katz, IDSA, recognized that they were in a state of transition with multivalent conjugate vaccines, but he wondered if the working group discussed hypo-responsiveness with repeated doses of polysaccharide vaccine.

Dr. Nuorti responded that it was one of the major factors, and a lot of discussion centered on the data pertaining to hypo-responsiveness. That was also a consideration that weighed heavily on the Alaskan Native / American Indian proposed recommendation. However, Vote #2 is not directly based on any direct evidence, but more on a practical clarification of the range of 3-5 years that was in the previous recommendation.

Dr. Judson inquired as to whether there was any evidence at all that the dosing intervals play out differently in terms of efficacy. If not, he did not believe it was useful to develop different or more complicated intervals when there is no clear-cut advantage of one over other. He thought they should keep it simple unless the data drove them to be more complicated.

Dr. Nuorti replied that there are no data suggesting a different degree of efficacy with these regimens. An alternative discussed by the working group was to state 5 years for all children, which would make the revaccination recommendation even simpler. To the best of his recollection, there were limited data on the response to the polysaccharide vaccine after the conjugate vaccine. There are approximately 14 pediatric studies that examined conjugate vaccine followed by polysaccharide vaccine, but the purpose of those studies was to show that priming had occurred after the conjugate vaccine. They were not designed to inform the hypo-responsiveness issue or address the efficacy of the vaccine.

Dr. Englund thought there were good data for other polysaccharide vaccines that a 5-year old responds quite differently than a 2-month old. As a practicing pediatrician, she thought the recommendations were good because frequently children are immunized at 2- and 5-years old and this fits in with when children are routinely seen. She also thought it was incumbent upon the ACIP to point out the incredible lack of data on any vaccines and need to state again that more immunological data are needed because they have a correlate of protection. There is minimal research funding for this type of studies, yet it is a critical need in the patient population.

Dr. Morse added that this was to attempt to clarify the recommendation to make it simpler than the previous one, which used a range of 3-5 years.

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Dr. Cieslak understood the desire to clarify what 3-5 means, and that it was good to pick a number, and he agreed with Dr. Englund that what she said made sense if the child received the vaccine at age 2, but if he or she received it at age 4, the age 5 visit would be difficult to implement.

Dr. Judson said his understanding was that immunologic responsiveness matured and was probably greatest from 11-13 years of age for many vaccines. He did not know of any studies that showed significant differences between 3 and 4 years or 5 and 6 years, which the recommendation under consideration would potentially imply.

Dr. Schuchat speculated that the issue may not have been the immunoresponse, but the age-specific risk of disease, because it is just in the healthy population that it is higher in under 5 than over 5.

Dr. Nuorti responded that the risk of disease decreases rapidly after age 2 and those children with high risk conditions may have high risk of disease during that couple of years before they reach age of 5.

Dr. Turner, American College of Health, thought the recommendation was suggesting that if a 13-year old had asthma, for example, this recommendation would call for PPV23 if the child had previously been vaccinated with conjugate.

Dr. Nuorti interjected that the recommendation did not include children with chronic illnesses who are not immunocompromised, including those with asthma.

Dr. Turner, American College Health Association, pointed out that if a pre-college individual who was 18 years old was given polysaccharide, it appeared that they would not be due for their next polysaccharide until they turned 65.

Dr. Nuorti confirmed that this was correct.

Dr. Morse clarified that this recommendation was an attempt to offer clarification because the current language includes the range of 3-5 years. However, it the ACIP was going to make changes for better clarification, they should be made based on science-based evidence. With that in mind, he suggested that this vote be tabled as well until ACIP could be presented with such data.

Dr. Nuorti reported that in the 1997 document, the revaccination interval for children ages 10 years or less was three years. It was changed in the 2000 document to 3-5 years. He did not believe there would be any conclusive data available to address the concerns.

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Motion #2: Pneumococcal Vaccine in Children (High-Risk)

This vote was tabled, given that a request was made for the working group to seek and present further data in terms of differences in immune response for younger age groups in order to warrant this recommendation.

Vote #3: HIV-Infected Children

For this vote, ACIP members were asked to consider the following:

> On the basis of available new immunogenicity and safety data, the Workgroup recommends the following permissive statement:
>
> "For HIV-infected children aged 5-17 years on HAART who have NOT been previously immunized with PCV7, practitioners may consider administering 2 doses of PCV7 followed by PPV23."

Discussion

Dr. Judson commented that there were fewer than 30 cases of new HIV infection in newborns as of 2007, based upon which this may be virtually eliminated in the next 3-5 years. Thus, they were making recommendations for a diminishingly small group of people whoa are often being seen by experts in field. Whether it is useful to simply tell an experts seeing one of a few cases in major city that they "may consider administering two doses of PCV7 followed by PPV23" did not seem beneficial. Experts are going to do what they believe they need to do based upon current information and knowing the immune status of their patient, which is the overriding issue.

Dr. Englund said that as former member of Pediatric Aids Clinical Trial Group that was involved in this study, she thought this was currently standard of care. However, most of these children have already been routinely immunized. This is common sense, there is a study to back it up

Dr. Schuchat pointed out that adolescents are still getting HIV, so it is not impossible in this age group to have new infections.

Dr. Cieslak expressed difficulty in seeing how the recommendation flowed from the data presented, which suggested that the risk is very low. He wondered if they were concerned about administering vaccine into individuals while they still have enough CD4 cells to make it count later. These recommendations are for children who are on HAART. Presumably, they are not at terribly elevated risk of invasive pneumococcal disease.

Dr. Nuorti responded that this is not a specific recommendation. It is a permissive statement.

Dr. Schuchat pointed out that HAART reduces the incidence with HIV-associated invasive pneumococcal disease greatly, but HIV-infected people still have much higher risk than similar age-matched populations. Therefore, this is one group that still has an on-going elevated risk.

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Cindy Whitney, Respiratory Diseases Branch, pointed out that there were other issues to consider. When using the two vaccines and wishing to use them together, the conjugate really needs to be given first or the opportunity is lost for maximum benefit for those antigens. The other evidence, the results from which are due out in a few months, is from a trial in Africa showing major benefit of conjugate vaccine in adults for pneumonia prevention. If thinking forward, the permissive statement makes sense.

Dr. Duchin, NACCHO, inquired as to why the working group chose to restrict the permissive statement to children on HAART and not HIV-infected children or qualified by immune status.

Dr. Nuorti responded that this recommendation was based on the one study in which all of the children were receiving HAART, the thinking being that they would probably respond to the vaccine better than if they were not on HAART.

Dr. Duchin, NACCHO, pointed out that since it was a permissive statement, it seemed that children who had comparable immune status should also be covered regardless of whether they are on HAART.

Dr. Englund responded that she thought it was to optimize their immune status before immunizing them. The study was conducted for children who had as robust an immune system for their age as could possibly be attained.

Dr. Stinchfield agreed that for those who do care for children with HIV, the population of HIV-infected children is decreasing. Those who would not previously have gotten PCV7 is small. This is straightforward, standard practice.

Motion #3: Pneumococcal Vaccine in Children (HIV-Infected)

Ms. Stinchfield motioned to approve the recommendation as written. Dr. Chilton seconded the motion. The motion carried with 15 affirmative votes, 0 abstentions, and 0 negative votes.

Combination Vaccines

Combination Workgroup Activities & Information

Patricia Stinchfield, RN, MS, CPNP
ACIP Combination Vaccines Workgroup Chair
Director, Pediatric Infectious Disease & Immunology,
Infection Prevention and Control,
Children's Hospitals and Clinics of Minnesota

Ms. Stinchfield reported that the ACIP Combination Vaccines Working Group goals were to review and communicate to the ACIP on combination vaccines new to the US market (e.g., Pentacel® vaccine (DTaP-IPV-Hib), sanofi pasteur; and Kinrix™ vaccine (DTaP-IPV), GlaxoSmithKline Biologicals); review issues surrounding the availability and use of combination vaccines in the U.S. market; and

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develop a revised statement, to replace the 1999 MMWR statement (*Combination Vaccines for Childhood Immunization MMWR Vol 48/No RR-5, May 14, 1999)* on use of combination vaccines for discussion and approval by ACIP. She then outlined the session and acknowledged workgroup members.

Pentacel®

Dr. David Greenberg
sanofi pasteur

Dr. Greenberg expressed sanofi pasteur's gratitude for the opportunity to present data for Pentacel® from their clinical trials. Pentacel® is an infant and toddler tetanus, diphtheria, acellular pertussis, polio and haemophilus influenza combination vaccine. The safety and immunogenicity of the combination vaccine, Pentacel®, compared to the standard of care and also to the Sweden 1 infant efficacy trial for pertussis, has shown 85% efficacy against WHO-defined pertussis. In addition, sanofi pasteur compared the consistency of three Pentacel® lots. They also studied the concomitant administration of Pentacel® with hepatitis B, pneumococcal conjugate, MMR, and varicella vaccines. The indication requested is for active immunization against diphtheria, tetanus, pertussis, polio and haemophilus influenza with a four-dose series beginning in infants at age 2 months with the 4th dose given between 15 and 18 months of age.

The composition of Pentacel® compared to the vaccines used in the controlled studies was as follows: Study P3T06 compared Pentacel to Daptacel, IPOL and Act-HIB, the licensed standard of care vaccines. Study 494-01 compared Pentacel to its formulation equivalent components HCPDT, Poliovax, and ActHIB. HCPDT is an unlicensed product, manufactured for this study to match the Pentacel composition and not used in any other setting.

Study P3T06 (N=1939), the safety and immunogenicity comparison with licensed vaccines, was a multi-center, randomized controlled, open label study in nearly 2000 infants who were vaccinated at 2, 4, 6 and 15 to 16 months of age with either Pentacel® or with the US licensed standard of care regimen (Daptacel, IPOL and ActHIB). About one-quarter of the children received Pentacel®, and each of the remaining three-quarters received one of three different lots of Daptacel®, because this was also a Daptacel® lot consistency trial. All of the subjects received hepatitis B vaccine at birth, 2 months, and 6 months of age, and most received Prevnar® at 2, 4 and 6 months of age. Study 494-01 (N= 3538) was the lot consistency study. It was a comparative group in which children received formulation components HCPDT (the DTaP portion of Pentacel®), Poliovax®, and ActHIB. The schedule was at 2, 4, 6, and 15 months of age. The most recent study is M5A10 (N= 2167),which is the immunogenicity comparison with licensed vaccines. The control vaccines are Daptacel, IPOL, and ActHIB. Data are available for the first three doses at 2, 4, 6 months of age.

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As an example of injection site reactogenicity, Dr. Greenberg referred to the data for the full four-dose series. The rates for local swelling were similar or lower at each of the doses after Pentacel® vaccination as compared to those observed with separate administration of control vaccines. This is also true for injection site redness and tenderness. Pentacel® did not cause any increased injection site redness as compared to separate vaccination. Fever is the most important of the solicited systemic reactions. The rate of fever, particularly at the first dose at 2 months of age, was not greater in Pentacel® recipients than in those receiving separate vaccines. There was also no increase in crying, fussiness, decreased appetite, decreased activity, vomiting, and diarrhea. In addition to the solicited reactions, unsolicited adverse events were monitored in all of the trials. In all of the trials, overall rates were similar between Pentacel® and control groups. Most non-serious unsolicited adverse events were common childhood conditions, the majority of which were assessed as non-related to vaccination by the investigators. There were a total of five deaths, all unrelated to vaccination. Thus, the safety profile of Pentacel® is similar to that of separate administration of standard US vaccines (e.g., Daptacel, IPOL, and ActHIB). Pentacel® is safe when administered alone or concomitantly with other age-recommended vaccines.

With respect to immunogenicity, Dr. Greenberg first discussed pertussis. Referring to study P3T06 (Pentacel versus Daptacel, IPOL, ActHIB) and post-dose 3 pertussis GMTs, he pointed out that for PT and FHA, the antibody levels were higher for the Pentacel® group. For FIM they were the same, and for pertactin they were slightly higher than the Daptacel® group. Following the fourth dose given to toddlers, the GMTs were somewhat higher for Pentacel®, for FHA, somewhat higher for the Daptacel® group and pertactin, and fairly similar in the two groups for PT and FIM.

Just as important, if not more so, is the comparison of Pentacel® to the efficacy trial originally performed with the five-component acelluar pertussis vaccine Daptacel® in the NIH-sponsored Sweden 1 Efficacy Trial from 1992-1995. Children in that study received Daptacel® at 2, 4, and 6 months of age and then were followed for two years for surveillance of pertussis. This study established 85% efficacy versus WHO-defined classic pertussis and 78% efficacy versus any pertussis (lab-confirmed, ≥1 day of cough). Pertussis antibody levels in the Sweden I Efficacy Trial were compared to those following four doses of Pentacel® in US pivotal trials P3T06 and 494-01. Sera from P3T06, 494-01, and the Sweden I Efficacy Trial were tested contemporaneously in same laboratory, under same conditions, using the same validated assay. Regarding the bridge to efficacy for P3T06, the response rates or the GMTs for PT, FHA, and FIM were higher than the sera from Sweden 1 and somewhat bit lower for pertactin. With regard to Study 494-01, the comparator is HCPDT, which is the formulation component of Pentacel®. that matches DTaP, Poliovax, and ActHIB. The GMTs were comparable for all of the antigens after the third dose. After the fourth dose, GMTs were comparable for PT, FHA, and FIM and somewhat lower for pertactin. The sera from this study were also re-assayed at the same time as the sera for Sweden 1, with the titers higher for Pentacil® against PT, FHA, and FIM and somewhat lower for pertactin.

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Study M5A10, looking at sera that have been collected from children following three doses, again the titers are higher with Pentacil® for PT and FHA and very comparable for pertactin and FIM. The children from these studies are now 4 to 6 years of age. Prior to the time that they received their 5th dose DTaP vaccine, their sera were drawn to examine antibody titers in these children in order to determine persistence of antibody to 4 to 6 years of age. The persistence of antibody levels in children who received four previous of Pentacil® or four previous doses of Daptacel® is comparable.

With respect to the Hib antibody responses, in Study P3T06 the benchmarks used were 0.15 mcg/mL and 1.0 mcg/mL post-dose three. In Pentacil® compared to Daptacel, IPOL, and ActHIB responses were essentially identical in the two groups. The GMTs were the same after dose three, and the titers were in the 18 to 20 range after dose four—well above the benchmark of 1.0 mcg/mL. Regarding the results for seroprotection in Study 494-01 (comparing Pentacil® to HCPDT) for Poliovax and ActHIB the seroprotection rate was ≥ 0.15 mcg/mL, after the third dose were equivalent, and were lower at ≥ 1.0 µg/mL after the third dose, but the same after the fourth dose. The results for the GMTs show the contrast for the antibody levels in these children, particularly after the third dose when there is a distinct difference.

When sanofi pasteur first reviewed the results for Study 494-01, there were not clear how to interpret them because there is nothing to compare these results to—there are no other studies that have ever given children HCPDT and Poliovax. HCPDT is a component that is not licensed or used in the US or elsewhere. Poliovax® is licensed in the US, but not distributed here. Thus, this is a unique study group that has never before been examined. Given this, they reviewed the results of P3T06. The Pentacil® GMT results for 494-01 are higher than the Pentacil® results from P3T06. The group who received the HCPDT Poliovax® with their ActHIB who seemed to have aberrantly high antibody response. With respect to M5A10 (comparing Pentacel® with Daptacel®, IPOL®, and ActHIB®), the responses of seroprotection rates following the third dose are nearly identical in the two groups as are the GMTs.

Looking across all three studies at the percent achieving anti-PRP seroprotection levels of ≥0.15 µg/mL and ≥1.00 µg/mL one month following the third dose, in studies P3T06 and M5A10, Pentacel® vaccine was compared to licensed, separately administered Daptacel®, IPOL®, and ActHIB® vaccines. In Study 494-01, Pentacel® vaccine was compared to separately administered HCPDT, Poliovax®, and ActHIB® vaccines. In all three studies, Pentacel® vaccine met non-inferiority criteria with respect to achieving anti-PRP levels of ≥0.15 µg/mL. With respect to achieving an anti-PRP level ≥1.00 µg/mL, non-inferiority criteria for Pentacel® vaccine were met in the two studies in which Daptacel® + IPOL® + ActHib® vaccines were used as the controls, but in the study comparing Pentacel® vaccine with separately administered HCPDT + Poliovax® + ActHIB® vaccines, non-inferiority criteria were not met. HCPDT, which as noted earlier represents the DTaP component of Pentacel vaccine, is not a licensed vaccine in the United States (Pentacel vaccine [Prescribing Information]. Swiftwater, PA, Sanofi Pasteur, Inc; 2008). Post-dose four and at age 4 to 6 years pre-dose five, Pentacel®

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recipients had titers about the same as ActHIB® recipients and GMTs were at least as high, if not higher, as those given ActHIB® in a previous study.

The Pentacel® immunogenicity conclusions are that Pentacel® efficacy against pertussis can be concluded based on the serological bridge to the Sweden I Efficacy Trial; Pentacel® produced Hib GMTs and seroprotection rates that were comparable to separately administered standard US vaccines; and immune responses were similar when Pentacel® was administered alone or concomitantly with other vaccines. With respect to the schedule and where Pentacel® fits in, with DTaP, IPV, and Hib being given at generally the same ages and visits. This has a number of benefits for patients, physicians, and public health.

Vaccine ▼ / Age ▶	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months
Hepatitis B[1]	HepB	HepB		*see footnote 1*	HepB			
Rotavirus[2]			Rota	Rota	Rota			
Diphtheria, Tetanus, Pertussis[3]			DTaP	DTaP	DTaP		DTaP	
Haemophilus influenzae type b[4]			Hib	Hib	*Hib*[4]	Hib		Hib
Inactivated Poliovirus			IPV	IPV	IPV			
Pneumococcal[5]			PCV	PCV	PCV	PCV		
Influenza[6]					Influenza (Yearly)			
Measles,Mumps, Rubella[7]						MMR		
Varicella[8]						Varicella		
Hepatitis A[9]						HepA (2 doses)		

Pentacel® Safety, Immunogenicity, Indications, and Use

M. Patricia Joyce MD
MVPD Branch, NCIRD
ACIP Combined Vaccine Work Group

Dr. Joyce reported that Pentacel®, a combination vaccine of DTaP, IPV, and Hib, produced by sanofi-pasteur, was approved by the FDA on June 20 2008, for active immunization against diphtheria, tetanus, pertussis, poliomyelitis and *Haemophilus influenzae* type b disease. The proposed Notice to Readers will refer to the vaccine by its full name, DTaP-IPV/Hib. The ACIP Combined Vaccine Workgroup reviewed the safety, immunogenicity, indications, and use of Pentacel®, for which Dr. Joyce summarized the highlights. Pentacel® vaccine has the same pertussis antigens as sanofi-pasteur Daptacel®, but has increased amounts of pertussis toxin and FHA antigens. The polio virus components are equivalent to IPOL® inactivated polio

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vaccine. The Hib component is equivalent to ActHIB®, a PRP-conjugated to tetanus toxoid. Notably, Pentacel® contains no thimerosal. Pentacel® is approved for use in infants and children for four doses (at ages 2, 4, 6, and 15-18 months).

With respect to the safety and immunogenicity issues considered by the working group, the solicited local and systems adverse events and serious adverse events were similar for Pentacel® as those observed following separately administered vaccines in the control group. Tenderness, swelling, and redness were the most common solicited adverse events. Approximately one third of subjects in Pentacel® and control groups reported increased circumferential limb swelling, although swelling greater than 20mm was rare. Fever of 38.5C degrees or higher occurred in 1.3% to 5.1% of study subjects.

With respect to the *Haemophilus influenzae* Type B disease, given that the immunogenicity data from three trials were inconsistent, the working group discussed them in great detail. An antibody level of $\geq$ 0.15 ug/ml is accepted as a marker of short-term protection following vaccination against Hib. A level of $\geq$ 1.0 ug/ml is accepted as a marker of long-term protection. With regard to seroprotection rates after dose 3 and dose 4 in Study P3T06, this study demonstrated non-inferiority after post-dose 3 and after post-dose 4 of Pentacel® as measured by levels of $\geq$ 0.15 and $\geq$ 1.0 ug/ml, as well as by geometric mean concentration titer or GMT ratio (From FDA, VRBPAC January 2007). Regarding Hib seroprotection rates post-dose 3 for P3T06, as well as for studies M5A10 and 494-01, Hib seroprotection was shown for the $\geq$ 0.15 and $\geq$ 1.0 ug/ml markers. The results for studies P3T06 and M5A10 also met non-inferiority criteria. This is in contrast to study 494-01. In study 494-01, markers of Hib immunogenicity did not meet criteria for non-inferiority for GMT post-dose 3, and did not meet the criteria at the $\geq$ 1.0 ug/ml antibody level after dose 4. Non-inferiority criteria at $\geq$ 0.15 ug/ml post-dose 3 and 1.0 ug/ml post-dose 4 were achieved.

With respect to indications and uses, Pentacel® is approved for use in children 6 weeks through 4 years of age (prior to fifth birthday), and is indicated in the childhood vaccination schedule at ages 2, 4, 6, and 15 to 18 months. Consistent with recommendations for other DTaP-containing vaccines, the working group believed the minimum interval between Dose 1 and 2 of Pentacel could be four weeks. Dose 3 should not be given before age 14 weeks. The working group also felt that dose 4 could be given as early as 12 months if the clinician believed an opportunity to vaccinate might be missed, and if 6 months had elapsed since Dose 3. DTaP-IPV/Hib can be administered at separate injection sites with other vaccines scheduled for age 12-18 months.

For prevention of poliomyelitis, four doses of IPV are recommended at ages 2, 4, 6-18 months and 4-6 years. Members of the working group felt that Pentacel® may be used for poliovirus vaccination in children who have received 1 or more doses of another IPV-containing vaccine. Doses of Pentacel® given at 2, 4, 6, and 15-18 months would provide 4 valid doses of IPV when an accelerated schedule is needed, such as recommended for use in pediatric travelers. However, working group members wanted to be clear they were not proposing an accelerated schedule for routine use. Any child

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who receives IPV vaccination on the accelerated schedule using Pentacel® may require an additional dose of vaccine at school entry.

With regard to DTaP interchangeability, in the 1999 Combined Vaccine Statement, the ACIP previously recommended that, whenever feasible, the same manufacturer's DTaP product should be used for the primary series, but that vaccination should not be deferred if the specific DTaP vaccine brand previously administered was unavailable or unknown. However, there were no data for Pentacel® upon which to base recommendations concerning interchangeability with other vaccine products in the infant and child schedule.

Consistent with prior recommendations for Hib vaccination, certain populations, such as American Indian / Alaskan Native children (AI / AN), are at increased risk for Hib disease, particularly in the first 6 months of life. Compared with other Hib-conjugate vaccines, PRP-OMP-containing Hib vaccine preparations lead to more rapid seroconversion and protective antibody concentrations within the first 6 months of life. Failure to use PRP-OMP vaccine for the first dose of the series, has been associated with excess cases in populations with high risk of Hib disease. For this reason, the Working Group felt it may be prudent for clinics that serve predominantly AI / AN children to use only PRP-OMP-containing Hib vaccines.

The Working Group prepared a Notice to Readers, "FDA Licensure of Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine (Pentacel®) in Infants and Children," a draft of which was provided to ACIP members in their meeting materials.

Discussion

Dr. Pickering reminded the group that because the individual components were already approved, the ACIP did not need to vote on the combined vaccine itself, only for the VFC.

Dr. Duchin, NACCHO, requested clarification on the statement about IPV and school entry. If child received Pentacel® at 2, 4, 6, and 15 to 18 months, it was not clear whether they required another dose prior to school entry.

Dr. Joyce responded that the FDA did approve this as the four-dose primary series. The problem becomes how this fits in with state laws, particularly for the pre-school dose.

Ms. Jane Seward added that about a quarter to a third of states still require a dose of polio vaccine to be delivered at 4 to 6 years. Thus, a child in those states would not be compliant and would need an additional dose delivered between 4 to 6 years of age.

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Stanley Plotkin indicated that there is table in the IPV chapter of the vaccines book concerning studies of persistence of antibodies after four doses in the first 18 months of life, which does suggest good persistence.

Confirming that she had no conflicts, Dr. Baker pointed at the wording pertaining to the AN / AI population, "it may be prudent for clinics that serve predominantly AI / AN children to use only PRP-OMP-containing Hib vaccines," seemed fairly weak. She asked for clarity if this was the actual wording to be included in the *MMWR*. It should be more definite that OMP is the preferred vaccine in that group.

Dr. Joyce responded that the wording was taken almost verbatim from the current Red Book.

Dr. Hosbach, sanofi pasteur, added that they would be providing the working group with additional historical data, as well as data on persistence of polio antibody out to five years post four doses of Pentacel®.

KINRIX™

Leonard Friedland, MD
Executive Director
Head, Clinical and Medical Affairs, Vaccines, NA
GlaxoSmithKline Biologicals

Dr. Friedland expressed his gratitude for the opportunity to review data on the immunogenicity and safety of GlaxoSmithKline's (GSKs) DTaP-IPV combination vaccine, KINRIX™. This combination vaccine received its first global licensure in 1996 in France, and is currently licensed in 32 countries worldwide, including the United States as of June 24, 2008.

KINRIX™ is intended for use as a fifth dose of DTaP vaccine and fourth dose of IPV vaccine in children 4-6 years of age. Current recommendations are for up to five vaccinations to be given to children in this age group. DTaP and IPV account for two of these. Combination vaccines, by reducing the number of injections needed to provide multiple immunizations, have been associated with improvements in vaccine coverage and vaccine timeliness. By combining DTaP and IPV vaccines into a single injectable, it reduces by one the number of injections required to provide the recommended immunizations to this age group. GSK expects this to have a beneficial effect on overall coverage and vaccine timeliness in this age group. Dr. Friedland noted that the antigen composition of KINRIX™ was included in the handout provided to participants. The DTaP antigen components are identical to those of GSK's Infanrix and Pediarix vaccines, in the same quantities, and the IPV components are identical to those of Pediarix in the same quantities.

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With respect to the studies providing data in support of KINRIX™ licensure, the bulk of the data comes from the pivotal Phase III Study 213503/048 conducted in the US in 2005-2006. This study included over 4000 children, over 3000 of whom received KINRIX™ as study vaccine. Primary objectives included assessments of safety and immunogenicity and manufacturing lot consistency. In addition, immunogenicity and safety were examined in a Phase II study, 213503/047, also conducted in the US in 2003-2004. This study, a supportive study of 200 children vaccinated with KINRIX™, also provided information on immunogenicity of co-administered MMR vaccine. Additional safety information comes from a small Phase II study conducted in Australia, Study 213503/046, includes 181 children vaccinated with KINRIX™. Dr. Friedland presented the immunogenicity and safety data from Phase III Study 213503/048, noting that in the interest of time, specifics of the study design for pivotal study 213503/048, and the primary and secondary immunogenicity and safety objectives in the KINRIX™ studies, were included in the handouts provided.

With regard to serum antibody concentrations for anti-D and anti-T antibodies and percentages of subjects with seroprotective antibody concentrations >=0.1 (represents seroprotection for D and T) and >=1.0, Dr. Friedland reported that following vaccination with either KINRIX™ or separately administered Infanrix and IPOL, GMCs increase many fold and proportions of subjects with antibody values exceeding these cutoffs approaches 100%. With regard to serum antibody concentrations for antibodies to the acellular pertussis antigens (PT, FHA, and PRN), serum GMCs also increase many fold following vaccination. Regarding percentage of subjects with post-vaccination booster responses, Diphtheria and Tetanus in Study 048, the primary immunogenicity comparisons for the diphtheria, tetanus, and pertussis components of the vaccine were based on booster responses. Both the diphtheria and tetanus groups showed a high booster response rate for both antigens. Regarding the booster responses to the acellular pertussis antigens, both treatment groups showed high booster response rates for all pertussis antigens. In noninferiority comparisons for DTaP booster responses, the between-group difference in percentage of subjects with booster response was determined for each vaccine component (slide 8; shown by the center point in each range, along with the 95% confidence intervals; limits of which are shown by the ends of the ranges). Noninferiority was defined as the upper limit of the 95% CI for the treatment difference being <=10%. The criterion was met for all DTaP antigens.

Regarding the percentages of subjects with seroprotective levels (titers 1:8 or greater) of antipolivirus types 1, 2 and 3 antibodies before and after vaccination, most subjects had seroprotective levels of one or more antibodies prior to vaccination. Following vaccination virtually all subjects were seroprotected for all 3 poliovirus types, except for a single subject in the KINRIX™ group not seroprotected for type one poliovirus. In terms of the pre-and post-vaccination titers for anti-poliovirus antibodies, antibody titers are similar prior to vaccination and are increased multi-fold after vaccination.

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In the noninferiority comparison for poliovirus GMTs, with respect to the between group GMT ratios with 95% confidence intervals for all three poliovirus antigens, the upper limit of the 95%CI for each ratio was less than the pre defined limit of 1.5. Thus, GSK was able to conclude that KINRIX™ is non-inferior to IPOL with regard to anti-poliovirus post-vaccination GMTs (Study 048).

In terms of solicited local events (e.g., pain, redness, swelling, and increased arm circumference) occurring at the DTaP based injection site within four days of vaccination, injection site pain was the most commonly reported local event, reported by 57% of subjects in the KINRIX™ group and 53% in the Infanrix + IPOL group. The difference was found to be statistically significant. Grade 3 pain was reported by 1.6% of KINRIX™ recipients and 0.6% of Infanrix plus IPOL recipients—also a statistically significant difference. No difference was observed between groups in reporting of pain resulting in a medical contact visit. For all other solicited local events, no clinically significant differences between groups were observed.

With regard to percentages of subjects reporting solicited general symptoms (e.g., drowsiness, fever, loss of appetite) within four days of vaccination, no statistically or clinically relevant differences in the incidence of drowsiness or loss of appetite, of any or Grade 3 intensity, were observed between the groups. GSK did observe a statistically significant difference in the incidence of fever with temperature greater than 38C, with a greater percentage of KINRIX™ recipients than Infanrix + IPOL recipients reporting temperatures in this range. No differences between groups were observed for the overall incidence of fever or of fever >39C, >39C. >39.5C, and >40C, nor were differences observed in the percentage of subjects seeking medical attention for fever or any other solicited general symptoms. GSK therefore considered the difference in fever >38C not to be clinically significant. Unsolicited adverse events and SAEs were reported by comparable proportions of subjects in both groups. No fatalities were reported during the study, and no clinically relevant differences between groups in reporting of unsolicited adverse events were noted.

In conclusion, GSK's data show that immune responses and reactogenicity were comparable between Kinrix vaccine and Infanrix coadministered with IPOL. No differential effect on immunogenicity of coadministered MMR vaccine was noted between Kinrix and coadministered Infanrix and IPOL vaccines. Kinrix is expected to provide protection comparable to Infanrix and IPOL, with one fewer injection required.

Discussion

Noting that it appeared that one shot was more painful than two shots, Dr. Schuchat inquired as to whether Dr. Friedland had a theory about this.

Dr. Friedland responded that for local reactions at any site, rates are very comparable between subjects. GSK's hypothesis is that there are additional antigens in the DTaP-

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IPV injection at that site, but there are injection reactions reported at the IPOL site as well.

Sam Katz asked how many more years the United States planned to immunize against polio. The question of polio eradication and the World Health Organization (WHO) program hangs on persistence of disease in areas such as Nigeria, yet eventually everyone will have to have an inactivated vaccine and oral vaccines will have to be eliminated. With that in mind, he wondered what the potential would be for the manufactures to develop an inactivated vaccine that would be affordable for the resource-poor world, which would enable them to stop the use of oral vaccines and eliminate circulating vaccine-derived polio viruses, and provide immunity through a DPT combination with IPV. The Expanded Program on Immunization of the WHO gives DPT to children; however, each time the question of combing it with IPV is raised, the WHO says that it is too costly.

Dr. Friedland responded that it is desirable for vaccine manufacturers to create opportunities for vaccines to be available to everyone who needs them on the planet. GSK and other manufacturers continue to work with the WHO and other groups to make that a reality.

Dr. Pickering suggested that ACIP request a presentation from the global group for an update on polio eradication progress internationally.

Dr. Englund requested that Dr. Friedland further discuss the fever profile.

Dr. Friedland replied that for the fever cutoff of >38.5C, 2.8 of the subjects in the KINRIX™ group reported that level of fever, 2.6% in the separate group. At >39C it was 1.1% in both groups. At >39.5C it was 0.4% in the KINRIX™ group, 0.5% in the separate group. At >40%, it was comparable in both groups. For medically attended fever (e.g., fever that required the parent to contact their health care provider), it was 1.2% in the KINRIX™ group and 1.1% in the separate group. Thus, it seemed to be related to just low-grade fever.

An inquiry was posed regarding the cost of the two single vaccines versus the cost of the combination vaccine.

Jane Quinn, GSK Marketing Team, responded that the price for KINRIX™ is additive of the two components. At list prices or wholesale acquisition prices are the two reference points for the top line list price. For DTaP these range from $21 to $22 and for polio $24 to $26. GSK is targeting a price of $45 at list.

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KINRIX™ Safety, Immunogenicity, Indications, and Use

Angela Calugar, MD, MPH
Centers For Disease Control and Prevention
Coordinating Center for Infectious Diseases
National Center for Immunization and Respiratory Diseases
Immunization Services Division

Dr. Calugar stated that the Safety Combined Vaccine Workgroup reviewed the safety and immunogenicity of Kinrix® vaccine and its components. On the basis of this data, expert opinion of the workgroup members, and the feedback from Kinrix® partner organizations, including the American Academy of Pediatrics and the American Academy of Family Physicians, the workgroup formulated a summary of indications for use of the DTaP-IP vaccine. This information was presented to ACIP for discussion purposes only, and a vote was not requested.

Recalling Dr. Friedland's presentation earlier, which detailed the trial data on Kinrix®, Dr. Calugar pointed out that the goal of her presentation was to emphasize the major topics to be included in the *Morbidity and Mortality Weekly Report* (*MMWR*) Notice to Readers. She also provided a brief overview of the Kinrix® vaccine composition, its safety and immunogenicity data, and indications and uses of the vaccine.

Kinrix® is a combined Diphtheria and Tetanus toxoid and acellular Pertussis inactivated poliovirus vaccine. The individual antigens contained in the combined DTaP-IPV are identical to the antigens contained in GSK Infanrix® and Pediarix, approved previously by the FDA. It is presented as a single injectable vaccine. DTaP antigens are identical to the antigens contained in GSK Infanrix®. In addition to DTaP, Kinrix® contains IPV antigen, which is identical to IPV in Pediarix®, and all components are GSK licensed.

Clinical trials conducted in the US on children aged 4-6 years showed that combined DTaP-IPV and separately administered component DTaP and IPV vaccines have comparable safety and reactogenicity profiles. Injection site pain was the most common adverse event in both groups. There was a reportedly small statistically significant difference for Any or Grade 3 pain in DTaP-IPV combined vaccine recipients. In addition, there were reports of large swelling, with severe Grade 3 functional impairment. There were seven cases among 3,156 DTaP-IPV recipients, and one case among DTaP and IPV recipients. There were no reports associated with other serious adverse events or deaths. The immunologic responses following Kinrix® were similar to those following separately administered component vaccines. When co-administered with measles, mumps, and rubella (MMR) vaccine, DTaP-IPV had no effect on immunogenicity.

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Mix and match issues have been discussed, especially in relation to DTaP. "The ACIP has recommended that, whenever feasible, the same manufacturer's DTaP product should be used for the primary series but that vaccination should not be deferred if the specific DTaP vaccine brand previously administered is unavailable or unknown" [*Childhood Vaccines for Childhood Immunization MMWR, Vol. 48, No. RR-5, May 14, 1999].*

Regarding indications and uses, DTaP-IPV is administered as an intramuscular injection into the deltoid region. It is indicated for use as the fifth dose of DTaP, the fourth dose booster of IPV, in children aged 4-6 years who receive DTaP and/or DTaP-HepB-IPV as the first three doses, and DTaP as the fourth dose.

Based on the information presented, the Combination Vaccine Workgroup proposed a Notice to Readers, soon to be published in the *MMWR* (e.g., Notice to Readers: FDA Licensure of Diphtheria and Tetanus Toxoids and Acellular Pertussis and Inactivated Poliovirus Vaccine (Kinrix®) for use as a Booster Dose in Children Aged 4 to 6 years). The ACIP committee members were provided with the draft of the Notice to Readers in their binders.

Discussion

Dr. Chilton noted that the recommendation that is to be published in the *MMWR* indicates that this is to be used as the fifth dose for children who start late and require only three doses prior to that. He wondered if those children should also be mentioned in the statement.

Dr. Calugar responded that they would work with the Immunization Schedule Workgroup to determine how to better formulate this statement.

Dr. Judson asked, in reference to the microgram weight of the adjuvants, whether everything was simply additive when combined versus separate.

Dr. Calugar replied that to her understanding it was. Dr. Friedland added that there was no additional adjuvant in this vaccine compared to those in the separate vaccines.

Dr. Englund expressed concern in that, in some offices, DTaP and IPV are given more often during infancy, even if given as three doses. However, Dr. Calugar said the IPV is a fourth dose. Dr. Englund thought it might be used in many circumstances as a fifth dose as well and thought it should be approved for that use. For example, a child may have had an extra IPV dose because, as is often the case with combination vaccines, offices might not stock separate DTaP and may have only DTaP-IPV.

Dr. Wallace responded that these types of issues regarding children who are behind or who are receiving extra doses with combination vaccines are covered in the General Recommendations. However, they can be referenced in the Notice to Readers as well.

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These issues are caveats, which is the reason for the General Recommendations—to deal with minimal intervals, late doses, extra doses, et cetera when using the combination. This is similar to the Pediarix® situation where one receives a birth dose of Hepatitis B.

With respect to the new combination vaccine and Pentacel®, Dr. Sawyer pointed out that this was adding to the number of combination vaccines in use and the challenge for documentation and confusion in offices about which one is pulled out of the refrigerator. He did not notice whether there was any specific language in the statement to advise or remind people to be careful about documentation of this vaccine compared to others. He also thought there should be on-going efforts to look for problems related to confusion, suggesting the possible use of registries as a way to monitor whether people are receiving extra doses of antigens potentially because of confusion in using the various combination vaccines.

Dr. Calugar stated that many conversations had taken place concerning administrative issues, especially with regard to additional issues for immunization providers. The more combination vaccines that come on the market, the more stipulations there will need to be in Notices to Readers.

Dr. Bocchini, American Academy of Pediatricts (AAP), concurred with the concept of a registry. The new vaccine scheduler now available through CDC might be an additional way for people to ensure that children are receiving the right vaccines and the right components at each time.

Dr. Wallace reminded everyone that a Notice to Readers is simply to announce the availability of a newly licensed vaccine, and that the issues that they were discussing were really the task of the Combination Workgroup going forward, given that there are many issues. The combination statement needs to be revised to address these very issues.

Dr. Friedland said that to assist public health providers with administration of vaccines, GSK is including stickers with their DTaP portfolio and other vaccines, as well including stickers on the pre-filled syringes that can be peeled off. The stickers include the lot number, the name of the vaccine, and a bar code that can be easily placed into the chart, so it is very simply to record and see what was given. Each of their vaccines has a different color and a different box, so it is simpler to not confuse them. GSK understands and is working on the issues continuously.

Dr. Stinchfield noted that the workgroup spent a considerable amount of time on documentation and administration. They understand that with combination vaccines, at the local level providers have many decisions to make (e.g., financial, storage, education of staff, et cetera). They are working in combination with the General Recommendations Workgroup in an effort to offer as much advise as possible to assist local providers.

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VFC Vote for Pentacel® & Kinrix®

Dr. Greg Wallace
(CDC / CCID / NCIRD / ISD)

Dr. Wallace stated that, with the licensure of the two new vaccines, the VFC resolutions must be updated to include them, so that the choice would be available for providers who deliver vaccines to VFC-eligible children. There were three VFC resolutions: One that covered Diphtheria, Tetanus, and Pertussis; one that covered Haemophilus Influenza type B (Hib); and one that covered Polio. He reiterated that there were no new recommendations to protect against any of those diseases. The purpose was merely to include the vaccines in the VFC.

With respect to the vaccines to prevent Diphtheria, Tetanus, and Pertussis, the previous resolution was being updated to add both Pentacel® and Kinrix®, with the addition of Pentacel®, given that it covers Hib (12-15 months) and the fourth dose of DTaP (15-18 months). Dr. Wallace emphasized that in the resolution, and already covered in the General Recommendations, was that the first booster may be administered as early as 12 months of age, provided that 6 months have elapsed since the third dose. This would allow flexibility for those who wanted to administer the Hib dose earlier.

Dr. Wallace pointed out that in the dosage intervals for vaccination for diphtheria, tetanus, and pertussis containing vaccines, Pentacel® was added with the minimum age and minimum intervals, which is driven by the DTaP. Also added were the Kinrix® minimum age and interval for that dose.

Directing attention to the caveat footnotes of the resolution as to dosage intervals, Dr. Wallace pointed out that the following language was added:

- The combined DTaP-Hib-IPV vaccine may be used when any component of the combination is indicated, and if the other components are not contraindicated. The combined DTaP-Hib-IPV vaccine is approved for the primary series and first booster dose (Doses 1-4). The combined DTaP-Hib-IPV vaccine is not indicated for children 5 years of age and older.

- The combined DTaP-IPV vaccine may be used when any component of the combination is indicated, and if the other components are not contraindicated. The combined DTaP-IPV vaccine is approved for the booster dose at age 4-6 years.

Similarly for Hib, Pentacel® was added. Dr. Wallace noted that there was an error in the age indication in that it should be “to five years” not “through five years.” Otherwise, there was no new information. It was simply reformatted to make it easier to understand. This included the basic schedule, age indications, and the addition of Pentacel®. This was vetted through the Bacterial and Viral Division to ensure its accuracy. With respect to catch-up information in terms of how to proceed when people begin late, information is included from an older version of the Red Book, given that some people find this format easier to understand and implement than using a catch-up schedule, particularly for Hib. The Hib and Pneumococcal catch-up issue can be

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confusing, depending on what age someone it. Thus, this is a slightly different format that some providers prefer.

Given that the polio resolution was a few years old, in addition to adding Pentacel® and Kinrix®, Dr. Wallace removed all of the references to oral polio vaccines, since there is not a licensed OPV in the US being distributed at this time, nor is there a routine recommendation. In the eligible groups, age caveats were added for the indications for Pentacel® and Kinrix®. The schedule was also reformatted in order to make it easier to read. The following caveats were added to the dosing schedule:

- For children who receive an all-IPV series, a fourth dose is not necessary if the third dose was administered at age 4 years or older.
- The combined DTaP-HepB-IPV vaccine may be used when any component of the combination is indicated, and if the other components are not contraindicated. The combined DTaP-HepB-IPV vaccine is approved for the primary series only (Doses 1-3). For adequate immune response, the last dose of hepatitis B vaccine should be given at ≥24 weeks of age and therefore this combination vaccine should not be administered as a complete primary series on an accelerated schedule at 4 week intervals for prevention of pertussis. The combined DTaP-HepB-IPV vaccine is not indicated for children >6 years of age.
- The combined DTaP-Hib-IPV vaccine may be used when any component of the combination is indicated, and if the other components are not contraindicated. The combined DTaP-Hib-IPV vaccine is approved for the primary series and first booster dose (Doses 1-4). The combined DTaP-Hib-IPV vaccine is not indicated for children 5 years of age and older.
- The combined DTaP-IPV vaccine may be used when any component of the combination is indicated, and if the other components are not contraindicated. The combined DTaP-IPV vaccine is approved for the booster dose at age 4-6 years.

Motion

Dr. Chilton made a motion that ACIP vote on the VFC as presented by Dr. Wallace. Dr. Neuzil seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions.

Measles, Mumps, Rubella, and Varicella (MMVR) Vaccine

MMRV Vaccine Safety Workgroup Update

Jonathan Temte, MD, PhD
University of Wisconsin
Chair, ACIP MMRV Vaccine Safety Working Group

Dr. Temte reported on the new MMRV Vaccine Safety Working Group. He reminded everyone that during the February 2008 ACIP Meeting, preliminary data were

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presented from two independent studies (Vaccine Safety Datalink and Merck) suggesting increased risk for febrile seizures in the first to second week after use of the combined measles, mumps, rubella, and varicella (MMRV) vaccine among children aged 12-23 months. In response to this safety concern, ACIP recommended removing the preference for MMRV vaccine over separate administration of MMR and varicella vaccines, and forming an ACIP MMRV Vaccine Safety Working Group. The recommendations were published in CDC's *Morbidity and Mortality Weekly Report* (*MMWR*) in March 2008.

Since that time, the working group was assembled, and subsequently developed terms of reference. The first objective of the working group is risk assessment, with the CDC's Immunization Safety Office serving as the lead. The working group's goals with regard to risk assessment are to evaluate post-licensure safety data on risk of febrile seizures after MMRV vaccine, identify data gaps, and propose additional analyses or studies; review encephalitis cases after MMRV vaccine; and communicate vaccine safety findings related to MMRV vaccine with ACIP and the public in a clear and transparent manner. The group's second objective pertains to risk management and policy, which will be under the lead of CDC's National Center for Immunization and Respiratory Diseases. The working group's goal pertaining to risk management are to formulate policy options for use of MMRV vaccine for ACIP, considering the benefit of vaccination and the risks of vaccine adverse events; and identify and reconcile potential inconsistencies in ACIP statements related to measles, mumps, rubella, varicella vaccination and febrile seizure prevention.

MMRV Vaccine Safety Working Group members have expertise in vaccine safety; epidemiology and vaccines for measles, mumps, rubella and varicella; statistics and pharmacoepidemiology; pediatric neurology; pediatric infectious diseases; primary care; vaccinology; and vaccine policy. Membership is made up of ACIP members and CDC and FDA representatives. Working group consultants include representatives from RTI International; Children's Hospital of Philadelphia; Kaiser Permanente Northern California; Maine State Health Department; Council of State and Territorial Epidemiologists; Columbia University; Duke University; University of Alabama at Birmingham; American Academy of Pediatrics; Kaiser Permanente Northern California; Harvard Medical School; Tufts University School of Medicine; and Brown University. Merck's scientists will be invited to present their final data from their Phase IV Post-Licensure Studies and will participate in working group calls discussing the safety data; however, they will not participate in the policy decision calls.

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The MMRV Vaccine Safety Working Group's proposed timeline is as follows:

Date	Topic
June 2008	Working Group (WG) - Introductory calls
June 25, 2008*	ACIP Meeting - Update
June – Oct 2008	WG – Presentation and discussion on Vaccine Safety Datalink and Merck postlicensure MMRV safety studies
Oct 22 – 23 2008*	ACIP Meeting - Update on vaccine safety studies
Nov 2008 – Feb 2009	WG - Presentation and discussion on policy options for MMRV use
Feb 25 – 26, 2009*	ACIP Meeting - MMRV policy option discussion
Spring 2009	WG - Additional calls as needed

Dr. Temte reminded everyone that it was important to keep in mind that the MMRV vaccine supply had been limited since 2007, having to do with manufacturing problems unrelated to safety or efficacy. The final data from Merck will be available in late August 2008 for review. The working group plans to have some basic responses ready on the safety data by the October 2008 meeting, and to bring policy recommendations to ACIP by February 2008. Hence, the timetable is very rapid.

Discussion

Amy Middleman, Baylor College of Medicine, inquired as to whether the working group planned to discuss any preference as it related to those over the age of 5 who are outside the age group for febrile seizures. Given that MMRV vaccine is licensed up to the 13th birthday and adolescents typically do not like shots, she wondered if he could comment about the use of the combination vaccine in that age group as well.

Dr. Temte responded that these issues were probably within their realm. However, data presented to the ACIP were for the first dose and the priorities were aimed at the first dose of MMRV vaccine. The data had not been very robust for adverse effects after the second dose.

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Rotavirus Vaccines

Rotavirus Vaccines Workgroup Update

Lance Chilton, MD, FAAP
Chair, Rotavirus Work Group

Dr. Chilton reported that during its meetings from July 2007-June 19, 2008, the Rotavirus Vaccines Workgroup had evaluated available data from independent studies, proprietary studies, and economic analyses. Where there were no data, expert opinion was gathered from committee members; the FDA action in licensing the vaccine; European Society for Paediatric Infectious Diseases / European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; the World Health Organization; and from Australian recommendations. Some of the principles under which the Rotavirus Vaccines Workgroup has operated over the past year include safety first, efficacy quickly after that, especially given the experience with Rotashield® in the past. To this end, the workgroup evaluates safety data, especially regarding intussusception. In addition, it is important to be able to get the rotavirus vaccine to as many infants as possible, consistent with safety, to prevent as much rotavirus disease as possible. Vaccine economics for practitioners are considered. The workgroup plans to continue with post-marketing evaluation of safety and efficacy data as they come out.

The workgroup has also made every effort to write clear, unambiguous recommendations whenever possible. Recommendations should stand on their own, without references to background being necessary. The reason for that is because many people who read the recommendations do not read all of the statement; therefore, the information should be encapsulated with the recommendations. The workgroup also attempts to make recommendations as user-friendly as possible. If at all possible, the workgroup prefers to make the age recommendations for dosing the vaccine the same for both vaccines. Issues that are especially carefully considered by this workgroup are whether recommendations should be made for preference for one vaccine over another in certain circumstances; age maximums for first dose and last dose; mixed series (RotaTeq® + Rotarix®); and special populations (e.g., premature infants, blood product recipients, immunocompromised infants, infants with immunocompromised household members, and infants with GI tract disease).

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Update on Safety Monitoring of RotaTeq®

Ms. Penina Haber
Immunization Safety Office
Office of the Chief Science Officer (ISO)

Ms. Haber reminded everyone that Rotashield® rotavirus vaccine was withdrawn from US market in 1999 after post-licensure monitoring identified increased risk for intussusception (IS). There was a 29-fold increase 3-14 days following the first dose (Murphy et al. NEJM. 2001). RotaTeq® rotavirus vaccine was licensed in 2006. No increased risk for IS was observed in clinical trials for RotaTeq® (Vesikari et al. NEJM 2006).

The Vaccine Adverse Event Reporting System (VAERS) is a national passive surveillance system, which identifies potential vaccine safety concerns. Its limitations include underreporting or reporting bias and lack of denominator data. With respect to the VAERS analysis for RotaTeq®, reports have been received from February 1, 2006 through March 31, 2008. Reports of intussusception (IS) are verified by chart review, using Brighton Collaboration criteria. The Vaccine Safety Datalink (VSD) Project is used to calculate expected rates for IS. Sensitivity analyses are also conducted (Haber et al. Pediatrics. 2008*).* Regarding the results from this timeframe, 14,274,551 doses RotaTeq® vaccine were distributed in the US (Merck, personal communication, February 1, 2006 – March 31, 2008) . There were 2,600 RotaTeq® VAERS reports, of which 683 (26%) were serious, and 44% of reports involved the first dose. The most frequently reported adverse events included diarrhea and vomiting (Merck, personal communication; February 1, 2006-March 31, 2008). IS was confirmed for 267 reports through 3/31/08, of which 91 reports were within 1-21 days following vaccine, and 48 (53%) of the 91 were within 1-7 days. One confirmed IS death was reported following the second dose, 18 days post-vaccination; this child who was four months old and had received other vaccines simultaneously.

Among the VAERS intussusception reports, the day of onset of intussusception after vaccination are almost evenly distributed over eight weeks. There is a small increase in days 5 and 6 after vaccination and also at 33-35 days after vaccination. With respect to intussusception cases by onset interval in days, it is important to note that more cases after dose 1 have been reported during week 1 compared to weeks 2 and 3. In contrast, reports after dose 2 and 3 were more stable across the weeks. Several possible explanations exist for this apparent clustering of IS reports during the first week after dose 1. First, this is a well known aspect of passive surveillance of adverse events that reporting tends to be better closer to the suspected exposure. Dose 1 is given to infants 6-12 weeks of age, when intussusception events are extremely rare, which might prompt better reporting. Because of Rotashield®, a heightened awareness of IS might also exist for the first dose. Another possibility is that this clustering could represent a 2 or 3-fold risk during week one. However, more cases were also reported during the fifth and sixth weeks, suggesting that the cases in week 1 could be a reporting artifact.

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Above all, it is important to keep in mind that overall, the number of reports in any given week are small and caution should be taken not to over-interpret them.

With respect to observed versus expected calculations, age-stratified analysis is important because the baseline intussusception rate varies 10-fold during the first six months of life. The three doses of RotaTeq vaccine are administered during this time period. The data assumptions include reporting completeness to VAERS and number of vaccine doses administered.

In terms of observed versus expected cases after RotaTeq® 1 to 21 days (any dose), using three scenarios of percentage reporting and percentage of doses given, at 100% reporting and 100% doses given, the number of VAERS cases is 92 versus the expected 242 cases with a reporting rate ratio of 0.37 (95% confidence interval (CI) 0.27-0.50), which is not significant. Due to publicity and maturity of the program, reporting is assumed to be at least around 75%. At 75% reporting and 75% doses given, the number of VAERS cases is 123 versus 181 expected cases with a reporting rate ratio of 0.65 (95% CI 0.49-0.88), which is not significant. At 50% reporting and 50% doses, the number of VAERS cases is 184 versus 121 expected, with a reporting ratio of 1.45 (95% CI 1.11 – 1.92) (VSD for background and age of vaccine administration and Merck distribution data; analyses adjusted for age).

With respect to observed versus expected cases after RotaTeq® 1 to 7 (any dose), at 100% reporting and 100% doses given, the number of VAERS cases is 49 versus the expected 81 cases with a reporting rate ratio of 0.58 (95% CI 0.39-0.84), which is not significant. At 75% reporting and 75% doses given, the number of VAERS cases is 66 versus 60 expected cases with a reporting rate ratio of 1.02 (95% CI 0.73-1.44), which is not significant. At 50% reporting and 50% doses, the number of VAERS cases is 98 versus 40 expected, with a reporting ratio of 2.25 (95% CI 1.65 – 3.07) (VSD for background and age of vaccine administration and Merck distribution data; analyses adjusted for age).

Regarding observed versus expected cases after RotaTeq® 1 to 7 (dose 1), at 100% reporting and 100% doses given, the number of VAERS cases is 22 with an expected 22 cases and a reporting rate ratio of 1.03 (95% CI 0.53-1.98), which is not significant. At 75% reporting and 75% doses given, the number of VAERS cases is 29 versus 16 expected cases with a reporting rate ratio of 1.81 (95% CI 0.98-3.34), which is not significant. At 50% reporting and 50% doses, the number of VAERS cases is 44 versus 11 expected, with a reporting ratio of 4.14 (95% CI 2.40- 7.19) (VSD for background and age of vaccine administration and Merck distribution data; analyses adjusted for age) (VSD for background and age of vaccine administration; Merck distribution data adjusted for age).

Regarding intussusception cases by onset interval, with substantially fewer doses administered (< 1 million), many more cases were reported after Rotashield®. While the cases reported after Rotashield® were stimulated by the *MMWR*, it is important to note that most clustered in time during the first week after vaccination. Approximately

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60% of the cases were within week one of Rotashield®. In contrast, only 20% of the cases after RotaTeq® were during week one. While a few more cases occur in the first week relative to week two and three, after RotaTeq®, there is not a similar signal as with RotaShield®. Cases are dispersed throughout the first eight weeks after vaccination (table titled "Proportion of IS reports to VAERS after RotaTeq® and RotaShield® Vaccines" taken from a recent *Pediatrics* manuscript: 2008, Haber et al).

After two years of monitoring, VAERS did not identify a safety concern for intussusception within 21 days after RotaTeq® for any dose. Because of VAERS under-reporting, and use of doses distributed instead of doses administered, VAERS can not rule out increased risk of IS after dose one within 1-7 days of RotaTeq® vaccination compared to week two and three. Safety monitoring is on-going. An evaluation has also been conducted in the VSD Project.

Update on Safety Monitoring of RotaTeq®

Dr. James Baggs
Immunization Safety Office
Office of the Chief Science Officer (ISO)

Dr. Baggs reminded everyone that the Vaccine Safety Datalink (VSD) is a collaboration between CDC and eight managed care organizations across the US (e.g., Group Health Cooperative, Northwest Kaiser Permanente, Northern California Kaiser Permanente, Southern California Kaiser Permanente, HealthPartners, Kaiser Permanente Colorado, Marshfield Clinic, and Harvard Pilgrim). Data from 8.8 million members are captured annually (2.9% of US population). The VSD was established in 1990 to improve the evaluation of vaccine safety through use of active surveillance and epidemiological studies. VSD addressed the limitations of VAERS and responded to the needs identified by two Institute of Medicine reports. VSD tests hypotheses suggested by VAERS reports and pre-licensure trials.

Recently the VSD has developed a method known as rapid cycle analysis (RCA). RCA is an alternative to traditional post-licensure vaccine safety epidemiologic study methods, which generally take years to complete. RCA can identify pre-specified vaccine adverse events in near real-time. It tests specific hypotheses with well-defined outcomes, and compares the number of events in vaccinated persons with the expected number of events. Data are available within weeks of vaccination, and weekly analyses are conducted with adjustment for repeated hypothesis testing. RCA is a method for the VSD to conduct surveillance for adverse events after vaccination on a real-time basis instead of waiting for years to complete the study.

The RCA study objectives for the RotaTeq® vaccine were to monitor for increased risk of intussusception (IS) during a 30 day window after receipt of RotaTeq®; and to monitor for increased risk of other pre-specified adverse events following receipt of RotaTeq®. Seven of the eight VSD sites participated. The exposed population included children who received any dose of RotaTeq®, with or without other vaccines,

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from age 4 through 48 weeks. The historical comparison group included children 4 through 52 weeks of age with a VSD enrollment record from 1991 through 2004. Baseline IS incident rates were calculated by week of age with adjustment for secular trend.

The outcomes of interest in the RCA include intussusception from emergency department, inpatient, and outpatient data sources (ICD-9 codes 543.9, 560.0); meningitis and encephalitis from inpatient data sources (ICD-9 codes 047.8, 047.9, 049.9, 321.2, 322, 323.5, 323.9); seizures from emergency department, inpatient, and outpatient data sources (ICD-9 codes 780.3, 779.0, 333.2, 345); myocarditis from inpatient data sources (ICD-9 codes 429.0, 422); gram negative sepsis from inpatient data sources (ICD-9 codes 038.4, 038.9); and Kawasaki syndrome from emergency department, inpatient, and outpatient data sources (ICD-9 code 446.1). All cases of IS were validated by medical record review. Brighton Collaboration criteria were used to validate IS cases, the guidelines for which are available at the following link: http://www.brightoncollaboration.org/internet/en/index/definition___guidelines.html Level 1 diagnostic certainty (surgical criteria and / or radiologic criteria, and / or autopsy criteria) was required to define cases.

Poisson maxSPRT analyses, a maximized sequential probability ratio test, is the statistical analysis that is conducted weekly to examine the data that have been collected. maxSPRT compares the observed number of events to the expected number from the historical control group. Each week, a log likelihood ratio (LLR) is calculated and is compared to a critical value. An association or “signal” is detected if the LLR exceeds that of the critical value.

Through May 24, 2008, 205,179 doses of RotaTeq® have been given in the VSD. That total includes 77,162 first doses, 67,977 second doses, 50,561 third doses, and 9,389 doses administered outside of recommended age range for dose 1, 2, or 3. For all doses 5 events were observed and 6.65 events were expected, with an RR of 0.75, and LLR of 0.00. The critical value for this comparison was 3.30. For Dose 1, 2 events were observed, while 1.39 were expected, for a RR of 1.44, an LLR of 0.12. The critical value was 2.86. For Dose 2, 2 events were observed while 2.27 were expected. RR=0.73, LLR=0.0. For Dose 3, 1 events was observed, 2.19 events were expected, RR= 0.46, LLR = 0.00. The critical value for both Dose 2 and 3 was 3.05. No signal was detected for any of the doses as a result of the surveillance. Dr. Baggs noted that the LLR is automatically set to 0 if the risk ratio is less than 1.

Of the five cases that were identified, only two of the case were validated upon medical record review. The first was a 28 week old male, with and IS diagnosis 16 days after Dose 3 was administered. The diagnosis was identified through emergency department data. The second was a 17 week old female, with an IS diagnosis 12 days after administration of Dose 2, who was identified through outpatient data. With respect to the other adverse events of interest, for meningitis and encephalitis, 8 events were observed and 12.91 events were expected, with an RR of 0.62. For seizures, 37 events were observed and 55.71 were expected, with an RR of 0.66. For myocarditis, no

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events were observed and 0.41 were expected, with an RR of 0. For gram negative sepsis, 3 cases were observed and 5.57 were expected, with an RR of 0.54. No signals were generated for any of these outcomes. Kawasaki Syndrome (KS) was added during the middle of the RCA analysis. Instead of using a historical comparison group, a concurrent comparison group was used. The concurrent comparison group consisted of children in the same age range who received any licensed vaccine (but not RotaTeq®) during the post-licensure period. Two cases of KS occurred after RotaTeq® vaccination within 30 days. Eight cases were identified in the comparison group. The risk ratio was 0.205 and no signal was generated.

In summary, five cases of IS were found within 30 days after RotaTeq® in the computerized data, which was not more than expected. No cases occurred within seven days of vaccination. Only two cases were validated after medical record review, neither of which occurred following dose 1. The results provide no evidence that RotaTeq® receipt is associated with an increased risk for IS or other pre-specified adverse events.

There were concerns about an increase in IS risk following dose 1 of RotaTeq® for days 1-7 identified from VAERS reports. However, no events in days 1-7 following any dose in the VSD population were identified.. The investigators more closely examined the probability calculations in a 1-7 day window after RotaTeq. These calculations were based on cases occurring within 1-7 days after 77,162 first doses administered, assuming this hypothetical risk were the true risk. When assuming a risk of 1 / 10,000 first doses, or an RR of 29, they would have expected 7.7 cases to date. The probability that the VSD would have observed zero cases, given that hypothetical risk was 0.00045. When assuming a risk of 1 / 50,000 first doses, or an RR of 6, they would have expected to observe 1.5 cases to date. The probability that the VSD would have observed zero cases, given that hypothetical risk was 0.214.

As noted, seven of the eight VSD sites participated in the study. Data have been obtained from the eight site regarding their use of RotaTeq® and the number of cases they observed. The eighth site observed zero cases within the 1-30 day window after all doses of RotaTeq® administration. The data from the clinical trial were also incorporated. The first dose probability calculations were then done for all VSD sites and the clinical trial. Assuming a risk of 1 / 50,000 first doses, or an RR of 6, the probability was 0.074 that the VSD would have observed zero cases with the inclusion of all eight sites. Assuming a risk of 1/50,000 first doses, or an RR of 6, the probability was 0.038 of observing zero cases with the inclusion of all VSD sites and the clinical trial.

The key points for RotaTeq® RCA are that there is virtually no possibility of observing zero cases given a level of risk comparable to that of RotaShield® vaccine, which was withdrawn from the US market in 1999 (~1 case per 10,000 first doses). The investigators were unable to rule out a small probability of observing zero cases given a true risk smaller than 1-2 cases / 50,000 first doses. The variable data suggests that risk of IS after RotaTeq® administration for the 1-7 day window after dose 1 is not great

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than that 1-2 cases per 50,000 doses. The investigators also examined some draft sample size estimates to detect small risks in the VSD for IS occurring in the 1-7 day window after the first dose of RotaTeq®. They estimated that it would take about 10 years in the VSD or 850,000 first doses to detect a RR of 3, and it would take 31 years or about 2.7 million first doses to detect a RR of 2.

The next steps in the VSD are to continue surveillance for intussusception occurring 1-7 days after RotaTeq® vaccination; and to begin the rapid cycle analysis for the Rotarix® vaccine if it is recommended. It would be monitored for the same adverse events as for RotaTeq®, with one additional outcome of hospitalized pneumonia. The VSD will be able to distinguish between the Rotarix® and RotaTeq® vaccinations.

The CDC Immunization Safety Office summary of the RotaTeq® VAERS and VSD post-licensure safety monitoring indicated that with >14 million doses distributed since 2006, VAERS passive surveillance did not identify a specific safety concern for IS during 1-21 days after any dose. An apparent cluster was observed 1-7 days after the first RotaTeq® dose. With >200,000 doses administered, VSD active surveillance did not identify an increased risk for IS or any other pre-specified adverse events during 30 days after vaccination. With >160,000 first doses administered in VSD and the pre-licensure trial, no cases of IS were identified during 1-7 days after vaccination. Available data suggest that the risk for IS after first RotaTeq® dose is not greater than 1-2 cases per 50,000 first doses administered.

Discussion

Dr. Judson wondered if the rate was known for natural infection within the first seven days of natural rotavirus infection. This pertained to attributable fraction of all IS and whether the investigators were actually observing an excess over what would occur from the natural history. When looking at control, it depends whether there is a periodic outbreak or outbreak year with rotavirus epidemiology being recently variable. This relates to what is normal in the presence of rotavirus infection and in the absence of rotavirus vaccine.

Dr. Baggs responded that in the VSD they did not calculate the rate after rotavirus infection specifically. They calculated the rate that occurs overall.

Dr. Cortese responded that the data are not conclusive with respect to whether rotavirus disease is an etiology of natural IS. The predominance of the evidence suggests that it does not induce IS. These background cases are historical rates from throughout several years of data that VSD has of intussusception from any cause. They were adjusted for secular trends because it is true that sometimes year by year there could be substantial variability in the number of cases that are reported in any population. No one is really clear on why that occurs. The rotavirus seasonality question does not directly impact this analysis because there is not clear evidence that rotavirus is an etiology of IS.

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Dr. Iskander added that the comparison group for the background was taken from a period during which there was no use of rotavirus vaccines within the VSD.

Update on 2007-2008 Rotavirus Season

Cathy Panozzo, MPH
Epidemiology Branch
Division of Viral Diseases

Ms. Panozzo reported on the delayed onset and diminished activity of rotavirus in the US from November 2007 to May 2008. Rotavirus seasonality was consistent prior to 2007-2008 season in the US. It typically followed a distinct winter-spring pattern, with a median start date mid-November (week 46), a median peak date in mid-March (week 12), and a median end date in mid-June (week 24). Also of note, vaccine coverage increased from last year. By March 2008, data from eight sentinel sites suggest that a mean of 56.0% of infants aged 3 months received 1 dose and a mean of 33.7% of infants aged 13 months received 3 doses.

The objective of this presentation was to characterize the unusual rotavirus season in the US from November 2007- May 2008. Investigators analyzed rotavirus data from two major sources. The first source, the National Respiratory and Enteric Virus Surveillance System (NREVSS), conducts passive laboratory surveillance and obtains real-time data for several viruses. Laboratories submit weekly reports by virus and test type on the number of specimens tested and the number of positive results. Since 1991, a median of 66 laboratories reported rotavirus to NREVSS annually.

Data from NREVSS for the past 15 years reveal the late onset of 2-4 months and the decrease in the percent positive of rotavirus tests during the peak week in 2007-2008 compared to the previous 15 years of aggregated data. Regarding the number of positive and total rotavirus tests from 32 laboratories continuously reporting to NREVSS from 2000-2008, during this season, the number of tests performed from January 1, 2008 to May 3, 2008 decreased by almost 40% and the number of positive results decreased by approximately 80%.

The second source of data upon which Ms. Panozzo reported was provided by the New Vaccine Surveillance Network (NVSN). NVSN conducts prospective surveillance for acute gastroenteritis (AGE) among children <3 years since 2006. Inpatient, emergency department, and outpatient clinic data are obtained. Fecal specimens are tested for rotavirus by enzyme immunoassay and epidemiologic and clinical data are collected. NVSN sites examined the number and proportion of children having rotavirus positive specimens from January to April from 2006 to 2008. In 2006, 51% of the specimens were positive for rotavirus; in 2007, 54% were positive for rotavirus; and in 2008 just 6% were positive, an approximate decline of almost 90%. Total all-cause AGE cases also declined by approximately 40%.

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Ms. Panozzo pointed out that the findings from this presentation were subject to several limitations. Given that the 2007-2008 season is still on-going, delays in reporting could affect results. Also, rotavirus testing is not usually routine. In addition, the results may not be representative of the entire US population.

In summary, compared to the 15 years of pre-vaccine data, the 2007-2008 rotavirus season was delayed by 2-4 months. The proportion of positive tests was also lower than any of the previous 15 years. Hospitalizations, emergency department visits, and outpatient clinic visits all observed reductions in rotavirus cases from the previous two years. These changes coincide with increasing rotavirus vaccine coverage, and appear to be greater than expected based on direct protective effects of vaccination alone. On-going surveillance and epidemiologic studies are needed.

Discussion

Ms. Stinchfield commented that she is on a listserv of the Childrens Hospitals Infection Control and Practitioners through which everyone was remarking on the dramatic decrease at Childrens Hospital of Minnesota. Two years ago they had 341 cases, last year 323, and this year 75. They monitor this because of nosocomial rotavirus in hospitals, but universally everyone commented on the dramatic decreases.

Dr. Temte reported that Wisconsin has been conducting rotavirus surveillance, with about 300 sites submitting their test results (e.g., emergency departments, hospitals, et cetera). They have made exactly the same observations. He became aware of this meeting with Wisconsin's state laboratory representatives in early April. Now rotavirus is not only delayed, but also the total number of detections is down by approximately 80-90%.

Dr. Paul Offit, Children's Hospital Philadelphia, agreed with the conclusions that given the number of children who have been immunized, the reduction of disease is much greater than what would have been expected. Perhaps it is true, but it is difficult to believe that this would be based on herd immunity, given the contagious and ubiquitous nature of this virus. He inquired as to how that decrease could be accounted for clearly beyond those who are vaccinated other than herd immunity.

Ms. Panozzo responded that they had not yet speculated in-depth on the mechanism. However, they do plan to conduct other studies to determine what the effect of herd immunity may actually be.

Dr. Baker indicated that Texas Children's Hospital in Houston, Texas has partenered with CDC to establish an active surveillance system and is examining vaccine effectiveness using the City of Houston registry. They have also observed a delayed and dampened season. Of children ages 15 days to 2 years, they have enrolled over 400 AGE cases and 90 rotavirus positive cases. Those cases will be sent for typing in order to know whether it is G1 or something different. It will be tied to registry they hope as a quick way to understand efficacy.

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Rotarix® Vaccine: Summary of Efficacy and Safety Data and GSK Post Licensure Monitoring Plans

Leonard Friedland, MD
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GlaxoSmithKline Biologicals
Head, Clinical and Medical Affairs, Vaccines, NA

Rotarix® vaccine is derived from a G1P[8] human rotavirus strain given orally as a 2-dose series. The vaccine is lyophilized and is reconstituted with a liquid diluent which contains CaCO3 as a buffer. Each oral dose is 1 mL and contains at least 10^6 $CCID_{50}$ of live attenuated human rotavirus strain. A second generation ready-to-administer liquid formulation is in development. Rotarix® is licensed in over 100 countries. The BLA for Rotarix® in the US was submitted to FDA last June. GSK has made multiple presentations to the ACIP rotavirus working group, and a detailed presentation was made to the ACIP meeting in October 2008. FDA approval occurred on April 3, 2008. Dr. Friedland thanked the ACIP for inviting GSK to this meeting to provide a brief refresher.

Following the withdrawal of RotaShield®, the World Health Organization called for manufacturers to extend their development programs with new rotavirus vaccines to countries with high medical need, where the risk-benefit would be clear. GSK chose a "South-to-North" approach, with initial Phase III studies and subsequent licensure in the countries of the developing world, including Latin America. It is important to note that prior experience with live, oral vaccines such as oral polio virus, cholera, and RotaShield®, demonstrated variable vaccine efficacy and immunogenicity in developed and developing world countries (generally lower in developing world countries).

Dr. Friedland reviewed data from the two Phase III studies conducted, which were pivotal to the US licensing application and form the basis of the prescribing information efficacy data in the US. The first was Study 023 conducted in Latin America and Finland in which 63,225 infants were enrolled and followed for assessment of safety, among which a cohort of 20,000 infants, all from Latin America, were followed for assessment of efficacy. The second was Study 036 conducted in Europe in which over 4000 infants were enrolled.

Rotarix® was highly efficacious in clinical trials. In the Latin American Phase III study (023), through the first year of life, vaccine efficacy was 85% against severe rotavirus gastroenteritis using both a clinical case definition and the widely used and validated Vesikari scoring system. Efficacy was 85% against rotavirus gastroenteritis hospitalizations, and 40% against all-cause severe gastroenteritis regardless of etiology. Efficacy was sustained at similar high rates through two years of age against all outcomes. In the European Phase III study (036) Rotarix® was also highly efficacious. Through the first rotavirus season after vaccination, efficacy was 87% against any severity of rotavirus gastroenteritis and 96% against severe rotavirus

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gastroenteritis. Rotarix® was 100% effective in preventing rotavirus gastroenteritis hospitalizations, and 92% effective in preventing rotavirus gastroenteritis that required medical attention. Vaccination also has the potential to reduce the overall burden of gastroenteritis disease during early childhood because rotavirus infections are the most common cause of severe gastroenteritis in young children. Reductions in hospitalizations in this study for all-cause gastroenteritis regardless of etiology were 75%. Efficacy was sustained through two rotavirus seasons after vaccinations against all outcomes.

In the European study, vaccine efficacy from the day of dose 1 up until dose 2 was 90% against any severity of rotavirus gastroenteritis and 100% against severe rotavirus gastroenteritis, with wide confidence intervals given the small number of cases. In the Latin American Phase III study, vaccine efficacy against severe rotavirus gastroenteritis was 51% from dose 1 to dose 2 and 61% from dose 1 to 14 days after dose 2, with wide confidence intervals given the small number of cases.

With respect to type-specific vaccine efficacy against severe rotavirus gastroenteritis through two years of age, in the Latin American study statistically significant efficacy was demonstrated for the most common circulating types: Types G1P[8], G3P[8], G4P[8], and G9P[8]. In the European study through two rotavirus seasons after vaccination, there were sufficient numbers of cases of all rotavirus serotypes to assess efficacy for the most common circulating types. Statistically significant efficacy was demonstrated for all circulating types in this study: Types G1P[8], G2P[4], G3P[8], G4P[8], G9P[8].

Rotarix® was investigated in US infants in a Phase III study when co-administered with the US-licensed routine infant vaccinations Pediarix®, Prevnar®, and ActHIB®. The design of this non-inferiority study was a randomized 1:1, controlled, open label study. The first objective was non-inferiority immunogenicity (Rotarix® + coads vs. coads alone). N=484 (1:1). Infants in the co-administration group received Rotarix® concomitantly with Pediarix®, Prevnar®, and ActHIB®, and infants in the separately administered group received Rotarix® one month apart from the routine vaccines. The pre-specified criteria for demonstrating non-inferiority of antibody responses at one month after dose 3 of Pediarix®, Prevnar®, and ActHIB® were met for all 17 coadministered antigens:

- anti-PRP, anti-HBsAg, anti-poliovirus 1, 2 & 3, anti-D and anti-T: LL of 95% CI for the treatment difference in seroprotection rate ≥ -10%
- anti-PT, anti-FHA and anti-PRN: LL of 95% CI for the GMC ratios ≥0.67
- *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F & 23F: LL of 95% CI for the GMC ratios ≥0.5

The results from this study demonstrate that Rotarix® does not negatively impact the immune response to any of these routine vaccine antigens.

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Dr. Friedland then reviewed data from the Latin Study (023), the pivotal study which evaluated intussusception. He also reviewed data from eight clinical studies incorporated in an integrated summary of safety which form the basis of the US prescribing information. Before reviewing the intussusception data from Study 023, Dr. Friedland noted that it was important to mention that the 63,225 infants enrolled in the study were followed for a median of 100 days after dose 1. The primary endpoint for safety was a case of intussusception diagnosed within 31 days of receiving the first or second dose of vaccine. All potential IS cases were reviewed by an independent Clinical Events Committee composed of a pediatric gastroenterologist, surgeon, and radiologist who remained blinded to treatment allocation and categorized cases as definite, probable, or possible using the Brighton Collaboration intussusception criteria.

Regarding the adjudicated definite IS cases, within 31 days of any dose, there were six cases in the Rotarix® group and seven in the placebo group. The relative risk was 0.85 (0.30 ; 2.42) and the risk difference was -0.32 (-2.91 ; 2.18) per 10,000. Within the safety surveillance period, which was a median of 100 days after dose 1, there were 9 IS cases in the Rotarix® group and 16 cases in the placebo group. The relative risk was 0.56 (0.25 ; 1.24) and the risk difference was -2.23 (-5.7 ; 0.94) per 10,000. With respect to the 13 definite intussusception cases within 31 days of any dose by day range in relation to dose, the cases occurred sporadically. There was no clustering of intussusception cases within 7 or 14 days after any vaccine dose. Specifically, there were no intussusception cases reported within 14 days of dose 1 in any group, which was the period of greatest risk of intussusception associated with RotaShield®. The safety results from this study demonstrate that Rotarix® is not associated with an increased risk of intussusception.

An integrated summary of safety of all randomized, placebo-controlled clinical trials submitted in the licensure application was performed. The core ISS includes eight randomized, placebo controlled trials and compares placebo to Rotarix® at licensure potency. The ISS includes data on solicited adverse events, unsolicited adverse events, serious adverse events, and forms the basis of the safety information in the US prescribing information. Relative risk accounting for study effect, with the exact 95% CI, of Rotarix® versus placebo was estimated for each safety endpoint. Statistical imbalances for each safety endpoint were defined as the 95% CI for the relative risk across studies excludes 1.

In the core integrated summary of safety including over 36,000 infants receiving Rotarix® and over 34,000 infants receiving placebo, at least one serious adverse event was reported by similar number of subjects in both groups. The most common serious adverse event s occurring within the 31-day post-vaccination period after any dose reported with a frequency of greater than 0.1% in either group were bronchiolitis, pneumonia, and gastroenteritis. Bronchiolitis and pneumonia were reported at a similar rate in both groups. As would be expected, given the protective effect of Rotarix® against gastroenteritis, gastroenteritis was reported more frequently in the placebo group. Compared to placebo subjects, Rotarix® subjects reported significantly less diarrhea, gastroenteritis, and dehydration, in keeping with the protective effect of

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Rotarix® against gastroenteritis. All other serious adverse events reported within the 31-day post-vaccination period, including deaths, intussusception, nervous system disorders, and as previously mentioned bronchiolitis and pneumonia, were reported by similar proportions of subjects in both the Rotarix® and placebo groups.

While the integrated safety summary did not show significant imbalances in favor of the placebo group, the company has identified events worthy of further exploratory analysis and follow-up. These events were identified either because they were highlighted in the context of another rotavirus vaccine, or because they were found to be occurring at higher rates following Rotarix® compared to placebo in single studies. The first event, bloody stools, was reported as part of the spectrum of gastrointestinal illnesses related to RotaShield®. Hematochezia is also a clinical sign of intussusception and information on hematochezia is included in the RotaTeq® US package insert. The second and third events, Kawasaki disease and convulsions, have been discussed in the context of RotaTeq®. Convulsions, and the remaining events, pneumonia deaths, pneumonia, and bronchitis, are events of clinical interest because an imbalance was found during exploratory analyses of single Rotarix® studies. It should be noted that for each of these events, the imbalance was only noted in a single study and not in any other study or the core integrated summary of safety.

The pivotal safety results reviewed by the FDA in support of licensure come from the pooled, integrated summary of safety. In the core integrated summary of safety there were no hematochezia severe adverse events or cases of Kawasaki disease within 31 days of vaccination. For the four events of clinical interest where an imbalance was noted in a single study, in the core integrated summary of safety within 31 days of vaccination there were no imbalances for convulsion severe adverse events, pneumonia deaths, pneumonia severe adverse events, or bronchitis severe adverse events.

Because of their clinical importance, Dr. Friedland discussed the clinical events of interest, convulsion and pneumonia, in more detail. The imbalances in convulsion and pneumonia deaths were seen only in a single study, Study 023, which enrolled over 60,000 infants in Latin America. In that study, as mentioned previously, the primary safety objective was the occurrence of the serious adverse event intussusception. Multiple comparisons of other severe adverse events were made between the Rotarix® and placebo group for exploratory purposes to evaluate potential imbalances. The reported serious adverse events were coded to 24 different system organ classes and 265 different preferred terms according to the MedDRA classification system. Asymptotic p-values were used as an aid to highlight potential imbalances worth further clinical evaluation. No adjustment for multiplicity was made, and the assessment of such imbalances should be based on thorough, qualitative clinical assessment.

In study 023, within the whole safety surveillance period from Dose 1 to 30-90 days after dose 2, 16 cases of convulsion were reported in Rotarix® and 6 in placebo subjects. Considering convulsions within 31 days after vaccination, the time window that might be considered the most relevant for biological plausibility, there were 7

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convulsions reported in the Rotarix® and 5 in the placebo group. The investigators in this study reported new onset seizures under 5 different diagnoses: convulsion, epilepsy, grand mal convulsion, status epilepticus, and tonic convulsion. To better capture all seizures, reports for all severe adverse events related to these 5 convulsive disorders were grouped together for an exploratory analysis which showed that during the whole surveillance period from Dose 1 to 30-90 days after dose 2, there were 20 convulsion-related cases in the Rotarix® and 12 in the placebo group. Within 31 days after vaccination, there were 7 convulsion-related cases in the Rotarix® and 9 in the placebo group.

This finding in study 023 was further investigated. A review of the individual case histories revealed that many subjects in both the Rotarix® and placebo groups had pre-existing or concurrent medical conditions as risk factors. Also, within 1 month after vaccination, fever was associated with the convulsion in 14% of the cases in the Rotarix® group and 22% of the cases in the placebo group. A temporal association related to vaccination was not established. Imbalances were not observed when pooled terms related to convulsions were analyzed. In addition, imbalances in convulsion-related severe adverse events were not observed in the other large Phase III study Rota-036, or in the core integrated summary of safety. Based on these evaluations, the currently available data do not suggest a causal relationship between Rotarix® and convulsions. Further assessment is planned in the post-marketing setting.

Study Rota-023 was conducted in Latin American countries (e.g., Brazil, Dominican Republic, Honduras, Nicaragua, and Peru) where neonatal mortality and post-neonatal infant mortality rates are very high. Study 023 was not designed to study the effect of vaccination on fatalities, and the study was not controlled for factors associated with higher post-neonatal fatality such as prematurity, age of mother, smoking exposure, and nutritional deficiencies. As expected in this study, when looking at the entire safety surveillance follow-up time, there were many deaths in both the Rotarix® and placebo group. Specifically, there were 56 deaths in the Rotarix® and 43 deaths in the placebo group, a difference that is not statistically significant. A blinded, independent safety review committee appointed by the study's Independent Data Monitoring Committee (IDMC) reviewed each death and assigned a primary cause of death. Among multiple exploratory analyses performed, the only potential imbalance noted was for death coded to the preferred term pneumonia. Several supplementary analyses were performed to assess the relevance of this finding. First, as pneumonia could be reported under various terms, an additional exploratory analysis was performed combining preferred term codes that were related to pneumonia. During the whole surveillance period from Dose 1 until 30-90 days after Dose 2 there were 16 pneumonia-related deaths in the Rotarix® and 6 in the placebo group. Second, GSK looked at whether this imbalance was replicable in other studies. There are no studies that have been completed to date in which a comparable number of deaths occurred.

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As a next step, GSK reviewed the individual cases to look for patterns that may suggest a relationship to vaccine. A review of the cases shows that there were no unique or distinguishing clinical characteristics, consistent patterns, or common chest x-ray findings. Seven of the 16 cases had symptom onset between day 0 to 30 after vaccination. Within 31 days after vaccination, the time window that might be considered the most relevant for biological plausibility, 2 of the cases occurred within 1 week of vaccination, 2 in the second week, 2 in the third week, and one in the fourth week after vaccination. This absence of any clustering does not suggest a causal association. Nine of the 16 infants had symptom onset beyond day 30 after vaccination, occurring between 31 and 199 days after vaccination. Five of the 16 infants had pre-existing conditions, risk factors, or alternative diagnoses that could have contributed to the pneumonia.

One would expect that a vaccine-associated signal in pneumonia deaths would be part of a clinical spectrum of vaccine-associated pneumonia-related disease, including non-fatal severe pneumonia resulting in hospitalization. Therefore, an additional analysis was performed to evaluate pneumonia-related hospitalizations. With respect to the additional exploratory analysis on all hospitalizations coded to the various pneumonia-related preferred terms, parents and guardians of the infants in this study were contacted by study personnel at least every four days, and emergency department and hospital admission logs were systematically reviewed. There were approximately 275 hospitalizations from pneumonia in both groups, numbers that would have been large enough to detect an imbalance if vaccination was associated with serious adverse respiratory outcomes. These data show that the observed imbalance in pneumonia related deaths among Rotarix® recipients was not supported by observation of other pneumonia related severe adverse events.

There are two studies on-going in Africa which have enrolled nearly 5000 infants in which, as can be expected given the high background infant mortality rate in that part of the world, a considerable number of deaths have occurred. GSK remains blinded to treatment allocation. In these two placebo-controlled studies, among all infants enrolled, 135 deaths have occurred in both the Rotarix® and placebo subjects, 60 of these deaths in both the Rotarix® and placebo subjects were pneumonia-related. GSK has asked the IDMC that oversees these studies to inform them of imbalances in deaths, and specifically pneumonia-related deaths it may observe. The IDMC met recently, and in their latest statement said that there are no safety concerns in these two on-going African studies, nor in other ongoing studies.

In study 036, conducted in Europe, pneumonia and combined pneumonia-related serious adverse events were reported by more subjects in the Rotarix® group than in the placebo group. The majority of these cases were reported to occur remotely from vaccination during the second rotavirus season. The relative risk through the two seasons after vaccination was 2.1, with the lower limit of the 95% CI being 0.95. In all of the other clinical trials, and in the ISS, an imbalance was not noted in pneumonia or

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combined pneumonia-related serious adverse events within 31 days, or regardless of time to onset after vaccination.

GSK has recently completed two large, placebo-controlled trials in Asia and Latin America which were not included in the BLA because they were on-going at the time the licensing application was submitted. In these two large, placebo-controlled studies, there is no imbalance in pneumonia serious adverse events within the 31 days post-vaccination period, nor during long-term follow-up.

Several sets of criteria to assess causality exist. Criteria that apply to vaccine safety include consistency, strength of association, specificity, temporal relationship, and biological plausibility. With respect to pneumonia deaths and non-fatal pneumonia serious adverse findings as they relate to these criteria, based on these evaluations, the currently available data do not suggest a causal relationship between Rotarix® and pneumonia deaths and non-fatal pneumonia serious adverse events. Further assessment is planned on this category in the post-marketing setting.

Shifting focus to reactogenicity, in the integrated summary of safety, in the eight day period after each of the two vaccinations similar percentages of infants in the Rotarix® group and placebo group reported any intensity of fever, cough / runny nose, diarrhea, vomiting, irritability / fussiness, and loss of appetite.

Since the launch of Rotarix® in Mexico in 2005, the company has distributed over 23.5 million doses of the vaccine. The majority of these, 22 million doses, have been distributed in Latin America, of which most were in Brazil. To conclude this presentation, Dr. Friedland reviewed the plans GSK has to monitor the safety and effectiveness of Rotarix® in the post-marketing setting worldwide. GSK is currently conducting a clinical trial to assess the frequency of transmission of the human rotavirus vaccine between twins in the Dominican Republic. A study is underway in South Africa to assess the safety and immunogenicity of Rotarix® in infants who are HIV positive, and a study is on-going in Europe to assess the safety and immunogenicity of Rotarix® in infants born prematurely. Results from these three studies will become available later this year.

More clinical data from large efficacy and safety trials of Rotarix® in Latin America, where Rotarix® is being co-administered with OPV, from Asia, and from a PATH-sponsored study in Africa are just now becoming available. In fact, vaccine efficacy data from an interim analysis of infants enrolled in the PATH study in South Africa were presented earlier this month at the 8th Annual Rotavirus Symposium held in Istanbul. The interim analysis results show that Rotarix® was highly efficacious in this impoverished population.

In addition to these clinical trials, GSK has put or is putting a place a number of observational studies to further monitor the safety and effectiveness of Rotarix®. GSK will be conducting an observational study in the US to monitor the safety of Rotarix® in relationship to intussusception, Kawasaki disease, hospitalizations for acute lower

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respiratory tract infections, convulsion, and death due to any cause. The study will be powered to detect an increased risk of intussusception due to vaccine of 2.5 or greater with 80% probability after any dose. The design of the study, as well as the site where the study will take place, are currently under discussion with the FDA.

In addition to the US study, GSK has initiated or is involved in a number of other studies. In Mexico, a large study has just started that intends to follow more than one million children vaccinated with Rotarix® to compare their risk for intussusception before and after vaccination. Besides IS, this study also has pneumonia deaths and hospitalizations as an additional outcome. Surveillance for IS conducted at the request of GSK and in collaboration with Merck and sanofi pasteur has just been terminated in Germany and is now taking place in the United Kingdom. The objective of this surveillance is primarily to obtain reliable background rates on IS in Europe. Three studies to assess the effectiveness of Rotarix® in preventing severe rotavirus gastro-enteritis in the real-life setting are about to start in Panama, Belgium, and Singapore. Finally, GSK has partnered with the European rotavirus surveillance network, Merck and sanofi pasteur to monitor the circulating rotavirus strains in Europe, with the objective of identifying any shifts as a consequence of vaccination.

GSK is and will be very closely following all adverse event reports that are made to them spontaneously. GSK has a worldwide network of safety personnel to receive such reports. All cases of IS are actively followed to obtain as much information as possible, and these reports are submitted in an expedited fashion to the FDA. GSK plans to engage in regular discussion with the FDA and CDC. In summary, a comprehensive pharmacovigilance plan is in place to further monitor the safety and effectiveness of Rotarix®.

In conclusion, the clinical trial data show that Rotarix® is highly efficacious. Rotarix® may be concomitantly administered with US-licensed infant vaccines. The safety profile of Rotarix® was clinically acceptable, with no safety signal related to intussusception. A comprehensive post marketing pharmacovigilance plan is in place, which will include active monitoring of adverse events of special interest.

Discussion

Dr. Pickering noted that G2 efficacy in the Latin American study was about half as efficacious as the European study, and he wondered whether that was of concern. In addition, he wondered if the 16 deaths in the randomized prospective study from pneumonia would be considered abnormal.

Dr. Friedland responded that in the study in which the pneumonia deaths occurred was in countries where infant mortality rates are very high. After all of the evaluations, there appears to be no evidence of causal association with Rotarix vaccination in the case of these deaths. Nevertheless, this is being followed in post-marketing settings. Regarding G2P[4] efficacy, this was the least commonly circulating type of rotavirus in all of the clinical trials. In the study in Latin America, only 5% of placebo subjects had

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G2P[4] as their cause of RVGE. In the European study, approximately 7% of placebo subjects had G2P[4] as the cause of their RVGE. Throughout all of the clinical trials in Phase II and Phase III, positive point estimates have always been observed for G2P[4] efficacy. When the data are pooled across all of the clinical trials, G2P[4] efficacy is approximately 75%. In the European study (036), when subjects were followed for two years after vaccination, enough G2P[4] rotavirus cases occurred so that G2P[4] efficacy was able to demonstrated with statistical significant efficacy. In the interest of time, Dr. Friedland agreed to share new data efficacy data from other studies and other parts of the world at another time (e.g., Hong Kong, Taiwan, Singapore, South Africa, and Latin America).

Dr. Judson inquired as to whether there was any information on the vaccine strains and whether they grow in respiratory epithelium.

Dr. Friedland responded that there was no consistent evidence that there is a respiratory syndrome associated with rotavirus disease. In particular, there is no association of mortality from non-GE etiology with rotavirus. Antigemia and systemic infection from rotavirus occurs commonly in wild type infection. In this vaccine, there are lower rates of antigemia and viremia compared to wild type infection.

Update on Cost-Effectiveness of Rotavirus Vaccination

Marc-Alain Widdowson
NCIRD / DVD / EB and NCPDCID / DEISS
Centers for Disease Control and Prevention
Advisory Committee for Immunization Practices

Dr. Widdowson presented an updated cost-effectiveness analysis of rotavirus vaccination in the US. He reminded everyone that a cost-effectiveness analysis of RotaTeq®, the 3-dose pentavalent vaccine, was presented to the ACIP in February 2006. RotaTeq® was recommended by the ACIP during that meeting. The results of that analysis are likely to be broadly applicable to the 2-dose vaccine as it presented CE ratios for any cost of a full vaccine course. However, several differences between the vaccines do exist, so an updated analysis was performed to address several potential differences: 1) Published efficacies of 2-dose monovalent vaccine are slightly different; 2) A 2-dose vaccine would provide full efficacy by 4 months of age (compared to 6 months of age with 3-dose vaccine); 3) Administration costs may be different for a 2-dose vaccine; and 4) Dose 1 efficacy of both 2-dose and 3-dose vaccines may be higher than previously estimated. The objective was to assess whether the cost-effectiveness of a 2-dose monovalent rotavirus vaccine was different than a 3-dose pentavalent vaccine, per case averted and life-year saved, from both healthcare and societal perspectives. A cohort model was used that was previously published for the 3-dose pentavalent vaccine. In this model, the number of outcomes experienced by an unvaccinated cohort of 100, 000 children from birth to age 59 months were calculated. The investigators then recalculated the number of outcomes in a cohort vaccinated at 2

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months, 4 months, and 6 months of age, giving them the number of outcomes prevented (Widdowson et al: Pediatrics, 2007:119:684-697).

With respect to the disease burden estimates upon which the model is based, Dr. Widdowson referred to a table reflecting the cumulative number of rotavirus disease outcomes with a range for the 2004 US birth cohort of 4,010,000 followed from birth to 5 years. From these, probability distributions were derived for each outcome for the cohort of 100, 000. For deaths, published estimates were used. For non-fatal outcomes requiring health care, the cumulative number of outcomes of diarrhea of any cause were multiplied by the rotavirus fraction. All outcomes resulting in heath care and death were subtracted from the total number of children who will get rotavirus disease to obtain the number of rotavirus cases that required home care only. For any rotavirus, the investigators assumed that three quarters of every cohort of about 4 million children would have some clinical rotavirus disease by age 5. Most of those would not need medical care; about 400,000 would need physician office or outpatient care; just over 200,000 would require emergency department care; just under 70,000 would require hospitalization; and 30 children a year in the US would die due to rotavirus.

The other model input was the efficacy that was assumed for the vaccine (Widdowson et al, Pediatrics 2007 † Vesikari et al Lancet 2007). Efficacy for different outcomes from the Rotateq® trial were used, and the investigators used a range of efficacy measures from 65% for mild diarrhea to 90% against hospitalization and death. Estimates were used for the two-dose monovalent vaccine, Rotarix®. Both of those were based on available data. The same point estimates of vaccine efficacy were used for various outcomes in a similar range for those used for Rotateq®, except a slightly higher vaccine efficacy was used against mild / moderate disease simply reflecting the published data.

Dr. Widdowson noted that the cost attributed to each outcome were included in the committee's handouts, and that they were the same as those presented in February 2006. The total cost of the program for each vaccinee in the model consisted of costs of vaccination (dose and administration) and costs of side effects. The investigators used a range of costs for a vaccine dose and $10 for administration. Based on information that the investigators had, a two-dose course Rotarix® would be $205.50 in 2008 (Personal communication: Dr M. Rennels). This was compared to a three-dose vaccine at the time of analysis of $206.52, so for practical purposes, identical costs for a full course of vaccination. In order to compare the two vaccines, the investigators reviewed the 2006 model and determined that the cost used in that model for RotaTeq® was $187.50. Since in 2008 the costs of the vaccines are the same, it was assumed that they might have been the same in 2006 as well. There is no evidence from large clinical trials that new rotavirus vaccines cause intussusception. However, they could not exclude the possibility of a very small risk, so they included the costs of a risk of vaccine-associated IS of up to 1 in 50 000, which is several times lower that the risk of IS associated with the previous vaccine. That added only 25 cents to the vaccine cost, so it is really negligible. Also included were the costs of negative outpatient workups for

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IS, to account for increased anxiety of physician and parents and desire to rule out IS in children with adverse advents.

In terms of results, in regard to the cost-effectiveness per case averted from the healthcare perspective, Rotateq® and Rotarix® follow each other very closely, and for both vaccines the cost per cases increases as the net cost of the vaccine course increases. Both have a cost-effectiveness ratio of about $300 per case averted. Of note also is that both vaccines are very unlikely to be cost-saving from the healthcare perspective, given that both are past the 95th percentile. Vaccination may be cost saving from $37 to $149 per vaccinee. At more than $67 per vaccinee, vaccination is increasingly likely to result in net cost from the healthcare perspective, but will definitely not be cost saving at $149 per vaccinee. With respect to cost-effectiveness per life-year saved from the societal perspective, vaccination will be cost savings from at under $110 per vacccinee and may be cost saving from $110 to $241 per vaccinee. Vaccination is increasingly likely to have net cost at more than $157 per vaccine, and will definitely not be cost-savings at $241 per vaccine. Both vaccines have a cost of over $100,000 per life year saved.

With respect to cost-effectiveness of 2-dose and 3-dose rotavirus vaccines, the 3-dose RotaTeq® vaccine at $218 per course is essentially what was estimated previous and the 2-dose vaccine is at $208 per course. From the healthcare perspective, the median cost per case averted (5th and 95th percentile) is $338 for RotaTeq® and $290 for Rotarix®. The median cost per life-year saved is $472,672 for Rotarix® and $392,550 for RotaTeq®. From the societal perspective, the median cost per case averted is $139 for RotaTeq® and $94 for Rotarix®. The median cost per life-year saved is $198,546 for RotaTeq® and $128,400 for Rotarix®. The fact that the societal perspective may possibly be cost savings is reflected by the fact that lower confidence intervals are in brackets.

A further sensitivity analysis was performed to examine how changing the parameter of days off work would affect the cost effectiveness ratio. A shift of $32 occurred when 50% was added and subtracted from the total number of days off. It was first assumed that the first dose had 50% effectiveness of the full course. So, if the full course was 80% effective, then the one dose would be 40%. The first dose was then made to be 25% as effective as the full course, followed by making the first dose 100% as effective as the full course. No appreciable difference was observed in the cost-effectiveness by varying the efficacy of the first dose.

In conclusion, the median estimates in this model suggest small increased cost-effectiveness of 2-dose monovalent vaccine over 3-dose pentavalent vaccine. The difference between vaccines is unlikely significant due to uncertainty of factors between vaccines. True cost of each vaccine is not known, given that there are various commercial arrangements, which means that the cost of one vaccine or the other may differ from what was assumed and the difference between them may be higher or lower than assumed. The cost of administration and shipping may be different. For example, the 2-dose requires reconstitution and may require more time, which has not been

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factored in. In addition, the vaccine efficacies are not really known. In the field, it is not known whether one will perform slightly differently from the other. These small differences are likely to obliterate any small difference in the median estimates presented here. If there is a high dose 1 vaccine efficacy for 3-dose vaccine, that will also make the difference between the two vaccines much smaller because RotaTeq® will also be able to protect children as of 2 months of age.

The conclusion is that the overall cost-effectiveness of rotavirus vaccination is not appreciably changed with a 2-dose vaccine. There are several limitations as well. While there is speculation of herd immunity, which has not been assessed and incorporated into the model. The field effectiveness of 2-dose vaccine is not known. It may not perform similarly to trials. There is a small fraction of children who may only ever receive one dose, so the field cost-effectiveness for both vaccines may actually be higher if the first dose has high efficacy in children who do not complete the course.

Older vaccines tend to be much more cost-effective than newer vaccines as reflected in the following references:

- MMR: Hatziandreu, 1994. Cost saving (societal & healthcare payer)
- DTaP: Ekwueme, 2000. Cost saving (societal & healthcare system)
- Hep B: Margolis, 1995. Cost saving (societal) $1522 / YOL for infants (healthcare payer)
- Varicella: Lieu, 1994 Cost saving (societal) $2500 / YOL (healthcare payer)
- Pneumococcal conjugate: Lieu, 2000. $80,000 / YOL @ $58/dose (societal) IPV (vs OPV) Miller, 1996 $3(m) / VAPP (incremental costs).

Comparing rotavirus with other vaccines from the societal perspective, in terms of life years saved, the rotavirus vaccine is very costly at $197,000 because very few children die of rotavirus in the US. However, from the perspective of cases averted, the cost is $138.

As per protocol, this analysis presentation went through CDC internal review. The following comments from that review were addressed in an earlier draft:

- Justification for redoing analysis for the 2-dose vaccine is not clear.
- Cost-effectiveness ratios should be presented and the high cost per life year saved made explicit.

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Discussion

Dr. Judson pointed out that there did not appear to be competition of the two vaccines based on price. However, he thought the model used an extremely low cost of administration as he did not know anyone in a modern American healthcare system who could administer vaccines for this amount.

Plans for Post-Marketing Safety Monitoring of Rotarix®

Ms. Penina Haber
Immunization Safety Office (ISO)
Office of the Chief Science Office (OCSO)

Ms. Haber reported that the infrastructure for Rotarix® vaccine post-marketing surveillance will include VAERS, VSD, and the vaccine manufacturer will submit monthly data on dose distribution. In terms of VAERS post-marketing surveillance for Rotarix® vaccine, CDC and FDA scientists will continue to receive and review daily alerts of serious adverse event reports as defined by the Code of Federal Regulation (CFR) and other medically important conditions (OMIC) including: age at vaccination, onset-interval (days), dose number, vaccine co-administration, and pre-existing medical conditions. VAERS nurses will obtain medical and immunization records and other relevant laboratory data for all serious and OMIC reports.

VAERS post-marketing surveillance will include review and verification of reports indicating any possible intussusception (based on Brighton case definition level 1); pneumonia and lower respiratory events (serious reports); GI bleeding outcomes, including gastroenteritis; Kawasaki disease; seizures; other outcomes. Comparisons will be made of a proportion of reported adverse events and safety profiles of Rotarix® versus RotaTeq® vaccines by age, dose number, and event severity. The observed versus expected reporting rates will continue to be calculated for intussusception after Rotarix®. VAERS safety concerns (signals) will be assessed through VSD studies and other analyses.

With respect to intussusception laboratory testing, CDC requests tissues samples when available for all reports of intussusception that occur within 1-21 days after rotavirus vaccine. Immunohistochemistry (IHC) testing is done for adenovirus and rotavirus in order to determine if there are potential causes of the intussusception other than the rotavirus vaccine.

Rotarix® VSD monitoring will begin rapid cycle analysis of Rotarix®, monitoring for the same adverse events as for RotaTeq® and including the additional outcome of hospitalized pneumonia. The VSD can distinguish between Rotarix® and RotaTeq® vaccinations.

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Proposed Rotarix Vaccine Recommendations and Updated Rotateq Vaccine Recommendations

Margaret M. Cortese, MD
Centers for Disease Control and Prevention

With regard to the rationale for rotavirus vaccination in US, Dr. Cortese indicated that routine rotavirus vaccine is the primary public health prevention for the prevention of severe rotavirus disease. Its goal is to mimic a child's first natural infection without symptoms and is not expected to prevent all subsequent disease, but should prevent most cases of severe disease and sequelae (e.g., physician visits, dehydration, hospitalizations, deaths). The US rotavirus disease burden among children is substantial. For one US birth cohort followed to age 5 years, there is an estimated 30 deaths; 67,000 hospitalizations; 214,000 emergency department visits; 424,000 outpatient visits; and 2,281,000 episodes with home care (Widdowson MA et al Pediatrics 2007; 119: 684-93).

The CDC laboratory, led by Jon Gentsch, genotyped a convenience sample of isolates collected from approximately 12 participating laboratories in different US areas (1996-2007). The distribution varies by site and by year. For all years, G1P[8] strains predominate on average making up about 75% of the total isolates. Annually, this ranged from 51% to 91%. On average each year, the remaining types each make up 10% or less of the total. G2P[4] made up approximately 20% of the isolates in three different seasons. G9P[8] reached 21% in the 2002-2003 season.

As noted earlier, the working group reviewed the available data on rotavirus disease and the two vaccines. These data will be summarized in the background section of the new 2008 statement. The working group drafted recommendations with the goal to provide guidance for providers, and considered programmatic aspects for the use of these vaccines. With the availability of two different rotavirus vaccine products available in the US, the working group considered whether there were circumstances under which ACIP would propose one vaccine to be recommended or preferred over the other product.

The vaccines differ substantially in their composition. RotaTeq® contains bovine-human strain reassortants and Rotarix® is an attenuated human strain. The working group recognized that the pivotal trials for both of these vaccines differed by study location and, therefore, by the populations studied; the number of infants studied; the number of doses in a series; the exact primary and secondary efficacy endpoints; the case definitions; and other aspects. It was also recognized that there are no studies that compare these two vaccines head-to-head.

With respect to the results from the major clinical trials for vaccine efficacy for data from the first year, or through the first rotavirus season, for both vaccines very good efficacy was demonstrated against severe disease, with generally lower efficacy when the endpoint was rotavirus disease of any severity. In terms of type-specific efficacy from

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the pivotal trials, for some strains the number of cases in the placebo groups and the vaccine groups were low. For type G2P[4], all of the point estimates were positive from the trials, but that the 95% confidence interval included 0 in several estimates. For Rotarix®, the 95% confidence interval did not include 0, so it was positive in the European trial when data from two years of follow-up were considered. Regarding the shedding of vaccine virus measured by antigen detection reported for Rotarix®, shedding was quite common in the first week following vaccination, particularly after the first dose, and was demonstrated up to 60 days after vaccination. Detection of live virus was measured in some infants. Among the infants studied who received RotaTeq®, virus was detected from 1 to 15 days following a dose. It is important to note that transmission of vaccine virus was not evaluated in any of these studies. Data for post hoc analyses of the trial have been reported for premature infants. The data are relatively limited, with fewer premature infants studied to date in Rotarix® recipients compared to those who received RotaTeq®. In drafting recommendations, the working group also considered that the series with Rotarix® is completed earlier in a child's age than with RotaTeq®. In addition, latex is included in the oral applicator of Rotarix®. These are just some of the issues that the working group considered. The group recognizes that there are other aspects of the vaccines that providers are also likely to consider in their own decisions, such as cost and ease of administration.

In terms of the general concepts of the working group's main proposed recommendations, these proposed recommendation are very similar to the draft recommendations presented to the full ACIP in February 2008. For the recommendation on routine administration, the working group proposed to summarize that safety and efficacy have been demonstrated for both vaccines in clinical trials, that the vaccines differ in composition and schedule of administration, and that ACIP expresses no preference for RV5 or RV1. With respect to the proposed schedule and age recommendations for the vaccine, the working group proposes to harmonize the maximum ages with one of the considerations being that the working group felt that harmonization, when reasonable, would be an advantage for the program overall. The proposed ages differ somewhat from the maximum ages in the trial protocols. For the interval between doses, the working group proposes to state that the minimum interval between doses is four weeks. The recommended ages for doses would define the usual interval as two months, so here the working group would be stating the minimal interval and not an upper limit. Four weeks is the minimum interval between doses for most vaccines in the current infant schedule. For RotaTeq® (RV5), the 2006 ACIP statement states that doses should be administered at four to ten week intervals, so this would be a slight wording change for that vaccine. It will not be a change in the way that the recommendation is likely to be interpreted in that it does not explicitly state that doses should not be given if ten weeks or more have elapsed. There are data from Merck on a limited number of infants in the RotaTeq® trial who received doses more than ten weeks apart, and generally data were similar to those from the study overall. The working group felt that harmonization between the vaccines on this issue was advantageous.

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For the maximum age for the first dose, the working group proposes that the first dose be given from age 6 weeks through age 14 weeks 6 days. Vaccination should not be initiated for infants aged 15 weeks 0 days or older. 14 weeks 6 days was the maximum age for enrollment in the Rotarix® efficacy trial in Europe. The working group recognized that the maximum age limit on the first dose does impact ultimate coverage with rotavirus vaccine among US infants. For RotaTeq®, the 14 week 6 day recommendation would be an expansion of two weeks from the likely interpretation of the 2006 recommendation stated as 12 weeks. The working group felt that this was an appropriate recommendation, given that the available data (trial, US post-marketing) do not indicate RV5 is associated with intussusception in the age groups recommended for vaccination. However, there are no safety data (trial, post-marketing) for Dose 1 in infants much older than those covered in the 2006 recommendation. Therefore, the working group felt that at this time, the maximum age for Dose 1 should not be greatly expanded for US infants with RotaTeq®. Again, the working group considered harmonization to be advantageous.

For the maximum age for the last dose, the working group proposes to state that all doses of rotavirus vaccine should be administered by age 8 months 0 days. For RotaTeq®, this would be an expansion of maximum age for last dose by approximately 2 weeks from the way the 2006 recommendation is likely interpreted (e.g., 32 weeks 6 days) and 8 months 0 days is approximately 34 weeks 6 days. The reasoning was that for providers, determining if infant is aged ≤8 months 0 days much simpler than determining if infant is aged ≤32 weeks and, therefore, to determine if the child is eligible for vaccine. The available data (trial, U.S. post-marketing) do not indicate RotaTeq® is associated with intussusception in the age groups recommended for vaccination. For Rotarix®, this would be an expansion of maximum age for last dose by approximately 10 weeks from that used in trials (8 months 0 days = ~34 weeks 6 days). Data from trial do not suggest that Rotarix® is associated with intussusception in the age groups studied. Background rates of intussusception among US children are similar at ages 24−34 weeks. If mixed (or potentially mixed) series is allowed and three doses are recommended, the 8-month age limit is practical. Again, harmonization is advantageous.

Regarding the interchangeability of the products in the vaccine series, the working group recognizes that there will be some infants who change providers after receiving dose 1 and before finishing the series by age 8 months and that the second provider may not have the same product or may not know which product was used. The workgroup's considerations took into account that there are no data available or expected on mixed series. In the working group's opinion, the mixed series would not be expected to pose additional risk, and may be more effective than incomplete series with one product. Programmatically, the working group thought this was a practical requirement. The working group proposes a recommendation for three total doses of rotavirus vaccine if any dose in series was RotaTeq® (RV5) or if the product is unknown for any dose in the series. The working group recognized that no data are available or expected, and although there are a lot of differences in rotavirus and Hib vaccines, this follows the general concept of ACIP Hib vaccine recommendations for mixed series.

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With regard to the recommendations, underlined text in this document represents where wording is different from the 2006 ACIP statement:

Proposed Wording-1
Routine Administration

ACIP recommends routine vaccination of US infants with rotavirus vaccine. Two different rotavirus vaccine products are licensed for use in infants in the United States, RotaTeq (Merck) (RV5) and Rotarix (GSK) (RV1). The products differ in composition and schedule of administration. Rotavirus vaccine efficacy studies demonstrated 85%–98% protection against severe rotavirus disease and 72%–87% protection against any rotavirus disease (see pages xx). ACIP expresses no preference for RV5 or RV1.

Discussion

Dr. Paul Cieslak expressed disappointment in the cost-effectiveness data. This translates to spending $800 million per year in the US to vaccinate 4 million children in order to prevent 30 deaths a year. Those types of data were used to limit the number of groups for which the ACIP recommended the meningococcal vaccination for.

Dr. Baker clarified that the recommendation of cohorts for meningococcal vaccine was not based on cost, it was based on supply. When the supply was adequate, the ACIP then recommended that the vaccine be administered to all adolescents 11-18.

Dr. Morse added that the cost per case prevented is very low, so there are other factors to be considered.

Paul Offit clarified that he was the co-inventor and co-patent holder of RotaTeq®. He indicated that the heterotypic immunity issue is one that anyone who has worked with rotavirus has dealt with for the last 25 years. When Dr. Friedland shows the data in the European trial, there is protection against G2; 2 cases in the vaccine and 7 in the placebo group (2:1 randomized). He thought that was real. There are clearly epitopes on both VP4 and VP7 that are cross-neutralizing. The problem is that as a general rule, the history of rotavirus vaccine shows that heterotypic immunity is inconsistent. For example, in the early development of Rotashield® by NIH, it was just the RV vaccine. RV is not a P8 strain and it is not a G1 strain. When tested in Finland and Sweden, it had excellent protection against the natural P1G8 outbreak. That was heterotypic protection. The problem was that when subsequent trials were conducted (for example, in Rochester, New York) there was very little protection. Therefore, for Rotashield® heterotypic immunity was inconsistent. When the Childrens Hospital Philadelphia group first developed the vaccine, it was a WC3 vaccine. It had excellent protection in Philadelphia, but when it extended to trials in the Central African Republic and in Cincinnati, heterotypic protection did not occur. When heterotypic protection against G2 is observed in the European trail, but do not see heterotypic protection in the Latin

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American trial, one could argue that this is to be expected. While he did not disagree with the decision not to distinguish the two vaccines regarding safety and efficacy, given that both are excellent vaccines that are very safe and none of this may matter. However, he did believe it was incumbent upon investigators to study areas with almost exclusive use of Rotarix® to determine whether there is G2 emergence. This occurred in South American, but there may have been a G2 emergence anyway independent of Rotarix® use.

Dr. Neuzil thought something that was missed in describing the clinical trials was the tremendous prevention of this vaccine against all-cause gastroenteritis, which is partially what they may be observing in some of Dr. Friedland's graphs as well. The morbidity of the cost-effectiveness studies may be under-estimated.

Dr. Chilton commented that with many of the other vaccines the ACIP has considered quality adjusted life years (QALYs) saved by a vaccines. It is more difficult to do that with respect to an infant disease, but he thought they would see that this is a cost-effective vaccine program if they take QALYs into consideration.

Dr. Lieu thought that for all vaccines ACIP should be attempting to translate the benefit of preventing morbidity into a standard metric. In the US that is QALYs. It can be done even when the vaccines prevent childhood morbidity.

Dr. Paul Cieslak responded that he appreciated the significant amount of morbidity that could be prevented, but the cost-effectiveness studies account for recouping all of that on the one side of the equation. Even with cost per life year saved, rotavirus vaccine is well above anything else that has been approved. He wondered if they had any ceiling or if they planned only to consider whether a vaccine was safe and effective no matter what the price.

Dr. Schuchat reminded everyone that there is a certain set of information that the ACIP committee is supposed to review: burden of disease, safety, immunoresponse, clinic protection, programmatic considerations, cost-effectiveness (not budget in terms of who is going to come up with the funds). These meetings are held in public where people can make additional comments so that they will ideally receive input from public voices. Some have wondered whether enough of a public voice is being included in the process in terms of the values because it does sound as if the discussion questions whether it is about death, dollars, things that are important to families, et cetera. Perhaps what is important to families is a factor that has not been incorporated enough. In terms of the strict cost-effectiveness, there is not a cutoff. Cost-effectiveness is merely one consideration the committee makes just as the performance of the vaccine, the clinical course of the illness, and many other factors are considered.

Dr. Beck thought one of the problems was that many of the members did not have expertise in this area, yet they were called upon to give some cogent review and response. They cannot really make a comparison the way the data come in. This cost-effectiveness report was particularly distant from what the ACIP had come to accept as

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the material they would review on cost-effectiveness. This pointed to the fact that they needed to see information in the same manner to make appropriate comparisons in order to do a satisfactory job in meeting their responsibilities for that part of their considerations which dealt with cost-effectiveness. He recognized that there was not magic bullet that reflected the perfect cost for every vaccine, but they must have some type of reality check.

Dr. Lieu said that by putting the value of preventing rotavirus cases in dollars in the numerator of cost-effectiveness analysis, they have not actually accounted for the psychological costs of pain and suffering in the denominator analysis in terms of benefits. Thus, the custom would be to include those costs. Without the QALYs, she did not believe they could get a fair comparison. The dilemma at the time the initial decision came before the committee was that they said they needed the QALYs in order to make a fair comparison or decisions on imperfect data. However, the CDC economists told them that the data on QALYs did not exist. It is possible to conduct a study to collect the values from people that are needed to generate the QALYs. This takes a while to do because it is primary data collection.

Dr. Baker stressed the importance of acknowledging that part of the cost of vaccines pertained to the fact that the trials for new vaccines are very expensive, but are necessary to be absolutely sure that they are adequately assessed for safety.

Dr. Vesta Richardson reported that Mexico had been using the monovalent vaccine since 2006, initially in 50% of the country and as of 2007 in 32 states. Their coverage rates are above 75% and they have administered greater than 2.5 million doses as of 2007. They are in the process of the analysis of burden of disease and cost-effectiveness. These data are expected by the end of the year, which she would be happy to present. They do believe that the vaccine is cost-effective, beneficial, and has saved a lot of lives in Mexico. In terms of surveillance for G2 serotypes, they have cyclic appearances every five or six years. The last time it appeared was in 2006 before they began the use of the vaccine and it has not been observed since.

Responding to Dr. Offit's comments, Dr. Friedland pointed out that in addition to biologic plausibility for heterotypic protection, there is evidence in natural disease studies that children who are infected with the most common G1P8 type are protected against all types during subsequent infections. All of the Rotarix clinical trials have always demonstrated a positive point efficacy for G2, including pooled analyses. GSK does plan to acquire additional data for G2 protection. The PATH group currently involved in the GSK study in Malawi and South Africa, recently presented interim analysis in which showed 83% efficacy in a highly impoverished population in South Africa. It is known that G2 is circulating in a frequency in South Africa that exceeds that which was circulating in the Latin America and European studies.

Dr. Offit applauded GSK for the monumental effort, recognizing that it is not easy to make vaccines. Although Rotarix® is a human virus, it is not a wild type. It is an attenuated virus. Therefore, its replication efficiency is far less than the natural virus.

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His point was that the expression then of those cross-reactive epitopes was likely to be less. The cross-reactive epitopes on VP4 and VP7 are really across mammalian strains. It is human, cow, mouse, primate, et cetera. The Latin American trial reflects the 25 year inconsistency with rotavirus vaccine of heterotypic immunity. It is a testable hypothesis and it is worth testing.

Dr. Friedland responded that it would be tested and that it is also possible that there will be emerging strains that are not covered by the Merck vaccine, so that will have to be tested in the future as well.

Penny Dennehy, Rotavirus Vaccine Working Group member and liaison from AAP, fully agreed that this vaccine does not save many lives in the US. However, having dealt with many of these families, it was gratifying to no longer see these children admitted to the hospital. It may be necessary to account for herd immunity in the cost-efficacy analyses. The drop in cases presenting to the hospital seems to suggest that there is herd immunity. It would be beneficial to have some input from the families who have been through this exactly what amount of money they would be willing to pay for a vaccine to prevent this disease.

Motion: Vote #1

Dr. Neuzil motioned that ACIP approve the recommendation as presented. Dr. Baker seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions.

Proposed Wording-2
Routine Administration

RV5 is to be administered orally in a 3-dose series with one dose at ages 2, 4, and 6 months. RV1 is to administered orally in a 2 dose series with one dose at ages 2 and 4 months (Table 8). The first dose of rotavirus vaccine should be administered from age 6 weeks through age 14 weeks 6 days; the maximum age for the first dose is 14 weeks 6 days. Vaccination should not be initiated for infants aged 15 weeks 0 days or older because of insufficient data on safety of the first dose of rotavirus vaccine in older infants. The minimum interval between doses is 4 weeks. All doses should be administered by age 8 months 0 days.

The recommendations would also include the following summary table:

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Proposed Wording-3
Routine Administration

Table 8

	RV5 (RotaTeq; Merck)	RV1 (Rotarix; GSK)
Number of doses in series	3	2
Recommended ages for doses	2, 4 and 6 months	2 and 4 months
Minimum age for Dose 1	6 weeks	
Maximum age for Dose 1	14 weeks 6 days	
Minimum interval between doses	4 weeks	
Maximum age for last dose	8 months 0 days	

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Proposed Wording-4 & 5
Interchangeability of Rotavirus Vaccines

ACIP recommends that the rotavirus vaccine series be completed with the same product whenever possible. There are no studies that address the interchangeability of the two rotavirus vaccine products. However, there are no theoretical reasons to expect that risk of adverse events would be increased if the series contained more than one product, compared to risk of adverse events of a series containing only one product. Further, although it is possible that effectiveness of a series that contained both products could be reduced compared to a complete series with one product, the effectiveness of a series that contained both products may be greater than an incomplete series with one product.

Therefore, ACIP recommends that vaccination not be deferred because the product used for previous doses is not available or is unknown. If the product used for a previous dose(s) is not available or is unknown, the provider should continue or complete the series with the product available.

If any dose in the series was RV5 or the vaccine product is unknown for any dose in the series, a total of three doses of rotavirus vaccine should be given. The minimum interval between rotavirus vaccine doses is 4 weeks. All doses should be given by age 8 months 0 days.

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Discussion

Dr. Englund inquired as to whether Rotarix® had ever been given as a second dose in any of the GSK studies in a child between 7 and 8 months old, or if they were making new recommendations on something that had never been done.

Upon checking the study reports, Dr. Friedland responded that in the Latin American study, in the arm that received Rotarix® there were children who had their second dose up to 36 weeks of age, so there are children in the database who were vaccinated at that late point. He also pointed out that with respect to the intent to treat efficacy data (which would include children at older ages) in all of the clinical trials, and particularly in the two Phase III trials, are virtually the same as the excellent efficacy data shown in the according to protocol analyses.

Stanley Plotkin said that he realized the stipulations (e.g., 14 weeks 6 days and 8 months) were because these are the only data from the efficacy trials. The efficacy trials were set up in light of the Rotashield® data and the idea that Rotashield® caused IS because it was given at older ages. However, this affects the administration of rotavirus vaccine in the US and overseas. He requested that CDC and the manufacturers to set up studies to accumulate data on non-protocol administration of these vaccines because based on the safety data available, they will be perfectly safe at older ages as well as the ages stipulated. That is not a trivial point.

If the recommendations were expanded beyond the clinical trial data. Dr. Morse inquired as to whether FDA would raise any objections.

Dr. Houn responded that they would likely have a situation in which the approved labeling would disagree with the practice recommendation. For RotaTeq® in the large trials, there was only a small number of children (n=99) in the BLA who received the first dose beyond the recommended 6-12 weeks. Of those, 3 received the product at 14 weeks, so most of them received it at 13 weeks. The recommendations differing from the labeling may cause some confusion in the practice community. That would just have to be understood.

Dr. Temte said he had as much difficulty figuring out 14 weeks and 6 days as for whatever was translated into 8 months. In terms of registries, it is difficult to translate language into specific dates. Programmers need very precise language in order for the registry to react appropriately in terms of prompting.

Dr. Chilton commented on the difference in 32 weeks and 8 months versus 14 weeks 6 days and three and a half months. Actually, three and a half months is 105 or 106 days while 14 weeks 6 days is 104 days. If the committee thought that 3 months 15 days would be easier, that change could be made.

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Amy Middleman, SAM, noted that 8 months and 0 days is very precise in terms of days, but if February is included in the 8 months versus a 31-day month, that could introduce a significant amount of confusion for practitioners. She suggested either making 8 months the parenthetical statement or 34 weeks 6 days. She thought there would be significant confusion by putting 8 months and 0 days.

Dr. Cortese responded that within the working group, all of the various options were discussed. This would be the anniversary of the child's 8-month birthday, which the working group thought was the clearest option.

Motion: Vote #2

Dr. Baker motioned that ACIP accept these further recommendations as presented. Dr. Sawyer seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions.

Although no vote was entertained on the following, the suggested changes were reviewed. Again, underlined text represents where wording differs from the 2006 ACIP statement:

Proposed Wording-9
Contraindications

Rotavirus vaccine should not be administered to infants who have a history of a severe allergic reaction (e.g., anaphylaxis) after a previous dose of rotavirus vaccine or to a vaccine component. Latex rubber is contained in the RV1 oral applicator, so infants with a severe (anaphylactic) allergy to latex should not receive RV1.

The RV5 dosing tube is latex-free. Some experts, therefore, prefer that infants at high risk of acquiring latex allergy, including those with spina bifida or bladder exstrophy, receive RV5 instead of RV1. However, if RV1 is the only rotavirus vaccine available, it should be given, as the benefit of vaccination is considered to be greater than the risk of adding to the likelihood of sensitization.

Proposed Wording-13, 14, 15
Special Situations: Premature Infants (<37 wks gestation)

ACIP considers the benefits of rotavirus vaccination of premature infants to outweigh the theoretical risks. Data suggest that premature infants are at increased risk for hospitalization from rotavirus or other viral gastroenteritis during their first year of life. In clinical trials, rotavirus vaccines appeared to be generally well tolerated among preterm infants, although a relatively small number of preterm infants have been evaluated (see pages xx).

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ACIP supports vaccination of prematurely born infants (according to the same schedule and precautions as full-term infants) under the following conditions: the infant's chronological age meets the age requirements for rotavirus vaccine (e.g., from age 6 weeks through age 14 weeks 6 days for the first dose), the infant is clinically stable, and the vaccine is given at the time of discharge from the NICU or nursery, or after discharge from the NICU or nursery. Although the lower level of maternal antibody to rotavirus in very premature infants theoretically could increase the risk for adverse reactions from rotavirus vaccine, ACIP considers that the benefits of vaccinating the infant when age-eligible, clinically stable, and no longer in the hospital outweigh the theoretical risks.

Vaccine strains of rotavirus are shed in the stool of vaccinated infants (see pages xx) so if an infant receives vaccine while still needing care in the NICU or nursery, there is at least a theoretical risk of vaccine virus being inadvertently transmitted to infants in the same unit that are acutely ill (moderate-to-severe illness is a precaution for vaccination) and premature infants who are not age-eligible for vaccine. ACIP considers that, in usual circumstances, the risks from shedding outweigh the benefits of vaccinating the infant who is age-eligible for vaccine but who will remain in the NICU or nursery after vaccination.

Discussion

With respect to the proposed wording for premature Infants (<37 wks gestation), Dr. Pickering expressed concern with the wording, "Vaccine strains of rotavirus are shed in the stool of vaccinated infants (see pages xx) so if an infant receives vaccine while still needing care in the NICU or nursery, there is at least a theoretical risk of vaccine virus being inadvertently transmitted to infants in the same unit that are acutely ill (moderate-to-severe illness is a precaution for vaccination) and premature infants who are not age-eligible for vaccine. ACIP considers that, in usual circumstances, the risks from shedding outweigh the benefits of vaccinating the infant who is age-eligible for vaccine but who will remain in the NICU or nursery after vaccination" as it seemed to send a mixed message.

Dr. Baker agreed that no live virus should be given in the nursery, and the way this paragraph is worded is confusing.

Dr. Paul Cieslak inquired as to what the recommendation would be for a child who has had confirmed rotavirus disease.

Dr. Cortese responded that the language in regards to vaccination after rotavirus disease is the same as that in the 2006 recommendations and no changes were made The recommendation is to complete the series, given that it is not known whether the first infection would provide complete protection.

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Neal Halsey, Johns Hopkins University, thought the wording about latex allergy would generate a lot of questions and concerns with regard to the second paragraph that states, “Some experts, therefore, prefer that infants at high risk of acquiring latex allergy, including those with spina bifida or bladder exstrophy, receive RV5 instead of RV1.” Historic data are correct that those children are at marked increased risk of acquiring latex allergy, but latex gloves and other latex products have been largely disappearing from hospitals over the past several years. He wondered whether the patient safety group would be willing to weigh in on this. The apprehensiveness on the part of many parents who fear that there may be latex and latex exposure from those vaccines far outweighs the risk, and they may not be willing to give either vaccine. With that in mind, he encouraged the working group to reconsider the language.

Dr. Cortese responded that this is included in the package label under the section of “Hypersensitivity.”

Dr. Iskander reported that the limited data available do indeed suggest that true anaphylactic reactions to latex in vaccines are quite rare. As he read the wording for those at high risk, it included a contraindication for prior allergy to latex and a precaution. Perhaps less wording to the second part and simply rephrasing it more generally in terms of a precaution would be one way to address the concern raised by Dr. Halsey.

Dr. Chilton reported that when the working group reviewed the wording of the approved labeling for Rotarix®, they were concerned about the fact the labeling suggested that there would be a problem with children who had experienced previous latex anaphylaxis. There would be very few of those by age 2 months. However, given the importance of having patients with spina bifida or bladder exstrophy avoid exposure to latex through any means, he asked experts in the care of children with spina bifida for an opinion about this, which is reflected in the paragraph.

Dr. Friedland read from the product insert under “Warnings and Precautions,” which states, “Hypersensitivity Reactions: Review the infant immunization history for hypersensitivity and other reactions for any component of Rotarix®, including latex rubber contained in the oral applicator.”

Dr. Judson requested input from FDA regarding whether ACIP was inconsistent with the approved labeling. He also noted that stating something about potential allergy to “any component” of the vaccine without defining what is meant will not be helpful to patients, their parents, or healthcare providers.

Dr. Houn responded that this is not included in “Contraindications,” it is included in “Warnings and Precautions.” The reason the FDA refers them to descriptions is that there are many components and ingredients in the vaccine such as amino acids, stabilizers, et cetera.

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Dr. Judson pointed out that the ACIP has a different charge from FDA, and public health practicality had to be considered as well. Using the wording "components" when talking about a number of amino acids that neither the clinician or the guardian may be able to interpret seemed remiss.

Given the time and that no vote would be entertained on these recommendations, Dr. Morse encouraged everyone to review these and submit their comments at a later time.

VFC Vote

Dr. Greg Wallace
CDC / CCID / NCIRD / ISD

Dr. Wallace reminded everyone that a VFC resolution was a vote to entitle those eligible for a vaccine to routinely recommend vaccines. He stressed that the wording voted upon must be specific for this, so if there were going to be any changes, this may have to be tabled for another vote. Or, they may decide to make the information briefer within the resolution, given that readers would be referred back to the recommendations eventually for more information. He explained that the purpose of this resolution was to add the newly licensed vaccine against rotavirus, Rotarix®, that replaces the initial resolution from February 2006. The revision reflects the language from the recommendations described by Dr. Cortese. Dr. Wallace stressed that he worked closely with Dr. Cortese and was part of the working group to assure that. The upper age limit is changed, and the table included is the same as the table included in the proposed language for routine administration.

The language for the severe allergic reactions, followed by the latex, differs slightly from the recommendations:

> Severe allergic reaction (e.g., anaphylaxis) after a previous dose of rotavirus vaccine or to a vaccine component. Latex rubber is contained in the Rotarix® oral applicator, so infants with a severe (anaphylactic) allergy to latex should not receive Rotarix®. The Rotateq® dosing tube is latex-free. Some experts, therefore, prefer that infants at high risk of acquiring latex allergy, including those with spina bifida or bladder exstrophy, receive Rotateq® instead of Rotarix®. However, if Rotarix® is the only rotavirus vaccine available, it should be given, as the benefit of vaccination ~~as the risk of rotavirus disease in these infants~~ is considered to be greater than the small additional risk of adding to the likelihood of sensitization.

If there were concerns about this wording or including "some experts" Dr. Wallace did not believe there was a legal reason all of the language needed to be included. Instead it could read, "severe allergic reaction after a previous dose or to any vaccine component," which is standard language for all VFC resolutions. The language could read simply, "Severe allergic reaction (e.g., anaphylaxis) after a previous dose of rotavirus vaccine or to a vaccine component. Latex rubber is contained in the Rotarix® oral applicator, so infants with a severe (anaphylactic) allergy to latex should not receive Rotarix®" and stop it there. He did not think this was an issue, given that the VFC resolution is not meant to encompass the hundred page R & R for anything and some of the other special circumstances are not considered, such as

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prematurity and so forth. All of the precautions remain unchanged from the previous resolution. There are simple re-ordered to be consistent. Some additional information is included about HIV. Otherwise this section is primarily some wordsmithing, some additional information, and a change in the order to be consistent with how the recommendations will eventually be published.

Discussion

Dr. Baker suggested that the contraindication language stop after "The Rotateq® dosing tube is latex-free" for informational purposes. Otherwise, she completely supported the idea of making this simple.

Dr. Wallace stressed that the VFC did not have to include all of the caveats. He restated that the contraindication language would be revised to read as follows:

> Severe allergic reaction (e.g., anaphylaxis) after a previous dose of rotavirus vaccine or to a vaccine component. Latex rubber is contained in the Rotarix® oral applicator, so infants with a severe (anaphylactic) allergy to latex should not receive Rotarix®. The Rotateq® dosing tube is latex-free.

Motion: VFC Vote

Dr. Baker motioned that ACIP accept the VFC resolution as presented by Dr. Wallace. Dr. Stinchfield seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions.

Human Papillomavirus (HPV) Vaccines

HPV Vaccines Workgroup Update and Session Overview

Janet Englund, MD
Chair, ACIP HPV Vaccine Workgroup

As discussed during the February 2008 ACIP meeting, Dr. Englund reminded everyone that the manufacturer of the currently licensed HPV vaccine, Merck, submitted a supplemental BLA for use of the quadrivalent HPV vaccine in women over 26 years of age in January 2008. Because of this, the ACIP HPV Vaccine Workgroup has been preparing recommendation options for use of the vaccine in this age group. FDA recently requested additional data regarding the Merck submission for licensure in women ages 26-44 years. An ACIP vote may occur in October 2008 or later if FDA approval is received.

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HPV Workgroup activities with respect to potential recommendations for women >26 years have included conference calls to review data on the following:

- Quadrivalent HPV vaccine in adult women: Haupt (Merck)
- Epidemiology of HPV in "older women": Winer (U Wash)
- Sexual behavior in the US: Leichliter (CDC)
- Cost effectiveness: Goldie (Harvard)
- Natural history of HPV: Schiffman and Rodriguez (NCI)

During the February 2008 ACIP meeting, the manufacturer's adult women vaccine trial data were presented. The committee also heard overviews of epidemiology and cost effectiveness related to this issue. The workgroup also presented recommendations options that had been considered. Since the February 2008 meeting, there has been further presentation and consideration of the modeling and cost-effectiveness data and multiple discussion regarding recommendations options. The workgroup has moved closer to consensus on some recommendations, and a draft notice to readers is being developed.

With respect to the data shown by the manufacturer during the February 2008 ACIP meeting regarding the quadrivalent HPV vaccine study in adult women, the study included over 3800 women age 24-45 years. This was a multi-center, international study (27% US participants) with the following key exclusion criteria: No history of LEEP, hysterectomy, or genital warts; no history of cervical biopsy in the past 5 years; and no limitation of lifetime sex partners. The primary end outcome is HPV 6,11,16,18-related persistent infection, cervical intraepithelial neoplasia (CIN), or EGL. In terms of efficacy shown in the per protocol population, which includes women who were negative to the respective vaccine type at baseline, the efficacy for HPV 6-,11-,16- or 18-related outcomes was 91%; efficacy against HPV 16- or 18-related outcomes was 83%; and efficacy for HV 6- or 11-related outcomes was 100% (Haupt, presented at February 2008 ACIP meeting). These are interim data analyses at 2.2 years of mean follow-up. The study is powered to evaluate composite endpoints of persistent infection and disease. At the interim analysis there were few disease endpoints (e.g., 1 in the vaccine group; 8 in the placebo group). Stratified analysis looking only at disease endpoints demonstrated high efficacy against CIN or EGLs attributed to vaccine HPV types. The study profile in the adult women was similar to that in the Phase III studies. There was no difference in serious adverse events overall no serious adverse events that were considered to be vaccine-related. Infection site AES were more likely in the vaccine than placebo group, as was seen in the integrated safety data previously reviewed.

During this ACIP meeting, the HPV session includes a cost-effectiveness analysis presented by Dr. Jane Kim. While this analysis examined cost-effectiveness of vaccination strategies through 26 years of age, it provides information relevant to the issue being addressed by ACIP concerning vaccination of women older than age 26 years. Dr. Chesson would review another cost-effectiveness model developed by Merck and discuss the differences between these two models. Both models provide

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useful information for policy makers. Dr. Dunne will discuss some epidemiologic issues and options for recommendations being developed by the workgroup.

With respect to the projected dates for an ACIP vote, Dr. Englund reported that the possible dates for a decision on quadrivalent vaccine in females 27 through 45 years would be October 2008 or later; for bivalent vaccine in females in 2009 or later; and for quadrivalent vaccine in males 2009 or later.

Cost-Effectiveness of HPV Vaccination in the US

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Dr. Kim reported that in terms of the HPV burden, infections with high-risk (oncogenic) HPV types are associated with 100% cervical cancer, 90% anal cancer, 40% vulva, vaginal, and penile cancers, 12% head and neck cancers, and 3% of mouth cancer. HPV-16 and -18 are the most common. Infections with low-risk (non-oncogenic) HPV types are associated with >90% genital warts and juvenile onset recurrent respiratory papillomatosis (JORRP). HPV-6 and -11 are the most common. The objective of this study was to evaluate the cost-effectiveness of vaccinating pre-adolescent girls (age 12) and temporary catch-up programs for women (up to age 18, 21, or 26) in the context of current cervical screening in the US.

The general analytic framework was to develop mathematical model(s) of the natural history of disease; synthesize epidemiological, clinical, and economic data from multiple sources; calibrate the model to achieve good fit to empirical data; validate the model by predicting outcomes consistent with observations from independent data; simulate different interventions to estimate consequences (e.g., quality-adjusted life expectancy, costs); and explore the influence of alternative scenarios, analytic assumptions, and uncertain parameters. Because of the inherent tradeoffs associated with different model types, the investigators elected to use multiple models for this analysis. The mathematical models used included (1) a dynamic sexual transmission model of HPV-16 and -18 infection among males and females, which captures direct and indirect (e.g., herd immunity) benefits of vaccination—this model was used to calculate the percent reduction in HPV-16 and -18 incidence over time from vaccination; (2) a microsimulation model of cervical carcinogenesis, to which the HPV-16 and -18 reduction were directly applied, and which captures cervical cancer outcomes associated with all HPV types and detailed screening strategies—this model was used to assess the cost-effectiveness of HPV vaccination in conjunction with cervical cancer screening in the US; and (3) a series of Markov models of other health outcomes to simulate the incidence of other cancers, genital warts, and JORRP.

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The dynamic model for females reflects sexual transmission of HPV-16 and -18. Those who are uninfected can acquire HPV-16 or -18 infection, develop pre-cancerous lesions classified as CIN1 and CIN2,3, and over time they develop invasive cancer. Those who clear their infections or lesions develop a natural immunity to that same type. They can re-acquire the same type at a reduced rate or acquire a new infection with the other type. The history of prior infection is tracked throughout the analysis. Once vaccination is introduced, women enter a corresponding vaccinated state. The model has a similar structure for men, reflecting HPV only. The model is age-structured and stratifies the population into four sexual activity levels. Females and males form partnerships over time depending upon age and sexual activity level. HPV incidence is a function of number of new sexual partners, HPV prevalence among partners, and the transmission probabilities of HPV-16 and -18 given an infected partner. The microsimulation model is an individual-based model that includes detailed screening and vaccination modules and tracks the history of each individual woman. All HPV types are included, stratified as HPV-16,-18, other high-risk types, and low-risk types. Unlike the dynamic model. HPV incidence in this model is a function of age and other individual level characteristics.

The investigators leveraged the strengths of both models by estimating reductions in type-specific HPV-16, -18 incidence with vaccination using the dynamic model, and then applying the generated reductions in each incidence to the microsimulation model. This linkage between the two models allowed the investigators to reflect herd immunity, all HPV types, detailed screening strategies, and individual level heterogeneities. The natural history input parameters were based on epidemiological studies, cancer registries, and demographic statistics primarily from the US. After initial parameterization, the models were calibrated to fit to empirical data using a likelihood-based approach. For the most part, the calibrated models produced trends that were consistent with the data. The single best-fitting sets from each of the models were selected to proceed with the analysis. Selected data on incidence of other HPV-related conditions, percent of cases attributable to the vaccine-targeted HPV types, five-year survival, and estimated cost per case in 2006 US were used as inputs in the Markov models to estimate vaccine effects on non-cervical conditions.

The primary analysis focused on outcomes related to cervical disease only; secondary analyses included other HPV-16 and -18 cancers and HPV-6 and -11 warts and JORRP. Analyses were conducted from the societal perspective, including direct medical and non-medical costs regardless of payer. Health and economic outcomes were discounted at a rate of 3% per year, which are consistent with the recommendations of the US Panel on Cost-Effectiveness in Health and Medicine. Health outcomes were expressed as quality-adjusted life expectancy, which is life expectancy that accounts for diminished quality of life due to disease. Health state utilities for invasive cancer (range, 0.48-0.76), genital warts (0.91), and JORRP (0.69) were obtained from the published literature. Economic outcomes included lifetime costs of interventions and were comprised of direct medical (e.g., vaccination, screening, diagnostic follow-up, treatment) and direct non-medical costs (e.g., patient time and

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transportation) were included. Patient time costs due to lost productivity were not included. The investigators assumed the cost per-vaccinated girl to be approximately $500 (e.g., three doses at $120 each, wastage, supplies, administration, patient time and transport). The results were expressed as an incremental cost-effectiveness ratio measured by the net increase in health care cost divided by the net gain in health effects when comparing one intervention to another. The cost-effectiveness ratio is a measure of value for resources and is used to compare the value across other diseases and interventions.

Intervention strategies included routine vaccination of 12 year-old girls and temporary catch-up vaccination to age 18, 21, or 26. All strategies include Pap screening based on current rates in the US (NHIS 2005). The time horizon was lifetime outcomes for all birth cohorts during the first 10 years of vaccination program. With respect to the assumptions about vaccination coverage, in program year 1, the 12-year old birth cohort gets covered at a rate of 25%. In a program without a catch-up campaign, in year 2 another cohort of 12-year old girls is vaccinated. This coverage increases linearly, and beyond the fifth year, constant 75% coverage was assumed for each incoming birth cohort. It was assumed that a catch-up program to age 18 would occur over five years, and that girls were covered at a rate of 25% per year. This implies that of the original cohort of girls starting at age 13 in vaccine year one, 76% will be covered in year five. After year five, the catch-up program ends and only incoming 12-year old girls are vaccinated. Temporary catch-up programs were evaluated out to age 26. Other intervention assumptions included 100% lifelong vaccine efficacy among those without prior infection with vaccine targeted types, and a composite cost per vaccinated girl of $500. In the booster analysis, a cost of $250 was assumed per vaccinated girl. These assumptions were varied considerably in sensitivity analyses to reflect uncertainty.

With respect to cervical screening, the base case analysis assumed Pap smear screening starting three years after sexual debut, consistent with current recommendations. Coverage rates were based on data from the National Health Interview Survey (NHIS). Pap test sensitivity ranged from 70% to 80% and specificity was 95%. The cost of the Pap screen, including test cost, office visit, and patient time and transport was $85. In secondary analysis, alternative screening strategies were explored, including HPV DNA testing for primary screening starting at later ages every one to five years. With respect to the base case cost effectiveness results, expressed as $ per quality adjusted life year (QALY) , routine vaccination of 12-year old girls had a cost per QALY of <$50,000 compared with screening alone when only cervical cancer outcomes were considered. Including a five-year catch-up program up to age of 18 provided additional costs and additional benefits, and increased the ratio to <$100,000per QALY. Extended catch-up to age 21 increased the ratio to >$100,000per QALY, and to age 26 increased the ratio to >$150,000per QALY. Although there is no consensus on an appropriate cost-effectiveness threshold, commonly cited benchmarks include $50,000 and $100,000 per QALY, in which case pre-adolescent vaccination alone and catch-up to age 18 respectively would be considered most cost-effective.

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When including the benefits of averting genital warts, morbidity, and costs, the general themes were consistent with the base case, with decreasing cost-effectiveness as catch-up age increased, and catch-up to age 26 well over $100,000 per QALY. When the vaccine impact was included on other non-cervical cancers, catch-up programs to age 18 and 21 fell comfortably below $100,000 per QALY, and catch-up to age 26 was slightly above $100,000 per QALY. Two scenarios were then evaluated, including all outcomes together, one in which vaccine efficacy for non-cervical cancers and JORRP endures with 100%, and one in which it was 50%. Only when the best-case scenario of 100% efficacy was assumed on all health conditions did the ratios for all strategies fall below $100,000 per QALY. However, vaccine efficacy has not yet been reported for many of these conditions. Looking across all scenarios, the trends within and between strategies are fairly robust. Vaccinating 12-year old girls is consistently below $50,000 per QALY, catch-up to age 18 is consistently below $100,000 per QALY, under most scenarios catch-up to age 21 is below $100,000 per QALY, and catch-up to 26 generally exceeds $100,000 per QALY and is only below this threshold under the most generous assumptions about vaccine efficacy.

In sensitivity analyses, the impact of uncertain vaccine properties was explored. When full vaccine protection was assumed for 10 years, after which protection wanes completely, the pre-adolescent vaccination strategy provided only slight improvements in health benefits compared to screening along and cost nearly $150,000per QALY. With a booster at 10 years that extends lifelong protection, the ratio decreased below $100,000 per QALY. For the catch-up strategies, however, the policy implications do not change and are unattractive in both scenarios. If a vaccine wanes at 10 years, the risk of cancer actually increases in some birth cohorts, and catch-up strategies are more costly and less effective and are, therefore, dominated by pre-adolescent vaccination alone. With a 10-year booster, these strategies are all well over $100,000 per QALY.

An additional sensitivity analysis was conducted on the interplay between vaccination and screening coverage. Vaccine coverage was assumed to be random irrespective of a woman's screening status. If 5% of women are neither screened nor vaccinated, all strategies that involve a catch-up program exceed $100,000 per QALY. The ratio became even less attractive when it was assumed that girls who are vaccinated are more likely to be screened frequently, (i.e.,annually, bi-annually, or tri-annually) as adults, with all vaccination strategies exceeding $100,000 per QALY.

As with all model-based studies, the analyses have several unavoidable limitations, including natural history uncertainties. There are limited data on HPV transmission by type, age, sex. Sexual behavior data are primarily based on population averages from large surveys. Incidence, mortality, and quality of life associated with non-cervical HPV-related outcomes are less well-known. In terms of vaccine uncertainties, long-term vaccine efficacy for cervical lesions and warts is unknown. Vaccine efficacy for most non-cervical HPV-related outcomes are not yet reported. Despite these limitations, several general themes have emerged from these analyses. The cost-effectiveness of HPV-16 and -18 vaccination in the US will likely be optimized by achieving high, equitable coverage in adolescent girls. Targeting catch-up efforts up to age 18 is

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attractive, and up to age 21 is likely cost-effective, when the potential benefits of other non-cervical HPV-related outcomes and / or modifications in screening are considered. The cost-effectiveness of extending catch-up to older women becomes increasingly unattractive with age.

Review of HPV Vaccine Economic Analysis in the US

Harrell Chesson, PhD
Division of STD Prevention, CDC

Dr. Chesson summarized the cost-effectiveness estimates of catch-up vaccination in the US, first reminding everyone of the estimates of the cost-effectiveness of HPV vaccination of 12-year-old girls. Vaccination of 12-year-old girls has been shown to be cost-effective by the usual standards, with most estimates ranging from $3,000 to $50,000 per QALY gained. These estimates are consistent across a range of different models in numerous published studies. One reason for this consistency is that the cost-effectiveness estimates for vaccinating 12-year-olds are less sensitive to uncertainty in natural history and epidemiology of HPV, assuming long duration of protection. For example, the acquisition of HPV before being vaccinated is not really an issue when considering the vaccination of 12-year olds; however, this does become an issue for vaccinating older age groups. If models have to address these and other issues, a wider range of estimates across the models is to be expected.

Two studies thus far have estimated the cost-effectiveness of HPV vaccination of females over age 12 years in the US: the Kim / Goldie model and the Merck model (Elbasha, Dasbach, Insinga, *Emerg Infect Dis* 2007; Elbasha, Dasbach, Insinga, *Bull Math Biol* 2008). Dr. Kim just reviewed her model, the results from which are not yet published, but there is some background information relevant to her model that is available (Kim et al., *Am J Epid* 2007; Goldhaber-Fiebert et al., *J Natl Cancer Inst* 2008; Goldhaber-Fiebert et al., *Population Health Metrics* 2007).

The Merck model utilized a dynamic transmission model from a previously published cost-effectiveness study of vaccination of ages 12-24 years in US (Elbasha et al., *Emerg Infect Dis* 2007; 13:28-41*).* The authors have extended this model to address vaccination of women 25-44 years of age. The Merck model assumed that the degree of protection for three doses would be 90% against infection with the vaccine types; 95% against CIN associated with the vaccine types; and 99% against genital warts attributable to the vaccine types HPV-6, 11. They assumed no protection for those receiving less than the full three doses, lifelong duration of projections, and a vaccine cost of $360 per series.

It was assumed that roughly 75% of those entering the model at age 12 years would be vaccinated (after a five-year phase-in in which coverage rates increase linearly). The annual probability of being vaccinated was assumed to be 35% for ages 12-19 years, 19% for ages 20-29 years, and 5% for ages 30-44 years. With respect to compliance, Merck assumed that 75% of those receiving the first dose received the second dose,

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and that 75% of those receiving the second dose received third dose. Health outcomes included: CIN, cervical cancer, genital warts, including prevention of genital warts in males as a result of female vaccination.

From the base case analysis, it was estimated that adding vaccination of 12-24 year olds would have an incremental cost per QALY gained of $8,600. The incremental cost effectiveness of expanding vaccination to include 25-29 year olds was estimated to cost $46,400 per QALY gained. As the cutoff age of catch-up vaccination increased, the cost per QALY gained increased as well to over $200,000 dollars when expanding the vaccination program to include those 40-44 years of age.

The vaccine becomes less attractive from a cost-effectiveness standpoint at a younger cut-off age in the Kim / Goldie model than in the Merck model. These cost-effectiveness estimates differ because of the different model structures and assumptions. In addition, the modeling of HPV requires complex models, made even more difficult by the uncertainty in the natural history and epidemiology of HPV. Also, the incremental health impact of HPV vaccination decreases as the cutoff age of catch-up vaccination increases, which could also increase the disparities in the cost-effectiveness ratios

In terms of the differences in the models and assumptions in the Merck and Kim / Goldie models, the Merck model was a dynamic model and they used the same model to address HPV incidence as well as the incidence of HPV-related health outcomes. The hybrid model described by Dr. Kim used a dynamic model of HPV transmission and then applied this information into the individual-based simulation model. The Merck model addressed the four vaccine types, while the Kim / Goldie simulation model examined HPV-16, -18, and also included two categories for other high risk types and low-risk HPV types. Because each model included a dynamic component, both models do address indirect effects; however, because the model structures are different, the degree of impact of these indirect effects may differ across the models. The base case parameter values in both models were based in part on the literature, and both models do yield results that are consistent with observed data. The selection of the base case parameter values for the Merck model was based in part on an expert review panel and on vaccine trial data; whereas the Kim / Goldie model used a likelihood based calibration as described by Dr. Kim earlier.

Both models included cervical cancer screening. In the Kim / Goldie model, the individual-based model allows the tracking of the individual's history of screening and treatment; whereas in the Merck model, the heterogeneity in screening frequency was approximated using age-based annual probabilities of screening. The age at which acquisition of new sex partners ceases varied across the two models. Both model did address a long-term horizon, although the methods that they used to do this differed. Effectively, the cost per vaccinated person was approximately $500 in both models. If the $360 vaccine cost in the Merck model is adjusted for compliance to take into account those who are vaccinated but do not receive any benefit, the effective cost per person vaccinated was approximately $500. In the Kim / Goldie model, the cost was

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$500 because they included administrative costs, patient time cost, et cetera. The patient time and travel costs that were included in the Kim / Goldie model not only applied to the cost of vaccination, but also to the cost of the HPV-related health outcomes. Both models addressed cervical cancer, CIN, and genital warts in females. However, the Merck model included an estimate of the impact of CIN on quality of life and also included the potential benefits of preventing genital warts in males.

With respect to the vaccine coverage assumptions, in terms of the annual probability of vaccination by age, the Merck model assumption of 70% coverage for those reaching 12 years of age after the fifth year of the program was similar to the estimate in the Kim / Goldie model in which vaccination coverage of 12-year olds increased to 75% after the fifth year. However, it is important to note that the Merck probabilities are not adjusted for compliance; therefore, taking into account that not all of those vaccinated will receive the full series, the effective coverage rate is lower than suggested. This is perhaps important because the sensitivity analyses that Merck has performed thus far suggest that as the coverage of 12-year olds increases, the cost-effectiveness of catch-up vaccination decreases.

The complexity of HPV and the uncertainty in the natural history of HPV contributes to the divergence in the cost-effectiveness estimates. Selected examples of parameters for modeling HPV incidence included: percentage of men, women in each sexual activity group, by age; number of new partners per year in each sexual activity group; sexual mixing matrix; HPV transmission probability; vaccine efficacy; probability of HPV clearance; probability of natural immunity; degree of protection offered by natural immunity; progression of invasive cancer; and cancer survival probabilities. The progression from HPV acquisition to the HPV-related health outcomes must be modeled as well. Selected examples of parameters for modeling HPV-related health outcomes included: progression of HPV to CIN1; progression of HPV to CIN2,3; progression of CIN1 to CIN2,3; progression of CIN2,3 to invasive cancer; HPV clearance; CIN1, CIN2,3 regression; probability of natural immunity; degree of protection offered by natural immunity; progression of invasive cancer; cancer survival probabilities; and probability of symptom detection. This reflects the complexity of these models, and the difficulty in comparing these across the models, given that these parameters are not accounted for the same way in the models. Changing one parameter value may require the change of more values in the model because of the calibration process. That is, the two modelers cannot be asked to come up with the exact same list of parameter values to determine how the results compare.

With regard to how the incremental health impact of quadrivalent HPV vaccination decreases as cutoff age of catch-up vaccination increases, and how this can have an impact on the divergence of the cost-effectiveness estimates, the vaccination of ages 12-24 has a major impact in terms of the gain in QALYs. However, the marginal impact of adding additional ages is relatively small.

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In the Merck model, vaccinating women over age 24 years provides less than 5% of the QALYs gained by vaccinating women 12-24 years old. The marginal cost associated with vaccinating older ages represents about 40% the marginal cost of vaccinating 12-24 year olds. Therefore, expanding the coverage to include women 25-44 provides about 5% of the benefit of vaccinating 12-24 year olds, but at 40% of the cost. It is also possible that this decreasing marginal benefit could account somewhat for the divergent cost-effectiveness estimates.

The cost-effectiveness ratio was derived by dividing the net increase in health care cost by the net gain in health effects. As the denominator becomes smaller; that is, as the numbers of QALY gained decreases, it is possible that two cost-effectiveness ratios can differ substantially even though the difference in the estimated number of QALYs gained is small in absolute terms.

In conclusion, cost-effectiveness of catch-up vaccination varies across the two models. However, the wide range of results across the different models is not completely unexpected due to the uncertainty of natural history, the epidemiology of HPV, and different modeling assumptions and methods. Vaccination becomes less cost-effective as the cutoff age of catch-up vaccination increases. Extending vaccination beyond the mid-20's would account for a small percentage of overall benefits of vaccination due to the decreasing incremental health impact as the cutoff age of catch-up vaccination is increased.

Discussion

Dr. Judson recognized that the ACIP was increasingly being asked to consider cost-effectiveness studies, and that as a public health agency it was imperative that this be done; however, he stressed that it must be done with great care. With that in mind, he requested clarity on what ACIP was recommending that the taxpayer buy for $50,000 per QALY and what that meant in terms of HPV infection. Someone has to pay for this.

Dr. Kim responded that one of the reasons they wanted to show the members a range of different outcomes and uncertainty analyses was to show whether the results are stable across various assumptions because the truth is not known. The models are used as a tool to help simulate the truth in order to address the policy question the best way possible. Everyone would say that all models are wrong because they are simplifications of reality. The best that can be done in terms of offering information for policymakers is to examine base case analyses, the best available data, and varying assumptions across a wide range. With respect to the $50,000 cutoff, it was shown across a wide range of assumptions that pre-adolescent vaccination strategy is stable at under $50,000. The purpose for conducting and presenting these analyses was not to determine what strategies fall under hard and fast rules because there are no hard and fast rules for decision making.

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Dr. Judson understood that without vaccine and with increasing screening and other efforts to prevent cervical cancer deaths, deaths have declined from approximately 12,000 per year to 3,000 to 4,000. If that trend was continuing, he wondered if or how that was factored into the cost-effectiveness studies examining 5-20 years into the future.

Dr. Kim responded that one of the results she had not shared in the interest of time was an analysis of the implications of different screening policies with the introduction of HPV vaccination. Based on this analysis, the cost-effectiveness of vaccination strategies is very sensitive to what society will do in terms of cervical cancer screening. With more aggressive screening, even without vaccination, it has been shown that annual screening as recommended by the guidelines is not very cost-effective. It is very expensive per QALY gained. If vaccination is added, a lot of resources will be expended on attempting to get the incremental cancer case.

Dr. Judson thought that gynecologists would argue that there are other benefits in terms of women's healthcare to a screening visit, so it should not be viewed totally in isolation.

Dr. Kim responded that part of the limitation of the models is that all of the positive externalities cannot be included. The model was presented as a single tool for providing more information. The decision will have to take into consideration the other positive externalities.

It appeared to Dr. Judson that each of the models, by taking an incrementally large range starting with 12 years, averages down the cost-effectiveness and averages up the cost. Without looking at that full range, he wondered what they should tell a 26-year old woman who has not been a part of this what it will cost her and what the benefits will be. For example, his own daughter recently had a low-grade CIN and her physician offered her $500 worth of vaccine.

Dr. Kim replied that exposure rates of HPV among women of different ages, as well as vaccine efficacy data by age, could be analyzed to help inform particular patients where they fall in terms of how may partners they have had, whether they are at high-risk, and if they would benefit from receiving the vaccine. Individual-based questions are very different from population-based policy questions that must be addressed.

Jim Turner, American College of Health, inquired as to whether there was a way to include in the cost of medical care some of the psychological trauma associated with acquiring a sexually transmitted infection. Working in college health, he has observed women and men struggling with these issues. This becomes a major relationship issue and relationships dissolve over it. This could impact the figures.

Dr. Kim responded that this was included to some extent as an impact on quality of life in both models. Direct medical costs for treating have been included, although additional costs for therapy or further management are not included.

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It was clear to Dr. Lieu that beyond the age of 26 the Kim / Goldie model predicted that the cost would be well above $100,000 per QALY saved to extend catch-up vaccination. There is a general observation that models created by academics tend to be more conservative, while models created by manufacturers tend to be more generous to vaccine. She wondered how conservative Dr. Kim thought the Kim / Goldie model was. If she was Merck, she might make the observation that the Kim / Goldie model did not give credit for preventing genital warts in males or for the impact of CIN on quality of life.

Dr. Kim responded that there were multiple dimensions of assumptions that they made. To the best of their ability, they relied on natural history data from recent studies, longitudinal studies, and collaborations with large epidemiological study groups. In terms of the vaccine efficacy and quality of life costs, they have been trying to use the published literature to the best of their ability. Interestingly, during the manuscript review process they received input from both directions, sometimes being told they were being entirely too generous to the vaccine and to non-cervical outcomes that have not yet been reported. They removed the analysis of males because there are no data reported for males at this point. They certainly have included assumptions about natural immunity that interacts with vaccine-induced protection that may be too conservative. There is a lot of uncertainty in the degree and duration of natural protection after infection and clearance. On balance, she thought they fell somewhere in between conservative and generous; however, it is difficult to assess this.
Dr. Judson pointed out that the models resulted in an order of magnitude difference for the age groups of interest. A lot of parameters are listed that might be feeding into that, but at the same time, he was impressed that the investigators attempted to have comparable models. He wondered what was driving the substantial difference.

Dr. Chesson responded that it was safe to say they did not know. Some of the differences are easy to interpret, such as the inclusion of the benefits of preventing genital warts in males, which would make the vaccine appear more cost-effective. There are many other differences and it is not yet clear how they drive the results.

Dr. Schuchat expressed surprise at the difference between the two models in the age at which new sexual partners cease. The Merck model used 85 and the Kim / Goldie model used 50. She wondered whether that was based on literature.

Dr. Kim responded that it was difficult to take information from the literature and turn those data into parameters that can be directly put into the models. The investigators attempted to base sexual behaviors on data from large national surveys. The age of 50 was an assumption that was made. The upside is that for the simulation model, they still calibrated HPV prevalence in the older age groups. It is not that it drops to zero, it is just that the herd immunity benefits are constant after that 50-year age group. It is not that someone could not acquire HPV after age 50, it is just that the mixing, which would result in the herd immunity benefit wanes to zero after 50.

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Erik Dasbach Merck, pointed out that one of the fundamental differences in the models is that they are very different structurally and they are very different in that Merck analyzed within a dynamic model all of the costs and benefits within a single model. The Kim / Goldie model is a series of models. He still did not believe they knew how the model structures contributed to the differences observed in the numbers. When they tried to harmonize the parameters between the models, Merck's results diverge further from the Kim / Goldie model.

Stanly Gall, American College of Gynecologists, noted that with respect to the cost of abnormal cytology in 26-year olds, the cost would be approximately $2,000 for a work up. However, it would not be known what type caused the abnormal cytology. That was the reason for the recommendation of the vaccination at that time.

Dr. Beck pointed out that ACIP was charged with making the best-informed recommendations they could based upon the evidence. This has been an area in which they have not had a mechanism for examining the evidence to assess it one way or another. With these models, what he was seeing for the first time was an ability to review a series of models in an organized way, understand the underlying assumptions, and be able to compare them. Prior to that, they had nothing to compare and a number without a comparative is irrelevant. He thought that while this was not perfect, it was a great step forward and that they would become better at it. He was encouraged by the presentations. He was resistant to the idea that they set a parameter of taking, for example, all QALYs of $50,000 or less and throwing out all those above that cutoff. That is too simplistic. The models offer them the ability to consider parameters and ranges and deal with some of the questions that had been raised during this discussion. For example, what other issues should be considered that might change the decision? From a business perspective, major decision are not made without having this type of modeling. While he stressed that he was not anti-manufacturers, they have a particular product or purpose that they are trying to get across and they are trying to present it in the best way possible and they should do that. However, it is incumbent upon the ACIP to assess that to determine how reasonable it is as the quality of life and effectiveness are put into the whole answer of their recommendations. He encouraged them to continue on this course.

Recommendations for Women Ages 26-45 Years: Issues and Options for Quadrivalent HPV Vaccine

Eileen Dunne MD, MPH
Division of STD Prevention, CDC

Dr. Dunne presented ACIP considerations for vaccination of women 27-45 years of age with the quadrivalent HPV vaccine, highlighting the data reviewed by the ACIP HPV workgroup over the last year. She began with a background on the existing recommendations for use of the HPV vaccine, discussed recent presentations to the ACIP on the HPV vaccine, and provided an overview of the considerations of the HPV

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workgroup for vaccinating 27 through 45 year old women—a process that began in preparation for FDA's possible licensure of the vaccine in this age group.

The workgroup reviewed the epidemiology of HPV and the burden of HPV-associated diseases among women; the efficacy, safety, and immunogenicity data of the HPV vaccine; population impact; economic models; and programmatic issues. In June 2006, ACIP recommended routine vaccination of girls 11 and 12 years of age, with catch up vaccination of 13 through 26 year old females. These recommendations emphasized immunizing girls at 11 and 12 years of age, given that many in this age group had not yet had sex and were likely to have the full benefit of the vaccine. In February 2008, there were presentations to ACIP that covered issues on epidemiology of HPV infection, cost-effectiveness, and efficacy / safety of the HPV vaccine in women 24-45 years.

With respect to the epidemiology of HPV infection, including acquisition of infection and development of cervical cancer in women, most women acquire HPV soon after sexual initiation. In the majority of these, infections clear. Persistent infection with cancer-associated HPV types can lead to the development of cervical cancer precursor lesions or CIN2,3 over many years, and up to decades later, cervical cancer. There are current recommendations for routine cervical cancer screening to detect and treat the cervical cancer precursor lesions early before they develop into cancer.

Cumulative incidence of HPV infection months after sexual initiation among young women is a reminder of the fact that much exposure to HPV is occurring soon after sexual initiation. In a relatively short time frame of 48 months, over 50% of young women had acquired any of 40 genital HPV types, and over 10% had acquired HPV 16 (Winer R, et al., Am J Epidemiol, 2003). It is important to frame the information on HPV acquisition around the data available on sexual behavior in the US. The percentage of females who have had vaginal sex increases each year through young adulthood. At 15 years of age, 26% of females have had vaginal sex, by age 17 this has increased to 49%, and by 24 years of age, 92% of females have had vaginal sex (Mosher et al. NCHS report. 2006).

Incidence data may provide information on the possible preventable vaccine-type infections in mid-adult women. There are no incidence data in adult women from the US, but there are available data from worldwide cohorts, and the clinical trials of the quadrivalent HPV vaccine. A study of women attending cervical cancer screening centers in Bogotá, Colombia demonstrates decreased incidence of HPV vaccine type infection in women after their mid 20s. The highest incidence of infection with HPV-16, -18, -6 or -11 occurred among the women in their late teens and early 20s, and generally decreased in their mid 20s. It is unclear whether this is due to immunity, lack of exposure, or other reasons (Munoz N, et al., JID 2004).

Other data on incident infection in older women come from the quadrivalent HPV Vaccine clinical trials. With respect to the data on incidence of HPV-16, -18, -6 or -11 infection from the placebo arm of the clinical trials and information on acquisition of vaccine-type infection during the trial, with increasing age, the incidence of infection with

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HPV-6, -11, -16 or -18 decreased from 7.4 infections per 100 person years in 24-29 year olds to 1.9 infections per 100 person years in the 40-45 year olds (Haupt R, Merck presentation to ACIP, Feb 2008).

Although there are no data on vaccine type acquisition in adult women from the US, there are prevalence data for the high-risk or cancer-causing HPV type prevalence among women from a representative survey of the US population (NHANES). These data show that the peak prevalence is in the early 20s, and prevalence generally declines in older age groups. The infections detected in older age groups likely represent persistent infection, rather than acquisition of infection. Data are also available on seroprevalence to HPV 16 from NHANES. HPV antibodies are a better measure of previous exposure to HPV then DNA prevalence, but antibodies do not develop in all women who have been exposed to HPV. Therefore, seroprevalence data is an under-representation of the percentage of women with previous infection to HPV 16. These data show an increase in HPV-16 seroprevalence among young women due to acquisition of infection. The seroprevalence to HPV-16 is as high as 25% among women in their early 20s, and then the seroprevalence remains constant or declines, possibly indicating limited new exposures to HPV-16 in the older women (Stone KM, JID 2002, Dunne EF, JID 2004).

With respect to data on CIN2,3 and genital wart diagnoses from two sources (e.g., claims data and an HMO), the peak in the genital wart diagnoses for women occurs in their early 20s and for CIN2,3 in the late 20s. Infection that can lead to these diseases is often acquired months before a wart diagnosis and years before a CIN2,3 diagnosis (Insinga RP, CID 2003, Insinga RP, Am J Ob Gyn 2004).

Regarding the efficacy data for the quadrivalent HPV vaccine in women 24-45 years, Dr. Dunne reminded everyone that approximately 3,800 women 24-45 years of age were evaluated over 2.2 years of follow-up. The vaccine efficacy for disease outcomes of HPV 6/11/16/18, CIN, or external genital lesions was 92%. Few CIN2,3 and adenocarcinoma events occurred in this smaller and shorter duration trial. It is important to note that these outcomes were the primary outcome of the trials in younger women. The vaccine efficacy for this outcome was 75.2%. There is no intent-to-treat analysis to date. As Dr. Chesson reviewed earlier, there is a decreasing incremental health impact of the quadrivalent HPV vaccine as the cut-off age of HPV vaccination catch-up increases. Some reasons for this are that more women will have already been exposed to HPV vaccine type infection, and the incidence of HPV decreases with increasing age. Also, as reviewed earlier by Dr. Chesson, the two models show that HPV vaccination also becomes less cost-effective as the cut-off age for catch-up vaccination increases. These models demonstrated that the age at which cost-effectiveness estimates crossed a certain threshold differed. For example, when using the $100,000 per QALY gained threshold, one model met that threshold at age 21 years, and the other model met that threshold at 34 years.

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At this time, most members of the workgroup did not support extending catch-up vaccination of women > 26 years, but would support a statement that women may elect to be vaccinated. One workgroup member supported extending catch-up vaccination of women through age 45 years. The workgroup will continue discussions of these options as they await further information provided from the vaccine trials, economic data, and FDA review.

Discussion

Dr. Temte thought that having data for all-comers would be a crucial requirement for making decisions.

Stanley Gall, American College of Gynocologists, disclosed that he was the individual on the workgroup who supported extending catch-up vaccination through age 45. It is anticipated that the vaccine will be shown to be safe and efficacious. At every meeting he attends where he speaks on this vaccine, the primary question from obstetricians and gynecologists regards when this vaccine will be approved to age 45. This comes from the requests they receive from their patients. The abnormal cytology that occurs with CIN1, CIN2,3 external genital warts, and cancer are largely treated by obstetricians and gynecologists. In the committee, it was stated that only 5% of HPV spectrum diseases occur after the age of 26. He did not believe that was true, nor did he believe that any of the 46,000 obstetricians believed it either. There is significantly greater incidence that 5% occurring after age 26. It was also interesting to him that in Dr. Dunne and Dr. Markowitz's paper on sexually transmitted diseases, studying 11,000 people, the largest incidence of external genital warts occurred in the 26-35 and 35-45 year old groups. A universal recommendation for a catch-up period to age 45 establishes a medical standard and should be available to all women regardless of whether they are private or public. The emerging evidence suggests that some adults are not receiving new vaccines because of increased costs. Many states' Medicaid programs are struggling with the vaccine even in the 19 through 26 year old age group. Prioritization is noticeable. This committee is advocating explicit prioritization of HPV vaccines based on funding, but is advocating no recommendations to prevent HPV spectrum diseases. The alarming number of 5% amounts to 200,000 Pap smears; 50,000 patients with external genital warts; 70,000 patients with CIN1; 16,500 patients with CIN2,3; 550 patients with cervical cancer who potentially will not be protected because of the recommendation not to vaccinate through age 45. He assured ACIP that ACOG's position was that if the FDA approves this vaccine to age 45, the ACIP should recommend it.

Dr. Sandy Fryhofer said that as a practicing physician, she has women in her practice who have been in a monogamous relationship who in their 40s become divorced or widowed, and then they venture out again. While one of the model suggested that there were no new sexual partners possibly after 50, this is not the case in practice. This discussion was thoughtful and fascinating, but when in a room with a patient it changes

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the scenario. She expressed her hope that the vaccination would be available for these women.

Dr. Dunne re-emphasized that most members of the working group did support a statement that women may elect to be vaccinated.

With respect to fulfilling some mission of decreasing disease burden in the 45 and older age group, Dr. Sumaya agreed to a point. While he recognized this as an important step, individuals are not receiving the vaccine in the age group that is already highly recommended. Hence, a more positive step would be to implement vaccination in the larger group for whom the vaccine is highly recommended. They observed this same type of approach with respect to PPV-23 and trying to expand indicators. That said, it seemed there would be a greater impact on disease burden if coverage was increased in the highly recommended group. While ACIP does not necessarily delve into the implementation or application of the recommendations, it seemed that this needed to be included in the context of QALY and in the total impact of reducing human disease via vaccines.

Dr. Judson thought a number of people would agree that if they wanted to accomplish the greatest public health benefit, they would do everything they could to develop recommendations to assure that the demographic groups of highest risk of cancer were being immunized immediately at age 12, well before their period of exposure. For the ACIP to concentrate its time on an almost infinitesimally declining benefit would be a misdirection of their charge. An easy way out for them, which he hoped they would never take, would be simply to approve every vaccine that has been approved by the FDA for any person for whom it is not contraindicated. While that overstated the point, he believed the ACIP's charge was simply somewhat different and probably narrower than the FDA.

Dr. Morse inquired as to whether there was evidence about how much of the burden of disease in the over 45 year old age group was due to new disease versus chronic disease from previous infection.

Dr. Markowitz said that the 5% figure that Dr. Gall mentioned was from Dr. Chesson's presentation. Dr. Chesson was not implying that only 5% of disease occurs in that older age group. Instead he was pointing out that vaccination of that age group would only result in a gain of QALYs equal to approximately 5% of the gain in QALYs associated with vaccinating the younger age groups. It is true that disease does occur in that age group, but it is due to infection acquired earlier.

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Quadrivalent HPV Vaccine Dose Intervals: VFC Vote

Dr. Greg Wallace
CDC / CCID / NCIRD / ISD

Dr. Wallace reminded everyone that with the original recommendation for the quadrivalent HPV vaccine, minimum intervals were established and placed in the catch-up schedule as part of the immunization schedule, as well as included in the VFC resolution. The HPV vaccine ACIP statement defined the minimum dosing intervals for HPV vaccine but only for doses 1 to 2 (4 weeks) and doses 2 to 3 (12 weeks). They became aware that some clinicians were routinely using these minimal intervals as a compressed schedule as a routine basis for 13-26 year olds, which was an unintended consequences of the minimum intervals. When the minimum intervals were established, it was done only for between doses 1 to 2 (4 weeks) and doses 2 to 3 (12 weeks) and not 1 and 3. The way that the studies were conducted, the intervals between 1 and 3 were also important. In March 2008, in order to make the routine recommendation consistent with the data available from the clinical trials, the *Catch-up Schedule* was updated to clarify that the third dose of HPV should be administered at least 24 weeks after the first dose. So, the interval between doses 1 and 3 is also important, at least with the information available. For those who only had a 16-week, or 4 + 12 week interval between 1 and 3, CDC is not recommending that they be re-vaccinated, but does want to emphasize that there should not be routine compressed for the routine recommended age groups. That will be dealt with in future publications of the general recommendations.

At this time, the ACIP was asked to vote upon an update of the VFC Resolution with the caveat that was added that is consistent with intended consequences and what is currently in the *Catch-up Schedule* to clarify that the third dose of HPV should be administered at least 24 weeks after the first dose.

Motion: VFC Resolution

Dr. Baker motioned that ACIP accept the VFC resolution as presented by Dr. Wallace. Dr. Stinchfield seconded the motion. The motion carried with 15 affirmative votes, 0 negative votes, and 0 abstentions.

Public Comment: June 25, 2008

No public comments were offered during this session.

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Thursday, June 26

Agency Updates

CDC / CCID / NCIRD

Dr. Schuchat indicated that CDC / CCID / NCIRD was completing transition of the immunization grantees, the state and local programs, to a centralized vaccine distribution and management system. The last of the grantees would be transitioning in the next week. The next major effort in the modernization will be updating the software for ordering and vaccine tracking, over the next year or two. It is well known that CDC / CCID / NCIRD conducts a very large, on-going telephone-based household immunization survey, with physician provider verification of vaccine history to track immunization coverage in young children, and more recently in teens, to provide state level and national data. Two modules have been added to the National Immunization Survey, in addition to the general immunization coverage, which pertain to: 1) socioeconomic status and financial, insurance, and economic barriers to vaccination; and 2) vaccine acceptance that gets at parental attitudes and behaviors, and can be linked to vaccine practice for their children. The vaccine acceptance component has been in the field this year, and data are expected next year on that. These will be on-going and will provide CDC with important information about trends in the country.

Center for Medicare and Medicaid Services (CMS)

Dr. Linda Murphy reported that states are slowly and painfully increasing their administration rates. She believed that two more will come up to nearly maximum administration fees. She encouraged everyone to keep working at this effort, even though it was slow. She also mentioned that in working with the CDC on the VFC Operations Guide, the importance of putting in place the fraud and abuse policies. With the cost of the program being in the billions currently, immunization and Medicaid must collaborate more closely to eliminate fraud and abuse. She expressed her constant amazement at how creative some people were at attempting to work the loopholes.

Department of Defense (DoD)

No update.

Department of Veterans Affairs (DVA)

No update.

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Food and Drug Administration (FDA)

Dr. Florence Houn reminded everyone that on May 29, 2008 the FDA published major proposed revisions to prescription drug labeling about pregnancy and breastfeeding. FDA is collecting public comments not only from ACIP, but also other liaison organizations by August 2, 2008. The FDA is proposing to eliminate the current pregnancy categories A, B, C, D and X. They have heard that practitioners find these confusing, which FDA recognizes as well. The FDA is also proposing to eliminate the labor and delivery section, and incorporate labor and delivery information into the pregnancy subsection, which will be more of a narrative summary with risk information, and a best data summary of what exists so that practitioners will have more information. The proposed rule is intended to create a consistent format. The FDA is also proposing that instead of the nursing mothers section, a lactation subsection with labeling of specific summary risk and summarization of risks of medicines to developing fetuses and breastfeeding infants be included. Data supporting that summary would be included in the labeling. This is a major change and comments on the proposed rule were welcomed.

Heath Resources and Services Administration (HRSA)

Dr. Geoffrey Evans reported that since the last ACIP meeting, the court has held the second theory general causation hearing, and two test cases in the autism proceeding. Leading up to that hearing, one of the potential test cases was reviewed by the department this past fall and entitlement was conceded in that case. It is still in active litigation, in terms of damages. That particular case created a great deal of media interest. The Special Master in that case has expressed an interest in getting further information out, and there is a good chance that that will be forthcoming, within the constraints of the law and the consent of the parties. The hearing took place for three weeks in May, and the entire audio files of every day of the proceedings, as well as transcripts, will eventually be posted on the court's website. Those interested could Google the "US Court of Federal Claims" and "autism" to find the site where there are various links to the files. Otherwise decisions will be forthcoming. HRSA expects the decisions for the hearings that took place in 2007 probably to be handed down by the three Special Masters either later this summer or in the fall. Decisions in last month's hearing, the two test cases and a third test case, that will be next month. These will be probably be handed down in about three-fourths of a year or longer. It takes a while with briefs going back and forth after an actual hearing. In conclusion, there is a third theory that is being pursued, which is that of theory of MMR vaccine only. It is not clear that that actually is going to be a general causation hearing, which was originally scheduled this September. There are further discussions between the court and petitioners on that matter.

Indian Health Service (IHS)

No update.

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National Institutes for Health (NIH)

Following the disappointment of the HIV vaccine trial, which really called into question a lot of the scientific theories, NIH has established a new branch in the Division of HIV / AIDS on vaccine discovery. This is a clear indication that they are going back to square one to develop the science for a new generation.

National Vaccine Program Office (NVPO)

No report.

National Vaccine Advisory Committee (NVAC)

Dr. Gus Birkhead expressed his gratitude for the opportunity to provide the ACIP with an update on the activities of the National Vaccines Advisory Committee. He recently assumed the Chair of the committee and found it helpful to review the Public Health Service Act that described the duties of the National Vaccine Program, and the NVAC, which he shared. He briefly reviewed part of the authorizing legislation for the National Vaccine Program (NVP) (Title XXI Public Health Service Act Sec. 2102: National Vaccine Program). NVP Responsibilities include vaccine research; vaccine development; safety and efficacy testing of vaccines; licensing of vaccine manufacturers and vaccines; production and procurement of vaccines; distribution and use of vaccines; evaluating the need for, the effectiveness, and adverse effects of vaccines and immunization activities; coordinating governmental and non-governmental activities; and funding of federal agencies. Dr. Birkhead assumed it was fair to say that the full panoply of these responsibilities had not totally been assumed at this level by the NVP, but it is a work in progress.

An additional item in the authorizing legislation is the development of a national vaccine plan, which establishes the priorities and research; development of new vaccines; optimal use of resources; et cetera. A national vaccine plan was developed in 1994, but has not been updated since that time. The process is underway to revise and update the 1994 version, which is expected to be completed in approximately one year. The National Vaccine Program also is to submit an annual report to Congress, and the National Advisory Committee is set up as the advisory committee to this process.

NVAC is charged with recommending ways to encourage the adequate supply of safe and effective vaccines; establishing research priorities and other measures to enhance safety and efficacy of vaccines; implementing implementation of Sections 2102 and 2103; and identifying annually for NVP the most important areas of government and non-government cooperation in implementing sections 2102, 2103, and 2104.

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Some recent accomplishments include a report, published in the last year, of information systems development, and also a report that was recently been finalized on adolescent immunization. In addition, they have established a new working group structure in NVAC, and currently have three active work groups: Vaccine Finance, Vaccine Safety, and Adult Vaccination.

The Vaccine Finance Working Group, chaired by Dr. Birkhead, attempts to examine the issues that have arisen due to the number of new and expensive vaccines that have been added to the schedule in the last five to six years that have put pressure on both the public and private sectors to cover the cost of the vaccines, as well as the administration of the vaccines. This has been a process with a very broad public stakeholder input. The Vaccine Finance Working Group convened a two-day stakeholder meeting in Rockville, Maryland in April 2008. The stakeholder meeting was very broad, including representatives from the pharmaceutical industry, insurance industry, large and small employers, state Medicaid directors, consumer and parent groups, and many other groups. He reported that it was a lively and productive meeting. Draft recommendations were presented to NVAC during its June 2008 meeting. The work group's plan is to revise the recommendations based on public comment, and to present them to NVAC for a final vote. The NVAC recommendations will be officially transmitted to the Assistant Secretary for Health during the September 2008 meeting.

With respect to the current framework for the finance recommendations, Dr. Birkhead thought that the general categories would hold. Issues have been identified in the public and private sectors. In the public sector, there are issues regarding how to pay for the vaccines themselves. While VFC is an entitlement, it does not cover all of the children that state and local immunization programs want to cover. The 317 Program has not historically kept pace with VFC, so there are a variety of issues pertaining to how to cover vaccines in the public sector.

In terms of the current issues regarding vaccine administration, the VFC program essentially covers vaccine administration for Medicaid-eligible children through the Medicaid program. However, the other VFC-eligible categories (e.g., uninsured, under-insured, Native Americans, et cetera) there is no administration fee. Providers can request payment from the parents, but cannot turn people away for inability to pay. Therefore, in a sense, there is a gap in the public program in terms of vaccine administration fees. There simply are some children for whom a vaccine administration fee is not available. In addition, for those children on Medicaid, most states do not reimburse at the maximum allowable level. In fact, many states are far below the allowable level. As more vaccines are added, this becomes an increasing problem for the provider community, given that they do not have adequate support for vaccine administration. In the private sector, there are similar issues relating to insurance coverage for vaccination in terms of how complete it is. States regulate the insurance industry within their states, but do not regulate the large employer, self-funded plans, which are exempt from state regulation. Many issues arise regarding how to assure

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that health insurance is fully covering both the cost of the vaccine and the cost of the vaccine administration. This is a complicated area and a number of recommendations are posted on the NVAC website, which will continue to evolve until the September meeting.

The Vaccine Safety Working Group's first goal is to review the CDC Immunization Safety Office (ISO) Scientific Agenda and provide feedback. This document is posted at the following address http://www.cdc.gov/vaccinesafety/agenda.htm. Once that goal is completed, the working group will take a broader look at vaccine safety across the federal agencies, and begin to develop recommendations for the federal government in general around the vaccine safety agenda. This process will involve active public engagement, with plans underway to consider the idea of having regional meetings or other forums where input can be obtained from the public about these issues. This is critically important in order to maintain trust in the vaccine system.

The Vaccine Safety Working Group will address four research topics (e.g., Specific Vaccine Questions; Clinical Outcomes; Special Populations; and Vaccines and Vaccinations). They will also address capacity topics within each of these research topics. For each of the research topics, sub-groups have been formed. They hope by the September meeting to have a report for the full group regarding the status of each of these groups in developing some feedback for CDC specifically.

The Adult Vaccination Working Group is charged with examining the broad public health adult immunization activities across all Health and Human Services (HHS) programs, identifying gaps, and recommending improvements, particularly in program implementation, coordination, evaluation and collaboration across agencies, that will lead to improved vaccination uptake in adults in these programs. This committee will also consider finance issues jointly with the Vaccine Finance Committee. The Adult Vaccination Working Group expects to develop recommendations throughout the next year. Dr. Birkhead encouraged ACIP members to provide input or comments on issues in any of these areas.

The National Vaccine Program office is drafting the plan with input from each of the federal agencies, including CDC. NVAC will provide input into that process, and the Institute of Medicine (IOM) has empanelled a committee to review the overall vaccine plan. The IOM link to review the plan is http://www.iom.edu/vaccineplan. The IOM has scheduled a series of stakeholder workshops, the first of which is July 24 in Chicago. There will be four other meetings held throughout this year and in early 2008 around the country. Dr. Birkhead invited ACIP members to attend any of these meetings. He stressed that this is a chance to provide input into the broader vaccine plan, and recommended that ACIP members go to the site to familiarize themselves with the overall components of the plan. The National Vaccine Plan Draft Priorities include the following topics: Enhance Vaccine Research and Development; Develop Specific Vaccines; Adult Immunization; Adolescent Immunization; Childhood Vaccination; Financial Barriers; Vaccine Supply; Vaccine Safety; Vaccine Injury / Compensation; Communication and Education; Surveillance; Preparedness; and Global Health.

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NVAC's future priorities are to assure a strong, continued commitment to the national immunization effort; advise during federal administration transition; carry out the mandates of Title XXI; participate in the development of the National Vaccine Plan; study of NVAC's effectiveness; and improve processes for stakeholder input and public engagement. Again, Dr. Birkhead welcomed input from members of ACIP and those in the audience with respect to how to make this advisory committee a more effective process. He stressed that acquiring stakeholder input and public engagement is going to be a major thrust across all of the areas in which NVAC is interested. In conclusion, Dr. Birkhead acknowledged the staff in the National Vaccine Program office who have worked diligently on a number of these working groups.

Discussion

Dr. Duchin, NACCHO, requested a reminder from CMS of what the maximum reimbursement fee is nationally, and how many states had reached that maximum.

Dr. Murphy replied that each state has its own maximum fee. It was set in the Federal Register of October 1, 1994, so there is no set fee for the nation. Each state has a different rate. She offered to make the list available, as it is not longer available on-line. She suggested that anyone who was interested email her a request for this information.

Dr. Baker inquired as to where the information Dr. Houn discussed could be found.

Dr. Houn recommended that everyone visit www.fda.gov and search "pregnancy and lactation." She said to look for dockets, pointing out that FDA now operates using an electronic docket room where one can submit comments electronically.

For clarification and as a corollary, Dr. Baker asked whether these general principles applied to vaccines as well.

Dr. Houn affirmed that they would apply to drugs and biologics.

Anthrax Vaccine

Anthrax Vaccine Workgroup Activities

Dale Morse, MD, MS
Workgroup Chair, Advisory Committee on Immunization Practices

Dr. Morse recognized members of the Anthrax Workgroup for their helpful contributions to the process. The Workgroup's charge was to examine Anthrax Vaccine Adsorbed (AVA), of which there is one manufacturer. This working group has been reviewing the existing 2000 and 2002 supplement to update them. During this process, they have

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been reviewing new data on the anthrax vaccine, including safety and immunogenicity data, recently published safety studies, publications about the 2001 anthrax attacks, post-exposure prophylaxis with vaccine and antibiotic recommendations, and pre-exposure vaccination with a charge of revising the existing statement and supplement into a single document.

Dr. Morse reminded everyone that in February 2008, the workgroup presented safety data and data supporting a dose reduction / route change, dropping one of the doses and going from subcutaneous to intramuscular (IM). Since that meeting, the workgroup has reviewed unpublished data on vaccine use during pregnancy, data on post-exposure prophylaxis, and reviewed data and drafted the first responder recommendations. During this meeting, the plan was to present the draft of the first responder recommendations and rationale to the ACIP Some additional presentations were postponed on pregnancy, awaiting clearance on some of that information.

During the summer, the workgroup will continue their efforts to update the draft of the statement, and to examine information regarding how to deal with missed doses. In September, the review statement will be drafted for presentation to ACIP. In October, the plan is to present to the ACIP the draft combined statement, review pregnancy information and recommendations, consider recommendations on missed doses and post exposure prophylaxis, and vote on the first responder recommendations and potentially on other components, depending upon the discussion during that meeting and the question of FDA final approval.

Draft Recommendations for the Pre-Event Use of Anthrax Vaccine in First Responders

Jennifer Gordon Wright, DVM, MPH
On behalf of the
Anthrax Vaccine Work Group

Dr. Wright presented an overview of the Anthrax Vaccine Workgroup's discussion over the last several months regarding the pre-event vaccination for first responders, as well as the draft recommendations from the workgroup. She explained that there are two situations in which Anthrax Vaccine Adsorbed may be used. The first is to protect high-risk persons prior to exposure to the *B. anthracis* spores. Pre-event vaccination requires 6 priming doses, administered over 18 months, plus annual boosters. Post-event usage follows exposure to *B. anthracis* spores, presumably primarily in a bioterrorism event, and consists of 3 doses of vaccine, plus at least 60 days of antimocrobials. The focus of this presentation was on the pre-event immunization of the specific group of first responders.

To provide some context, Dr. Wright reviewed the current recommendations as provided in the 2000 statement and the 2002 supplement, which was developed during the 2001 bioterrorism events. In 2000, ACIP stated that "Routine pre-exposure vaccination with AVA was indicated for persons engaged in work or activities involving

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production quantities or aerosol concentrations of *B. anthracis* with a high potential for aerosolization." Further, AVA may be indicated for persons in otherwise low-risk occupations when in certain situations. For example, veterinarians practicing in areas of high endemnicity and persons who encounter imported animal products, such as hides, furs, or wools in the workplace when the standards and restrictions in those workplaces are insufficient to prevent exposure. Because BSL-2 laboratorians routinely processing clinical samples were not at increased risk for exposure to *B. anthracis* spores, ACIP at the time said that pre-event vaccination was not indicated and therefore not recommended for this group.

In a separate section of the 2000 statement focused on bioterrorism preparedness, ACIP did not recommend pre-event vaccination for first responders, federal responders, medical practitioners, and private citizens. ACIP said that recommendations should be based on a calculable risk assessment. In the case of anthrax exposure, the target population at risk cannot be predetermined, the risk of exposure cannot be calculated, and there is low risk for exposure due to secondary aerosolization. The ACIP said that for groups for whom a calculable risk could be quantified, such as the military or other select populations, pre-event vaccination may be indicated.

In late 2001 the ACIP revisited the pre-event recommendations, as well as the concerns of a limited supply of vaccine at the time. In this statement, the ACIP recommended that groups at risk for repeated exposure be given priority for pre-event vaccine, including specific laboratory personnel and workers making repeated entries into known contaminated areas. Persons who were not at risk for repeated exposures were not recommended to receive pre-exposure or pre-event vaccination. The current pre-event schedule follows the FDA licensed regimen of 6 priming doses administered subcutaneously over 18 months and requires annual boosters. As the workgroup reported to ACIP in February 2008, FDA is currently reviewing data from the AVRP clinical trial, which demonstrated that it was possible to drop the second (or 2 week) dose from the 6-dose priming series, and the IM administration produced an equivalent immune response to subcutaneous administration, while decreasing the occurrence of injection site side effects. No ruling has yet been made on this application, and the workgroup is currently still discussing a 6-dose, subcutaneous priming schedule with annual boosters.

There are currently limited civilian pre-event vaccination programs. A previous program to vaccinate laboratorians, initiated in 2002, has been suspended. However, the vaccine is currently commercially available and could be purchased from the manufacturer for administration by a private practitioner. This practice, while possible, likely occurs rarely.

In addition to the fact that the 2000 / 2002 statements needed updating and merging, and that the BLA is pending with FDA, some groups have recently requested a clarification of the supply language in the 2002 document, as well as clarification of the recommendation for pre-event vaccination of first responders. Making a recommendation is not a straightforward process, in part due to several complicating

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factors. There is no single organization representative of the first responder community. There are multiple types of first responders and defining this group can be difficult. Depending on how one chooses to define "first responders," the population may number as great as 3 million individuals and, and there are also some complex programmatic implications.

With regard to whether ACIP should recommend routine pre-event vaccination for first responders, issues such as burden of disease risk, vaccine safety, vaccine efficacy, vaccine supply, and programmatic implications, influenced the Workgroup's decision. In terms of the burden of disease, currently there is virtually no naturally occurring human disease in the U.S. In 1979, there was an accidental release from a military microbiologic facility, believed to be a bio-warfare facility, in the Soviet City of Sverdlovsk, resulting in at least 60 deaths. As is well known, in 2001 attacks were mounted through the US Postal system, resulting in 22 suspected or confirmed cases and 5 deaths. The workgroup thought that, while there is virtually no naturally occurring disease in the US at this time, there have been two precedents for the use of anthrax as an agent in bioterrorism. If there were to be another bioterrorism attack utilizing anthrax, the burden of disease could be high for those involved.

The risk of an individual first responder acquiring anthrax through a bioterrorism event is undefinable. It varies by location in the country, and is always evolving. The risk varies, even based on individuals' roles and duties. The magnitude of inhalation risks due to secondary aerosolization of previously settled spores is uncertain and thought to be low, but some risk may exist. Because of this, the Workgroup concluded that at this time the risk due to anthrax exposure is currently undefinable.

As was presented to ACIP in February, multiple reviews and studies have demonstrated the vaccine to be safe. There have been 7 independent reviews, over 35 published reports, and the military experience with greater than 7 million doses administered to nearly 2 million persons. There is also the safety data from 1564 participants in the on-going AVRP clinical trial, which was presented to the ACIP in February of this year. Although multiple studies have demonstrated the vaccine to be safe, there is always the potential for a rare adverse event to occur, especially when vaccinating a large number of persons.

Colonel Cieslak reported on VAERS and AVA in February 2008, and the workgroup revisited military associated AVA VAERS data as part of their discussion. VAERS is a passive reporting system and does not establish causality. Through June 2008, there were 10,640 VAERS reports filed as military-associated. Of these, AVA accounted for 4,705, or approximately 44%. There were 61.1 reports filed to VAERS per 100,000 doses of AVA administered, compared to 117 reports per 100,000 doses of smallpox vaccine. Approximately 10% of military-associated AVA reports were filed for "serious" adverse events. The vast majority of reports, however, as presented by Colonel Cieslak, were for local or generalized nonspecific events.

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A 2002 IOM report compared the percent of persons experiencing adverse events with AVA administration to other common vaccines. Reports for subcutaneously administered AVA were consistent with other vaccines. Data presented to ACIP in February 2008 demonstrated a significant decrease in the reporting of local adverse events when AVA was administered intramuscularly. These data regard IM administration rather than subcutaneous, so one would expect to observe decreases in erythema and swelling for AVA. Reports for AVA were consistent with the other vaccines. The workgroup thought that the available data suggested that the vaccine is safe and that the reported local adverse effects will be diminished if the IM indication is approved.

The workgroup next considered efficacy, first reviewing the Brachman study, which was conducted in four wool mills during the 1950s, when anthrax infection was common among wool sorters. This study demonstrated a combined efficacy against cutaneous and inhalation anthrax of 92.5%. During the study, there were no cases of inhalation anthrax among vaccinees, but 5 cases of inhalation anthrax did occur among unvaccinated persons. This study was affirmed as the best evidence for efficacy of the vaccine by an independent advisory panel in 1985.

The same independent advisory panel reviewed 12 years worth of data collected by CDC from nearly 7,000 persons. In the CDC data, there were 27 cases of anthrax noted, with 0 cases occurring among those fully vaccinated. The panel concluded that no cases occurred in fully vaccinated subjects while the risk of infection continued. They felt that these observations offered further support of the effectiveness of the product, and believed that there was sufficient evidence to conclude that the vaccine is effective. In addition to the Brachman and CDC data, there is an on-going clinical trial at CDC, which was reported on in February to the ACIP. While the trial is not collecting human efficacy data, it is collecting efficacy data from Rhesus Macaques, and plan to compare that macaque data to human data. This may provide a better picture of the actual correlate of protection against anthrax, but this data will not be available until late 2009. The workgroup felt that the available vaccine efficacy data suggested that the vaccine is effective and provides protection against inhalation anthrax.

The 2000 statement mentions the limited supply of AVA. During 2002, there were approximately 2 million doses manufactured, and the DoD utilized the majority of those doses. During 2007, 9 million doses were manufactured. There is a single manufacturer for AVA, Emergent BioSolutions, and the vaccine is currently manufactured in one plant, although a new facility is currently undergoing qualification and validation. The current manufacturing facility has been renovated, with an improved production process and quality systems resulting from the renovations. Current annual production capacity is 8-9 million doses, with future capacity possible of reaching 30-35 million doses once the new facility is on line. The vaccine is commercially available for purchase. The workgroup felt that at the current time, vaccine supply was sufficient to support vaccination for a large group of individuals.

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The workgroup also reviewed programmatic implications, specifically schedule, risk versus benefit, responsibility for campaign, responsibility for post-vaccination surveillance, and impact on preparedness. As discussed during this meeting and in the February 2008 meeting, the licensed schedule for AVA is complicated. To be fully immunized, one must receive all 6 priming doses over the 18 months, and there are annual boosters to maintain. To successfully implement immunization, someone must be in charge of tracking personnel to ensure individuals stay on schedule and return when their next dose is due.

The workgroup also considered the risk-benefit. A national, single risk benefit analysis is likely impossible, given that risk varies by first responder subgroup and location in the country, and requires a definition of "first responder," one that appears to be constantly evolving. While the workgroup believe the vaccine is safe, rare adverse events do occur and a serious adverse event is not a small matter, regardless of whether it is vaccine-associated. A risk assessment would require access to classified information and is always changing. It must be conducted at the local level, as the pre-event risk for persons in one city would likely be far different for the risk in persons of other locales. Furthermore, the perception of risk / benefit varies based on perspective. Societal perspective likely varies from the perspective of the first responder organizations, which in turn varies from individual citizen perspectives. All will have differing views as to the risk of acquiring anthrax, and the benefits received from a pre-event vaccination.

The next programmatic issue considered by the workgroup was the implementation itself. Someone would be responsible for immunizing the first responders if a recommendation were made. Private providers can administer vaccines to individuals, but could not likely mount large-scale vaccination efforts. The responsibility could fall to public health, whether at the local, state, or federal level, or to the occupational health programs of the individual responder organizations. In addition, educational materials would need to be crafted and distributed to vaccinees. While first responder occupational health programs may be able to administer the vaccinations, developing materials will likely require the input of public health partners.

Vaccination must be sustainable, and this is a complicated vaccine to administer, especially on a large scale when the population of vaccinees could reach 3 million persons. There will always be new entrants to the program, and tracking of personnel could be difficult. Additionally, this is not a vaccine that will be given just once or twice in a lifetime, but something that is going to be continually on-going with the annual boosters. There is also the issue of who could provide liability coverage if someone were to be injured. There must also be a mechanism for adverse event monitoring and for providing care for those who do experience adverse events. This responsibility must be made clear *before* vaccinations have begun, and should involve the same groups previously noted. There should be a mechanism to monitor and report adverse events, especially to VAERS, and there must also be a mechanism to provide care in the event of a serious adverse event, whether truly related to the vaccine or not. Again, there remains the issue of who provides worker's compensation or liability insurance.

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Post-event vaccination in combination with antibiotics is an effective intervention following exposure to *B. anthracis* spores, but the workgroup felt that pre-event vaccination could offer additional protection beyond that afforded by antibiotics and post-vaccination by providing early priming of the immune system. Some respondent organizations have stated that their members would be more willing to respond to a bioterrorism event if they were vaccinated prior to the occurrence of the event. Pre-event vaccine may also be beneficial if antimicrobial post-exposure prophylaxis (PEP) is unable to be delivered rapidly, in the event that the attack strain has been bioengineered for antimicrobial resistance, or in the instance of a covert release.

The workgroup felt that implementing a recommendation for pre-event vaccination of first responders would be difficult, but it may have a positive impact on first responder preparedness. Therefore, the workgroup reviewed several options for recommendations, which included: 1) not recommended, which is the current language; 2) may consider; 3) should be encouraged; and 4) recommended. There was some support for option 3 among the workgroup, but in general the members preferred option 2.

The Workgroup would like for ACIP to consider its recommendation and to provide feedback prior to a vote in October. Specifically, the workgroup proposes that:

> "Groups for whom potential contact with aerosolized anthrax is a reasonable expectation based on occupation and duties (e.g. first responders expected to be called to the scene of a bioterrorist event) and for whom a calculable risk is not available <u>may consider</u> pre-event vaccination on the basis of an <u>estimated</u> risk benefit and <u>in the context of an occupational health and safety program</u>."

Discussion

With respect to the case fatalities in the Brachman study, Dr. Stinchfield noted that it appeared that four or five cases were fatal. However, the CDC data from 1962-1974 reported 27 cases of anthrax, but not how many deaths.

Dr. Wright responded that the CDC data did not include the data from Brachman—it was a separate population of persons. The CDC data was only for cutaneous cases. There were no inhalation cases during the time period reported.

With respect to safety, Dr. Baker inquired as to whether there were any gender differences.

Dr. Wright responded that they showed in the February 2008 presentation that women tended to report a higher rate of local adverse events with subcutaneous administration. With IM administration, there is still a reporting gap between men and women, but with fewer women reporting IM events than subcutaneous events. She believed that women had a higher magnitude of antibody response, but there was no one in the audience to provide specific data.

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Col Cieslak added that in DoD data there was a markedly increased incidence of local reactions, of subcutaneous nodules, in women as compared to men. However, there was not a difference in significant adverse events.

Dr. Gellin pointed out that this was all about risk and benefit. If there were letters "flying around," this would be getting a lot more attention than it is now. He wondered what the current risk was and whether there was an equivalent of a code orange, for example.

Dr. Richard Besser, Director of The Coordinating Office for Terrorism Preparedness & Emergency Response (COTPER) responded that by first pointing out that he thought Dr. Wright laid out the current situation very well in that it is very difficult to define a risk for various groups. A number of first responder groups have assessed that their risk may lead them to want to vaccinate their workers, but the existing recommendation of "do not recommend" is viewed is an impediment. Therefore, this recommendation, which allows various first responder groups to self-define their risk, would meet the need of those organizations that have assessed risk, either based on information they have or based on what their role would be if there were an aerosol release. That is, the proposed recommendation would allow them to move forward.

Dr. Baker congratulated Dr. Wright and the workgroup. She thought the proposed recommendation was a very reasonable compromise, given the unknowns.

Dr. Morse added that the workgroup did add a clarification. It is just not self-identified risk. The feeling was that it needed to be in the context of an occupational health and safety program.

Dr. Temte also commended the working group on developing a very reasonable recommendation. With any issue such as this, there are many ramifications. For example, this recommendation may require the use of public funds, which will defer funds from other important immunization programs. Allowing smaller groups to consider their own risks is a very worthwhile approach, as opposed to the other options.

Dr. Stinchfield pointed out that there are a lot of bioterrorism grants and funds available. She wondered what would preclude EMT first responder groups from going ahead with pre-vaccinations using some of those funds.

Dr. Besser's understanding was that the existence of a "do not recommend" was an impediment to using those funds. However, they would need to seek official word from the Department of Homeland Security (DHS) on that. He acknowledged that there was some interest in using some of those funds for that purpose, and groups eagerly await the recommendation from the ACIP. The issues that were laid out in terms of pre-vaccination versus post-vaccination, use of antibiotics, and post-exposure are all being considered, but a great deal more is known now than when these recommendations were first issued about the challenges around post-release counter measure distribution. It will be challenging. In pretty much all communities, there will be a desire

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to have first responder groups (e.g., police, fire, EMS, public health, et cetera) available very quickly to maintain order, and also to participate in antibiotic distribution.

Dr. Neuzil appreciated the workgroup presenting this ahead of the meeting in October where ACIP will need to vote on it because she was feeling a little uncomfortable about the recommendation and needed some time to think it through further. She saw this issue as somewhat analogous to the discussion around pre-pandemic use of that vaccine, where not only is the risk unknown, but also the time period is unknown. The anthrax situation requires careful tracking of vaccines and administering annual boosters.

Dr. Judson indicated that at the local level in Colorado, he has been involved in exercises for a Governor's Expert Emergency Bioterrorism Response Committee regularly since 2000. They have been through many exercises where they attempt to deal with the unknown / unquantifiable risks. He thought there were two options for ACIP, the first being to say nothing. Based on information, that would probably be the correct scientific response, because no one locally in most places is able to establish any credible estimate of risk, time of attack, or timing for pre-exposure prophylaxis. The second option was what had just been done, which did not say much, but indicated that ACIP had thoughtfully considered the evidence, a lot of which remained inadequate. While he could support the recommendation as stated, practically it would do little at the local level.

Dr. Sumaya was uncomfortable with the wording, "may consider pre-event vaccination on the basis of an estimated risk benefit and in the context of an occupational health and safety program." There should be some type of algorithm to make risk determinations that can be useful to the practitioner and at the local level.

Dr. Besser noted that earlier in the year, the Homeland Security Council issued Homeland Security Presidential Directive 21, which calls on the Department of Homeland Security to prepare a threat briefing for use throughout the country for public health and other groups. Prior to that, there really was not anything available to assist people in weighing the risk equation. While the threat briefing has not yet been developed, it is underway. Since the recommendation was made, there have been some changes, one of which is that the vaccine supply has increased dramatically. The other is based on the AVRP work, based upon which it appears that the safety profile has changed. Those two factors lead to a reconsideration of the earlier recommendation.

Dr. Schuchat commented that in the context of occupational health and safety programs, it struck her that while programmatic concerns were within the purview of ACIP's considerations, public health and private provider groups are also represented. However, it was not clear whether occupational health and safety stakeholders for responders had been given an opportunity to weigh in or comment on this issue.

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Dr. Wright responded that there is not a single organization for first responders that could be brought to the table to weigh in. However, they do have a National Institute of Occupational Safety and Health (NIOSH) representative, who has links to the community from whom they have presented feedback. In addition, they receive feedback from NACCHO and CSTE.

Reflecting on Dr. Sumaya's observation, Dr. Paul Cieslak inquired as to whether some verbiage could be added to refer readers to resources regarding risk assessment.

Dr. Wright responded that this was mentioned in the workgroup and they can work on including something in the statement.

Dr. Judson suggested including an illustration of an outbreak or proven and credible threat identified by Homeland Security, both in time and in place, along with the recommendations. Otherwise, the recommendations would be free-floating, interpreted variably, and would not lead to cost-effective actions or increased security.

With respect to other constituents who have a stake in this issue, Nancy Messonnier, CDC, pointed out that this is a commercially available vaccine. Therefore, as with many other vaccines, even if it is not recommended by ACIP, an individual can pay for the vaccine themselves. The problem is that the current ACIP language is viewed by these groups as an impediment to getting the vaccine because it is distinctly recommended against. While the workgroup would like to provide the concrete language and risk data desired, they are unable to do so based on the currently available information. There are also constraints due to the fact that local risk is ever-changing. The intent of the workgroup was to open the door, knowing that the vaccine is commercially available and that first responder groups are at liberty to call the manufacturer to obtain the vaccine themselves. This is really meant to give them more impetus by saying that even if they do not have a calculated risk assessment, individuals or groups can assess their own risk, and weigh the risks and benefits of the vaccine with their occupational health and safety programs. The revised language would simply provide more flexibility.

Dr. Lett wondered whether people who stopped receiving their annual booster would simply need one booster should there be an event, or if they would have to restart the entire series.

Dr. Wright responded that the workgroup had not yet discussed what the recommendation would be should someone miss a booster. They plan to present on this at the October 2008 meeting. Waiting until there is a credible threat to begin vaccinating is problematic, however, given that it takes the full 18 months and the full 6 doses to be considered fully immunized.

Dr. Judson did not believe all doses were needed 18 months in advance of an event, given that a couple of doses with the combination of antibiotics would at least set the immune response. It was not practical, cost-effective public health for ACIP to make

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statements about self-determination of risk and need for a vaccine based on no science and no true objective risk information.

Dr. Katz, Infectious Disease Society of America, wondered whether the vaccine research unit at NIAID was attempting to develop a better vaccine that does not take 6 doses and require annual boosters.

Dr. Curlan responded that NIAID has had a recombinant protective antigen program underway for a long time, built upon the similar work that Art Friedlander did at the US Army Medical Research Institute of Infectious Diseases (USAMRIID). There is one company left in the competition from the UK, which is in the scale-up phase of their production. Like any new vaccine coming on the market, the process takes a long time. Evaluations are underway in primates and other models to compare and contrast various schedules with AVA and other programs. Although well underway, the vaccine is not ready at this time. Therefore, it is appropriate for the workgroup to base their recommendations on what is currently available. Other research is underway about small molecules, et cetera to affect the treatment of anthrax.

Bill Brandis, a retired Fire Chief of St. Louis County, Missouri, indicated that he coordinated the St. Louis regional response for the Chemical, Biohazard, and Radiation Team He covered two World Series with 92 of their responders (e.g., fire, EMS, HAZMAT, law enforcement, bomb technicians). Their Civil Support Teams, whose primarily mission is to back up the local responders, were invited as well. His local first responders did not know what they were responding to when they responded to over 2,000 calls of white powder incidences in the greater St. Louis region. Responders cannot spend their money on vaccines because they must use it to purchase trucks, HAZMAT suits, respirators, APRs, boots, gloves, et cetera required to respond to calls. He brought two letters with him for the ACIP members, one from the State of Missouri's Chief Medical Officer and the other from their Homeland Security Coordinator. He requested that the role of his responders be considered, and emphasized that they are the first responders when someone calls 911. Although the military teams, their brothers and sisters in arms, have the vaccine and his people are standing side-by-side with the military, they are not offered the same opportunity. He suggested that the language state "shall recommend" or "should recommend" and thought the proposed language was better than no recommendation.

Update: Measles Outbreak, United States 2008

LCDR Amy A. Parker, M.S.N., M.P.H.
Division of Viral Diseases, NCIRD

LCDR Parker reported on the epidemiology of measles in the United States in 2008, noting that in the pre-vaccine era, 3-4 million people in the US developed measles annually, of whom 400-500 died, 48,000 were hospitalized, and another 1,000 developed chronic disability from measles encephalitis. The measles vaccine was

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licensed in 1963, which caused a dramatic reduction in cases. However, a resurgence occurred from 1989-91. During this timeframe, a second dose of measles vaccine was recommended. By 2000, measles was declared eliminated from the US–a remarkable public health success. Elimination is defined as the absence of endemic disease transmission.

With respect to the average number of measles cases by month for 2000-07 versus 2008, from post-elimination data in the US, the 2008 data show an upsurge of measles cases, with 123 cases reported through June 20th. That is the largest number to date since 1996. Of these 123 patients, 16 (13%) were hospitalized; no deaths were reported. The June data are incomplete and are, therefore, underestimated. The 2008 resurgence is occurring across the country. LCDR Parker shared a map illustrating the wide geographic distribution of cases that have been reported. There were seven outbreaks in Arizona, California, Illinois, Michigan, New York City, Washington, and Wisconsin. The outbreak in Illinois is on-going and the most recent case count as of June 26, 2008 was 26. All of these outbreaks ranged in size from 4-26 cases, with a median of 14 cases.

It is not believed that endemic transmission has been reestablished. Of the cases reported in the US, 106 (or 86%) were import-associated. The remaining cases are also thought to be import-associated, but links for these have not been identified. US residents, rather than foreign visitors, account for 94% of all cases. Additionally, of the 18 cases for whom there is genetic sequencing information, the viruses isolated have a variety of genotypes from different countries, including D4, D5, and H1. Another key point is that 11 (69%) of the imports came from the WHO European region. Often, travelers to this region do not think about being up-to-date on their vaccinations prior to their departure. Yet, this region has reported more than 2,800 cases in 2008 from numerous large outbreaks in Austria, Germany, and Switzerland. Additionally, over 1,000 cases have been reported in Israel.

Regarding the proportion of cases by vaccination status, only 7% of case-patients were vaccinated, and 24% were unvaccinated, but were not eligible for vaccine (e.g., less than 1 year of age, born before 1957, or foreign). The largest portion at 69% was unvaccinated, but eligible for vaccine. This group included 8 unvaccinated U.S. residents who became infected while traveling abroad, as well as an unvaccinated healthcare worker. Among unvaccinated case-patients who were eligible for vaccine, 59% claimed a personal belief exemption. A personal belief exemptor was considered to be a person not vaccinated for religious or philosophical reasons. Of the 50 personal belief exemptors, 48 (96%) were children. Also among unvaccinated but eligible case-patients, 20% had unknown vaccination status or unknown reasons for being unvaccinated. Persons in this group were all adults 20-49 years of age. The remaining groups comprised 11% each, and represent the infants who were 12-15 months of age, and therefore not technically considered delayed, and the children who missed their opportunity for vaccination, but whose parents do not hold personal beliefs against vaccination.

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Much has been done in the past 6 months to communicate with state and local partners, as well as to the public. Two *MMWR*s were written in February and May 2008, and an additional one is planned for this summer. These have focused on the association of personal belief exemptors and the increase in measles outbreaks in 2008, the effectiveness of measles vaccine, that unvaccinated US residents are at risk for contracting measles, especially persons traveling abroad, and that measles diagnosis should be considered in travelers. In addition, a Webinar on measles was held with the National Association of County and City Health Officials (NACCHO). Travel alerts have been issued on CDC's website, particularly highlighting the risk to unvaccinated travelers who attend the European Football Championships and the Olympics. Finally, because of its elimination status, measles was made an immediately notifiable disease at the June 2008 CSTE meeting.

Although measles has been eliminated from the US since 2000, import-associated cases are on the rise and are primarily affecting unvaccinated US residents. The primary reason for lack of vaccination is personal belief exemptions. Until better global control is achieved, especially in highly traveled developed countries, cases will continue to be imported into the US and outbreaks will persist as long as there are communities of unvaccinated people.

Discussion

With respect to people born before 1957, Dr. Baker wondered whether there were any cases in people who had had natural measles before the vaccine was introduced, which would include the elderly, for example.

LCDR Parker responded that there were only 5 people over the age of 50 who were cases; however, she was not sure what their disease history was.

Dr. Seward added that some of them were not vaccinated because of birth before 1957, so they did not report any vaccination. Also, birth before 1957 is evidence of immunity for measles. It is possible that the affected individuals never had measles.

Dr. Sawyer emphasized that a very important group is the 24% under 12 months old who are unvaccinated and ineligible. In his state's outbreak these statistics held true. He also stressed that there are some very strong feelings among those parents who were inadvertently subjected to the measles because of the decision of others to exert personal belief exemption. He asked that those in a position to emphasize that in their communities to do so because it resonates with a lot of people, and may help to decrease the rate of personal belief exemptions, at least among a subset of that group.

LCDR Parker added that, in fact, some of the infants who were too young to be vaccinated became infected in their pediatricians' offices.

Dr. Temte recalled his very first vaccine-related activity as being in the measles elimination meeting in 2000. He was also part of the rubella elimination meeting.

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Coming from a state that not only has had a number of measles cases, but also one rubella case, he pointed out that the US is now three generations beyond the last case of measles, and are observing the benefit of having widespread immunity. However, a case of measles is an incredibly expensive activity for public health departments, tying up immunization programs and public health practitioners. The dollars expended must be tracked to better understand this. In terms of personal belief waivers, he wondered how many of these were from parents who have fear of the safety of the vaccine. This highlighted the importance of taking safety concerns seriously, and approaching them with transparency from this committee.

With regard to the issue of economic cost, LCDR Parker responded that containing an outbreak is, indeed, very expensive. Public health officials in San Diego have estimated the cost for that outbreak as nearing $100,000. The public health containment costs alone among the vaccine refuser community in Indiana in the 2005 outbreak was estimated to be $167,000. Regarding the proportion of the parents who are expressing safety concerns, San Diego has been conducting focus groups, and are finding that safety concerns are the issue. Moreover, safety issues have received significant media attention lately.

Dr. Iskander stated that, while he was not an expert on research conducted on personal belief exemptors, some of the work that has been documented by scientists and journalists in the past has suggested that these communities actually have broader concerns than simply safety. For example, many have preferences for the natural version of disease. Clearly there are linkages with safety issues, but the evidence does suggest that there is a broader set of issues.

Dr. Schaffner, National Foundation for Infectious Diseases, assured everyone that his comments were not to divert attention from domestic responsibilities, or to incite an international incident. However, he expressed concern that their colleagues in Europe and in Israel tolerate on-going outbreaks of measles and other childhood communicable diseases.

David Salisbury, Department of Health: United Kingdom, responded that it is true that, for a number of those countries, the perception of the seriousness of measles is different from what one might wish it to be. It is also true that coverage in a number of countries is low for many different reasons. The immunization program in Israel, to its credit, has actually been one of the better performing immunization programs for a very long time. Whether their outbreak is actually linked with one in a North London Jewish community remains to be fully understood, the community in North London has very close links with Israel. There currently are a lot of measles in Europe. The issues of how to raise the perception of the seriousness of measles, as well as the need to maintain very high coverage, have been a challenge for many years within the European region, and it is a reality that a number of countries have either not taken measles as seriously as they should or have not been able to do as much as they would like. The UK does take measles very seriously and has done as much as they could reasonably have done in the face of what has been an extraordinarily difficult decade

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over issues to do with vaccine safety, particularly focusing on MMR. Immunization coverage is increasing, but they do continue to have measles. With the Euro so strong, it is likely that many Europeans will visit the US.

Dr. Katz pointed out that 123 cases was a lot since 2000, but reminded everyone that 250,000 children died of measles last year throughout the globe, and that a former CDC officer was instrumental in organizing the measles initiative, which has been successful through the collaboration of the Red Cross, the World Health Organization, CDC, UNICEF, the United Nations Fund, the Church of Latter Day Saints, and a number of others in reducing measles mortality—not just the number of cases, but also of mortality from over a million at the end of the 20th century to about 250,000 in 2006.

Dr. Gellin inquired as to what the travel advisory levels were, noting that it is important to understand how this is playing out in the travel industry in terms of what the average travel agent know about this and how they would advise travelers. The CDC travel advisory is not particularly easy to find.

LCDR Parker responded that the European Football Championship website had a message about measles occurring in Switzerland and Austria, and recommended that people to be up-to-date on their vaccinations. It was also on the European Football website. On the CDC website, on the travel page, the advisory is one of the blurbs that pops up on the first page with a link.

Dr. Seward pointed out that the current policy recommendation is for measles vaccine for travelers. It is very difficult to keep websites updated as to outbreaks. There is endemic transmission in India, and in a number of countries in Africa. Therefore, it has been highlighted in the *MMWR*s that every traveler 6 months and older who does not have other evidence of immunity, should be protected through vaccination.

LCDR Parker stressed the importance of highlighting travel to areas that people would traditionally think of as safe. For example, one would not typically think of traveling to Switzerland as requiring up-to-date vaccinations. It is important to get the message out that outbreaks are occurring in these countries. Practitioners are apprised of travel advisories, so travelers should not experience difficulties in requesting and receiving updated vaccines.

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Vaccine Safety

Update: Immunization Safety Office, CDC

John K. Iskander, MD, MPH
Acting Director
Immunization Safety Office (ISO)
Office of the Chief Science Officer (OCSO)

Dr. Iskander welcomed everyone to the vaccine safety session on behalf of the Immunization Safety Office (ISO), which operates out of the Office of the Director, and which leads vaccine risk assessment activities at CDC. He thanked ACIP for the opportunity to provide some updated general information about immunization safety topics of interest, and briefly outlined upcoming speakers and topics for the remainder of the session.

Because issues related to the safety of quadrivalent human papillomavirus vaccine, Gardasil®, continue to attract attention from public health partners and the media, ISO now frequently posts safety updates for Gardasil® on its website, found at www.cdc.gov/vaccinesafety/vaers/gardasil.htm.

Dr. Iskander reported that the current status of CDC-sponsored research related to thimerosal and autism was as follows:

- Neurodevelopmental status at age 7-10 years
  - → Published in *NEJM* September 2007 (Thompson et al.)
- Italy neurodevelopmental status study
  - → Data submitted for publication by Italian researchers
- Autism case / control study
  - → Data collection completed early 2008
  - → External advisory panel recommending additional analyses

The components of vaccines (e.g., thimerosal, aluminum, formaldehyde, gelatin, yeast, and latex) have been a recent focus of attention. Dr. Iskander reminded everyone of the discussion within the committee related to this issue the previous day. He acknowledged and thanked scientific and communication colleagues at the FDA for their leadership on this issue, and for the key factual summary points and information resources they provided to him. FDA is the lead agency for vaccine component information. FDA requires manufacturers to extensively test for safety, purity, potency and efficacy. Testing includes laboratory, animal, and clinical studies. Data are reviewed by FDA scientists and clinicians. Inquiries and requests for information should be directed to octma@cber.fda.gov, 800-835-4709 or 301-827-1800. Supplemental web-based resources and recent vaccine publications of interest include the following:

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- www.cdc.gov/vaccines/vac-gen/additives.htm (NCIRD)
- www.vaccinesafety.edu/components.htm (Institute for Vaccine Safety, Johns Hopkins University)

The following recent publications are noted for the ACIP's awareness:

- Haber P, Patel M, Izurieta HS, et al. Postlicensure monitoring of intussusception after RotaTeq vaccination in the United States, February 1, 2006, to September 25, 2007. Pediatrics. 2008 Jun;121(6):1206-12.
- Nachamkin I, Shadomy SV, Moran AP, et al. Anti-Ganglioside Antibody Induction by Swine (A/NJ/1976/H1N1) and Other Influenza Vaccines: Insights into Vaccine-Associated Guillain-Barré Syndrome. J Infect Dis. 2008 Jun 3.

The work presented the previous day on behalf of the Rotavirus Workgroup extends the data published by Penina Haber and colleagues in this month's *Pediatrics*. The laboratory based study by Nachamkin and colleagues in response to an IOM recommendation, and conducted with the support of NVPO, may provide important clues to the pathophysiology of vaccine associated Guillain-Barré Syndrome (GBS).

Dr. Iskander summarized the upcoming presentations of Dr. Broder, who will provide an update on the ISO scientific agenda and Dr. Jim Nordin from Health Partners, who will provide updated Tdap safety data from Vaccine Safety Datalink (VSD). He noted that this would be the third time since the vaccine's licensure in 2005 that post-licensure safety data on this vaccine would be presented to this committee. Dr. Popovic, CDC's Chief Science Officer, will provide some additional comments about CDC vaccine safety activities.

Update: CDC's Immunization Office Scientific Agenda

Karen R. Broder, MD
Immunization Safety Office
Office of the Chief Science Officer (OCSO), CDC

On behalf of the Immunization Safety Office, Dr. Broder expressed her appreciation for the opportunity to update the ACIP about the Immunization Safety Office draft scientific agenda and its development process, and clarified that the upcoming presenters would refer to the draft scientific agenda as "the agenda."

In 2005, the Institute of Medicine (IOM) released a report on vaccine safety research, data access, and public trust. In this report, the IOM recommended that the National Vaccine Advisory Committee (NVAC) review and provide advice on the VSD research plan. In response to this recommendation, and to guide ISO's scientific activities, ISO developed a draft ISO Scientific Agenda that covers the VSD, as well as the office's other scientific and research components.

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To develop this agenda, the ISO received input from three planned scientific meetings with external consultants, federal scientists, and vaccine manufacturers. They also received input from numerous day-to-day partners, literature, and other sources. NVAC is currently facilitating a scientific review of the draft agenda and formed a Vaccine Safety Working Group, which is conducting the review. The working group held a public meeting on April 11, 2008 to begin this process. Information pertaining to the agenda and the public meeting may be located at the following:

- Immunization Safety Office Scientific Agenda http://www.cdc.gov/vaccinesafety/agenda.htm
- CDC, Vaccine Safety http://www.cdc.gov/vaccinesafety/
- National Vaccine Advisory Committee, http://www.hhs.gov/nvpo/nvac/index.html
- Institute of Medicine, Vaccine Safety Research, Data Access, and Public Trust, available at http://www.nap.edu/catalog/11234.html

The working group will advise on the content and priorities of the agenda. After the NVAC scientific review is complete, ISO and CDC will respond to the feedback and finalize the agenda. Their objective was to develop a comprehensive five-year ISO scientific agenda, with extensive expert input. The scope includes vaccine safety research, selected surveillance, and selected clinical guidance activities that are part of the ISO's mission, are within ISO's realm to lead, and could be implemented during the next five years with infrastructure generally accessible to CDC. The agenda does not cover all areas of vaccine safety, including some very important areas such as communications. It focuses on the ISO's scientific activities. Work is underway in many of the areas to be represented in this draft agenda.

The draft agenda has three main recommendations. The first is to respond to emerging issues and conduct core required scientific activities. One of the core basic activities includes monitoring newly licensed and newly ACIP-recommended vaccines. The previous day, the committee heard an example of this through the rotavirus vaccine presentations, and following her own presentation the committee would hear another example from Dr. Nordin's presentation on Tdap.

The second recommendation is to enhance vaccine safety, public health, and clinical guidance capacity in seven areas, and the third recommendation is to address five-year needs. The seven capacity areas, not in any order of priority, are as follows:

A) Infrastructure for Vaccine Safety Surveillance: Vaccine Adverse Event Reporting System (VAERS).
B) Infrastructure for Vaccine Safety Surveillance and Research and the Vaccine Safety Datalink (VSD) Project.
C) Epidemiologic and Statistical Methods for Vaccine Safety

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D) Laboratory Methods for Vaccine Safety
E) Genomics and Vaccine Safety
F) Case Definitions, Data Collection, and Data Presentation for Adverse Events Following Immunization
G) Vaccine Safety Clinical Practice Guidance

Thirty five-year research needs for the draft agenda were identified, which fall into four categories:

1. Specific Vaccine Safety Questions
2. Thematic Area: Vaccines and Vaccination Practices
3. Thematic Area: Special Populations
4. Thematic Area: Clinical Outcomes after Immunization

The seven vaccine safety questions, also not presented in any order of priority and available to the public through the website, are:

A-I Are vaccines (e.g., influenza vaccines, meningococcal conjugate vaccine [MCV4]) associated with increased risk for Guillain-Barré Syndrome (GBS)?

A-II Is live, attenuated influenza vaccine (LAIV) associated with increased risk for asthma and/or wheezing, particularly in young children or persons with history of wheezing?

A-III Is exposure to thimerosal associated with increased risk for clinically important tics and / or Tourette syndrome?

A-IV Are acellular pertussis vaccines associated with increased risk for acute neurological events, particularly hypotonic-hyporesponsive episodes (HHE)?

A-V Is immunization associated with increased risk for neurological deterioration in children with mitochondrial disorders?

A-VI Is combination measles, mumps, rubella, and varicella (MMRV) vaccine associated with increased risk for febrile seizure and, if so, are there sequelae?

A-VII Are varicella vaccines (varicella and MMRV) associated with increased risk for clinically important events related to varicella vaccine virus reactivation?

In the thematic area of vaccines and vaccination practices, the areas identified were:

B-1 Bivalent human papillomavirus (bivalent HPV) vaccine (Cervarix™)

B-II Zoster vaccine (Zostavax®)

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B-III Annual influenza vaccination in children and adolescents (trivalent inactivated influenza vaccine [TIV] and LAIV)

B-IV Non-antigen components of vaccines
(other than thimerosal and ASO4 adjuvant HPV vaccine)

B-V Simultaneous vaccination

B-VI Safety of different products within the same vaccine category

B-VII Off label use of vaccines

B-VIII Vaccine-drug interactions

In the thematic area of special populations, the following populations were identified: premature and low birth weight infants; pregnant women; adults 65 years and older; persons with primary immunodeficiency; persons with secondary immunodeficiency; persons with autoimmune disorders; and children with inborn errors of metabolism.

In the area of clinical outcomes, the following were highlighted: autoimmune diseases; central nervous system demyelinating disorders; encephalitis / encephalopathy; neurodevelopmental disorders, including autism spectrum disorder (ASD); vasculitis syndromes; myopericarditis (not associated with smallpox vaccine); clinically important outcomes related to postimmunization fever; and postvaccination syncope and sequeale.

The NVAC Safety Working Group is reviewing the draft agenda to provide recommendations on the content and the priorities, and will look forward to this feedback. Dr. Broder expressed gratitude to the more than 100 immunization experts and stakeholders who contributed to developing this draft agenda.

Rapid Cycle Analysis in the Vaccine Safety Datalink for Adverse Events after Tdap Vaccination

Dr. James Nordin
HealthPartners Research Foundation, Minneapolis, Minnesota

Dr. Nordin is the site Principal Investigator for the Vaccine Safety Datalink (VSD) Project. He reported on the rapid cycle analysis of adolescent and adult use of Tdap (tetanus-diphtheria-acellular pertussis vaccine) in the VSD. The VSD is a collaboration between CDC and eight managed care organizations: Group Health Cooperative in Washington State, Northwest Kaiser Permanente in Oregon, Northern California Kaiser Permanente, Southern California Kaiser Permanente, Kaiser Permanente Colorado, HealthPartners in Minnesota, Marshfield Clinic in Wisconsin, and Harvard Pilgrim in Massachusetts. Data from 8.8 million members are captured annually, making it about 3% of the population. The VSD was established in 1990 to improve the evaluation of

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vaccine safety through the use of active surveillance and epidemiological studies. It was designed to address some of the shortcomings of Vaccine Adverse Event Reporting System (VAERS) and responded to the needs identified by two Institute of Medicine (IOM) reports.

The VSD tests hypotheses suggested by the VAERS reports and pre-licensure trials. A few years ago, with a fair amount of effort, the Rapid Cycle Analysis System was developed. This is an alternative to traditional post-licensure vaccine safety study methods, which generally take years to complete. With this system, pre-specified vaccine adverse events can be identified in near real-time. Specific hypotheses are tested with well-defined outcomes. The number of events in vaccinated persons are compared to the expected number of events. Data are available within weeks of vaccination, and there are weekly analyses with adjustments for repeated hypothesis testing.

For the Tdap study design, the investigators wanted to identify associations between Tdap vaccine in adolescents and adults, and a pre-specified list of outcomes. The exposed cohort included people who received the Tdap vaccine. The comparison groups was a historic cohort included of subjects receiving Td. The incidences are adjusted for age and HMO site. The analysis is a Poisson maximized sequential probability ratio test (MaxSPRT), which was developed by the VSD statistical staff, and builds on quality control methods that are used in industry. The observed number of events are compared to the expected number from a historical control group, and an association or signal is detected if the critical value of the log likelihood ratio (LLR) is exceeded. In order to determine the outcomes of interest, the investigators reviewed the literature, pre-licensure data, and VAERS data on Tdap; whole cell and acellular pediatric pertussis vaccines (DTP and DTaP); out of age range previous pertussis vaccination; and reports with Td and tetanus toxoids. The two major outcomes of interest identified from this review were facial paralysis and encephalopathy. Outcomes included in rapid cycle analysis studies should have the following characteristics: clinically well-defined, serious in nature, and suggested by earlier studies or surveillance to be biologically plausible as a consequence of vaccination.

The categories considered for the Tdap study were encephalitis / encephalopathy / meningitis (ICD-9 codes: 047.8, 047.9, 049.9, 321.2, 322, 323, 348.3, 348.5); paralytic syndromes (ICD-9 codes: 342, 344, 781.4); seizures (ICD-9 codes: 345, 780.3); cranial nerve disorders, including Bell's Palsy (ICD-9 codes: 350, 351, 352); and Guillain-Barré Syndrome (GBS) (ICD-9 code: 357). A post-vaccination window of 1-42 days was established for each category, with the exception of seizures, which was 0-7 days. Most of these outcomes were studied in outpatient, inpatient, and emergency department (ED) settings; however, seizures were considered only for medical encounters in the inpatient and ED settings, given that most of the seizure diagnoses in outpatient data are follow-up visits that are not new events or new seizures.

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The background incidences for comparison were somewhat complex. GBS is rare enough that there are not good data from the VSD, so age-specific rates from the Healthcare Cost and Utilization Project (HCUP) hospital discharge data were used for all GBS, not just the primary diagnosis, during the years 2000-2004. For seizures, slight adjustments had to be made with the age-specific rates on Days 1-7 after Td, increasing by 1/7th, or 14%, because they dropped out the Day 0 events in the VSD historical data for the same years. The Day 0 problem is that a fair number of patients who were seen in EDs with seizures had fallen, hit themselves, received a Td, and had a seizure diagnosis on Day 0, which was not an outcome for a vaccination. For all other outcomes, age and VSD site-specific rates were used on Days 1-42 after Td in the historical data for the years 2000-2004. It was preferred to use concurrent data, but this was not possible because most of the sites fairly rapidly switched from Td to Tdap, making concurrent rates unusable. With the study that was set up, statistical power was calculated to detect a relative risk of 1.5 and a relative risk of 2. The ability to detect a relative risk of 2 or greater was very high for all outcomes except GBS, and the ability to detect a relative risk of greater than 1.5 was quite high, again for all outcomes except GBS. No signals were observed after about 660,000 doses of Tdap. All of the LLRs and observed ratios were considerably lower than the critical value of LLR. The investigators continue to monitor for GBS and will have somewhat increased power over time. There was adequate power to determine 1.5 or 2 relative risk over background for encephalopathy, encephalitis, meningitis; paralytic syndromes; seizures; and cranial nerve disorder. However, there was inadequate power for GBS for relative risk of <5. With approximately 660,000 doses of Tdap administered over 145 weeks, no evidence was found of increased risk of predetermined adverse events for encephalopathy, encephalitis, meningitis; paralytic syndromes; seizures; cranial nerve disorder; or GBS.

Dr. Nordin thanked the principal investigators of participating VSD sites, members of the VSD Rapid Cycle Analysis working group, and members of the VSD project for their contributions to this study.

Discussion

Dr. Morse noted that with the rapid expansion of the electronic medical records and health information exchanges, it would soon be potentially possible to expand real-time analysis on a much larger scale than currently possible. Given that rare events can only be recognized over long time periods through VSD, he wondered if there were plans to increase the size of the population followed by tapping into this emerging resource.

Dr. Nordin responded that there will be incremental increases. While large databases are important, it takes a considerable amount of funding and expertise to analyze these data. It is not a straightforward and easy process to analyze data such as these. Analyses of these data have taken two to three years. VSD does expect to work cooperatively with the FDA project.

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With respect to the representativeness of the VSD population, Dr. Temte requested a breakdown of the racial and ethnic composition compared to the overall US population.

Dr. Nordin responded that a conclusive answer was not possible because not all of the sites are collecting racial and ethnic data, but this is a project upon which they are currently working. He suspected that Caucasians were somewhat over-represented, but there are significant numbers of the various minorities in some of the populations.

Update on CDC Vaccine Safety Activities

Dr. Tanja Popovic
Chief Science Officer
Centers for Disease Control and Prevention

Dr. Popovic expressed appreciation for the opportunity to report on three immunization safety-related activities: 1) Establishment of an Federal Immunization Safety Task Force; 2) Recent efforts and thinking regarding mitochondrial disorders 3) Organizational changes at CDC.

Over the past few months, an increased level of discussions has occurred about the need to maintain the public and parent confidence and trust in immunizations. That has been highlighted, especially with a few highly publicized measles outbreaks recently. While everyone understood that trust and confidence were paramount for maintaining the high levels of immunization enjoyed in the United States, providers are being asked increasingly more questions about vaccines and recommended immunization schedules. To ensure responsiveness to partners, immunization providers, healthcare providers, parents, and the public, the Secretary of Health asked the Assistant Secretary of Health to establish a Federal Immunization Safety Task Force to be led by NVPO, with Dr. Bruce Gellin. The Task Force will have representatives from all HHS organizational units, as well as the Department of Defense and Veteran's Affairs. The charge of the HHS Immunization Task Force includes assuring that all federal resources are used and mobilized in the area of immunization safety; assuring that there is a coordinated response to emerging and urgent immunization safety issues; assisting with the development of the federal immunization safety research agenda; and facilitating public engagement in immunization safety research areas and topics.

In the past months, there has been much publicity and discussion related to mitochondrial disorders in general, as well as whether they have any associations with vaccines and/or autism. There are a few ongoing activities that will help us better understand the state of science and knowledge, and identify potential research priorities. HHS is sponsoring a workshop on Sunday, June 29, 2008, titled, "Mitochondrial Diseases in Childhood" at the close of the United Mitochondrial Disease meeting in Indianapolis, Indiana. The sponsors and participants at the workshops include NIH, FDA, and CDC. A number of invited mitochondrial experts will discuss areas of neurology of mitochondrial disease and how it may inform autism research, and triggers for neurological deterioration in patients with mitochondrial disorders.

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CDC's Clinical Immunization Safety Assessment Network (CISA) has also experienced a great deal of recent activity in this area. CISA's mission includes studying pathophysiologic mechanisms and biologic bases of adverse events following immunization, as well as providing evidence-based immunization safety assessments. Aligned with that mission, CISA experts formed a work group about a year ago to focus on metabolic disorders, and now have another one that is focusing on mitochondrial disorders in order to identify key research questions and study methods related to these conditions. Specifically, they plan to develop clinical protocols that will help to assess how immunization may affect or trigger these conditions. They also will consider the feasibility of developing clinical guidelines for assessment of patients with these conditions. Discussions are also underway at CDC regarding a feasibility and validation study to examine health and medical information in children who have died or who are suspected to have died of mitochondrial disease to determine whether information is available that could help assess how the health outcomes of these conditions were affected.

CDC is working towards changing the organizational home for our Immunization Safety Office. This update is provided early on while there are still a number of operational details that need to be worked out. That is because CDC wants to be transparent about our immunization safety efforts and wants you to know about this first-hand as immunization safety is critical to what ACIP does. Many thoughtful people with diverse perspectives have discussed this extensively and extended a recommendation to the CDC leadership that CDC could provide better scientific and program leadership and support by housing ISO in the Division of Healthcare Quality Promotion (DHQP). Our belief that this move will help and strengthen our immunization safety activities is based on a number of factors:

- Organizationally, CDC's major scientific and program activities are housed in the Divisions within our National Centers: this is where our science and activities best flourish.

- DHQP is the focal point for CDC's patient safety efforts and activities, and as such, contains knowledge, expertise and scientific leadership that is related to, and supportive of, immunization safety science and activities.

- The experience we've gained in the past three years: when ISO has been housed in CDC's Office of Science- allowed us to both strengthen the office and gain much helpful insights in vaccine safety issues and research, but the broad scope of the offices in the CDC Office of the Director usually are not well suited, over the long-term, for housing specific programs or activities

Dr. Popovic stressed that CDC is interested in working with ACIP with respect to how immunization safety activities could be further strengthened. She assured the committee that she would remain in contact with the ACIP Chair and Executive Secretary to determine how best to keep the lines of communication open. The ISO

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move is expected to take place in the fall. Dr. Popovic offered to update ACIP during the October 2008 meeting.

Discussion

Dr. Stephan Foster supported the move to DHQP. This should be a positive move, which continues to ensure the safety of vaccines. However, he cautioned that patient safety issues are not necessarily the same as vaccine safety issues. To equate the two could prove to be problematic. For example, current vaccine safety concerns are primarily grounded in fundamental, basic science and are addressed by fundamental science such as immunology and epidemiology. Many current patient safety issues have systems-based approaches and innovations. With that in mind, he stressed that the two issues should be treated separately at the division in terms of separate resources.

Dr. Iskander responded that ISO is clearly aware that the scientific underpinnings of a patient safety systems approach are different than the traditional vaccine safety model. However, with increasing numbers of vaccines, especially with increasing numbers of combination vaccines, preventable adverse events are also on the rise (e.g., vaccine administration errors, post-vaccination syncope). These issues may, in fact, be amenable to a more patient safety-centered approach. Working side-by-side with colleagues who are well-grounded in those alternative approaches should be extremely beneficial.

Dr. Dixie Snider, Co-Chair of the Patient Safety Work Group at CDC, assured everyone that this working group had also considered and understands the patient safety versus vaccine safety issue. DHQP has components that are focused on drug safety, tissue safety, organ safety, and general expertise in pharmaco-vigilance, which are very compatible with some of the expertise and activities of ISO. While there are similarities in patient versus vaccine safety issues, there clearly are systems issues upon which true healthcare quality promotion would focus that differ. He welcomed comments on the new organizational structure in terms of configuration and operation in order to take advantage of the synergies that are already intrinsically potential, and at the same time not to cause damage to either endeavor.

Dr. Curlin observed that, based on the material Dr. Broder presented and the discussion pertaining to standing up the Federal Immunization Safety Task Force, research ideas seemed to be divided into the activities which ISO would undertake versus activities that others would carry out. He cautioned that the list of draft recommendations was very ambitious and that the thematic areas were ideas rather than a research plan per se. Instead of dividing up turf, the entire federal research enterprise must be brought to bear.

Georges Peter, Brown University applauded the changes taking place and the increased attention to immunization safety. While he recognized that a science-based research agenda was critical, it was not apparent who would be coordinating and

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responsible for communications in immunization safety within CDC. This is extraordinarily important with respect to the public, parents, and pediatricians, particularly with so much media attention devoted to the allegations about autism and vaccine schedules.

Dr. Snider agreed and explained that there are continuing conversations within the CDC about where communications should come from, and it is not always from one place. For example, the National Center for Birth Defects and Developmental Disabilities (NCBDDD) has been very helpful in communicating certain issues. Also, as mentioned previously, implementation involves setting up three working groups to deal with various issues, one of which is policy and communications. While the details have not been worked through at this point, the Federal Immunization Safety Taskforce which recently met under the leadership of the ASH, identified communications as the number one priority for that task force. While they do not have all of the answers, they do have everybody's attention around this issue.

Rabies Vaccines and Biologicals

Rabies Vaccines and Biologicals

Dr. Charles Rupprecht
(CDC/CCID/NCZVED/DVRD)

Dr. Rupprecht thanked the committee for the opportunity to present an update on the human rabies biologicals supply. One can envision essentially three phases in regard to this topic: a green phase where all ACIP recommendations can be met; the current yellow phase, in which not all current ACIP recommendations can be implemented; and a critical red phase of a shortage, whereby it is projected that the most critical risk groups, exposed humans, would likely not be receiving adequate prophylaxis on the basis of supply.

There has been a series of concomitant unfortunate events: a disease that is relatively unpredictable because of wildlife reservoirs, animal rabies cases being on the rise according to 2007 surveillance data, and at the same time forecasted supply and demand being out of sync. These events converged to result in the current situation that was described during the February 2008 ACIP meeting. Since that time, on the basis of the recommendations of the committee, an ad hoc national interim working group was formed to deal with the most critical phase—an imminent shortage.

Since February 2008, the first case during 2008 of human rabies was diagnosed in California. There have been publications of major documents to assist with rabies prevention and control in the US, including the 2008 National Association of State Public Health Veterinarians (NASPHV) Compendium published on April 18, 2008. On April 24, 2008, draft interim plans in the event of shortage were developed. The 2008 ACIP rabies prevention document was published on May 7, 2008. On May 19, 2008 sanofi pasteur announced restrictions of vaccine for post-exposure prophylaxis (PEP)

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use only. On June 4, 2008 a zoonoses conference call was convened. On-going discussions have been held with states and at the NASPHV and CSTE meetings on June 8, 2008. Further restrictions were issued to the Novartis supply on June 17, 2008, such that it will only be released upon consultation with State Public Health Veterinarians and CDC based upon need.

The objective of the ad hoc working group was to draft interim recommendations for human rabies prevention in the event of a forecast shortage of biologicals, predominantly for human PEP. Based upon a combination of historical animal rabies surveillance data, prior mass human rabies exposure situations, and conventional aggregate commercial seasonal distributions of product over time, a national shortage in biologicals would be forecast when expected PEP needs were projected to out strip the estimated rate of use of available supplies of human rabies vaccines or immune globulins. The epidemiology of exposures is known, and there are aggregate records from both manufacturers as well, so it is possible to essentially determine what the supplies have been seasonally and when disjunctions occur between supply and demand.

The primary focus of the ad hoc working group included coordination and communications, diagnostic and animal control, risk assessments under various scenarios, alternative schedules and routes, travel medicine, economic implications, and investigational products. Dr. Rupprecht thanked the members of the ad hoc working group, acknowledging their activities. The ad hoc working group is predominantly made up of liaison groups whose focus is daily rabies prevention and control activities and non-governmental organizations (NGOs) in the states. The HHS working group is made up of CDC (e.g., National Center for Immunization and Respiratory Diseases, National Center for Preparedness, Detection and Control of Infectious Diseases, National Center for Zoonotic, Vector-borne & Enteric Diseases; and FDA representatives (e.g., Center for Biologics Evaluation & Research).

Contingency plans during a shortage situation include revised health communications and assessments; getting back to basics in terms of animal rabies prevention and control activities; a focus upon the actual administration of products that would entail alterations in criteria and triaging for the most critical groups at risk; changes in pre-exposure vaccination administration; and management modification of PEP. Actions in a shortage forecast would include mandated centralized national-state health communications with the manufacturers to maximize the limited use of supply, defining a true exposure versus much lower risk, mandatory consultations with knowledgeable public health officials related to disease risk and need for PEP, and renewed education and outreach for key medical providers—even during a yellow phase. Basic rabies prevention principles would include postponed PEP administration until animal control could locate and capture any suspects; forestalling any PEP during the observation period of domestic dogs, cats, and ferrets; and withholding PEP until timely diagnostic results are obtained for rabies suspect animals.

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In terms of reassessment of exposures, interim guidelines would provide a new risk-stratified approach to human rabies PEP decisions. Such modifications conserve supplies by curtailing use in low risk situations, such as non-bite exposures. Moreover, PEP may be withheld after bites from certain animals where adequate surveillance exists and documents no local terrestrial rabies reservoir. For bat scenarios, PEP should only be administered to individuals with a strong belief that they would not awaken from a bite, or be unable to report that actual physical contact occurred. Where available, all suspect bats should be captured, tested, and PEP deferred until diagnostic confirmation.

Gradually, over the 20th Century, there has been a gradual move from more than 14-21 doses of vaccine to 6 doses, to 4-5 doses. Over the last 30 years, recommendations have been in place to move to more evidence-based assessments in a shortage forecast. Rabies vaccine options in a shortage include administering only one booster in prior vaccinates; dropping the fifth (final dose) of vaccine in naïve patients; using alternative schedules (e.g., 2-1-1); utilizing ID route for immunization; and considering other biologicals, based on investigational new drugs (INDs). With respect to pre-exposure vaccine issues in a shortage, most of the supply would be diverted to a primary PEP focus; would focus primarily upon true first responders (e.g., those involved in minimizing and mitigating PEP; and those potentially exposed by soliciting, finding, sedating, restraining, euthanizing, necropsy, and rabies diagnosis); and would use alternate routes for administration. First responders are already defined by ACIP risk groups; however, not all ACIP risk groups are true first responders. There are a number of potential at-risk groups who would not be receiving pre-exposure vaccination under such considerations.

Pre-exposure needs directly determine the need upon those potentially exposed in the public at large. Vaccines would be required in first responder subjects at risk, before occupational exposure to rabies. Subjects include animal control workers, diagnosticians, veterinary staff, et cetera. Staff activities directly determine potential PEP management of other exposed patients. Minimization would occur in members of the general public. For example, pre-exposure vaccination would normally have been recommended for those who wished to go on a bat outing, expatriates, state department employees, and people going into at-risk canine and zoonotic situations. For these individuals, there would instead be a greater focus upon primary education with regard to avoiding such exposures, as opposed to carte blanche use in individuals who otherwise probably could have prevented such exposures by additional risk communications, and postponing activities that might place an individual at risk.

With respect to travel situations in the event of a shortage, it would be prudent to de-prioritize vaccination for any international travel indications in favor of reserving supplies for use in PEP regimens. Primary education of travelers about rabies occurrence abroad and primary bite avoidance (e.g., not approaching mammals, and avoiding encountering them accidentally by being more aware of their presence) is critical. People who take up residence overseas, longer term travelers, and frequent at-risk

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travelers may obtain vaccination abroad where safe injection practices are used with an approved cell culture vaccine.

The economic implications were previously vetted in the ACIP 2008 publication, as well as one in-press publication (P. Dhankhar et al Vaccine 2008;26:4251-5). It is always cost effective to administer PEP if a patient is bitten by a known rabid animal or a major reservoir. For all other transmission risk situations, net cost ranges from ~ $4 million to $4 billion per life saved. The supply could be conserved by administering PEP up to a maximum defined risk of rabies virus transmission. However, precise risk estimates of rabies virus transmission do not exist. Until more precise estimates for transmission are obtained, it is probably not advisable to use health economic strategies to limit the use of biologicals by pre-set thresholds of risks alone.

There are many less alternative biologicals if there is a projected shortage of rabies immune globulins, although there is not a projected shortage of immune globulins currently. However, there may be some aftermath post-2009 from some of the restricted pre-exposure utilizations that are currently in place. For example, if human rabies immune globulin applications for defined cell culture products are limited, there could be future restrictions on rabies immune globulin. Similarly, there are other forces at work that may provide some need for greater focus upon rabies immune globulin alternatives, some of which are currently under consideration.

In summary, supplies of biologicals used in human rabies prophylaxis are expected to remain less than ideal over the next several years. CDC, FDA, HHS, industry, state health departments, and national stakeholders continue to work together toward productive solutions to mitigate current human rabies vaccine supply issues. Deliberations of an ad hoc national rabies working group has resulted in the development of draft interim recommendations related to contingency actions that would be utilized in the event of any forecast actual shortages in the future.

Discussion

Dr. Morse pointed out that in New York State, about 2500 people are given PEP per year. If there was a campaign to reduce that by 10%, given the number of doses, that would be over 1200 doses saved. He wondered if there were plans to implement some of the recommendations of the work group immediately to educate health care providers and consumers in an effort to decrease the use of vaccine.

Dr. Rupprecht responded there were plans to do so. Given that some of the ACIP recommendations already are not being met, there are major plans afoot to assess needs, disseminate education, and ensure that the critical aspects of the 2008 ACIP recommendations are in the hands of medical providers. Some of the recommendations that would be utilized in a red phase, critical shortage, are already underway. They also await word from the manufacturers regarding whether apparent limitations in current supply, case-by-case utilization, and pre-exposure vaccination limitations will be alleviated later in the summer and into the fall.

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Dr. Duchin, NACCHO, reported that during this ACIP meeting, he had received multiple calls from his location in Seattle, Washington about patients who had been turned away from hospitals stating that they were out of rabies vaccine. Subsequently, these patients contacted the local health jurisdiction asking where to acquire rabies vaccine. His staff spent a lot of time and he attempted to intervene in an effort to facilitate access to the vaccine. He believed that more aggressive outreach was required to health care facilities and providers administering the vaccine to help them understand the procedure to acquire the vaccine and to encourage them not to send patients searching elsewhere for the vaccine. A problem traditionally encountered is that very few outpatient physicians and health care providers are willing to order the vaccine because of the tremendous up-front cost required, as well as the uncertainty of reimbursement once the vaccine is ordered. Predominantly all vaccines are administered in emergency departments and urgent care facilities; however, outpatient providers may need to be encouraged to order vaccine when they have an established relationship with patients.

Dr. Sandra Fryhofer , American College of Physicians, stated that from a practicing physician's point of view, the rabies vaccine shortage represented another example of the fragile balance between vaccine supply, demand, and availability. She worried that everyone's patients might encounter difficulties. She serves the ACIP as a delegate to the American Medical Association and also was elected to the Council on Science and Public Health. The council is developing a report on vaccine financing and funding issues because at the end of the day, it is all about money and how to keep pharmaceutical companies interested in making vaccines.

Dr. Morse inquired as to whether there was any additional information on how imminent the more serious shortage would be, or if there were too many factors to make a prediction in terms of vaccine production.

Dr. Rupprecht responded that everyone was cautiously optimistic that supplies would begin to improve to the extent that pre-exposure needs for critical first responders would be met. Plans are underway to meet demands for secondary groups at risk (e.g., veterinary schools) by August on the basis of supplies and lots that have been released. Within the next month and continuing into the fall, additional doses of vaccine should be coming into the market. Although it may be perceived that there is a shortage, instead supplies are simply being strictly managed to ensure against a shortage. With respect to patients being turned away, there are available supplies such that anyone who has truly been exposed will be vaccinated, receiving both vaccine and rabies immune globulin. He stressed that based upon the information available at this time, and barring any unforeseen events, supplies are expected to increase.

Rajiv Di Silva, Novartis Vaccines & Diagnostics, Inc., reiterated Novartis's long-term commitment to being in the rabies vaccine arena, and certainly part of all public health efforts in the area of rabies prevention in the US. He concurred that from the beginning of 2008, there had been a situation of short supply with respect to Rabavert®, Novartis's human rabies vaccine for the US. There have been multiple dialogues with CDC,'s the

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National Vaccine Program Office, as well as the FDA regarding the current situation. As Dr. Rupprecht mentioned, they have had a PEP limitation on their vaccine since the beginning of the year. They have certainly used that limitation with respect to distributors of the vaccine. In the meantime, Novartis has been working very closely with the FDA on certain steps to allow them to return to supply this year. He reminded everyone that in February, he communicated to the ACIP that Novartis was hopeful that they would be in a position to supply some material in July 2008 and supply more in the fall. He said he was happy to announce that this first lot of material that they expected in July had been released. As of that time, it had been shipped from their existing Marburg, Germany facility, was physically in the US, and should be in their warehouses by the following Monday. Therefore, a reasonable quantity of materials should be available through the summer months. There will continue to be a PEP- limitation on these materials until there is more comfort around the additional supplies coming in the fall. He reported that Dr. Rupprecht and others at CDC agreed to use a small proportion of the vaccine that had just arrived for high priority pre-exposure use as well. Novartis remains cautiously optimistic about the materials that they believe they can bring to the country later in the fall as well, although that is subject to further regulatory approvals by the FDA. From a longer term prospective, he was also happy to announce that just the week before they had broken ground on a new manufacturing facility in Marburg, Germany which will produce rabies vaccines for the US, and they will invest in excess of $200 million to fast-track the building of this plant to have it online as soon as 2011. In the meantime, they are working very closely with FDA to put in place some interim remediation measures with respect to their existing facility in Marburg so that they can supply adequate amounts in 2009 and 2010. That being said, several more complex actions need to be implemented and several more regulatory actions are required before they can say that they are safely back to supply as normal.

Dr. Pickering asked whether some quantification data could be provided on supplies for July and for the fall, perhaps in relation to what would normally be expected.

Rajiv De Silva, Novartis, responded that while he could not speak to the national supply, the material Novartis currently had coming into the country would be approximately about 40,000 doses. Under normal circumstances, that would certainly be sufficient to supply half the nation's needs. If they put some PEP limitations on that, even if the need is for more than 50% of the national supply, they could probably get through the summer at least.

David Johnson, sanofi pasteur, echoed what was said from their colleagues at Novartis that they are very committed at sanofi pasteur long-term to the rabies vaccine business. However, their situation is somewhat different in that they had planned a stoppage in production beginning in 2007 to renovate their production facilities in France to keep up with the evolving FDA and French regulatory standards there. Therefore, they created a stockpile based on historical demand for their rabies vaccine. However, other production supply problems were encountered during this time period causing them to have to go to the PEP only for their vaccine. Until approximately mid-2009, they will not be back in production and will have to continue in consultation with CDC and ACIP to

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focus, at least for the time being, on PEP. He said he was very happy to hear about the additional supplies from Novartis, which may allow sanofi pasteur to expand the use of their vaccine as well.

Dr. Morse thanked Dr. Rupprecht and the working group for tremendous rapid response to the potential shortage, and for developing a number of guidelines. He encouraged them to implement some of the strategies suggested immediately to reduce the potential need.

Dr. Rupprecht requested that committee members submit any additional substantive comments to the working group.

Vaccine Supply

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Dr. Wallace briefly discussed some of the issues pertaining to influenza vaccine production, distribution, administration, and disease. In addition, he presented an update on vaccines currently experiencing supply issues, and reviewed a survey conducted about the utilization of Hib vaccine and adherence to the interim recommendations during the Hib supply issues.

With regard to historical cumulative monthly influenza vaccine distribution from the years 2000 and 2004-2007, in 2000 there was a severe delay with the number of doses not reaching 70.4 million until December. 2002 represented the historical standard of getting about 80 million doses out by October. In 2003-04, manufacturers were more conservative with their production, but there was late demand due to reports of pediatric deaths. That was followed by 2004, which was a shortage year, with just over 40 million doses out by October and only 57 million doses out by January 2005. There was an initial recovery in 2005 in which there were 83 million doses out by November, but there was still a relative delay. Production rose to record levels in 2006 with 102.5 million doses out by December, but depending on product utilized and other pipeline issue there were still delays in October, which is still a critical month in terms of demand and distribution. In 2007, there were over 100 million doses out by October and 112.8 million doses out by January. Although some areas may experience relative delays, the US is at a high level historically speaking. The capacity to distribute does seem to be able to ramp up, although it is not clear what the capacity to administer doses would be.

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Projecting demand in a changing world is difficult, given that the doses produced can be increased, but the demand does not necessarily follow. In the 2003-2004 season, some manufacturers dropped out and production dropped down to predict more accurately the demand; however, that was followed with the shortage year in 2004-2005. In the three influenza seasons since, both production and distribution ramped up tremendously, but where the true demand ultimately will be is difficult to predict. It is likely to be affected by the ACIP recommendation to include all children through age 18 years made during the February 2008 meeting. In the decade between 1999-2007, production grew to 140.6 million doses, with the distribution having grown to 112.8 million doses. While there was record production, distribution, and administration in 2007, the gap between these numbers has also grown. In the last two years FluFinder SVN, a new tracking system to the level of major distributors, has been used. In the past, distribution was self-reported by the manufacturers. This system includes another layer of detail in which not only is self-reported by manufacturers included as they distribute directly, but also the seven major distributors are included. Thus, while influenza has presented challenges in the past several years, increased production and distribution capacity has alleviated some of these challenges. Nevertheless, administration capacity remains unknown and is of concern. It is also unclear where demand and the market will go from here.

Demand was high in 2003, the year before the shortage. Early disease was observed in pediatric populations, particularly reported through CNN. During that time, there was a tight matching of the distribution and production, some gap between administration and distribution, and gaps likely attributable to a certain amount of basic inefficiencies that would be expected in any year. The 2004 shortage year showed tight production and distribution, with a small gap with administration even during a shortage. Some of the gaps are due to timing, getting the patients in, holidays (e.g., Thanksgiving and Christmas), et cetera. Coming out of the shortage, Chiron was engaged in remediation steps and Flurarix®, Fluvirin®, and Afluria® were progressively added; and production, distribution, and administration were increasing. While the supply situation was more stable, there was a growing gap between production, distribution, and administration. While Dr. Wallace did not draw conclusions about what would happen next, this was somewhat similar to what was observed in the 1990s with some separation, although the magnitudes are greater now. While things are moving in the right direction, there are growing pains.

Regarding some of the current supply issues with the VZV bulk vaccines (e.g., Varivax®, ProQuad®, and Zostavax®) in 2007 bulk manufacturing was temporarily suspended. Merck is now producing bulk and is in the latter stages of the remediation process with FDA. There are currently adequate supplies of Varivax® and Zostavax®, but Dr. Wallace pointed out that just within the last week there had been some backorder status with the Zostavax®, much like from the summer of 2007 with the juggling of supply and demand, projecting demand, and dealing with all of the Varivax® issues. Orders are still being taken for Zostavax® by Merck, although orders are being put in back order status. Merck is working to get those out of back order status, and will

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be supplying more information in the coming weeks. ProQuad® is projected to be back on the market in early 2009, pending the remediation process with FDA. Currently, there are no interim recommendations despite there being no ProQuad® because there is enough Varivax® to meet the ACIP recommendations. Merck has also experienced production delays with Hepatitis A vaccine. They are now projected to return with their pediatric vaccine in the fourth quarter of 2008, and the adult vaccine in the first quarter of 2009. GSK is currently meeting the national demand for that vaccine and there are no interim recommendations, meaning that the routine ACIP recommendations are still in place.

Regarding the Hib vaccine (PedVaxHib & Comvax), Dr. Wallace called attention to the voluntary lot recalls in December, stating that they are currently projecting a return in the fourth quarter of this year. The interim ACIP recommendations are in place, and sanofi pasteur is meeting the need for those interim recommendations. The approval of Pentacel® does not change the current overall supply of Hib vaccine. Although Pentacel® will be ramped in with the new licensure, there is no excess supply of Hib-containing vaccines, so there are no plans to relieve the interim recommendations at this time. The Hib interim recommendations are to defer the 12-15 month dose, except for specific high-risk groups, such as those with immune deficiency issues. High-risk groups should continue to receive 12-15 month booster dose (e.g., asplenia, sickle cell disease, HIV infection, immunodeficiency syndromes, and malignancies). Providers who use PRP-OMP Hib (PedVaxHib & Comvax) to serve AI / AN children in AI / AN communities continue to use PRP-OMP, including administration of the 12-15 month booster dose.

Dr. Wallace then reported on the response of the health care provider community to the interim recommendations. Although initially there were not many complaints compared to other shortages, feedback was received about providers who were continuing to give the 12-15 month dose to healthy individuals, as well as some who did not have enough vaccine to reach the full 2-4-6 month recommendation. To investigate this issue, CDC turned to a Colorado research group who surveyed a group of family physicians and pediatricians—a group of providers with whom they have conducted other surveys. Dr. Wallace acknowledged that the survey was the work of Allison Kempe's group, for whom he was presenting the information as she was unable to attend.

The objectives of the "Hib Vaccine Shortages: A National Survey of Attitudes and Practices of Pediatricians and Family Medicine Physicians," were to determine pediatricians' and family medicine practitioners' knowledge and attitudes about ACIP recommendations regarding Hib use during shortages; reported practice regarding Hib administration in different age groups; and factors associated with adherence to recommendations. With respect to the study setting, the survey was conducted in a sentinel physician network, developed as part of the Vaccine Policy Collaborative Initiative. The network is recruited from a random sample of American Academy of Pediatric (AAP) members and American Academy of Family Physicians (AAFP) members. The survey was designed to be representative of AAP and AAFP region of

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country (MW, NE, S, W); location (urban, suburban, rural); and setting (private, community / hospital / clinic-based, managed care / HMO / Other)—AAP only.

Of the total response rates of 373 participants, 68% (n=220) were pediatricians and 51% (n=153) were family medicine practitioners. With respect to knowledge of the recommendations, it appeared that pediatricians and family doctors received the message and understood what the recommendations were. Regarding whether the vaccine should be given to healthy 2, 4, 6 month olds, 100% of pediatricians and 89% of family doctors understood the recommendation. In terms of whether vaccine should be deferred in healthy 12-15 month olds, 100% of pediatricians and 99% of family doctors understood the recommendation. With respect to whether the vaccine should be given to 12-15 month olds with high-risk condition, 98% of physicians and 98% of family doctors understood the recommendation. However, for those who had private insurance or non-VFC vaccine who reported and demonstrated that they understood correctly what the recommendations were, there were 12-13% who were not giving the full primary series. Although it was not clear exactly why that occurred, Dr. Wallace hypothesized that it was because practitioners did not have enough vaccine when the child presented. About 20% of those who understood the recommendations continued to vaccinate their healthy 12-15 month olds. From the community perspective, those ignoring the interim recommendations may actually be impacting their colleagues and the children they serve. Data from those using the VFC vaccine who understood the recommendations indicated that 12-15% were not giving the full primary series, and 19-20% continued to give the 12-15 month dose for healthy children. The initial conclusions were that the majority of physicians were aware of the recommendations and understood the specifics of them. Despite this, including both those who did and did not understand, almost a quarter of the pediatricians and a third of the family medicine doctors reported that they were not deferring. Even those who knew, 20% across the board, were not deferring the 12-15 month dose despite understanding the recommendations.

Open-ended questions at the end of the survey revealed that there was some misunderstanding that the recommendation only applied at the practice level, so that if one had enough vaccine, it was not necessary to defer those doses. This highlighted the issue that with this particular shortage, with two manufacturers, the extent of following the recommendations may have depended to some extent upon which manufacturer a practitioner used. Also, there may have been a hangover effect from the first Prevnar® shortage during which recommendations were made based upon how much supply practitioners had. No one could adhere to those recommendations because they were not easily understood. With the second Prevnar® shortage, national recommendations were made, although some work is still needed to make clear that the recommendations are national recommendations.

In conclusion, all pediatricians and the majority (80%) of family physicians were aware of interim recommendations during Hib shortages. Of those who were aware, almost all were knowledgeable about specific recommendations. Despite this, almost one fourth of pediatricians and one third of family medicine practitioners report they are not

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deferring in healthy 12-15 month olds. Of each specialty, 20% are not deferring despite knowledge of the recommendations. Reported attitudes suggest misunderstanding that the recommendations are based on Hib supply at the level of the practice, especially among family medicine practitioners. There are concerns about inadequate protection among children receiving three doses of ActHib and no booster, especially among pediatricians. Based on reported experiences, providers have had to make significant changes in the type and number of vaccines related to shortages, especially among pediatricians.

There are significant challenges at the physician level that impact their day-to-day work at the practice level. One recurring theme in the feedback from physicians was that they were not being provided any updates. In response to this survey, additional outreach efforts were made through CDC and the provider academies to reach out to providers to reemphasize that the recommendations are national, they must be adhered to, and to explain why. Clearly, a lot of work remains to be done regarding communication, especially in terms of updates. CDC's website is always up-to-date, but if providers don not see anything new, they think CDC is not communicating. Dr. Wallace invited input from the ACIP membership.

Discussion

Dr. Lett suggested using McKesson, the distributor, as a vehicle to send out periodic updates about even non-VFC vaccine.

Dr. Wallace responded that this was part of the original contract. CDC worked with sanofi pasteur on flyers and started putting those in every box. This has been done to announce the replacement program for FluMist® for the upcoming year. They have also been putting in flyers about upcoming webcasts from the education branch to determine whether that will help.

Dr. Judson stated that he may have a conflict, given that he was from the University of Colorado. He pointed out that critically, the sample sizes were small for the survey. A 50% or 68% response rate is not large. If people tended to respond when they were compliant, that would result in a major bias. If the survey is actually measuring practice reality, it was incredibly encouraging to reach 80% compliance in deferring the 12-15 month dose when almost all of the incentives for the practicing physician would be in the direction of non-compliance (e.g., they may have the patient in the office, there are expenses to rescheduling, they are well aware of compliance if appointments have to be rescheduled, they have the vaccine available, et cetera).

Dr. Wallace replied that part of the motivation for CDC to conduct the survey was due to information that sanofi pasteur was receiving from their customer base from a separate source (e.g., insurance claims, et cetera). In the second Prevnar® shortage, compliance was less poor than the first shortage, given that the manufacturer (Wyeth) and CDC were able to closely monitor and maintain ordering and inventory levels and the recommendation was simpler. Also with Prevnar®, there was always some coming

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out, just not in a smooth fashion. However, Hib has a shared market, plus a dropout, plus a recall, which affected some providers more than others. He stressed that it was important to convey the message to practitioners that their actions could impact children being cared for by their colleagues'.

Dr. Chilton wondered if there was any perceived impact of the shortage on Hib disease in the US, and if not, whether there was any possibility of dispensing with the booster dose of Hib vaccine.

Dr. Wallace answered that through the ABCs surveillance system, CDC has a good mechanism to monitor that. The working hypothesis is that because the vaccine is so good, coverage is also good, and there is some herd effect. That has bought some time. Based on the immunogenicity studies for Hib, the 12-15 month booster would not be the one to eliminate for long-time maintenance of low disease. There are still some pockets of Hib disease occasionally from communities that do not vaccinate. Based on that, he did not think anyone was entertaining the notion of dropping the booster permanently.

Dr. Sawyer was not surprised by the 20% non-compliance rate, in part because of the Prevnar® experience that was referred to and also because, in his opinion, physicians have held up the haemophilus program as the poster child of modern day immunization success and they are very afraid to let that go. The study from Colorado excellently illustrates that knowledge of the recommendation is not sufficient to assure compliance, and that perhaps there is a role for the public health community and the Vaccine for Children Program activities in private provider offices to take the next step to monitor compliance and provide feedback that this is a major problem, and that without their cooperation the problem could become worse.

Dr. Wallace acknowledged that there remained a great deal of work to be done in that area.

Dr. Morse wondered what the possibility would be, with one distributor, of better managing the inventory and stockpiling to avoid shortage situations.

Dr. Wallace thought that while having more moving parts helped in some ways, it could also serve to further complicate matters. There are many other procurement issues. CDC has a workgroup that is examining how to model the right amount of stockpile doses for each disease, what the real costs are, what the actual impact would be of falling short to different degrees for different vaccines, et cetera. The workgroup is vetting that through NVAC and will present the information to the Office of Management and Budget (OMB). Perhaps it had less to do with managing inventory and the number of manufacturers and more to do with having a logical way to determine true need and true costs. He offered to present on those issues in the future.

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Influenza

Update on Influenza Surveillance

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Dr. Fiore reminded everyone that the sentinel provider system consisted of a group of providers distributed nationally who agree to report to CDC each week what proportion of office visits they have for influenza-like illness (ILI). As would be predicted, there is a winter peak each season. Based on the percentage of visits for ILI and ARI reported by sentinel providers from 2005-06 through 2007-08 influenza seasons, in the previous two seasons the peak was above the baseline threshold. There was a much higher peak in the past influenza season.

Through the Emerging Infections Program, CDC also tracks laboratory-confirmed influenza and cumulative hospitalization rates for children ages 0-4 and 5-17. For 2007-2008 and the previous four seasons, given that the hospital rates are cumulative, the rates go up as the season progresses and then flattens out as the season ends. For the past season, the cumulative hospitalization rate was something higher than it has been in the previous three seasons, but not as high as it was in the 2003-2004 season. The New Vaccine Surveillance Network also tracks laboratory-confirmed influenza and cumulative hospitalization rates for children 0 - 4 years. Because there is a somewhat more sensitive case-ascertainment for this system, the rates are somewhat higher, but they show basically the same sorts of trends as the Emerging Infections Program. There was a higher rate this season than in the previous two seasons, and in this system it was similar to the rates observed in 2004-2005 and in 2003-2004. The Mortality Reporting System tracks pneumonia and influenza mortality for 122 US cities based on death certificate data. Based on these data, the 2007-2008 influenza season was well above the epidemic threshold for much of the winter in comparison to the previous two seasons, which were somewhat milder. This past season looked more like 2004-2005 and 2003-2004.

Since 2004, there has been a reporting system for deaths due to laboratory-confirmed influenza among children. Typically, these data are updated over the summer as the case reports are completed, so it could still increase somewhat higher. As of June 19, 2008, CDC has received 83 reports of influenza-associated deaths among children <18 years old. The median age is five years (range, 29 days – 17 years). Of 65 children tested for bacterial co-infection, 28 (43%) had *S. aureus* infection, of which 15 were due

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to MRSA. Of these children, 53 were unvaccinated, 9 were ineligible (< 6 months old), 5 were vaccinated (5), 5 were partially vaccinated, and 11 had an unknown vaccine status. There were 76 deaths in 2006-2007, 47 in 2005-2006, 46 in 2004-2005, and 153 in 2003-2004.

Antiviral Resistance Among Influenza A H1N1 Viruses

Anthony Fiore, MD, MPH
Influenza Division
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Coordinating Center for Infectious Diseases
Centers for Disease Control and Prevention

With respect to influenza virus surveillance and antiviral resistance observed in the 2007-2008 season, Dr. Fiore reported that the percent positive for acute respiratory illness was over 30% during the peak of the season, which is somewhat higher than observed in several previous seasons. Although most initial influenza A isolates early in the season were H1N1 subtype, H3N2 ultimately predominated. There was also considerable influenza B activity. Thus, the 2007-2008 was predominantly an H3N2 and B season with very little H1N1 left by the end of the season (U.S. WHO / NREVSS Collaborating Laboratories).

CDC has antigentically characterized 1,161 viruses collected by US laboratories since October 1, 2007 in order to determine how well the circulating viruses match the vaccine viruses and to collect viruses that potentially could be used in vaccines in the future. Amongst the 407 Influenza A (H1N1) strains that have been characterized, 66% are similar to A/Solomon Islands/3/2006-like viruses (2007-08 vaccine strain) which was in the vaccine this past season, and 29% are similar to A/Brisbane/59/2007 that was selected for the 2008-09 vaccine strain. Of the 404 Influenza A (H3N2) strains tested, 23% were similar to A/Wisconsin/67/2005-like viruses (2007-08 vaccine strain), and 60% were similar to A/Brisbane/10/2007 (selected 2008-09 vaccine strain). Each year, the vaccine has one of the two lineages represented. Of the 264 Influenza B strains, 2% were in the Victoria lineage (represented in 2007-08 vaccine by B/Malaysia/2506/2004), and 98% were in the Yamagata lineage. 89% were similar to B/Florida/4/2006, which was selected for the 2008-09 vaccine strain.

Antiviral resistance has been tracked much more closely over the past few years, and is tested against both the adamantane (rimantadine and amantadine) classes of anti-influenza drugs and the neuraminidase inhibitor medications (oseltamivir and zanamivir). 1,392 virus isolates have been tested for sensitivity to adamantane medications. Of the 487 influenza A (H3N2) viruses tested, 99% were resistant. Of the 905 influenza A (H1N1) viruses tested, 11% were resistant. Influenza B viruses are inherently not sensitive to adamantanes. Therefore, adamantanes are not recommended for treatment or chemoprophylaxis. 1,705 virus isolates have been tested for sensitivity to neuraminidase inhibitor medications. Of these, 109 (11%) of 1003 influenza A (H1N1) viruses were resistant to oseltamivir. All of the resistant

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viruses have H274Y mutation. In the 2006-2007 season, 4 (0.7%) of 588 influenza A (H1N1) viruses isolated in US were resistant, 0 of 397 influenza A (H3N2) viruses were resistant to oseltamivir, and 0 of 305 influenza B viruses were resistant to oseltamivir. All tested viruses were sensitive to zanamivir. There is a low prevalence of oseltamivir resistance overall, given type/subtype distribution (~2%). Oseltamivir or zanamivir continue to be the recommended medications for treatment or for chemoprophylaxis.

Oseltamivir resistance is not just a US phenomenon. It was initially identified in Europe. Referring to a world map from the WHO showing the prevalence of oseltamivir-resistant H1N1 viruses in the last quarter of 2007 through the first quarter 2008, a number of countries had greater than 25% resistance (e.g., Canada, Russia, several European countries). In Norway resistance is over 60% and in France it over 40%. Thus, the US is at somewhat lower levels of resistance than other countries. Based on preliminary data from the WHO and CDC, the characteristics of influenza caused by oseltamivir-resistant influenza A (H1N1) viruses are that persons were typically not taking oseltamivir at the time resistant virus was isolated. Most persons infected with resistant influenza A H1N1 did not have an epidemiologic link to other persons taking oseltamivir or to each other. Symptoms and severity are similar to illness caused by oseltamivir-sensitive viruses. Oseltamivir-resistant viruses are transmissible between persons, similar to other influenza A viruses.

Interim Vaccine Effectiveness Estimate, 2007-2008 Season

Dr. David Shay
Influenza Division
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Coordinating Center for Infectious Diseases
Centers for Disease Control and Prevention

Dr. Shay reported on the interim within-season estimate of the effectiveness of trivalent inactivated influenza vaccine from Marshfield, Wisconsin's 2007-08 Influenza Season (MMWR 2008;57:393-8). The objectives of this set of studies were to estimate vaccine effectiveness for preventing medically attended acute respiratory illness (MAARI) that is confirmed as influenza; provide interim and final estimates of vaccine effectiveness for the 2007-2008 influenza season; and include all groups for which ACIP recommends annual vaccination in the vaccine effectiveness estimates.

With regard to the methods, patients living in a 14 postal-code area surrounding the Marshfield Clinic were eligible for the study (N=49,712 residents). Enrollment began on January 21, 2008, with interim data through February 8, 2008 reported. Patients with MAARI (including feverishness, chills, or cough) were recruited during or after a clinical encounter. Patients with illness duration $\geq$ 8 days were excluded. Consenting persons were tested for influenza by real-time RT-PCR with nasal (children) or nasopharyngeal swab specimens. RT-PCR positive specimens were also cultured. CDC antigenically characterized isolates. Immunization status was determined using a regional electronic

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vaccine registry. Individuals were classified as immunized beginning 14 days after receipt of vaccine.

This was a case-control study design. Cases were enrolled MARRI patients with influenza diagnosed by RT-PCR, and the controls were enrolled MAARI patients who tested negative by RT-PCR, so a so-called test negative control design. One of the reasons that this design was adopted was because the investigators found that the likelihood of vaccination is associated with the propensity to seek healthcare in the Marshfield Clinic, particularly among their older patients. For example, vaccinated persons age 65 and above were twice as likely to have a MAARI visit as unvaccinated persons during January and February 2008. The use of a test negative control strategy in this situation helped to adjust for the source of bias and vaccine effectiveness, as all study subjects sought care for MAARI at a particular point in the season. The analysis used logistical regression models that adjusted for age, week of enrollment, and the presence of any chronic ECIP-defining medical condition. Vaccine effectiveness was determined in the usual manner: 100 x (1 – adjusted odds ratio).

During this timeframe (January 21 to February 8, 2008) 1,779 MAARI patients were assessed for eligibility. Almost half of these patients were not eligible, and the majority of those exclusions were either due to the absence of feverishness, chills, or cough, or an illness duration of 8 days or longer. Of the eligible patients, 639 (69%) were enrolled. The typical reason for those who did not enroll was because they did not want to participate and have a swab drawn. After exclusion of 23 partially immunized children, for which the investigators did not have the power to make separate vaccine effectiveness estimates, enrollment was 616. Of the enrolled patients, 191 (31%) of the enrolled patients tested positive for influenza by RT-PCR, and 75% of these people had influenza A. The following chart briefly presents some of the results:

Data from 8 Jan – 21 Feb 2008	Influenza positive cases (n=191) % Vaccinated	Influenza negative controls (n=425) % Vaccinated	Adjusted VE % (95% CI)
All influenza			
All case	19	39	44 (11-65)
ACIP	35	51	34 (-31-67)
Healthy	11	24	54 (12-76)
Influenza A			
All cases	15	38	58 (28-76)
ACIP	35	50	49 (-14-77)
Healthy	8	24	68 (29-86)
Influenza B			
All cases	30	33	-35 (-172-33)
ACIP	39	49	-32 (-287-55)
Healthy	7	18	-33 (-241-48)

Of all cases, 19% were vaccinated against influenza versus 39% of controls, for an adjusted vaccine effectiveness of 44%, with a confidence interval of 11-65%. There is an indication that in the predominantly older ACIP group, the vaccine effectiveness may fall to 34%, but is a little bit higher in the otherwise healthy group (54%). In terms of

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influenza A versus influenza B, for all of the cases in influenza A subset there was 58% effectiveness, which was statistically significant. This was somewhat lower at 49% in the ACIP group, and somewhat higher at 68% in the otherwise healthy individuals. There are no indications in these preliminary data of any effectiveness at all against influenza B.

With regard to the preliminary laboratory data available, the subtyping is finished. Subtyping by RT-PCR found that all submitted influenza specimens were H3N2, so there was essentially no H1N1 circulation in this area in this past season. Most of the H3N2 viruses that have been characterized to date were A/Brisbane/10/2007-like, a drift variant of the vaccine strain. All B viruses characterized thus far have been B/Florida-like, in the Yamagata lineage, distinct from the B/Victoria lineage that was in the 2007-2008 vaccine.

There are a number of limitations to this study. An important limitation to keep in mind was that the vaccine effectiveness estimates presented were only for medically attended influenza, not for all symptomatic influenza infection as typically would be done in a trial situation. Given the technical and resource matters, the investigators do not believe it is feasible to produce interim assessments in a clinical trial scenario. However, that leads also to the possibility in the study design used that false-negative test results are important. Despite using RT-PCR, there is still a chance that there are some false-negatives. False-negatives in this test design become controls as opposed to just missed cases. Therefore, particularly over time as more data are accumulated, the investigators are examining how the influence of onset of symptoms to the time the swab is taken may influence the vaccine effectiveness estimates. This is one site that is not necessarily powered to examine vaccine effectiveness by each group or severity of the influenza infection. Results apply to patients enrolled only in one specific area of the US, and there is some indication that the distribution of influenza strains may differ geographically. For example, there were no H1N1 viruses in circulation in the Marshfield area during the past season.

Despite a suboptimal match between two of the three vaccine strains, interim vaccine effectiveness was 44%. Vaccine effectiveness for H3N2 medically attended infections was 58% versus no demonstrated effectiveness for B infections. There is a need to interpret the antigenic characterization data with clinical effectiveness data, and that work is still on-going. Based on the interim data for this study, it appears that it is feasible to produce within-season estimates of vaccine effectiveness in the US.

With respect to future steps, final estimates from this past season will be available soon, pending the integration of the laboratory results with the available epidemiologic data. There are enough cases this year to examine vaccine effectiveness by age group. Through a new cooperative agreement, the investigators plan to use the rapid vaccine effectiveness methods that have been developed with the Marshfield Clinic in the past few seasons at four sites, beginning in the 2008-2009 season. The team hopes to make interim assessments by age group with that larger, more geographically dispersed group of sites. It is possible that there will be sufficient power for effectiveness against

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more severe hospitalized outcomes depending upon the severity or non-severity of the next season.

Discussion

Dr. Neuzil expressed appreciation for the presentation of effectiveness data during the last two ACIP meetings. She suggested that the control groups could be a bias, pointing out that there was very strong evidence in certain age groups that a clinical diagnosis of influenza, when influenza is circulating, is very strong. Therefore, there are almost certainly undiagnosed cases in the Marshfield control group. She suggested considering the use of more than one control group in future seasons, and then comparing the estimates.

Dr. Shay responded that the investigators have done this. While there was not time during this meeting to present on this topic, they have taken alternative methods and control groups into consideration. For example, when compared with people who are asymptomatic, contacted by telephone in the community and matched by age very similar estimates are observed in some age groups, particularly younger individuals where good concordance would be expected between circulating flu and a clinical diagnosis of influenza. However, in some older age groups, there is still the problem of bias by propensity to seek healthcare in that people who present for healthcare are substantially different from those who do not. This must be taken into account in order to avoid falsely decreasing the estimated vaccine effectiveness.

Noting that this study was heavily covered in the press during the past flu season, Dr. Chilton wondered whether there might be an effort in subsequent seasons to communicate the limitation of having the study located in just one site, or in the future four sites. The demonstrated efficacy of 44% was reported in the press, which negatively affected immunization efforts within the season in New Mexico where there was much more H1N1 disease and higher vaccine efficacy.

Dr. Shay responded that perhaps as a group, the Influenza Division must ensure that they present antigenic characterization data together with the vaccine effectiveness data. There was actually a perception among physicians and the public, with the release of the preliminary antigenic characterization data that showed two out of three strains appeared not to be well-matched to the circulating strain, that the vaccine would have no effect.

Dr. Schuchat stressed that while the science of influenza is complicated, communication about influenza and influenza vaccine is even more complicated. As more and better data become available during the flu season, the priority of strong communication is very high. A broader group beyond the Influenza Division is deeply engaged in examining and learning from the last two seasons in order to think ahead about the next flu season's data and communications. There are many issues from which they must recover (e.g., changing supply, timing, new formulations, new recommendations).

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While this is a major job, it is also a major priority for CDC and others as they plan next year's messages.

Influenza Vaccines Workgroup Report

Anthony Fiore, MD, MPH
Influenza Division
National Center for Immunization and Respiratory Diseases
Coordinating Center for Infectious Diseases
Centers for Disease Control and Prevention

Dr. Fiore reported that the following vaccines are approved in the US for the upcoming 2008-2009 influenza season: Fluzone® (sanofi pasteur), Afluria® (CSL), Fluvirin® (Novartis Vaccines), Fluarix® (GSK), FluLaval® (GSK / IDB), and FluMist® (MedImmune). These are the same trade names of vaccines as were utilized in the past influenza season). The projected influenza vaccine supply for the 2008-2009 season is approximately 150 million doses, up from the estimate of last year's supply of 130 million doses. All six manufacturers have reported that their manufacturing processes are proceeding appropriately. Based on reports from the manufacturers, the estimated total of thimerosal- or preservative-free capacity is expected to increase to approximately 50 million doses.

Dr. Fiore reminded everyone that a major change was made to the influenza vaccine recommendations during the February 2008 ACIP meeting, which will be rolled out during the 2008-2009 season. The new recommendation is that "all children aged 6 months through 18 years should receive annual influenza vaccination, beginning in 2008 if feasible, but beginning no later than during the 2009-2010 influenza season." This will allow a provision for the difficulty in implementing such a major change in recommendations. There has been a fairly rapid advance of influenza vaccine recommendations up to the recommendation for the upcoming season. Before 2000, the focus was on the elderly, those with chronic medical conditions, pregnant women, and healthcare workers. Beginning in 2000, the focus shifted to adults aged 50 and older. In 2004, the recommendation included children aged 6–23 months, contacts (household and out of home caregivers) of children aged 0–23 months, and women who would be pregnant during the influenza season. In 2006, the recommendations included children aged 6–59 months, and contacts (household and out of home caregivers) of children aged 0–59 months.

With these changes in recommendations, vaccine coverage data is tracked. Dr. Fiore reported on data recently received from the Immunization Services Division. From the past influenza season, the only influenza coverage information available is from the registries because they are more timely than the gold standard coverage data obtained from the National Immunization Survey. Vaccine coverage information from immunization information systems has limitations, including that it is usually from limited geographic areas. Over the past four years, these registries have been participating in

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the sentinel site project, and have worked with CDC to ensure data quality.. Hence, they probably predict fairly well what the vaccine coverage is.

Oregon, Michigan, and Arizona participated in the IIS Sentinel Site Project from 2004-2007. With respect to the vaccination coverage rates in children (ages 6-23 months) who received one or more doses of influenza vaccine in Oregon, Michigan, and Arizona, receipt of one or more doses is approximately 40%. Coverage rates were slightly lower in Oregon in the 2007-2008 influenza season compared to 2006-2007. Rates remained stable in Michigan and Arizona. Approximately 20% of children during this time period received two doses, or are fully vaccinated. Coverage rates were slightly lower in Oregon in the 2007-2008 influenza season compared to 2006-2007, while rates remained stable in Michigan and Arizona. For 24-59 month olds coverage rates were slightly lower in Arizona in the 2007-2008 influenza season compared to 2006-2007, while rates remained stable in Oregon and Michigan. Full vaccination coverage is still approximately 20% in this age group. This slow rate of increase in coverage is not just among 6-23 month olds, and not just for newly recommended age or risk groups. There are minimal increases or even decreases in coverage in each of the priority groups (e.g., 65 and older, high-risk 50 to 60 year olds, healthy 50-64 year olds, pregnant women, and healthcare workers).

For the adult groups, preliminary data are available from the 2007 National Health Interview Survey, which shows that vaccination coverage in the older adults, 65 and older, is still at approximately 70%. Among 50-64 year olds with chronic medical conditions, coverage is at approximately 40-45%. Among the healthy 50-64 year olds, coverage is approximately 30%. There are no 2007 data on healthcare workers, but their coverage rate has remained at approximately 40% for a couple of years. Coverage in pregnant women remains at approximately 12-14%, which has not changed much in the last five years.

There have been many efforts to improve vaccination coverage by extending the influenza vaccine season beyond the traditional Thanksgiving ending period. The primary reason for this is because influenza seasons typically do not peak until January or February. In 2008, the flu season did not peak until February. This leaves ample time for an extended vaccination period. 2006-2007 was the first season during which there was a major communications effort to extend the vaccination season. During that time frame, there was a slight increase in coverage during December and January. Hopefully, trends will continue toward a rise in vaccinations during this extension effort.

With respect to ACIP Influenza Vaccine Workgroup activities and discussion topics for the next 6-12 months, a major topic will be to discuss annual vaccination for healthy adults ages 19-49. During the February 2008 meeting, Dr. Morse requested that the workgroup report on this topic to the full ACIP within one year. To meet that goal, the workgroup is now assessing the evidence base, examining the impact of the current recommendations on disease among healthy adults, and thinking about the potential impact of the new recommendations for all children on disease among healthy adults. It is possible that reducing illness in children will have an impact on reducing illness

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among healthy adults. The workgroup will also take into consideration the timeframe of when such a recommendation might be moved forward. Critical factors to be addressed with respect to an annual influenza vaccination recommendation for healthy young adults include vaccine supply, vaccine safety, vaccine effectiveness, disease burden, cost-effectiveness, feasibility of sustained implementation, and timeframe.

The workgroup has a number of other activities to address as well. Pandemic and pre-pandemic influenza vaccine issues will continue to be deliberated based on the recommendations put forward by HHS and other federal agencies, and the group will provide comments on their findings. The workgroup will also continue to monitor trends in antiviral resistance to determine whether ACIP recommendations for influenza treatment or prophylaxis need revision. Toward that end, the workgroup will need to assemble clinical experts on an "as needed" basis. Consideration is also being given to issues related to new influenza vaccine recommendations for children with respect to implementation challenges and measuring the impact of these new vaccination recommendations among children and amongst the communities where children are achieving high rates of vaccination coverage.

Discussion

Dr. Neuzil pointed out that the coverage data was new and that the working group had not had time to discuss it. With regard to 6-23 month olds, it is known that this is a group with high morbidity. As Dr. Shay reported during the last meeting, vaccine effectiveness is above what was anticipated in this group. It was also hypothesized that there would be fewer barriers to giving influenza vaccination to children as compared to adults. However, rates in this high-risk group of children are a half to a third what is being observed in high-risk adults, which still is not optimal. Although they could speculate the possible causes of low coverage rates, she believed that the workgroup and others must take a scientific approach. She noted that the National Immunization Survey has added a vaccine acceptance component, and she expressed hope that this would seek to understand vaccine-specific acceptance. She also noted that Allison Kempe's group had been helpful in assessing provider recommendation logistical issues. She strongly encouraged aggressive pursuit of these topics for influenza vaccine in children.

Dr. Schuchat added that the vaccine acceptance module is designed to better understand vaccine-specific concerns.

Dr. Strikas, National Vaccine Program Office, announced that the HHS, led by Assistant Secretary for Health Dr. Garcia, is launching an initiative to attempt to improve vaccination of healthcare personnel, which lingered at 42% in 2006. The target for 2010 is 60%. An attempt will be made to increase coverage among federal employees, nursing homes healthcare practitioners, and healthcare professional schools. The vaccination rates for nursing homes are less than 30%, and it is unknown how well healthcare students are vaccinated. There will also be broader outreach to healthcare organizations with colleagues at CDC. He anticipated that many of those present would

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be invited to meetings at HHS to discuss how better they can increase rates in each of these groups to reach 60% coverage by 2010.

Dr. Judson requested further clarification about the number of doses produced but not administered this year.

Dr. Wallace responded that while he did not have the exact numbers readily available, he believed that it was approximately 25 to 30 million doses that were produced and not distributed. However, the gap (usually is around 10%) between distribution and administration had increased. There are three numbers: produced, distributed, and administered. There was the greatest number produced ever, and there was the greatest number produced and not distributed. Last year the amount produced was a little more than 140 million, the amount of doses distributed was just under 113 million, and the amount administered was probably in the high 90 millions, though those are rough, preliminary estimates.

In regard to the Marshfield study, Dr. Judson commented that it appeared that the vaccine caused influenza B. While it probably did not, that looked significant to him. He wondered how the investigators would explain what appeared to be a significant 33%.

Dr. Shay responded that it was not significant. The confidence intervals were very broad around a negative point estimate. The investigators would interpret that as no evidence of effectiveness. Negative 33% was the point estimate. The overall was minus 35% and the confidence interval was -172 to plus 33%, so a very broad confidence interval. The investigators are often asked to take these preliminary data where they were not originally intended to go. The interim assessment was powered to make an assessment against all influenza isolated up to this point in the season. The investigators happened to observe a substantial difference by A versus B, so that was reported.

Dr. Wallace added that, in the future, there would be ways to deal with the healthy person bias that has caused discussion and embarrassment. For instance, regarding the study for the elderly and an exchange over the winter in the *New England Journal of Medicine* that purported to show that influenza vaccination reduced mortality by 50%, all of the differences were before the vaccine was actually administered and surmised that healthy people were getting vaccinated and that was why they were not dying.

Dr. Shay pointed out that in other studies particularly examining the elderly that the Marshfield investigators are planning to conduct to follow-up on the study discussed during the last ACIP meeting (e.g., on effectiveness through the EIP consortium against laboratory-confirmed hospitalizations). A similar study will be conducted in adults 50 and above, and the investigators certainly plan to collect data in that study on some of the factors that have been hypothesized (e.g., functional status, eating assistance, bathing) as potentially important confounders of the relationship between receipt of vaccine and all-cause mortality.

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Dr. Judson pointed out that people who are voluntarily seeking vaccine or being offered it by their physicians are not, in fact, healthier in many ways than those who do not seek it and are not offered it.

Dr. Sandra Fryhofer, American College of Physicians, commented that with respect to the separation between production and administration of the flu vaccine, the distribution is "wacky." The number one universal theme among practicing doctors is that they cannot get the vaccine. She implored the vaccine manufacturers in the room to help physicians acquire influenza vaccine for their offices instead of sending it first to that "well-known health institution called Wal-Mart."

Dr. Wallace responded that with the new FluFinder distribution system, distribution is tracked over time by provider types. Practicing physicians receive approximately 40% of the doses that are distributed, which is consistent throughout the entire season. He offered to report on this data during a future meeting. There is not a bias, at least on a national level.

Dr. Whitley-Williams, National Medical Association, stated that in the past there have been health disparity gaps with regard to adult influenza vaccine coverage levels. She asked for information about what occurred during the past season, and if that gap remained the same or was narrowing, particularly among ethnic minorities. If that gap continued, she suggested that it be included as a workgroup topic.

Dr. Fiore responded that they did not yet have these data, which comes from the Immunization Services Division. They received the NHIS data in the past couple of weeks. He offered to share that data when it became available.

Dr. Foster, American Pharmacist Association, pointed out that from Dr. Wallace's statistics last year, pharmacy only received about 7-8% of the total dosage for flu vaccine. However, he proudly announced that as of the past Monday, New York became the 49th state that allows pharmacists to administer vaccines. He stressed that they were not doing this to take vaccine supply away or compete, but instead were attempting to increase vaccination coverage, which was what the goal should be.

Dr. Temte reported that he had just completed his education and clinic from the National Asthma Education Program that was administered by a nurse from the American Lung Association, and that at no point was there any comment on the value of influenza immunization; this was something he had to bring up during the session. This highlighted the importance of proactive outreach. He inquired of Dr. Houn when they could expect to see pregnancy removed from product inserts as a relative contraindication. This remains a major stumbling block for many obstetrical care practitioners.

Dr. Houn answered that this is not a contraindication. It is simply absence of information. All flu labeling contains information from that data either from animal or human studies. If there were no animal studies conducted, it is Category C. It is also

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Category C if animal studies were conducted and there were findings that showed adverse events in animals. That is why there is movement away from categories to simply explaining the information.

Public Comment: June 26, 2008

No public comments were offered during this session.

Certification

With no further business posed, Dr. Morse officially adjourned the meeting.

I hereby certify that to the best of my knowledge, the foregoing Minutes of the June 25-26, 2008 ACIP Meeting are accurate and complete.

_____
Date

_____

Dale Morse, M.D., M.S. Chair,
Advisory Committee on
Immunization Practices (ACIP)

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Arboleda	Nelson
Atkins	Jennean
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Bandell	Allyn
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Beck	Robert L.
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Bowser	Andrew
Boyce	Donna
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Brier	Nicole
Brooks	Dennis
Bruce	Kelly
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Campos-Outcalt	Doug
Cary	Donna
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Cieslak	Paul
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Clover	Richard
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Colquitt-Hall	Karen
Conway	Sarah
Cooney	Lenore
Cooper	David
Curlin	George
Dalrymple	Donald "Dack"
Dasbach	Erik
De Silva	Rajiv
Dempsey	Tina

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Gellin	Bruce
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Gurunathan	Sanjay
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