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

## Advisory Committee on Immunization Practices (ACIP)

## Summary Report
## February 25-26, 2009
## Atlanta, Georgia

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# Acronyms

| | |
|---|---|
| AAFP | American Academy of Family Physicians |
| AAP | American Academy of Pediatrics |
| ACIP | Advisory Committee on Immunization Practices |
| AGS | American Geriatrics Society |
| ALS | Amyotrophic Lateral Sclerosis |
| ATP | According to Protocol |
| AVA | Anthrax Vaccine Adsorbed |
| AVWG | Anthrax Vaccine Work Group |
| 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 |
| CID | Committee on Infectious Diseases (CID) of the American Academy of Pediatrics (AAP) |
| CIN | Cervical Intraephithelial Neoplasia |
| | Centers for Medicare and Medicaid Services |
| DBD | Division of Bacterial Diseases (of NCIRD) |
| DGMQ | Division of Global Migration and Quarantine |
| DHQP | Division of Healthcare Quality Promotion |
| DoD | Department of Defense |
| DSMBs | Data Safety Monitoring Boards |
| DSTDP | Division of Sexually Transmitted Diseases Prevention [of NCHHSTP] |
| 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 |
| GID | Global Immunization Division |
| GMCs | Geometric Mean Concentrations |
| GMTs | Geometric Mean Titers |
| GSK | GlaxoSmithKline |
| HICPAC | Healthcare Infection Control Practices Advisory Committee |
| 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 |
| HZ | Herpes Zoster |
| 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 |
| ISD | Immunization Services Division (of NCIRD) |



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| ISO | Immunization Safety Office (of CDC/OD/Office of the Chief Science Officer) |
| ITT | Intent to Treat |
| MCO | Managed Care Organization |
| MCV4 | Meningococcal Conjugate Vaccine |
| MDH | Minnesota Department of Health |
| MMRV | Measles, Mumps, Rubella, Varicella |
| *MMWR* | *Morbidity and Mortality Weekly Report* |
| mOPV1 | Monovalent Polio Vaccine Type 1 |
| NACCHO | National Association of County and City Health Officials |
| NACI | Canadian National Advisory Committee on Immunizations |
| 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 Diseases |
| 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 |
| OCSO | Office of the Chief Science Officer |
| OD | Office of the Director (of CDC) |
| ODCER | Office for Disease Control and Emergency Response (Of China) |
| P&I | Pneumonia and Influenza |
| PCV | Pneumococcal Conjugate Vaccine |
| PEP | Post-Exposure Prophylaxis |
| PhRMA | Pharmaceutical Research Manufacturers of America |
| RCA | Rapid Cycle Analysis |
| SAGE | Strategic Advisory Group of Experts |
| sBLA | Supplemental Biologics License Application |
| SHEA | Society for Healthcare Epidemiology of America |
| SMEs | Subject Matter Experts |
| VAERS | Vaccine Adverse Event Reporting System |
| VFC | Vaccines for Children |
| VSD | Vaccine Safety Datalink |
| VZV | Varicella-Zoster Virus |
| WG | Work Group |
| WHO | World Health Organization |



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## MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

Centers for Disease Control and Prevention
1600 Clifton Road, NE, Tom Harkin Global Communications Center (Building 19), Atlanta, Georgia
February 25-26, 2009

| | AGENDA ITEM | PURPOSE | PRESIDER/PRESENTER(s) |
|---|---|---|---|
| **Wednesday, February 25, 2009** | | | |
| 8:00 | **Welcome & Introductions** | | Dr. Dale Morse (Chair, ACIP)<br>Dr. Larry Pickering (Executive Secretary, ACIP; CDC) |
| 8:30 | **Anthrax Vaccine** | | |
| | • BioThrax® (Anthrax Vaccine Adsorbed): reduced dose/route change study – immunogenicity results | Information | Dr. Robert Hopkins (Emergent BioSolutions) |
| | • Draft recommendation for route/schedule of Anthrax Vaccine Adsorbed (AVA) | Information<br>Discussion<br>Vote | Dr. Jennifer Wright (CDC/CCID/NCIRD/DBD) |
| 8:55 | **Hepatitis Vaccines** | | |
| | • Hepatitis A vaccination among contacts of internationally adopted children | Information<br>Discussion<br>Vote | Dr. Mark Sawyer (ACIP, WG Chair)<br>Dr. Sandra Chaves and Dr. Cindy Weinbaum (CDC/CCID/NCHHSTP/DVH) |
| 9:55 | *Break* | | |
| 10:25 | **Influenza Vaccines** | | |
| | • Introduction | | Dr. Kathy Neuzil (ACIP, WG Chair) |
| | • Influenza surveillance update<br>• Antiviral resistance<br>• 2009 influenza vaccine recommendations | Information<br>Discussion<br>Vote | Dr. Anthony Fiore (CDC/CCID/NCIRD/ID) |
| 11:25 | **Rabies Vaccine** | Information<br>Discussion | Dr. Paul Cieslak (ACIP, WG Chair)<br>Dr. Charles Rupprecht (CDC/CCID/NCZVED/DVRD) |
| 12:10 | **Update: Pertussis Vaccines Work Group** | Information | Dr. Mark Sawyer (ACIP, WG Chair)<br>Dr. Jennifer Liang (CDC/CCID/NCIRD/DBD) |
| 12:15 | *Lunch* | | |
| 1:15 | **Pneumococcal Vaccines** | | |
| | • Use of PPSV23 for prevention of pneumococcal pneumonia during an influenza pandemic | Information<br>Discussion | Dr. Matthew Moore (CDC/CCID/NCIRD/DBD) |
| | • An economic analysis for use of PPSV23 for prevention of pneumococcal pneumonia during an influenza pandemic | Information<br>Discussion | Dr. Mark Messonnier (CDC/CCID/NCIRD/ISD) |
| | • Update on PCV13 pediatric phase 3 trial results<br>• Use of pneumococcal vaccines | Information<br>VFC Vote | Dr. Peter Paradiso (Wyeth)<br>Dr. Jeanne Santoli (CDC/CCID/NCIRD/ISD) |
| 2:35 | **Measles, Mumps and Rubella** | | |
| | • Proposed changes in MMR vaccine evidence of immunity requirements for healthcare personnel | Information<br>Discussion | Dr. Jane Seward (CDC/CCID/NCIRD/DVD/OD)<br>Ms. Amy Parker (CDC/CCID/NCIRD/DVD/EB) |
| 3:05 | *Break* | | |



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| 3:20 | **General Recommendations** | | Dr. Ciro Sumaya (ACIP, WG Chair) |
| | • Storage and handling of immunobiologics | Information | Dr. Andrew Kroger |
| | • Vaccination of people with altered immunocompetence | Discussion<br>Vote | (CDC/CCID/NCIRD/ISD) |
| 4:05 | **Human Papillomavirus (HPV) Vaccines** | | |
| | • Introduction | Information | Dr. Janet Englund (ACIP, WG Chair) |
| | • Update on bivalent HPV vaccine: ASO4 adjuvant mechanisms of action and safety meta-analysis | Information | Dr. Tom Verstraeten (GSK) |
| | • Burden of HPV related disease in males | Information | Dr. Mona Saraiya |
| | • Update on quadrivalent HPV vaccine: efficacy data in males | Information | (CDC/NCCDPHP/DCPC)<br>Dr. Rick Haupt (Merck) |
| | • Work Group plans for upcoming recommendations | Discussion | Dr. Lauri Markowitz<br>(CDC/CCID/NCHHSTP/DSTDP) |
| 4:55 | **Pediatric *Haemophilus influenzae* B Cases in Minnesota, 2008-2009** | Information<br>Discussion | Ms. Kris Ehresmann (ACIP, MDH)<br>Dr. Jeanne Santoli<br>(CDC/CCID/NCIRD/ISD) |
| 5:15 | **Vaccination of Immigrants and Refugees** | Information<br>Discussion | Dr. Martin Cetron/Dr. Katrin Kohl<br>(CDC/CCID/NCPDCID/DGMQ) |
| 5:30 | **Public Comment** | | |
| 5:45 | **Adjourn** | | |

## Thursday, February 26, 2009

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| 8:00 | **Unfinished Business** | | Dr. Dale Morse (Chair, ACIP) |
| 8:30 | **Agency Updates (CDC/CCID/NCIRD, CMS, DOD, DVA, FDA, HRSA, IHS, ISO, NIH, NVAC, NVPO)** | Information | |
| 8:45 | **Meningococcal Vaccine** | | |
| | • Update: Meningococcal Work Group | Information | Dr. Carol Baker (ACIP, WG Chair) |
| | • Meningococcal conjugate vaccine post-licensure safety update - Vaccine Adverse Event Reporting (VAERS) | Information<br>Discussion | Dr. Angela Calugar (CDC/OD/OCSO) |
| 9:15 | **Update: Herpes Zoster (Shingles) Vaccine** | | |
| | • Update: herpes zoster (shingles) vaccine | Information | Dr. Rafael Harpaz |
| | • National provider survey regarding barriers to implementation of zoster vaccine | Information | (CDC/CCID/NCIRD/DVD)<br>Dr. Allison Kempe<br>(University of Colorado) |
| 9:55 | **Vaccine Supply** | Information<br>Discussion | Dr. Jeanne Santoli<br>(CDC/CCID/NCIRD/ISD) |
| 10:10 | *Break* | | |
| 10:40 | **MMRV Vaccine Safety** | | |
| | • Introduction | Information | Dr. Jonathan Temte<br>(ACIP, WG Chair) |
| | • Update on Work Group activities for developing policy options for MMRV vaccine use | Information | Dr. Mona Marin<br>(CDC/CCID/NCIRD/DVD) |
| | • Provider survey regarding opinions on the use of MMRV vaccine | Information | Dr. Allison Kempe<br>(University of Colorado) |
| | • Discussion | Discussion | Dr. Jonathan Temte |



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| 11:25 | **Polio: Update on the Global Polio Eradication Initiative and Domestic Policy Issues** | Information Discussion | Dr. Steve Wassilak (CDC/CCID/NCIRD/GID)<br>Dr. Gregory Wallace (CDC/CCID/NCIRD/DVD) |
| 12:10 | **Update: Yellow Fever Vaccine Work Group** | Information | Dr. Carol Baker (ACIP, WG Chair) |
| 12:15 | **Public Comment** | | |
| 12:30 | **Adjourn** | | |

## Welcome & Introductions



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**Dr. Dale Morse (Chair, ACIP)**
**Dr. Larry Pickering (Executive Secretary, ACIP; CDC)**
**Dr. Richard Besser (Acting Director, CDC)**
**Dr. Samuel L. Katz (ACIP Liaison Representative, Infectious Diseases Society of America)**

Dr. Dale Morse, Advisory Committee on Immunization Practices (ACIP) Chair, welcomed those present and called the meeting to order at 8:00 a.m.

Dr. Larry Pickering, ACIP Executive Secretary, extended his welcome to those in attendance. With great pleasure and gratitude, he introduced Dr. Richard Besser, Acting Director of the Centers for Disease Control and Prevention (CDC). Dr. Pickering noted that Dr. Besser had worked with and had been involved in the career development of several of the committee members, and that he had been intimately involved in ACIP activities. Dr. Besser then presented a special award.

Dr. Besser stressed what a privilege and an honor it was to deliver the opening remarks during this meeting of the ACIP. As a general pediatrician, he said he has benefited greatly from the work of ACIP, and as the Acting Director of CDC and a long-term CDC epidemiologist, has appreciated the scientific deliberations that the ACIP has undergone to develop very thoughtful recommendations. He then presented an award to Dr. Samuel L. Katz, pointing out that CDC and ACIP were honored during this meeting to offer appreciation to Dr. Katz, who has contributed enormously to ACIP in several capacities, and who likely holds the record for longest running involvement with ACIP's activities from 1982 to the present.

Dr. Katz served as a voting member of the ACIP from 1982 through 1993, which included chairmanship of the committee from 1985 through 1993. This period was notable for remarkable progress in vaccinations to prevent invasive *Haemophilus influenzae* type b (Hib), the leading cause of pediatric meningitis in the United States (US) at the time. Dr. Katz played a key role in leading the ACIP constructively and rapidly to assess the controversy on the strategy and effectiveness of the Hib polysaccharide vaccine, as well as moving ahead with prompt recommendations for use of the newly licensed Hib conjugate vaccine, which eventually led to a 99% decrease in this devastating disease. During his tenure as chair, Dr. Katz played a major role in evaluating the safety of the whole cell pertussis vaccine and set the stage for transition to acellular pertussis vaccines. Also during his tenure, Dr. Katz guided the ACIP through an extensive evaluation of the need for a second dose of the MMR vaccine, which was recommended in 1989 following almost a decade of deliberations.

Since 1998, Dr. Katz has represented the Infectious Diseases Society of America (IDSA) as liaison member to the ACIP. In this capacity, Dr. Katz has participated actively as a member of several ACIP workgroups where his years of experience in vaccine research and implementation of immunization programs have proved invaluable in the development of options for policy recommendations. After graduating *cum laude* from Harvard Medical School, Dr. Katz completed his medical internship at Beth Israel Hospital and his pediatric residency at Massachusetts General Hospital and Boston Children's Hospital, where he also served as a research fellow in virology and infectious diseases. He then became a staff member at Children's Hospital and worked with Nobel Laureate John Enders for twelve years. Together, they developed the attenuated measles virus vaccine currently used worldwide.



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Early in his career, Dr. Katz became fascinated with the measles virus and was instrumental in developing a vaccine for the disease using cell culture techniques and egg inoculations. In fact, after fastidiously preparing safety tested material for use in humans, he first inoculated himself and then his colleagues in the laboratory. After a series of clinical trials proved the vaccine effective and safe, it was licensed in 1963. By 1968, the incidence of measles plummeted to low levels. Once the vaccine was proven to be effective domestically, Dr. Katz was eager to see its success taken globally, conducting studies that contributed to the use of measles vaccines internationally. As well as chairing the ACIP, Dr. Katz previously chaired the Committee on Infectious Diseases (CID) of the American Academy of Pediatrics (AAP), the Red Book Committee; the vaccine priority study of the Institute of Medicine (IOM); and several World Health Organization (WHO) and National Institutes of Health (NIH) panels. He also chaired the committee that in 2000 declared that measles was no longer endemic in the US.

For 22 years, Dr. Katz was Chairman of Pediatrics at Duke University. In addition to mentoring students and residents for over two decades, Dr. Katz established an exchange program with Oxford University and provided training for an annual succession of residents from the American University of Beirut. Graduates of this program hold positions in the Food and Drug Administration (FDA), CDC, NIH, university departments, state health departments, research institutes, and in private practice. Dr. Katz has shared numerous scientific activities with his wife of many years, Dr. Catherine Wilfert, also an infectious disease expert who is currently the senior technical advisor to the CEO of the Elizabeth Glazer Pediatric AIDS Foundation, and who preceded Dr. Katz as ACIP chair during the 1980s.

Tremendous gratitude was expressed to Dr. Katz for his years of tireless dedication, enthusiasm for the work, and his unfailing good humor. In his work with ACIP, he has been remarkable, not only for his graciousness and inclusiveness, but also for his effective committee management abilities. Dr. Katz brings a unique mix of skills and attributes that include expertise in virology and vaccinology, modesty and team spirit, and an ability to translate basic scientific knowledge into sensible public health policy. Dr. Besser concluded that it gave him great pleasure to present an award to Dr. Katz for his tremendous accomplishments, which read, “Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention. In recognition of the invaluable service of Samuel L. Katz, MD, ACIP member 1982-1993, ACIP chair 1985-1993, ACIP liaison representative 1998-present.”

Dr. Katz thanked CDC and ACIP, noting that this award was totally unexpected. He said he had enormously enjoyed his years working with ACIP in various capacities, and in getting to know many of the CDC staff members. He quipped that while many of his colleagues send their best and brightest to the National Institutes of Health (NIH), he always sends his to CDC. Those present thunderously applauded Dr. Katz.

At this time, Dr. Morse officially opened the meeting, thanking Dr. Besser for taking time out of his busy schedule to address the committee and present the award to Dr. Katz. He pointed out that one of the perks of being an ACIP member and attending these meetings is to bask in the wisdom of the icons in the world of immunization. Dr. Sam Katz is one of those icons and while he is not a giant in height, he is a giant in stature, and his comments and actions have prevented untold illnesses and saved many lives. Due to his many accomplishments, it was only fitting that they honor Dr. Katz for his career of service to CDC and ACIP, although that paled in comparison to how his presence, comments, and actions honor the agency and committee more.



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Dr. Pickering indicated that Dr. Besser's remarks were being circulated around the room for those who wanted to sign them and / or write their thoughts to Dr. Katz. He reminded everyone that the "Call to Order Bell" was given to ACIP by Dr. Katz in 1993, so every time they ring it, they will forever think of him.

He pointed out several individuals who were to be present throughout the meeting to assist with meeting functions (Antonette Hill, Natalie Greene, Tamara Miller, Stephanie Renna, and Suzette Law) 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, Notice to Readers, and other information related to immunization and ACIP activities also can be found on this site. CDC has updated its vaccine safety web site (www.cdc.gov/vaccinesafetv). Members of the press interested in conducting interviews with ACIP members were instructed to contact Tom Skinner. Dr. Pickering noted that their long-time friend and colleague, Curtis Allen, had taken another position outside CDC. He also welcomed visitors from China's Office for Disease Control and Emergency Response (ODCER) Dr. Zijian Feng, Director; Dr. Luzhao Feng and Dr. Xuesong Pei.

Dr. Pickering congratulated ACIP's immediate past chair, Dr. Jon Abramson, who was nominated and chosen to serve as a representative from the Americas to the Strategic Advisory Group of Experts (SAGE). Dr. Abramson served from 1999 to 2003 as an ACIP liaison representative from AAP, as an ACIP member from 2003 to July 2007, and as ACIP chair from 2005 until July 2007.

He welcomed new member Dr. Linda Kinsinger from the National Center for Health Promotion and Disease Prevention (NCHPDP), who has been chosen to represent the Department of Veteran Affairs (DVA) as the *Ex Officio Member*. *Ex officio* members Dr. Gus Birkhead from the National Vaccine Advisory Committee (NVAC) and Dr. George Curlin from NIH were unable to attend this ACIP meeting. It was noted that Dr. Gellin would present the NVAC update, while Ms. Carolyn Deal and Ms. Barbara Mulach were in attendance on behalf of Dr. Curlin. Liaison representatives Dr. David Salisbury from the Department of Health in the United Kingdom (UK), Dr. Alexis Elward from the Healthcare Infection Control Practices Advisory Committee (HICPAC), and Dr. Joanne Langley from the Canadian National Advisory Committee on Immunizations (NACI) were also unable to attend this meeting.

To avoid interruptions during the meeting, Dr. Pickering requested that all business not directly related to discussions of ACIP be conducted in the hall to avoid disturbing people in the audience, and that all cell phones be turned off or placed in the vibrate mode to avoid disruption. He stressed the importance of all members remaining throughout the meeting to maintain a quorum, requesting that appointed members return from breaks and lunch in a timely manner to participate in the meeting to help facilitate an efficient and productive meeting. In addition, he reminded everyone that the ACIP charter gives the Executive Secretary, or his 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 to vote due to financial conflict of interest. If necessary, the *ex officio* members would be formally requested to vote when necessary. If this occurred, they would be asked to disclose any potential conflicts of interest.



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The ACIP home page URL is www.cdc.gov/vaccines/recs/acip. The website is updated at frequent intervals with the current version of the meeting agenda, meeting minutes, and presentations, as well as ACIP recommendations and other information related to immunizations and ACIP activities. CDC continues to update its vaccine safety web page for which the URL is www.cdc.gov/vaccinesafety. Since the last meeting the Rotavirus Vaccine Recommendations have been published in the *Morbidity and Mortality Weekly Report* (*MMWR*) The adult and childhood immunization schedules also have been published. The adult schedule was published in the *Annals of Internal Medicine* for the second year in a row, as well as in the *American Family Physician Journal and* the *MMWR*. The interactive catch-up immunization schedule has been updated to reflect the 2009 childhood schedule. A standardized list of vaccine abbreviations has been posted to the ACIP website. Dr. Bill Atkinson will ensure that the vaccine abbreviations will be included in the Pink Book, and these will be included in the Red Book.

Topics presented at ACIP meetings include open discussion with time reserved for public comment. In certain circumstances, a formal comment period may be scheduled during the deliberation of a specific agenda item. Comments from the public may be received during open discussions depending on the amount of time available. Dr. Pickering requested that those who planned to make public comments sign in at the registration table at the rear of the auditorium where Antonette Hill would record their name and provide information on the process. Those who registered prior to the meeting were instructed to check the list to ensure that their names appeared. Microphones were placed at each end of the committee tables for members of the audience to use when addressing the committee. Dr. Pickering requested that anyone making comments identify himself or herself and organization before comments were made. He stressed that both CDC and 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. For this reason, CDC encourages people at the beginning of comments to advise the committee of any financial relationship that he or she may have with any company or any organization that is likely to be impacted by the topic being discussed. For example, the financial information may include the company's or organization's payment of travel, lodging, or other expenses in connection with attendance at the meeting. Likewise, CDC encourages individuals at the beginning of their statements to advise the committee if they do not have any such financial relationships. Although encouraged, choosing not to address the 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



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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 applications for membership appointment, the ACIP Secretariat solicits applications throughout the 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 of applications for ACIP membership, which begins in July 2010, are due no later than November 15, 2009. ACIP meeting registration dates are established for security reasons. The CDC complex is a secured environment and pre-registration for meetings is posed on the ACIP website. This pre-registration is time-sensitive for international visitors, given that the Office of Security and Emergency Preparedness (OSEP) is required to pre-approve access for all non-US citizens visiting CDC facilities. Dr. Pickering requested that everyone register early for the June 24-25, 2009 meeting by visiting the ACIP website.

Dr. Pickering then turned the meeting over to Dr. Morse, who welcomed members and requested that any conflicts of interest be indicated. The following conflicts of interest were declared: Dr. Marcy is serving as a consultant to Merck through April 2009; Dr. Englund is receiving research support from Novartis, MedImmune and sanofi pasteur; Dr. Meissner indicated that payments are made to Tufts Medical Center by Wyeth and MedImmune. All other ACIP members present declared that they had no conflicts of interest.

## Anthrax Vaccine

### BioThrax®: Reduced Dose / Route Change Study—Immunogencity Results

**Robert Hopkins, MD, MPH, TM**
**Vice President, Clinical Development US**
**Emergent BioSolutions Inc.**

Dr. Hopkins expressed his gratitude to the ACIP for permitting Emergent BioSolutions to discuss some of the immunogenicity results from the trial conducted and sponsored by CDC. His involvement was to interact with the Food and Drug Administration (FDA) in implementing the recent labeling change pertaining to route and schedule that occurred with the FDA approval on December 11, 2008. With regard to the clinical trial, Dr. Hopkins described the study design and objectives, populations and analytic datasets, the non-inferiority criteria, and the immunogenicity results from the following time points:

- At Week 8: After 0-2-4 wks SQ vs. 0-2-4 wks IM
- At Week 8: After 0-2-4 wks SQ vs. 0-4 wks IM
- At Month 7: After 0-2-4-26 SQ vs. 0-2-4-26 IM
- At Month 7: After 0-2-4-26 SQ vs. 0-4-26 IM



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The trial was a randomized placebo controlled double blind multi-center study conducted in the US at five academic institutions. There were seven study arms. The first arm (A) was the previously approved subcutaneous (SC) route and schedule, six doses over eighteen months followed by two additional booster doses at months 30 and 42. The second arm (B) was the same schedule using intramuscular (IM) route administration. The next three arms (C) were combined for the purposes for this analysis. This arm examined the IM route, dropped the two-week dose, and evaluated different booster schedules. These arms will be further investigated and analyzed in the 43-month analysis that will be conducted by CDC later in 2009. The last two arms (D) were saline placebo given IM and subcutaneous. Dr. Hopkins' discussion during this ACIP meeting was limited to two time points: Week 8 and Month 7 following each vaccination.

As outlined in the study protocol drafted in 2002, the primary study objectives were to: 1) demonstrate that BioThrax® (Anthrax Vaccine Adsorbed) administered by the IM route elicits antibody responses that are non-inferior to that achieved by the currently licensed schedule (Group A vs. Group B); and 2) to demonstrate that BioThrax® (Anthrax Vaccine Adsorbed) administered by the IM route and containing fewer numbers of doses (no 2-week dose) elicits antibody responses that are non-inferior to that achieved by the currently licensed schedule (Group A vs. Group C). The primary study endpoints included: Geometric Mean Concentrations (GMCs): Anti-PA specific IgGl; Geometric Mean Titers (GMTs): Anti-PA specific IgG; and seroconversion: ≥ 4 fold rise in anti-PA specific IgG titer.

There were two primary study populations: 1) Intent-to-treat (ITT) population, which included those subjects who received at least one dose. This was used for safety; and 2) According to Protocol (ATP) population, which consisted of those subjects who at a particular time point must have received all injections up through that time point; injections within the windows defined by the protocol; the correct agent administered by the correct route according to subject's assigned study arm; and the correct injection volume (0.3 mL or greater considered valid). Dr. Hopkins noted that immunogenicity analyses included data from blood draws that occurred within defined windows at a particular time point.

Non-inferiority criteria were established prospectively in the study. With respect to immunogenicity analyses performed at Week 8 and Month 7, for GMC and GMT the criteria for non-inferiority of comparisons were based on the mean antibody GMC / GMT ratio (Group A /Group X). Non-inferiority was achieved (passed) when the upper 97.5% confidence limit was ≤ 1.5. For seroconversion criteria for non-inferiority of comparisons was based on differences in rates of a four-fold rise in antibody titer (Group A – Group X). Non-inferiority was achieved (passed) when the upper 97.5% confidence limit was ≤ 0.10. Baseline values below LLOQ were set to ½-empirical LLOQ to calculate post-vaccination four-fold rise in titer.

Regarding the Week 8 Response: SQ (0-2-4 Wks) versus IM (0-2-4 Wks), the point estimates for IM were somewhat lower for both GMCs as well as GMTs; however, all three primary end points met the criteria. For the Month 7 Response: SQ (0-2-4-26 Wks) versus IM (0-2-4-26 Wks), the point estimates were somewhat higher for the IM route of administration versus subcutaneous, and all non-inferiority criteria were met. In the Week 8 Response: SQ (0-2-4 Wks) versus IM (0-4 Wks) in which the two-week dose was dropped and there was a change to an IM route of administration, there was a drop in the point estimates for the IM route and the dropping of the two-week dose (Group C versus Group A), and the prospective defined non-inferiority criteria was not passed for GMCs and GMTs. However, the criteria were passed for a four-fold rise seroconversion. In Group C, with the dropped two-week dose and move to IM route administration, non-inferior criteria are easily passed for all end points. Again, the IM



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route, as well as dropping the two week dose, have point estimates that are numerically higher and easily pass the non-inferiority criteria for all three endpoints.

In conclusion with respect to immunogenicity for this trial, at Week 8 Group B (IM 0-2-4-26 weeks) was non-inferior to Group A (SQ 0-2-4-26 weeks) for all three primary endpoints. Group C (IM 0-4 weeks) was non-inferior to Group A (SQ 0-2-4 weeks) for the percentage with a four-fold rise in titer but not non-inferior to Group A for GMC and GMTs. At Month 7 Group B (IM 0-2-4-26 weeks) was non-inferior to Group A (SQ 0-2-4-26 weeks) for all three primary endpoints. Group C (IM 0-4-26 weeks) was non-inferior to Group A for all three primary endpoints. Thus, the elimination of the Week 2 dose did not impact the immune response following the 6-month vaccination.

With respect to the approved labeling that occurred on December 11, 2008, these results essentially allowed a change from 6 doses to 5 and a change from SQ to IM administration. The recommended dosing schedule is now 0, 1, 6, 12, 18 months with annual boosters. The route of administration is now intramuscular, unless when medically indicated, such as in persons with coagulation disorders or receiving medications that affect coagulation (e.g., Coumadin® / Warfarin), the subcutaneous route may be used.

## Draft Recommendations for the Pre-Event Use of Anthrax Vaccine Adsorbed (AVA): Route of Administration Number of Doses

**Jennifer Gordon Wright, DVM, MPH**
**ACIP Anthrax Vaccine Work Group**

On behalf of the Anthrax Vaccine Work Group (AVWG), Dr. Wright thanked the ACIP for giving her and Dr. Hopkins the opportunity to present the final piece of this statement and the AVWG's final recommendation. She recognized all of the AVWG members, especially the two ACIP members Drs. Morse and Beck.

Dr. Wright reminded everyone that in October 2008, ACIP voted to approve approximately 20 recommendations for the use of Anthrax Vaccine Adsorbed (AVA) both pre-event and post-exposure. During this meeting, she explained that the AVWG would be requesting an ACIP vote on the route change and dose reduction recommendation. This would allow the workgroup to finalize the statement, a draft copy of which all ACIP members received for review on February 3, 2009. Comments were received from most of the ACIP members and the AVWG was working to finalize the document, with plans for submission to the *MMWR* in the near future.

The workgroup reviewed the dose reduction and route change data, and the data were previously presented to ACIP in their entirety on several occasions. The workgroup's position was that IM administration, as presented to the ACIP in October 2008, was associated with fewer injection site adverse events than subcutaneous administration. IM administration also elicited an immune response equivalent to that elicited by subcutaneous administration. Removing the second priming dose administered at Week 2 had no negative impact on immune response in the pre-event regimen. Therefore, the workgroup presented the following draft recommendation for pre-event use of AVA for consideration by ACIP, "ACIP recommends 5 IM doses administered at day 0, week 4, months 6, 12, and 18, followed by annual boosters. Subcutaneous administration is allowable only when medically indicated, such as in persons with coagulation disorders." At this time, there was no recommendation to change the dose or the route recommendation for the use of AVA in the post-exposure setting.



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## Discussion

Dr. Marcy noted that based on Page 23 of the statement that 6,000,000 doses were administered and presuming that in the Army all 5 doses were given to everybody, it appeared that approximately 1.2 million personnel received AVA. With that in mind, he wondered whether anyone was concerned about the 25 deaths, three of which were due to Amyotrophic Lateral Sclerosis (ALS). To Dr. Marcy, this seemed like a high number of ALS cases.

Col Cieslak replied that the number of personnel receiving doses was greater than 1.2 million. Not everyone received all of the doses. Many personnel left the military after receiving only 2 or 3 doses. He thought it was probably closer to 1.9 to 2 million personnel who received at least some doses. He then looked up the incidence of ALS per year in the general population, reporting that this appears to range between 1.4 and 2.7 per 100,000. Rounding that off to 2, in a population of 2 million, 40 cases of ALS would be expected. While that is not controlled for age and the military is a younger population than normal, the 3 ALS deaths did not appear to be unusual.

Also troubled by the number of ALS cases, Dr. Temte looked up the incident rate in the general population. Given that there is usually a fairly short latency between onset and death in ALS, the numbers seemed to him to be within what could probably be expected with the number of doses administered.

With respect to the post-exposure, inhalational situation, Dr. Lett requested clarification about what would remain under Investigational New Drug (IND) Protocol versus what constituted licensed use.

Dr. Wright responded that licensure is only for pre-event use. Post-exposure use at 0, 2, and 4 weeks administered subcutaneously is under an IND. The group that holds the IND is in the process of submitting a request to the FDA for consideration to change to IM administration. She believed a ruling was expected in April 2009.

Dr. Cieslak requested information about the subjects who were in this trial and their demographics (e.g., age, sex, and race).

Dr. Wright replied that the subjects in this trial were 1,563 US civilians. Across the study groups, the subjects were approximately 50/50 male and female, approximately 80% Caucasian, and the majority were less than 30 years of age. The next highest age group were 40 to 50 years old.

**Motion: Pre-Event Use of AVA Recommendation**

Dr. Neuzil made a motion to approve Option 1 Pre-Event Use of AVA Recommendation as written. Dr. Baker seconded the motion. The motion carried with 15 affirmative votes, 0 abstentions, and 0 negative votes.



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# Hepatitis Vaccines

## Overview

**Dr. Mark Sawyer, Chair**
**ACIP Hepatitis Workgroup**

Dr. Sawyer introduced the first action item brought to the ACIP by the Hepatitis Vaccine Workgroup, which was formed in the Fall of 2008, and on which Drs. Cieslak and Ehresmann also serve. Liaisons represented on this workgroup include: American Academy of Pediatrics (AAP), National Association of County and City Health Officials (NACCHO), Infectious Disease Society of America (IDSA), American Geriatrics Society (AGS), Healthcare Infection Control Practices Advisory Committee (HICPAC), Society for Healthcare Epidemiology of America (SHEA). Expert contributors include: Brian McMahon, Rafi Ahmed, and Myron Levin. CDC staff include: Sandra Chaves, Cindy Weinbaum, and Trudy Murphy.

The Hepatitis Workgroup's terms of reference are to determine the advisability and extent of hepatitis A vaccination recommendations for families adopting children from other countries; review data from recent hepatitis B outbreaks among diabetics in institutional care to determine whether vaccination is appropriate; review data related to long-term immunity of hepatitis B vaccine to determine if additional vaccine doses are necessary and if so, under what dosage and schedule; and review hepatitis A vaccine long-term immunity to determine whether updating recommendations is warranted.

## Hepatitis A Among Contacts Of Internationally Adopted Children

**Sandra Chaves, MD, MSc**
**Division of Viral Hepatitis**
**NCHHSTP / CDC**

During this session, Dr. Chaves described the morbidity of hepatitis A associated with international adoption by providing some examples of recent cases, discussed some background features of hepatitis A virus infection, and discussed the characteristics of international adoptees.

In June 2007, CDC was notified of a case of fulminant hepatitis A in a 51-year-old grandmother of 12-month old adopted twins. The twins were not jaundiced, but were both confirmed to have hepatitis A by IgM testing (anti-HAV IgM+). This case prompted further investigation, with 20 cases of hepatitis A in non-traveling contacts of international adoptees identified from six different states between 2006 and 2007 [Fischer et al., Clin Infect Dis. 2008 Sep 15;47(6):812-4].

In 2008, CDC learned about hepatitis A in both non-traveling parents of an international adoptee in Minnesota. This child was an 18-month old who was non-jaundiced, but who was confirmed to have hepatitis A by IgM testing (anti-HAV IgM+). Both parents were hospitalized due to hepatitis A, were sick for almost two months, were too ill to care for their child, were too ill to work, and had substantial medical care costs [International Adoption Medicine Program, MN – *Cynthia R. Howard*]. Also in 2008, CDC was informed of a community spread of hepatitis A related to an international adoptee. This child was a non-jaundiced 10-month old who was confirmed to have hepatitis A by IgM testing. Overall, 12 cases of hepatitis were associated with this outbreak, all in non-traveling contacts. Of these, 6 were household members (attack rate 100%), 4 cases resulted from contact with household members who attended the local



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elementary school (3rd and 5th grades), there was documented exposure in a pre-kindergarten class, 2 cases were identified among extended family members, and 2 adult cases were hospitalized (one with fulminant hepatitis). Two vaccination clinics were set up in response to this outbreak [Maine State Health Department, unpublished data].

In January 2008, another cluster of hepatitis A in non-traveling contacts of an international adoptee was reported to CDC. Two children, aged 8 and 14 months, were adopted. The 14-month old was not jaundiced, but was confirmed hepatitis A by IgM. Both parents, who were vaccinated before travel following ACIP recommendation, did not become ill. However, there were 3 hepatitis cases among 5 non-traveling household contacts for an attack rate of 60%. IG and immune globulin (IG) and vaccine were offered to the close contacts to control the spread of infection.

In summary, international adoptees have been recognized as an important source of hepatitis A for their unvaccinated, non-traveling contacts in the US. In fact, international adoption as a source of infection for hepatitis A is likely to be underestimated, primarily due to the incomplete ascertainment of cases. Based on surveillance, it is known that cases of hepatitis A are substantially underreported. Moreover, the current hepatitis A surveillance system does not capture international adoption as a risk factor.

With respect to transmission of hepatitis A, the incubation period is 4 weeks on average. The range is 2 to 8 weeks (~60 days). The greatest period of communicability is approximately 2 weeks before jaundice. In the US, transmission is most common by person-to-person contact, especially in household settings [Bell BP et al. J Infect Dis 1998;178(6):1579-84]. The highest risk of hepatitis is associated with infected children in diapers ages 0-3 years [Hadler S et al. J Infect Dis 1982; 145: 255-61]. In fact, infected, non-jaundiced children under age 6 have been described as the most likely source of hepatitis A for adults without any other risk factors [Staes CJ et al. Pediatrics 2000;106(4):E54; Smith PF et al Epidemiol Infect 1997; 118:243-52].

In terms of the probability of symptomatic (jaundice) hepatitis A virus infection by age, up to 70% of children under the age of 6 may be infected without having jaundice, but are a source of infection for other age groups. Of children ages 6 to 17 years, 20% to 50% could also be infected without jaundice [Armstrong GL et al. Pediatrics 2002;109:839–45]. The severity of hepatitis A increases by age. The overall fatality rate of hepatitis A is considered to range between 0.3% to 0.6%, but is at least 3 times higher (1.8%) among adults 50 years and older [Adapted from MMWR 2008; 57 SS-2]. The estimated cost of a case of hepatitis A, based on 2004 US dollars, ranges from $800 to $300,000 if a patient requires a liver transplant due to fulminant hepatitis. In terms of the public health costs, one reported case is estimated to cost approximately $700, excluding outbreak control (e.g., vaccination clinics) [Rein et al.; Pediatrics, 2007].

In summary, approximately 70% of infected children <6 years, and approximately 20% to 50% of infected older children are not jaundiced. The incubation period can be as long as 8 weeks or approximately 60 days. Diaper-wearing aged children are the most efficient source of transmission to older age groups. Death and hospitalization due to hepatitis A is more likely to occur among infected adults.



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With regard to the at-risk population of contacts of international adoptees, hepatitis A vaccine was first available in the US in 1995. ACIP recommendations targeted vaccination for children in high endemic areas, and high risk groups, e.g., travelers (1996 &1999). Nationwide childhood immunization for 12-23 month olds was recommended in 2006. Although the program has primarily targeted children, a strong herd immunity effect has been described related to hepatitis vaccine [Samandari et al.Vaccine, 22 (2004) 4342-50].

There was a dramatic decrease of hepatitis A incidence among the US population from the pre-vaccine era to 2007. Due to lack of circulation of virus and the herd immunity effect of the vaccine, adults are now less likely to be exposed to circulating virus and, therefore, may be more susceptible to hepatitis A [NNDSS, CDC unpublished]. Based on the National Health and Nutrition Examination Survey (NHANES) conducted from 1999-2004, less than 40% of adults ages 20 to 59 have markers of immunity to hepatitis A. While hepatitis A infections decreased in all age groups in the US, over 60% of adults 20-59 years of age are susceptible. In addition, this is the age group most likely to be adoptive parents.

The annual number of internationally adopted children coming to the US from 1998-2008, estimated from immigrant visas issued to orphans, is approximately 18,000. Of these internationally adopted children ages 0-17 years old, it is estimated that 40% are under 1 year of age, 85% are under 5 years of age, and 16% are 5 years and over. Countries with the greatest number of adoptions have changed over time. For instance, in 1990 South Korea was the most common source for US adoptions. Russia and China became preeminent in international adoption in the late 1990s. More recently, countries such as Guatemala and Ethiopia made their adoption process easier, so they became a popular destination for international adoption. For example, in 2003 only 135 children were adopted into the US from Ethiopia. In 2008, almost 2,000 children came from Ethiopia. While it is impossible to predict which country international adoptees will come from in any given year, Dr. Chaves considers all countries in which international adoptions occur to be endemic for hepatitis A. [Source: http://adoption.state.gov/news/total_chart.html].

In terms of the medical requirements for internationally adopted children, before admission into the US, children must undergo a medical examination in their country of origin by a US State Department designated physician. Basically, the examination focuses on serious physical or mental defects and there is no screening for hepatitis A virus (HAV) infection. Since 1997, international adoptees 10 years of age or younger are exempt from immunization requirements for entry into the US [Immigration and Nationality Act: October 21, 1997].

To estimate the risk of hepatitis A transmission for international adoptees, CDC has reached out to adoption clinics in the country that are screening this population routinely for hepatitis A. Data pertaining to the seroprevalence of antibody to hepatitis A among international adoptees under age 6, by their country of origin and at their first medical encounter, show that 50%-70% of children coming from Ethiopia have been exposed to hepatitis A by the time they turn 6. In Russia and China, infection may be acquired at a later age. While this illustrates that the risk of infection will vary by age and by country of origin for adoptees, it would be very difficult to predict infections based on these parameters [Data unpublished: Cincinnati Children's Hospital Medical Center, Mary Staat; and University of Minnesota, International Adoption Medicine Program, Cindy Howard]. Three adoption clinics have tested more than 600 internationally adopted children for Anti-HAV IgM+ [Cincinnati, Ohio 2006-2008; Lexington, Kentucky 2007-2008; Minneapolis, Minnesota 2008]. Data from these facilities demonstrate that most of the IgM+ children are clustering around younger ages, most of them under age 6. However, there are also IgM+ children ages 6-17. The percentage range of IgM positivity among adoptees of



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all ages across these three clinics varied from 1.1% to 6.5% [Data unpublished: Cincinnati Children's Hospital Medical Center, Mary Staat; A Caring Touch Pediatrics & International Adoptions, Lexington, Shawn Taylor; and University of Minnesota, International Adoption Medicine Program, Cindy Howard]. In summary, approximately 18,000 internationally adopted children come from hepatitis A endemic countries every year. Most of them will be exempt from immunization requirements before entry in the US. Of these international adoptees, 1.1% to 6.5% are infectious or may be infectious on arrival in the US based on the data from these three clinics.

Using the information available, the risk of hepatitis A among close contacts of international adoptees was estimated. The assumptions used to estimate risk of hepatitis A infection among close contacts of international adoptees ages 0 to17 years were that 18,000 children will arrive in the US every year from endemic countries and each adoptee will have, on average, 7 contacts for a total of 126,000 people at risk. Based on the NHANES data, it was assumed that 50% of these contacts may be susceptible to hepatitis A, varying from 30% to 90% for the sensitivity analysis. A 30% baseline estimate was used for attack rate, with 10% to 50% used for the sensitivity analysis, which is likely to be a conservative assessment. Although a much higher attack rate was reflected in one example earlier in the presentation. The assumption for the proportion of infectious adoptees on arrival in the US was 1.2% at baseline and 0.6% to 3.9% in the sensitivity analysis. This estimate took into account the rates of IgM positivity that was observed from the adoption clinics and was corrected by using a 60-day window period for risk of infection, with 60 days being the upper limit of the incubation period.

Given these assumptions, 136 cases of hepatitis A associated with international adoption could occur every year ranging from 113-1,031. The risk of hepatitis A was estimated at 106 cases per 100,000 among contacts exposed to an international adoptee during the first 60 days after arrival in the US, which could range from 90 to 819 per 100,000. Thus, the rate of infection in this group is substantially higher than the incidence of hepatitis A in the US in 2006 which, was estimated to be 1.2 per 100,000 [*MMWR* 2008; 57 SS-2]. However, there are limitations in the risk assessment that must be considered. The risk of transmission may vary by age of adopted child (highest among children in diapers ages 0-3 years), by country of origin of the adopted child, and by time of arrival of the adopted child related to the infectiousness period. In addition, the estimate of number of close contacts (e.g., denominator) may not be accurate.

Dr. Chaves concluded that international adoptees come from countries endemic for hepatitis A. A substantial proportion of US adults are susceptible to hepatitis A and are, therefore, at risk for severe disease. Adoptees with unrecognized hepatitis A virus infection, on arrival in the US, are a source of hepatitis A for their close contacts. Current recommendations for pre-exposure hepatitis A vaccination do not address non-traveling close contacts of international adoptees.

## Proposed Recommendation

**Cindy Weinbaum, MD MPH**
**Division of Viral Hepatitis**
**NCHHSTP / CDC**
**Advisory Committee on Immunization Practices**

On behalf of the Hepatitis Vaccine Work Group, Dr. Weinbaum posed the following question to the full ACIP, “Should current ACIP guidelines include hepatitis A pre-exposure prophylaxis for non-traveling contacts of international adoptees from areas of high and intermediate hepatitis A virus endemicity?” The current recommendation covering prospective adoptive parents



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traveling to foreign countries states, "All susceptible persons traveling to or working in countries that have high or intermediate Hepatitis A endemicity should be vaccinated or receive IG prior to departure" [*MMWR*, 2006/Vol.55/No. RR-7]. Making the new recommendation would rely on the previously published map that appeared in the 2006 ACIP guidelines. Basically, countries with intermediate or high endemicity of hepatitis A include most of the world except for North America, Western Europe, Australia, New Zealand, and Japan. The workgroup presented two options for this recommendation:

Option 1
Recommend hepatitis A vaccination for all previously unvaccinated non-traveling persons who anticipate having close personal contact with an international adoptee, within 60 days of arrival of the adoptee in the US, when the adoptee is from a country of high or intermediate endemicity and under age 6 years.

Option 2
Recommend hepatitis A vaccination for all previously unvaccinated non-traveling persons who anticipate having close personal contact with an international adoptee, within 60 days of arrival of the adoptee in the US, when the adoptee is from a country of high or intermediate endemicity.

Partners would be needed to facilitate provider awareness and vaccine uptake among parents including: US Department of State, adoption clinics, adoption agencies, travel agencies, American Academy of Pediatrics (AAP), and American Academy of Family Physicians (AAFP). Many adoption clinics already recommend that contacts of adoptees be vaccinated, and are giving advice to adoption and travel agencies that are subsequently advising adoptive parents. Also important to consider is the financial burden of vaccination that would be added to the cost of adoption. The cost of adoption was estimated at $20,000, but ranges between $20,000 and $30,000 for the family. The cost contributed by vaccinating 7 contacts (the average number of contacts estimated by the model) at a cost of $140 in the private sector for 2 doses plus an administration fee would represent 3% to 5% of the total costs of an adoption.

The following advantages and disadvantages are associated with each of the proposed options, with Option 2 being supported by the majority of the Hepatitis Vaccines Workgroup:

Option 1: Advantages and Disadvantages
*Advantages:*
- ❑ Children <6 years likely to be non-jaundiced (~70%)
- ❑ HAV transmission efficient; high attack rates in susceptible close contacts
- ❑ ≥85% of international adoptees are <6 years
- ❑ Less costly than recommending hepatitis A vaccine for contacts of all-aged adoptees

*Disadvantages:*
- ❑ Will not prevent cases associated with older adoptees
- ❑ Recommendation for target age group may be more difficult to implement

Option 2: Advantages and Disadvantages
*Advantages:*
- Acute hepatitis A infection can occur in any age group
- ≥ 20% not jaundiced with acute infection
- Patients are infectious prior to onset of jaundice
- All-age recommendation easier to implement
- Would prevent cases associated with older adoptees



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*Disadvantages:*

- ~15% increased vaccination costs
- Older adoptees more likely to be immune to hepatitis A; are less likely to have asymptomatic infection

The current definition of "Close Personal Contact" in the context of post-exposure prophylaxis is, "*Close personal contact.* Hepatitis A vaccine or IG should be administered to all previously unvaccinated household and sexual contacts of persons with serologically confirmed hepatitis A. In addition, persons who have shared illicit drugs with a person who has serologically confirmed hepatitis A should receive hepatitis A vaccine, or IG and hepatitis A vaccine simultaneously. Consideration also should be given to providing IG or hepatitis A vaccine to persons with other types of ongoing, close personal contact (e.g., regular babysitting) with a person with hepatitis A [MMWR 2007;56(41):1080-1084].

> *Close personal contact.* Hepatitis A vaccine *[or IG]* should be administered to all previously unvaccinated household *[and sexual]* contacts *[of persons with serologically confirmed hepatitis A. In addition, persons who have shared illicit drugs with a person who has serologically confirmed hepatitis A should receive hepatitis A vaccine, or IG and hepatitis A vaccine simultaneously. Consideration also should be given to providing IG or hepatitis A vaccine to]* and to persons with other types of *[ongoing,]* close personal contact (e.g., regular babysitting) with *[a person]* adoptees from countries of high or intermediate endemicity of *[with]* hepatitis A.

The underlined words would be retained from the current definition of "Close Personal Contact, italicized words would be removed, and the remainder of the words represent new language that would need to be added to make the definition applicable to this recommendation." That is, "Close Personal Contact" would be defined as, "Hepatitis A vaccine should be administered to previously unvaccinated household contacts and to persons with other types of close personal contact; for example, regular babysitting, with adoptees from countries of high or intermediate endemicity of hepatitis A.

## Discussion

With respect to the three clinics, Dr. Morse requested clarification regarding whether the IgM positive children were all asymptomatic. It seemed that there was a significant rate of positivity in the older age groups.

Dr. Chaves responded that this was correct, although she was not certain whether this was also true for the Lexington clinic, given that they had only recently collected these data. She thought two were asymptomatic and two actually developed symptoms. Given that the Lexington clinic did not provide all of the data provided by the other two clinics, she also did not know whether there was anything different about these children that differed in terms of where they came from geographically. It may reflect the country of origin.

With regard to the anti-HAV IgM, Dr. Sumaya inquired as to what type of test was used, whether it was commercially available, and if done in a reference lab whether there was validation.

Dr. Chaves responded that while they did not have information on test sensitivity of the tests used in the study described, it is a commercially available test. This is in the context of a



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population that can have a hepatitis infection without symptoms, and who come from countries where prevalence of disease is higher.

Dr. Judson pointed out that targeting this vaccine in a way that is going to be cost-effective is obviously difficult because such small groups have been tested, there are variations in age and country of origin, and from time to time secular trends are probably changing as well. Another issue pertaining to cost regarded when the vaccine patents expire.

Peggy Reynolds (GSK) responded that her understanding was that vaccines never come off patent.

Merck clarified that it is what goes into making a vaccine, not simply the intellectual property that is involved in the foundation of it. It is the technical know-how which is not really covered by intellectual property that is generally considered proprietary information. Given the significant expense that goes into developing a vaccine, there is no reason to believe that it could be made in a more cost-effective or lower price than the currently available vaccines.

Dr. Temte asked the Workgroup to consider two additional insertions of language: 1) Include language that endorses many other groups' approach to providing universal testing for children coming from intermediate and high endemic areas; 2) Based on a case in his clinic of a child coming from Ethiopia, and despite prompt warnings about not placing this child in daycare prior to the time that serologies came back, 50-60 children and adults had to be immunized. With that in mind, include language to suggest that children should not be placed in day care situations until serologies are known.

Dr. Weinbaum indicated that the workgroup considered an option of testing all children adopted from other countries.. The group basically concluded that for close contacts, by the time the test was done and the results were received, exposure would have already occurred. The workgroup would likely consider the recommendation of not placing a child in a daycare situation until the seriologic results were known.

Dr. Temte clarified that the suggestion was not to supplant the recommendation for immunization of close contacts, but as an addition to suggest that children adopted internationally from intermediate to high areas of endemicity be tested. Once that language is published, at least some insurers will cover the cost and some physicians will be inspired to do the testing. While there are several adoption clinics throughout the country that do a very good job, there are many practitioners in rural settings who have no knowledge about what to do. The backing of ACIP would lend credence to what they do.

Given that approximately half of the people ACIP was proposing to immunize were adults, Dr. Poland (ACP) extended ACP's partnership support. He was surprised that the number of contacts was just 7, particularly given that many of these children go into preschool. He seconded Dr. Temte's suggestion to add more language about placement in daycare / preschool settings. In addition, he thought perhaps other examples should be included in addition to babysitters, such as preschool workers. In addition, he wondered whether a cost-benefit analysis had been done.

Dr. Chaves responded that it was a learning process to understand how international adoption occurs and the dynamic of receiving and spending time with the child. Various adoption clinics that engage in pre-consultation before adoption say that in most cases they suggest that children not be placed in day care as soon as they arrive in the country. The clinics' reasoning



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behind this is that it is very important to have at least one of the caretakers with the child for the first three months or so to develop an emotional bond. The University of Minnesota interviewed almost 2,000 adoptive parents and found that this issue was addressed with parents. Less than 10% were going to place their child with a caregiver for the first three to four months. The article describing this survey was included in members' packages. In the examples provided during her presentation, the siblings were infected and were attending school before it was known that they were infected with hepatitis A. Although the analysis was not yet complete, the group examined cost-effectiveness and did not believe it would be cost-effective based because there would be very few cases to prevent, a small population at risk, and a short period of risk for those in contact.

Dr. Sawyer stressed that it was very difficult to develop a formal cost-effectiveness analysis, and noted that the workgroup discussed this extensively. He explained that the slide showing the estimate of number of cases among contacts at roughly 100 per 100,000 was meant to compare to the previous cost-effectiveness discussions regarding the general recommendation when overall rates were approximately 20 per 100,000, in which case it was considered to be cost-effective.

If trying to stop hepatitis A before it was introduced into the US, it seemed to Dr. Beck that Dr. Temte's recommendation seemed appropriate. Of concern to him was that they were relying upon the good auspices of people to acquire vaccinations after the child was already in the US. To him the hook was the child. It seemed more appropriate to make vaccination part of the entire adoption package (e.g., anyone who will be exposed or potentially will be exposed to the child should be vaccinated before the child arrives). If one child could affect 50 or more other children and their caretakers, such as in the preschool setting, this would mean an additional large number of people who could geometrically impact many other people. It seemed that this would also have an impact on cost-effectiveness.

Dr. Weinbaum reminded everyone that the preferred proposal from the workgroup was to recommend vaccination of all who would be expected to have contact with the child (within 60 days of arrival) as soon as possible after the adoption is planned, prior to the arrival of the child. For example, this would include a babysitter who would begin taking care of the child within 60 days of after arrival in the US. This person should be vaccinated as soon as the adoption is planned if they are known at that time.

Dr. Baker suggested revising the language because it appeared to recommend that people be vaccinated within 60 days after arrival rather than prior to arrival.

Dr. Ehresmann stressed that it was important for this recommendation to specifically address non-traveling close contacts. Recently in Minnesota a physician interpreted the recommendation as pertaining only to those who were traveling and did not vaccinate a non-traveling mother of an international adoptee. The mother subsequently developed hepatitis A. She also thought the estimation of 7 close contacts was very conservative. Minnesota has experienced a number of outbreaks of hepatitis A associated with international adoptees. In one situation, the grandparents were exposed. The grandfather worked in a group home as a cook where everyone had to be prophylaxed. There was one case of fulminant hepatitis A in one of the group home members who nearly needed a transplant. This has significant impact when it occurs. From the public health department's perspective, an exposure / outbreak takes a great deal of time and attention and the impact is considerable.



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Dr. Temte noted that the upper Mid-West has had many international adoptees. Wisconsin and Minnesota are greatly over-represented. He sees many of these families in his practice and finds them to be highly motivated. If he suggests vaccinations, this is the one group that will comply. He agreed that better language was needed to clarify that at least the first dose should be completed at least two weeks prior to the arrival of the child. Even a single dose within two weeks is highly effective in preventing hepatitis A.

Dr. Poland clarified that he favored the intent of the recommendation, but stressed that the committee must be consistent in their efforts. A complete cost-benefit analysis should be conducted. The average out-of-pocket expense for an adoption is approximately $40,000. Each cost that is added is not trivial. Wording in ACIP recommendations typically states something about being cost-effective or not and might include wording such as, "Hepatitis A vaccination is recommended for those who wish to avoid becoming ill with Hepatitis A." For the sake of consistency and because these recommendations tend to set precedent, he thought the committee should be consistent in its approach.

Dr. Englund pointed out that adoption itself is not cost-effective and these parents clearly realize this. This is indeed a specific and highly motivated group of people. They need the best medical advice possible regardless of whether cost-effectiveness is known. While cost-effectiveness information should be pursued, she did not believe ACIP should wait for cost-effectiveness information to make a recommendation. As someone who cares for many foreign-born adoptees, she strongly agreed with Option 2, with the revision of the language to make it clearer about vaccination of potential contacts "prior to arrival." She also thought the recommendation should address adoptees of any age, given that there are no firm birth records for children from some countries and many come from orphanages where the risks are even greater. Therefore, the recommendation should not be restricted to adoptees under the age of 6.

With respect to the travel medicine aspect, Dr. Grogg pointed out that frequently, families return to the country. Grandparents who did not go originally may not have been vaccinated. With that in mind, he supported Option 2 with the proposed wordsmithing.

Dr. Duchin (NACCHO) requested further information regarding the clusters described by Dr. Chaves with respect to how many had an indication for vaccination already.

Dr. Chaves responded that most of the clusters were in areas that did not have a recommendation for vaccination from the earlier ACIP recommendation, so many of these children missed the opportunity to be vaccinated. There were no children born in the cohort of children to be vaccinated based upon the 2006 recommendation. Based on the Minnesota article, the workgroup learned that most of the adult contacts (88%) of adoptees who actually travel to their adoptee country of origin were vaccinated before departure. There is room for improvement in terms of the recommendation to vaccinate travelers, but the uptake is reasonably good already.

Dr. Sawyer summarized the workgroup's discussion about Option 1 versus Option 2 with regard to the age cutoff. He thought it was fair to say the majority opinion was that Option 2 was preferred because it was simpler and for the reasons that had already been raised. However, a significant number of workgroup members preferred Option 1 on the strength of the cost-effectiveness considerations (e.g., it would reduce the costs somewhat, although only by about 15% overall).



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Ms. Stinchfield (NAPNAP) stressed that there is vaccine fatigue from a clinical standpoint. Therefore, simple is better, and with that in mind she supported Option 2.

Dr. Neuzil pointed out that this is a safe and effective vaccine and a small captured population. She also supported Option 2, reminding everyone that this issue came to light because a grandmother died. Referring to the map shown earlier about the effective decline in hepatitis A incidents in the US in the last 10 years, she wondered whether there were any plans to systematically examine the remaining cases, particularly the severe cases, to determine who these are to better target prevention / elimination efforts.

Dr. Chaves responded that while it was early to discuss elimination of hepatitis A - there are currently no catch-up vaccination recommendations - the epidemiology of hepatitis A has changed significantly since the introduction of the vaccine. CDC / Division of Viral Hepatitis is looking at the national surveillance system for hepatitis A to understand and address the current risk factors. Approximately 60% of reported hepatitis cases do not know where they contracted the disease.

John Ward, Chief, Division of Viral Hepatitis, added that death certificates reflect that those who are dying from hepatitis A tend to be adults with pre-existing liver disease.

To clarify that the “within 60 days statement” Dr. Sawyer suggested the following revision to the proposed wording: “Hepatitis A vaccination is recommended for previously unvaccinated, non-traveling persons who anticipate close personal contact with an international adoptee during the 60 days following the arrival of the adoptee in the United States when the adoptee is from a country of high or intermediate endemicity.” With additional input from other members, Dr. Sawyer suggested that the last sentence be changed to read, “Ideally, the first dose of Hepatitis A vaccine should be administered at least two weeks prior to the arrival of the adoptee.”

Dr. Ehresmann commented that most close contacts will not be identified until after arrival of a child, and that a recommendation for post-exposure prophylaxis following exposure would be sufficient. Therefore, it was not clear why the recommendation needed to read “two weeks prior to arrival.”

Dr. Englund disagreed. These children often arrive at the airport with 40 people there to greet, hug, and kiss them. They will know who the potential close contacts are because they have to make their airplane reservations at least two weeks ahead of time. Perhaps a new babysitter will also have been hired ahead of time. The recommendation must be clear for providers and parents.

Dr. Plotkin suggested removing the word “non-traveling” because some travelers will not have been vaccinated. Perhaps it should read “unvaccinated persons.”

Dr. Sawyer responded that the primary emphasis of this recommendation was to focus on non-travelers. There is an existing recommendation for travelers to be immunized, so they should be careful not to dilute or shift the focus away from that.

Dr. Baker thought everyone agreed that ideally the contacts should be fully immunized before arrival; therefore, she was comfortable with the language proposed by Dr. Sawyer.

Dr. Morse suggested taking a short break to flesh out the wording, to be able to reach consensus.



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Following a 20-minute break to further develop Option 2 wording, Dr. Weinbaum indicated that the group proposed a preamble to better define who this recommendation addresses, "Persons who will have close personal contact with the adoptee during the first 60 days following arrival of the adoptee in the US should be identified." The actual recommendation language would state, "Hepatitis A vaccination is recommended for all previously unvaccinated persons who anticipate close personal contact with an international adoptee from countries of high or intermediate endemicity during the first 60 days following arrival in the US." In addition, the recommendation would include the wording, "The first dose of hepatitis A vaccine should be administered as soon as adoption is planned. Ideally, the first dose of hepatitis A vaccine should be administered at least two weeks prior to the arrival of the adoptee." This recommendation would also refer to the currently existing recommendations for travelers and for post-exposure prophylaxis. The post-exposure prophylaxis recommendations would apply to those individuals who are not vaccinated two weeks prior to the arrival of the adoptee.

**Motion: Hepatitis A Among Contacts Of Internationally Adopted Children**

Dr. Ehresmann made a motion to approve Option 2 Hepatitis A Among Contacts Of Internationally Adopted Children with the newly suggested revisions to the language. Dr. Temte seconded the motion. The motion carried with 14 affirmative votes, 1 abstention, and 0 negative votes.

## Influenza Vaccines

### Introduction

**Kathy Neuzil, MD, MPH**
**Chair, Influenza Vaccine Workgroup**

Dr. Neuzil introduced the session on Influenza Vaccines. This session included an update on workgroup activities, the influenza season, antiviral resistance issues, and highlights and changes for the 2009-2010 influenza vaccine recommendations. The Influenza Vaccine Workgroup has been very busy in the last few months. The group has engaged in discussions on a number of topics, including: influenza activity, improved vaccines for older adults, vaccine safety issues, and adult vaccination recommendations. During this time, they heard presentations from the manufacturers as well.



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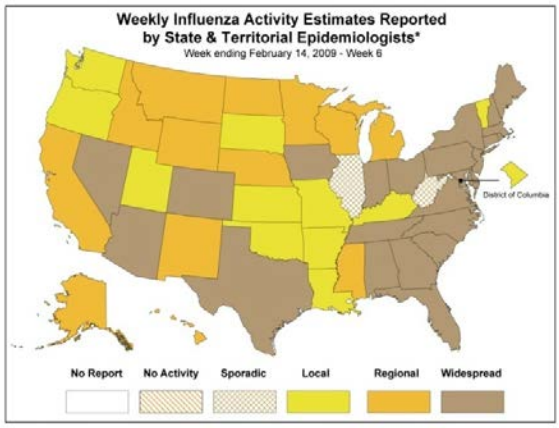
## Influenza Surveillance Update, Antiviral Surveillance, and 2009 Influenza Vaccine Recommandations

**Anthony Fiore, MD, MPH**
**CDC / CCID / NCIRD / ID**

Dr. Fiore first presented on the influenza positive tests reported to CDC from the WHO / National Respiratory and Enteric Virus Surveillance System (NREVSS) collaborating laboratories through February 14, 2009. As of Week 6, there were 1313 (24.4%) specimens positive for influenza virus among specimens submitted for testing from persons with acute respiratory illness. The types and sub-types thus far in this season have been dominated by influenza A(H1N1), with some influenza Bs appearing in the past few weeks, and relatively little influenza A(H3N2) thus far. Based on pneumonia and influenza mortality surveillance conducted in 122 US cities using weekly reports from death certificates, the past influenza season (2007-2008) was well above the epidemic threshold during the peak influenza season. This has not yet occurred in the current season.

Pediatric deaths for laboratory-confirmed influenza have been a reportable disease since 2004. Thus far in this season only 9 deaths have been reported. Of these 9 deaths, 6 were in children who had bacterial co-infection. Death reporting typically lags behind by one to two weeks, so unfortunately more reports of death can be anticipated. With respect to the hospitalization surveillance data from the Emerging Infections Program Surveillance, this season hospital laboratory-confirmed influenza is being reported for hospitalizations in all age groups. At the time of this presentation, an increase in persons hospitalized for laboratory-confirmed influenza was just beginning in hospitalization surveillance. This also tends to be a somewhat lagging indicator of influenza activity, so an additional increase would be expected over the next few weeks. With respect to the percentage of visits for influenza-like illness (ILI) reported by the US Outpatient Influenza-like Illness Surveillance Network (ILINet), conducted among over 2,000 central providers across the US, reports have exceeded the seasonal baseline over the last several weeks.

Influenza activity is reported to CDC by state and territory epidemiologists each week. The following map reflects week 6. At this time, 24 states were reporting wide-spread activity, while the majority of the rest of the states were reporting regional or local activity. At this time last year, all of the states were reporting widespread activity with the exception of Florida:




* This map indicates geographic spread & does not measure the severity of influenza activity



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CDC laboratories do strain characterization of the influenza viruses that are submitted to the agency. From October 2008 through February 14, 2009, 390 viruses have been characterized. The bulk of the viruses characterized are Influenza A(H1N1) [n=239]. Of these, 239 (100%) are similar to A/Brisbane/59/2007 (2008-09 vaccine strain). This includes H1N1 resistant to oseltamivir. Influenza A(H3N2) was characterized in 37 cases, of which 37 (100%) were similar to A/Brisbane/10/2007 (2008-09 vaccine strain). Of the total characterized, 114 were Influenza B. Of these, 33 (29%) were in the B/Yamagata lineage, similar to B/Florida/04/2006 (2008-09 vaccine strain); and 81 (71%) were in the B/Victoria lineage. With respect to Influenza B, there are always some strains that do not match the vaccine because over the last 10 years there has been co-circulation of the two major influenza B lineages.

The major issues thus far in the current influenza season has been resistance to antivirals among influenza viruses. In October 2008, CDC was concerned about antiviral resistance among the (H1N1) viruses. Over the course of the season, the majority (264 of 268) Influenza A (H1N1) viruses tested have been resistant to oseltamivir. All influenza A (H1N1) viruses were sensitive to zanamivir. All H1N1 resistant to oseltamivir were sensitive to adamantanes (rimantadine and amantadine). All 51 influenza A (H3N2) viruses were sensitive to oseltamivir and zanamivir, and resistant to adamantanes. All 110 influenza B viruses tested were sensitive to oseltamivir and zanamivir.

With regard to oseltamivir resistance, data suggested that development of resistance is probably not driven by oseltamivir use. There is no correlation between oseltamivir use and prevalence of resistance by country [WHO 2008]. Most persons with H1N1 infections have no exposure to oseltamivir [Hauge Emerg Infect Dis 2009; Dharan JAMA 2009]. From a clinical perspective, oseltamivir-resistant viruses are similar to oseltamivir-sensitive viruses in terms of transmissibility, virulence (severity of illness and types of complications) [Hauge Emerg Infect Dis 2009; Dharan JAMA 2009], and antigenic similarity to the 2008-09 vaccine strain.

As a result of this large increase in oseltamivir resistance among the (H1N1)s that has been observed in the current influenza season, CDC issued interim guidance in late December 2008. The rationale for “CDC’s Interim Guidance for Use of Antivirals in the Treatment and Prevention of Influenza, 2008-09 Season” was that oseltamivir-resistant H1N1 is the most commonly isolated virus thus far; clinicians need to know that oseltamivir alone might not effectively prevent or treat influenza; and there are no rapid tests for influenza A sub-typing or antiviral resistance testing. Key points made by this guidance are that local influenza surveillance data and influenza diagnostic testing can help with physician decision-making regarding the choice of antiviral agents for their patients. Treatment with zanamivir or a combination of oseltamivir and rimantadine (amantadine acceptable in place of rimantadine) is preferable in some situations (influenza subtype is likely to be H1 or unknown). Oseltamivir-resistant H1N1 strains are antigenically similar or identical to the strains in the vaccine.

CDC has conducted additional activities with regard to the oseltamivir resistance issue. Enhanced viral surveillance has been developed in partnership with state public health labs. Throughput and timeliness of antiviral testing in CDC labs have been increased. Updates are made through FluView (weekly) and the *MMWR*. The issues have been discussed with antiviral manufacturers. ACIP workgroup activities for antiviral recommendations are to monitor antiviral resistance data; consult and coordinate with antiviral experts and medical professional organizations; develop draft ACIP recommendations for antiviral treatment and chemoprophylaxis; present to the full ACIP in June 2009; and publish a separate ACIP guidance before the 2009-10 season.



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Dr. Fiore shared highlights in the proposed vaccination recommendations from the ACIP for the 2009-2010 season. Strain selection occurred in the past two weeks, first at the WHO meeting on February 11, 2009 and then during the Vaccines and Related Biologic Products Advisory Committee (VRBPAC) meeting the week prior to ACIP's February meeting. The selections were as follows:

- An A/Brisbane/59/2007 (H1N1)-like virus (same as 2008-2009)
- An A/Brisbane/10/2007 (H3N2)-like virus (same as 2008-2009)
- A B/Brisbane/60/2008-like virus (new; this is a Victoria lineage virus which is different from the Yamagata virus that is currently in the vaccine)

Some sections of the prevention and control of influenza draft vaccine recommendations have been revised to update them according to new data. The age or risk groups recommended for annual vaccination remain unchanged. Approximately 84% of the US population currently is recommended to receive annual influenza vaccination. The permissive recommendation will be continued for persons not specifically targeted (e.g., healthy adults ages 19-49 who do not have a contact-based recommendation). Vaccination is recommended for "All persons who want to reduce the risk of becoming ill with influenza or of transmitting it to others." Full implementation of annual vaccination for all children ages 6 months through 18 years is now expected, rather than "if feasible."

Revisions of vaccine immunogenicity and effectiveness background sections, with respect to immunogenicity among hospitalized persons, support will be included for routine vaccination of hospitalized persons [Berry et al, Vaccine 2001; Gurfinkel Eur Heart J 2004]. Some of CDC's colleagues in the quality assurance arena suggested that ACIP should be more clear in the guidance about its support for routine vaccination of persons who have vaccine indications during hospitalization. With regard to reductions in laboratory-confirmed influenza among infants born to vaccinated women, support will be included for vaccination of pregnant women [Zaman et al, N Engl J Med 2008]. Regarding reductions in absenteeism or illness in vaccinated populations, support will be included for community-level indirect benefits with increased vaccine use in younger persons [King et al, Pediatrics 2008; Kwong et al, PLoS Med 2008]. .

As part of the expansion of the safety background section, information has been added about ocular and respiratory symptoms that can occur following the trivalent inactivated influenza vaccine (TIV). The rationale for this is that ocular and / or respiratory symptoms after TIV are described in some prescribing information statements and are noted in some clinical trials; however, they are not adequately discussed in ACIP influenza vaccine statements. With respect to the US experience with ocular or respiratory symptoms after TIV, persons with red eyes and / or one or more respiratory symptoms after TIV are reported each year to the Vaccine Adverse Event Reporting System (VAERS). Fortunately, these are typically acute and mild self-limited reactions, which likely occur at low frequency.

Also described in the safety background section is oculorespiratory syndrome (ORS) after TIV. This was initially described as a syndrome occurring after a single TIV formulation in Canada during the 2000-2001 season that was discussed in 2004 and with the ACIP in the past. ORS study case-definitions include acute onset after TIV of a variety of ocular and / or respiratory symptoms (e.g., bilateral red eyes, cough, hoarseness, sore throat, facial edema, wheezing, difficulty breathing or swallowing, or chest tightness) that are typically acute, mild, self-limited, reactions occurring within 24 hours after TIV. Most published information on ORS is based on



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the Canadian experience during and after the 2000-2001 influenza season. This was associated with one product in 2000-01. Although it was reported after a variety of products in subsequent years, it was less frequent. Hoarseness, ocular soreness / itchiness and cough were the only symptoms significantly associated with vaccination in one placebo-controlled study. ORS can recur with TIV in following seasons, but many people were revaccinated without incident. The pathogenesis is uncertain. Some US VAERS reports meet screening criteria for ORS, including some before and after the 2000-01 season. Less than 2% of reports after TIV were for ORS-like symptoms occurred in 2008-09.

With regard to draft revaccination information and additional plans for ocular and respiratory symptoms, the proposed wording for the ACIP statement is, "Guidance on influenza vaccination in subsequent seasons for persons who have had ocular and respiratory symptoms is under consideration by ACIP." Additional consideration is needed regarding how to distinguish immediate hypersensitivity from ORS or other causes of ocular or respiratory symptoms. There are on-going discussions with the CDC Immunization Safety Office, Clinical Immunization Safety Assessment (CISA) Network consultants, FDA, manufacturers, and ACIP influenza vaccine workgroup. Plans for the June 2009 ACIP meeting are to expand the presentation and possibly request an ACIP vote on revaccination guidance if warranted, and to include the evaluation of VAERS reports among persons vaccinated with TIV during 2007-08 and 2008-09 with ocular and respiratory symptoms meeting screening criteria for ORS.

Vaccination recommendations for children and adolescents will include full implementation of universal recommendations:

- All children aged 6 months through 18 years should be vaccinated annually.
- Children and adolescents at higher risk for influenza complications should continue to be a focus of vaccination efforts, including those:
  - aged 6 months through 4 years;
  - who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological or metabolic disorders (including diabetes mellitus);
  - who are immunosuppressed (including immunosuppression caused by medications or by human immunodeficiency virus);
  - who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration;
  - who are receiving long-term aspirin therapy who therefore might be at risk for experiencing Reye syndrome after influenza virus infection;
  - who are residents of chronic-care facilities; and,
  - who will be pregnant during the influenza season.
- Note: Children aged <6 months cannot receive influenza vaccination. Household and other close contacts (e.g., daycare providers) of children aged <6 months, including older children and adolescents, should be vaccinated.



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There are no changes in the adult recommendations, which will remain as follows:

- Annual vaccination against influenza is recommended for any adult who wants to reduce the risk of becoming ill with influenza or of transmitting it to others.

- Vaccination is recommended for all adults in the following groups, because these persons are either at higher risk for influenza complications, or are close contacts of persons at higher risk:
  - persons aged ≥50 years;
  - women who will be pregnant during the influenza season;
  - persons who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological or metabolic disorders (including diabetes mellitus);
  - persons who have immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus);
  - persons who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration;
  - residents of nursing homes and other chronic-care facilities;
  - health-care personnel;
  - household contacts and caregivers of children aged <5 years and adults aged ≥50 years, with particular emphasis on vaccinating contacts of children aged <6 months; and,
  - household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza.

**Discussion**

With regard to the ocular and respiratory symptoms, Dr. Baker inquired as to whether CDC planned to conduct viral surveillance in these children. It seemed to her that some non-influenza virus might be causing these symptoms.

Dr. Fiore responded that further studies planned largely pertain to examination of the safety databases and consultation with a variety of allergists and others about revaccination. He knew of no plans at this point to study other potential causes.

Dr. Sawyer pointed out that healthcare workers often state the vaccine makes them sick. It appeared that the revisions would emphasize more clearly known side effects versus newly recognized side effects. With that in mind, he made a plea that the revisions be made very clear so as not to come across as addressing newly identified side effects. He also inquired as to whether the language concerning ORS would clearly distinguish respiratory symptoms related to LAIV.

Dr. Fiore responded that both of these issues would be addressed and that LAIV has its own section.

Dr. Neuzil indicated that the working group discussed this extensively. They raised some of the same concerns about proactively addressing this issue. There are a number of placebo controlled trials of influenza vaccine, which show that large percentages of the population have a headache and cough regardless of whether they receive vaccine or placebo. The difficulty is



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that some of the specific symptoms were not asked in many of these large studies, so the working group is relying on the Canadian experience and the passive databases. She encouraged members to read the language that is proposed in the *MMWR* to determine whether they struck a balance.

Peggy Reynolds (GSK) indicated that in approximately one month, the results would be published of a placebo controlled trial of the FluLaval™ TIV Vaccine (n=7500) for which ORS signs and symptoms were prospectively solicited. No significant difference was found between the vaccine and placebo groups. GSK would be happy to provide those data to the working group.

Dr. Temte pointed out that zanamivir is basically unavailable this year. He also had heard of a quadrivalent vaccine, and requested further information about this. In addition, the recommendation for up to 18 has been wonderful, given that he no longer has to think about who should be vaccinated in his practice. With that in mind, he wondered when they would simply recommend universal coverage.

With regard to zanamivir Dr. Fiore, CDC discussed availability with the manufacturer, GSK, before the season began and during the season. GSK has greatly increased the amount of zanamivir available to the US market; however, there appears to be a disconnect between what is ordered and what is available at the local level. He encouraged those experiencing difficulties to contact GSK to learn about availability. Shortages can be reported to the FDA. Regarding the quadrivalent vaccine, CDC engaged in discussions during the FDA Advisory Board meeting the week before the ACIP meeting about a quadrivalent vaccine. This information will be presented to the workgroup and the full ACIP as merited. The initial results suggest that there would be some modest benefits from the addition of a B strain that represents the B strain from each of the lineages. There are many other issues to work through with regard to licensure, safety, et cetera. Given the continued interest in this, Dr. Fiore believed that these discussions would continue with the FDA. The workgroup continues to discuss universal adult immunization recommendations. As indicated in the October 2008 ACIP meeting, the workgroup preferred to see how the universal childhood vaccination recommendation played out, and to gather additional information pertaining to why adults currently recommended for and who have access to vaccination do not acquire vaccines.

Dr. Cieslak wondered about the wisdom of dubbing ocular respiratory syndrome as a syndrome when it seems instead to be a minor side effect. He also wondered whether comments should be made on the potential differential effectiveness of why the attenuated influenza virus vaccine seemed to show a difference in the Belshe study, which is a randomized head-to-head placebo controlled trial.

With regard to the ORS, Dr. Fiore encouraged ACIP members to review an updated draft, which he planned to send them shortly, in which he thought they had struck a better balance between describing a variety of different ocular and respiratory symptoms that can occur at a relatively low frequency after TIV, with the Canadian experience which might be somewhat different because it was elicited by the one year when ORS was associated with one manufacturer. With regard to LAIV versus TIV, the randomized controlled trial from Belshe for 2004-2005 influenza season shows that LAIV had a better efficacy than TIV in children between the ages of 6 months and 6 years. There are also other randomized controlled studies in young adults, such as Arnold Monto's, that showed that TIV has better efficacy among young adults. There is no LIAV preference from a labeling point of view at this point.



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Paul Offit reinforced Dr. Fiore's communication with regard to supply and availability of zanamivir in the marketplace. GSK has more than ample supplies to satisfy current and future demand in this season's antiviral marketplace. Challenges at the start of the season in early January occurred with encouraging wholesalers and retail pharmacies to order zanamivir and put it on their shelves. He reassured everyone that this situation has been largely resolved. On-going challenges are occurring with thousands of independent pharmacies; however, that situation is improving each day.

Dr. Neuzil pointed out that the LAIV issue has been discussed in the past. The references are continually updated, so the workgroup has been provided with the Belshe study and others. One difficulty with regard to influenza is that it changes from year to year and there are three strains in the vaccine. Anytime a one-year study is reviewed, there is no evidence of efficacy for all three strains.

Dr. Marcy requested that the dashes be removed from age groups, given that these are confusing. For example, it is not clear whether 6 months-5 years means up to the 5th birthday or through 5 years.

Dr. Pickering responded that they are in the process of doing away with dashes. These have all been removed from the childhood immunization, and will be removed from all ACIP statements. They will no longer be used in the Pink Book or the Red Book either.

Dr. Sumaya inquired as to whether CDC was quantitatively following the sites where vaccine is administered (e.g., public health facilities, private physician offices, pharmacies, et cetera) to determine where there are any trends, consequences, et cetera.

Dr. Fiore responded that CDC gathers information through coverage data overall. There is a particular focus in the ISD on studying school-based vaccination recommendations to better understand best practices, barriers, et cetera. That has been the major focus of a Request for Application (RFA) that was published during the past season. In some of the coverage information, CDC does identify where people received their vaccines.

Dr. Meissner pointed out that the 1% or 2% of the H1 strains that are resistant to adamantanes, and isolates that are resistant to both oseltamivir and adamantanes, pose a major issue for a patient who cannot tolerate zanamivir (e.g., an intubated patient). If increasing oseltamivir resistance was not related to oseltamivir use, he wondered what CDC thought was driving this increased resistance pattern.

Dr. Fiore responded that in past seasons there has been a fair amount of oseltamivir resistance among H1N1 viruses on the order of 10% to 15%. This has not been observed during the current season. Last season, there was an 11% or so resistance to oseltamivir. In the past, resistance has been observed among H1N1s to adamantanes on the order of 10% to 15%. This season, whatever is currently circulating seems to have dropped that particular resistance pattern. CDC is concerned that there could be H1N1s that are resistant to both classes of antiviral drugs (e.g., neuraminidase inhibitors and adamantanes). Such viruses have sometimes been observed in global surveillance. The potential for this is one of the reasons for the advice that if zanamivir cannot be used, rather than simply switching to an adamantane if there is thought to be an H1N1, both oseltamivir and one of the adamantane drugs should be used. With regard to what drives resistance if not oseltamivir use, emphasis has always been placed on the role of antigenic drift, but beyond that, input is needed from virologists.



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Dr. Katz (IDSA) inquired as to what data CDC has related to uptake by hospital and clinic workers.

Dr. Fiore responded that CDC has no information for the current influenza vaccination season about health care workers at this point. There are a number of initiatives being implemented in hospitals and other systems, the results from which have been presented at the National Immunization Conference, and which have described ways in which uptake has increased beyond the national level of approximately 40%. CDC will receive national level data on healthcare worker coverage of influenza vaccine sometime in the summer, which will reflect 2008.

James Turner (ACHA) called Dr. Fiore's attention to an article by Dr. Ed Ellinger of the University of Minnesota published in early December in the *Archives of Pediatric and Adolescent Medicine* that discusses decreased absenteeism on college campuses and better academic success among vaccinated college students. For parents spending $20,000 to $40,000 a year for students to attend college, it is worth the $25 to have them vaccinated. In terms of vaccine effectiveness, the University of Virginia has a close population of 20,000 students. They know who is and is not vaccinated, and they can track vaccine effectiveness. During the poor match, they experienced approximately 30% effectiveness, but are approaching 60%-70% effectiveness this season with A strains. Anticipating the need for zanamivir, the college contacted local pharmacies and the hospital to ensure that an ample supply was available for this community.

Regarding vaccine effectiveness, Dr. Fiore indicated that this season CDC and partners are working to develop rapid vaccine effectiveness estimates. However, they are at the mercy of the influenza season. It was only in the past few weeks they had begun to observe an increase in activity.

Dr. Poland (ACP) pointed out that no one really knows what leads to antiviral resistance. ACP is attempting to publish an editorial in *Clinical Infectious Diseases* in the next few weeks. Resistance occurs against a background of use and abuse of single antiviral drugs. It may well have been a de novo mutation, but it occurs against a background in which there is mutational and selective pressures due to antivirals. He shared the concerns raised about ORS in terms of highlighting this as a seemingly "now we're concerned" type of side effect. While he knew that was not the intent, he cautioned the committee to use careful wording to stress that this was based on observations made in a limited timeframe and with respect to one product and a couple of lots. While the ACIP has functionally said that there should be universal immunization, there seems to have been a reluctance to state this out loud. At this point, there is basically a universal recommendation for influenza vaccine with three tiers: the tier of those who are at greatly increased risk of morbidity and mortality, the tier of contacts, and the tier of everybody else who wishes to avoid all the consequences. The three reviewers who reviewed the editorial insisted that a call be put forth for universal immunization, particularly given what is occurring with antiviral resistance. He suggested including health care providers in any surveys conducted regarding implementation.

Dr. Neuzil agreed that ACIP is encouraging vaccination for the entire population. The concern that has arisen is that regardless of how these recommendations are made (e.g., by high risk, age-based, et cetera) the vaccination rates continue to be dismal. Thus, there is nothing to suggest that going to a universal recommendation will actually result in improved vaccination rates. This is why the working group made the intentional decision to review the effects of



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various recommendations, and to attempt to obtain further information on coverage to better understand why coverage rates are not where they should be.

Tamara Lewis (AHIP) offered a plea from front line administrators who are trying to deal with the expanded recommendations and are seeking assistance with surveillance. While the National Immunization Survey (NIS) offers the ability to examine what is occurring with young infants, there are not good measures for the school-aged child to better understand what is occurring locally. In the interim, people look to the Behavioral Risk Factor Surveillance System (BRFSS) for information; however, on the BRFSS website the only information available is on those over 65 years of age. Even in the adult population it is not clear at the local level what is occurring.

David Kimberlin (AAP Red Book) indicated that the National Institute of Allergy and Infectious Disease's (NIAID's) Collaborative Antiviral Study Group recently convened a meeting on antiviral resistance. The summary of this is that virologists do not understand this much better that anybody else. In terms of the emergence of resistance of oseltamivir on such a widespread scale, it truly does not seem to be related to use of oseltamivir, given that it also occurred in countries with very low utilization of oseltamivir. While there may be a rationale for dual therapy, and he certainly understood CDC's recommendations on December 19, 2008, more information is needed on safety, pharmacokinetics, and efficacy in terms of whether these classes of drugs can be used together safely without any type of antagonism. Secondly, the use of rimantadine and amantidine is the same sort of situation that zanamivir has posed in that many pediatricians are experiencing difficulty in acquiring these two drugs.

Regarding immunization rates in school aged children and surrogate markers, Phil Hosbach (sanofi pasteur) pointed out that claims data could be used to ascertain a private sector number. Anecdotally from the experience they have had during the pre-booking season for influenza, the needle has not moved much with pediatricians in terms of preparing to implement the recommendation for 9- to 10-year olds. He seconded Dr. Poland's advice to include health care providers in any surveys conducted regarding implementation.

Patricia Whitley-Williams (NMA) inquired as to whether any increases had been observed in vaccine coverage, particularly among underrepresented minorities in the older age adult population. She also wondered where there had been any narrowing of the health disparities gap that exists in influenza burden of disease, particularly among adult minority populations. She encouraged the working group to continue to consider these issues, particularly as recommendations are changed. She also supported a universal recommendation.

Dr. Fiore responded that he would probably need to develop a presentation and consult with his colleagues about this topic, particularly with regard to coverage and ISD.

Dr. Bell added that CDC collects disparities information from the National Health Interview Survey (NHIS) every year (e.g., coverage by race, ethnicity, and age group). The previous season's findings were published in the *MMWR* last fall.

Dr. Chilton wondered whether information about the current problem with oseltamivir resistance had had any impact on the use of this particular agent.

Dr. Fiore responded that CDC plans to study this. They recently had a survey sent out through the Emerging Infections Network asking members of that network what drugs they were using and whether they had seen the interim guidance. They could conduct surveys similar to those



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that were administered regarding the adamantanes. However, it is difficult to quickly change course.

Dr. Judson inquired as to whether all inactivated vaccines are now thimerosal-free. While this is not an issue for ACIP scientifically, it remains an issue in the public. Perhaps at some point it would be beneficial to be able to state that no influenza vaccines contain thimerosal.

Dr. Fiore responded that the multi-dose vial of the inactivated vaccines still contain thimerosol. There are numerous thimerosal-free or trace thimerosal presentations in single use vials. Live attenuated vaccine does not contain thimerosal.

Phil Hosbach (sanofi pasteur) reported that this year, sanofi pasteur will have the capability of making 30,000,000 doses of thimerosal-free influenza vaccine based upon demand. For the 2010-2011 season, they anticipate being able to make 50,000,000 doses thimerosal-free, or virtually all of sanofi pasteur's supply in the US.

Peggy Reynolds (GSK) reported that all Fluarix™ doses will be thimerosal-free by the next season, and they anticipate that all FluLaval™ will be thimerosal-free by the season after that.

Malik Manzoor (CSL Biotherapies) reported that they plan to have 10,000,000 doses in 2009, 80% of which are thimerosal-free. They have the capacity to switch to 20,000,000 thimerosal-free doses over the next two years.

With the expansion of recommendations, Dr. Temte noted that Wisconsin has observed a near linear increase in vaccine utilization from 2002, with the one exception of 2004 with the shortage. They are over 1,000,000 doses in the registry this year for the first time ever. Most of their vaccine (95%) is being provided between August and December. At the end of December, people stop seeking vaccines. Thus, they must do a better job of educating people about the ability to acquire vaccines beyond that timeframe.

Dr. Fiore responded that each of the last three years, there has been an Influenza Vaccination Week. This past season it was in mid-December and encouraged people to vaccinate through January and February. This season was a great example of why vaccinating later in the vaccination season would be effective, given that influenza really did not appear in most communities prior to that and has not appeared in some communities until January or February.

Dr. Morse commended the working group on continuing its efforts with respect to adult immunization. He thought a strong case was made in October 2008 to move forward with a universal recommendation based on disease burden, safety, efficacy, and cost-benefit. While he understood the rationale behind further assessing feasibility, he expressed his hope that the search for the best did not become the enemy of the good.

**Motion: 2009 Influenza Vaccine Recommendations**

Dr. Baker moved to approve the 2009 Influenza Vaccine Recommendations as stated. Dr. Chilton seconded the motion. The motion carried with 14 affirmative votes, 1 abstention, and 0 negative votes.



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# Rabies Vaccines

## Introduction

**Paul Cieslak, MD**
**Oregon Public Health Division**
**ACIP Committee Member**

Dr. Cieslak explained that the Rabies Vaccine Work Group came into existence largely as a result of potential difficulties with the rabies vaccine supply. Since 2007, the availability of human rabies vaccine remains much less than ideal, for a variety of complex, interrelated reasons. Increased public health demand and seasonal limitations in vaccine supply over the past two years have created a very volatile public health environment. A variety of public health strategies have prevented the development of a true shortage.

A draft of interim recommendations prepared by a national working group on human rabies prevention, in the event of a forecast shortage of biologics used in prophylaxis, was previously distributed to ACIP. Use of alternative schedules, such as the elimination of the 5$^{th}$ (final dose) of vaccine in a naïve patient during prophylaxis, was one of the recommendations proposed by that working group. Based upon a review of the draft document by ACIP members, the suggestion was made to evaluate this option for more routine use, regardless of a vaccine shortage.

The focus of the ACIP Rabies Work Group was to review the available evidence related to a proposal for eliminating the last dose of rabies vaccine during post-exposure prophylaxis; provide a draft document to the ACIP for review of any altered schedule, based upon the data; discuss the findings during the February 2009 ACIP meeting; and prepare a statement for consideration of a vote at a future ACIP meeting, which is likely to be presented during the June 2009 ACIP meeting.

In conclusion, Dr. Cieslak thanked the members of the workgroup, without whose expertise and a variety of disciplines, consideration of this particular topic would not have been possible.

## Human Rabies Biologics: Consideration of a Reduced Vaccine Schedule in Post-Exposure Prophylaxis

**Charles E. Rupprecht, VMD, MS, PhD**
**National Center for Zoonotic**
**Vector-Borne & Enteric Diseases**

Dr. Rupprecht reported that the sources of the evidence for the Rabies Vaccine Workgroup were based upon preliminary studies, basic studies on rabies virus pathogenesis, applied immunization principles and kinetics, published literature on human clinical trials, epidemiological surveillance data in the US and abroad, and consultation with industrial and international and national subject matter experts (SMEs).

As an acute, progressive encephalitis, due to highly neurotropic RNA viruses, the modern rationale for preventive prophylactic action in rabies focuses upon timely intervention against the initial events in viral pathogenesis, prior to invasion of the central nervous system. The recommended rabies post-exposure regimens emphasize the early provisions of wound care and passive immunity (e.g., infiltration of rabies immune globulin at the bite site), combined with



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administration of rabies vaccine, to stimulate the development of active immunity in the days following exposure.

The rapid induction of rabies virus neutralizing antibodies during prophylaxis is accepted as a critical surrogate for predicting successful survivorship. In a review of clinical trials of rabies vaccination, all healthy individuals developed detectable rabies virus neutralizing antibodies by Day 14. No significant differences were documented between a 4- versus a 5-dose rabies vaccine schedule in the amount of detectable rabies virus neutralizing antibodies produced using temporal serological comparisons. In comparison of studies using 4 doses of vaccine, when given in a regimen that included rabies immune globulin, equivalent outcomes were found.

No record of failure of human post-exposure prophylaxis has been identified in the U.S. since the advent of modern cell culture vaccines and immune globulins 30 years ago. Worldwide, the clear majority of documented cases of human rabies cases have occurred in patients who either did not receive any post-exposure prophylaxis, or for whom there were documented substantial delays in the initiation of prophylaxis and / or significant deviations from current recommendations; no failures have been attributable to an absence of the last (fifth) vaccine dose in prophylaxis.

From the time of Pasteur, animals have been used as important surrogates in preclinical testing of rabies vaccines. Such research on basic immune response and efficacy outcomes with a variety of species has provided significant inferences to human clinical trials. Models from laboratory rodents to non-human primates demonstrate that the absolute number of doses of a potent vaccine are not critical if timely intervention occurs after experimental infection, including the use of immune globulins. In fact, all current biologics have first been used with surrogates from comparative animal models, and no animal models have demonstrated greater efficacy of 5 versus 4 doses. Provided that wound care, infiltration of immune globulin, and at least the 'prime-boost' vaccination scheme are given, the same outcome is observed in a variety of species: no evidence suggests the necessity of a 5th dose.

Preliminary assessments support the positive national health benefits associated with a reduced schedule of rabies vaccination. Overall, there is no anticipation that changing the current recommended schedule of 5 vaccine doses to 4 vaccine doses during rabies post-exposure prophylaxis would substantially alter the health economics of rabies prophylaxis. Recognizing that there are no national or international comparative clinical human trials that specifically compared 4 versus 5 doses, the work group's approach had to be inferential based on a review of published and unpublished studies related to rabies virus pathogenesis, experimental animal studies, human clinical trials, and national and international epidemiologic surveillance data. The work group concluded that based upon the available evidence *in toto*, no additional cases would result from a reduced schedule of 4 vaccine doses applied during post-exposure prophylaxis, compared to the *status quo* recommendations of 5 vaccine doses. After discussion and deliberations of the ACIP on the provided evidence, a vote should be considered at the next meeting based upon the draft document prepared by the rabies working group.

The work group recognizes that the 2008 ACIP recommendations did not take reduced doses into consideration. Considering lag times, the work group began work in 2005 to produce the 2008 recommendations. Nearly an entire year passed with the additional deliberations, clearance processes, et cetera after the primary vote and acceptance by ACIP the prior year. In addition, the supply limitations gave the group a new appreciation for the utility of dose-saving measures. Similarly, they do not wish to focus upon this as any conflict with label per se as



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opposed to a focus upon the evidence for support of any reduced schedules in the future. No substantive data have been produced internationally or nationally from the FDA, industry, or at the WHO Collaborating Center level that would suggest that a reduced dosing schedule from 5 to 4 would lead to any more cases. In regards to compliance issues, the work group recognizes from sentinel studies in the US that compliance with 5 doses is not 100%. In fact, from one retrospective study in New York, approximately 3% to 5% of patients did not report for the fifth dose. Extrapolating that across the US population, there have been no documented repercussions. Similarly, in enzootic dog rabies countries where compliance is less because of travel distances and because of cost, there have been no associated epidemiological repercussions from the reduction of 5 to 4 doses.

**Discussion**

Dr. Morse thought a highly convincing argument had been made to go to 4 doses. He reminded everyone that this was only one component of a multi-faceted approach to address the potential shortage of vaccine should it arise, and to reduce the potential overuse of vaccine. If ACIP recommends this reduction Dr. Morse wondered whether it would be implemented, given that it is licensed as a 5-dose regimen. Given the 5-dose series will be printed on the package insert, it is possible that this may be viewed as off-label use.

Norman Baylor (FDA) clarified for the record that while the FDA has a representative on this working group, the agency cannot endorse off label use. The package insert states 5 doses and until data are presented by the manufacturers to change that to 4 doses, the FDA cannot change the package insert as doing so would be inconsistent with the label as licensed.

Dr. Judson wondered whether anyone had compared the use of neutralizing antibody immune surrogate.

Dr. Rupprecht stressed that they had to appreciate the historical legacy that 5 to 6 doses were better than 14-21 doses. Vaccines have certainly improved over nerve tissue vaccines that continue to be used in the developing world. Based on all of the available evidence, the inclusion of wound care, infiltration of immune globulin, and at least the prime boost strategy are much more important than the necessity for 5 doses. The median incubation period for US cases is 35 days, which calls into question the scientific utility of a dose at day 28 when most people are not demonstrating illness at one month. While they cannot compel industry to change labels and recognize that there is a potential perceived conflict with FDA, on the basis of the data that industry and FDA have shared, there have been no substantive public health repercussions.

Dr. Cieslak pointed out that there are no data that either the 4$^{th}$ or the 5$^{th}$ dose is needed, so it might be a bridge too far to change the recommendation in that regard. There are no data to suggest what percentage of physicians would follow a recommendation for a reduced schedule if the FDA labels were not changed.

Dr. Rupprecht reminded everyone that many practicing physicians were not even aware of the current ACIP recommendations. Part of the outreach is at least to get the recommendations in place into the hands of the stakeholders.

Dr. Morse noted that Canada's committee recommended changing a different rabies issue, although this may not be implemented.



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Dr. Pickering added that the "bat in the bedroom" recommendation was changed in Ottawa so that it does not appear as a risk criterion.

Dr. Rupprecht pointed out that this working group has many issues to address (e.g., bat in the bedroom, risk assessments, stockpile issues, et cetera). The potential reduction in doses was simply the first issue the working group undertook for resolution. Similarly, the working group feels that even with its limitations, the 2008 attempt at an evidence-based approach is an improvement from the previous 1984 ACIP recommendations, which also included the utility of intradermal vaccination a full two years before it was actually licensed.

With respect to the question of 5 versus 4 versus 6 doses, Dr. Decker (sanofi pasteur) summarized what the package insert currently states with respect to indication, "WHO established a recommendation over 6 intramuscular doses based on [various studies that are listed]. Studies conducted at the CDC have shown that a regimen of 1 dose of human rabies immune globulin (HRIG) and 5 doses of human diploid cell rabies vaccine (HDCV) induce excellent antibody response. Based on this data, ACIP recommends a 5 dose regimen . . ." The US already deviates from WHO recommendations based on studies conducted by CDC. There are no studies to support further deviation. This proposal was not an accommodation merely for a shortage, but a permanent change in routine recommendation, which is an entirely different issue. sanofi pasteur fully expects that the FDA would not find it reasonable to change the package insert based on inferences with no specific studies. There is going to be incredible confusion if ACIP makes this recommendation and the label remains the same. There is a legal regulatory issue and a clinical practice issue. From a clinical standpoint, a clinician might reasonably assume that 4 doses are more than enough in the US system giving of HRIG, but as a matter of law, that is not adequate. The law must be complied with. As a matter of faithfulness to the procedures ACIP has followed in the past, this recommendation is not the basis on which they have made prior statements and is not what is embodied in the current package insert.

Dr. Rupprecht responded that the committee was cognizant of these nuances from an administrative and regulatory standpoint for a long time, and took the evidence-based approach based upon ACIP discussion regarding the utility based upon the evidence in toto of 4 versus 5 doses or other reduced schedules. They also recognize that no one can compel a manufacturer to change a label.

Clement Lewin (Novartis Vaccines) indicated that a 4-dose regimen is not on the label for RabAvert®. Novartis has not generated the data to support the 4-dose schedule. As a company, Novartis does not promote or support off label use, nor are they planning to collect clinical data to justify the change in the label that Dr. Decker discussed. If ACIP makes this change, Novartis will continue to tell anyone who calls in that the currently licensed regimen is 5 doses.

Dr. Plotkin commented that if this recommendation is put into effect, there will be a problem with regard to testing for antibody. There is a problem with immunosuppression, HIV, and perhaps people who receive the vaccine in the fatty tissue. Thus, he anticipated that there would be more demand for antibody testing. Perhaps some information about that should be included in any statement made regarding the 4$^{th}$ dose.

Dr. Rupprecht responded that the information supplied to ACIP members does recommend antibody testing, and that until additional supportive data become available, particularly for the immunocompromised, the current regimen of 5 doses should be continued.



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Dr. Sawyer encouraged the committee to consider making a recommendation that is off label as long as the data support it; however, as a clinician who deals with this question in talking to pediatricians about whether to give prophylaxis, this is a very stressful and emotional topic. For local public health authorities or clinicians to follow an off label recommendation, there must be very strongly stated data and language in the recommendation. Therefore, he encouraged the committee to be very clear about the points that had been raised in the draft statement. He thought they would clearly have to show that in the US, where everyone receives immune globulin, a 4-dose regimen is still likely to be successful and there will be no significant change in antibody titer.

Dr. Rupprecht replied that in regard to the immunosuppression issue, for example, with rabies immune globulin (RIG) as to the possibilities for interference from some of the licensed products used in the US, there are prior data showing a lack of interference of HRIG in regard to those doses. In addition, the working group believes that there will be some additional information coming out from an alternative product in the near future that will also support those claims.

Dr. Marcy said he thought most Americans contracting rabies would acquire it overseas. He was very concerned last year about the statement that post-exposure prophylaxis is a medical urgency not a medical emergency. This has implications for those who are traveling because a travel insurance company has to expend $50,000 to fly somebody back to the US. Otherwise they have to get nerve tissue vaccine and no rabies immune globulin is available.

Dr. Rupprecht clarified that this was a statement inserted in 2008 after the ACIP review and vote; however, the working group will be considering additional language based upon updating the recommendations. The implicit rationale behind that was to allow time for risk assessments as opposed to everybody receiving prophylaxis or any of the other strategies currently used. It is not clear whether prophylaxis is needed at all. The working group will consider alternative strategies.

Dr. Lett inquired as to whether the FDA would consider amending the package insert language to describe the ACIP recommendation or endorsement, given that it already states that the ACIP has recommended a schedule that is one dose different from the WHO's schedule.

Dr. Baylor (FDA) responded that they would not do so unless the manufacturers submit data supporting the 4-dose regimen. It has been the FDA's practice to drop the ACIP recommendations from the label if they are inconsistent with the data FDA has reviewed to support the indication.

Dr. Duchin (NACCHO) agreed with the recommendation put forward. While he thought the evidence presented was convincing, the discrepancy between the package label and the ACIP recommendation would likely create problems with respect to implementation. Therefore, he urged everyone to reconcile this before creating a final statement.

Dr. Decker (sanofi pasteur) indicated that to satisfy FDA requirements to effectuate a label change, sanofi pasteur would first have to decide that they wanted a label change. That is not a foregone conclusion because it was not clear to them whether dropping the 5$^{th}$ dose was prudent. Assuming they did agree, they would first have to determine what such a study would cost, and they would have to prioritize it. Many good projects are already going undone due to the lack of resources. This label change effort would delay or defer something else, so they would have to weigh whether it is important to do. They only engage in about half of the



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projects each year that would like to already. If it did become prioritized, it would take approximately three years from the day the decision is made to go forward to the day that there is actually a decision from the FDA about a label change. This is a highly effective vaccine for an otherwise fatal disease. There may be a difference in antibody levels downstream. The literature shows instances of people developing rabies years after exposure who are not prophylaxed, so it is not clear they would answer the question that a critic might raise, which is the most important aspect in determining whether someone has zero risk of disease later.

Dr. Rupprecht acknowledged that there are fundamental fears about rabies that the working group appreciates. He reiterated that there was none of the international SMEs consulted, including the SMEs from Novartis and sanofi pasteur, provided any data demonstrating the utility of 5 versus 4 doses. There are differences between administrative and regulatory issues, the evidence based upon the literature, what is understood about the disease, basic immunogenicity, the way forward for additional manufacturers and additional products, et cetera on the basis of the evidence. The working group does not wish to prolong the discussion about a conflict between the evidence and the label because these are two different arenas.

Clement Lewin (Novartis Vaccines) indicated that Dr. Rupprecht was correct on subject matter experts who were consulted. It was his understanding that the SMEs communicated that there are no data to support 4 doses. There is clinical data to support 5 doses. Novartis does not disagree with the scientific conclusions that Dr. Rupprecht shared; however, in practical terms, this will create an issue for practitioners because the ACIP recommendation will conflict with the product insert.

Dr. Chilton pointed out that there is a conflict in the labeling and in the recently published statement for rotavirus vaccine in the age at last dose, so there is precedent for differences between the FDA and the ACIP recommendations.

Having been on the Anthrax Working Group, Dr. Morse pointed out that it took years to reduce the number of doses based on clinical data. It seemed as though there was strong evidence for 4 doses, but without the clinical data, it will take numerous years to make this change. One of the issues driving this discussion was the potential for a vaccine shortage. He requested that the vaccine manufacturers comment on supply.

Joel Ward (UCLA) noted that over the decades, this committee had faced an issue many times in which there has been a discrepancy in a published precedent or the data used to develop the drug inserts. ACIP should develop some policy issues regarding how to deal with these generically.

With regard to supply, Clement Lewin (Novartis Vaccines) indicated that based on current projects and forecasts for demands in the marketplace, Novartis Vaccines believes that it can supply enough vaccine for pre-exposure prophylaxis and for selected first responders (e.g., veterinarians, students, animal control officers, et cetera). Novartis is currently not supplying for travelers for pre-exposure prophylaxis, but continues to evaluate the situation. In terms of long-term supplies, Novartis is upgrading its facility in Marburg, Germany. The new building is scheduled to be complete in 2010 and to start production in 2011, which will result in a significant increase in capacity.

Dr. Rupprecht indicated that there is one update for pre-exposure for travelers. Currently, individuals posted in enzootic rabies countries, because of the lack of pre-exposure vaccinations, are recommended to receive whatever local vaccines are available even if they



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are not on the ACIP list or licensed in this country rather than receive no pre-exposure whatsoever.

Phil Hosbach (sanofi pasteur) indicated that sanofi pasteur is currently providing post-exposure product only. They have made public announcements that their facility is in the midst of a planned shut down for upgrades. They have built a stockpile, but are reaching the end of it due to ins and outs of the other manufacturer. They are currently at post-exposure doses, with state health department assistance and screening only. The new facility is expected to be on-line and approved by the FDA in the second half of 2009.

Dr. Decker (sanofi pasteur) added that in a shortage situation there is substantially more flexibility in how sanofi pasteur responds. A deviation from the package insert can be handled much more easily in the context of a temporary shortage recommendation. They cannot handle a permanent ACIP change that conflicts with the package insert.

Dr. Gellin recognized that off label recommendations in this medical environment is not a simple thing to do. As part of the body of evidence to make the case for dropping the fifth dose, health economics was addressed. There is no question that less of something with an equal result is beneficial. He agreed that they should also develop a general framework for dealing with these issues regardless of the topic.

Dr. Pickering reminded everyone that the FDA licenses vaccines and ACIP recommends those vaccines without typically wandering too far from the FDA licensures. He said he felt very uncomfortable in doing that, particularly for large population recommendations. With smaller issues such as in sub-groups of travelers and post-exposure to hepatitis A, there have been differences from the labels. However, as a general rule it is not a good idea for ACIP to differ from FDA indications for vaccines.

Dr. Judson pointed out that one problem was that pharmaceutical manufacturers would never have as a high priority determining the minimal effective dose of anything. If ACIP had to rely upon manufacturers to go back to the FDA with an application to change the label to lower the dose to a new minimal effective does, it was not likely to happen. This leaves ACIP either to go against the label or go against the FDA to meet the practicalities of limited supply.

Clement Lewin (Novartis Vaccines) responded that Novartis was not declining to move forward with a label change request because they would lose money. They view rabies vaccine and the investment in terms of the cost per series and the value that they create by immunizing. Clearly, there is an advantage to fewer doses and there are actually savings that might be recouped. The challenge and concern is that there is a significant investment in capacity, as well as competing priorities. Given that the investments that both companies have made, it appears that the supply will be sufficient.

Dr. Friedland (GlaxoSmithKline) commented on the statement about manufacturers not being interested in establishing a minimum effective dose in that he though it was an over-generalization and was not accurate. Speaking for his company and others, they are interested in finding vaccines that prevent and eliminate disease for children and all age ranges. The approach is to find the proper dose.

Dr. Marcy emphasized that this issue was going to continue to arise. Last October, they were informed that there was a reduction in the dose of rotavirus vaccine with RotaTeq® from 3 to 2



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doses based on South American studies. It was his understanding that there are also on-going studies with HPV vaccine to support moving to 2 instead of 3 doses.

Dr. Katz indicated that there was no difference in the dosimetry of rabies vaccine for a 2-month old who is exposed versus a 200-pound adult. Speaking from personal experience, his granddaughter was exposed at 2 months to a rabid bat that the cat brought in the house. She received the full series of rabies vaccine (5 doses). He was convinced that if anyone conducted antibody studies, they could save vaccine also by having reduced doses depending on size and weight similar to other products. Influenza vaccine is given at a reduced dose to children in the first years of life. Perhaps the same could be done with rabies.

Dr. Decker (sanofi pasteur) indicated that manufacturers conduct studies to develop improved versions of products, with the intent to get the license changed. The problem was that the rabies vaccine process was flowing backwards with the functional indication of a recommendation without any studies. He emphasized that he totally agreed with Dr. Rupprecht's review of the literature as to what would be clinically reasonable. If someone asked him as a clinician, this would be his response. However, in the regulatory environment changing a package insert is a major endeavor that will take years. The change will not occur without an explicit study demonstrating satisfactory criteria on a pre-agreed endpoint that the change is adequate. It is not clear whether such a study could be conducted other than in Thailand, India, or elsewhere where rabies is so endemic an experiment could be conducted among people who have been bitten by rabid animals.

Dr. Baylor noted that moving forward with newer vaccines, the doses can be optimized at that point. It is very difficult to go backwards with old vaccines.

Dr. Cieslak pointed out that all of these concerns have been discussed in the working group, which has come far in terms of reviewing the data. The working group members believe the data are compelling and feel an obligation to place them before the committee in June 2009.

## Update: Pertussis Vaccines Workgroup

**Mark Sawyer, MD**
**University of California, San Diego**
**Chair, ACIP Pertussis Vaccines Working Group**

Dr. Sawyer indicated that his sole purpose was to introduce the new Pertussis Vaccines Workgroup, which is in the process of begin formed. The background is that pertussis remains the least well-controlled reportable bacterial vaccine-preventable disease in the US. There is a series of ACIP statements for infants and young children, adolescents, adults, and pregnant and postpartum women that refer to use of various products with pertussis vaccine in them.

The Pertussis Vaccines Workgroup's terms of reference are to: 1) review existing statements on infants and young children (1997), adolescents (2006), adults (2006), and pregnant and postpartum women and their infants (2008) and consolidate these into a single statement; and in the process of doing so 2) review new data on Tdap, including effectiveness of ACIP recommendations with respect to uptake of recommendations and barriers to uptake, interval between Td booster and Tdap, reactogenicity, use of vaccine for pregnant and breastfeeding women, and vaccinated healthcare workers and the need for post-exposure prophylaxis.



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The workgroup includes the following members and continues to take suggestions for any additions: ACIP: Mark Sawyer (Chair), Carol Baker, Lance Chilton; CDC: Jennifer Liang (Lead), Nancy Messonnier, Thomas Clark, Stacey Martin, Tami Skoff, Lucia Tondella, William Atkinson (ISD), Beth Hibbs (ISO); Liaisons: Richard Beigi (ACOG), Geoffrey Evans (HRSA), Theresa Finn (FDA), Stanley Gall (ACOG), Christine Hahn (CSTE), Harry Keyserling (SHEA), Tom Koinis (AAFP), Sarah Long (AAP); and Consultants: Scott Halperin (Canada), Bruce Meade.

## Pnuemococcal Vaccines

### Use of PPSV23 for Prevention of Pneumococcal Pneumonia During an Influenza Pandemic

**Matthew R. Moore, MD, MPH**
**Commander, USPHS**
**CDC / CCID / NCIRD / RDB**

During this session, Dr. Moore discussed the use of PPV23 for prevention of pneumococcal pneumonia during an influenza pandemic, specifically focusing on the role of this vaccine in critical infrastructure personnel. To set the stage, he explained that he would present a model used to estimate the burden of PPV23-type pneumococcal pneumonia among critical infrastructure personnel during an influenza pandemic and that, after his presentation, he would pause to answer questions about the specifics of the model. Next, Dr. Messonnier would present a cost-effectiveness model of PPV23 use in this same population during a pandemic.

The reason this issue is important is because it is known that pandemic influenza infection predisposes individuals to secondary bacterial pneumonia [Brundage, Lancet Infect Dis 2006]. Also known is that *Streptococcus pneumoniae* (pneumococcus) was identified in approximately 50% of secondary bacterial pneumonia cases and about 20% of deaths in 1918 [Soper, JAMA 1918; Morens, JID 2008]. Currently recommended pneumococcal vaccines were not available during any of the 20$^{th}$ Century influenza pandemics. Therefore, pneumococcal vaccines may play a role in reducing morbidity and mortality during the next pandemic.

The ACIP Pneumococcal Working Group considered three policy options regarding this issue. The first was to assume that a pandemic will occur in the near future, and to expand the current recommendations for use of PPV23 as soon as possible. This posed some challenges such as thinking through the target groups that would be involved and the benefit in vaccinating those target groups, the programmatic challenges of expanding target groups, and concerns about re-vaccination and the potential issue of hyporesponsiveness. The second option recognized by the working group was to encourage implementation of the current recommendations [http://www.pandemicflu.gov/vaccine/pneumococcal.html], which has essentially been done. This document is posted on the influenza website, which advocates for continuing to use polysaccharide vaccine according to the current recommendations. The third option, the topic of this discussion, is to administer PPV23 to critical infrastructure personnel targeted for pre-pandemic influenza vaccine when a pandemic is actually declared. This has several advantages. The first is that this is a relatively young, healthy population that is likely to respond robustly to PPV23. Programmatic efficiency would also result from administering pre-pandemic influenza vaccine. In addition, this particular approach fulfills the planning objective of maintaining critical response functions during a pandemic.



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Dr. Moore stressed that he wanted to be clear and careful about distinguishing between pandemic influenza vaccine and pre-pandemic influenza vaccine. Pandemic influenza vaccine is manufactured after sustained person-to-person transmission has been identified. It is targeted against a novel influenza A virus, which may not necessarily be H5N1. The objective of the pandemic influenza vaccine program is to minimize morbidity and mortality by providing an opportunity for the entire US population to be vaccinated. Pre-pandemic influenza vaccine is manufactured and stockpiled before a pandemic begins, and is targeted against strains that have pandemic potential, such as H5N1. Currently, HHS's goal is to stockpile 20 million 2-dose regimens with an objective to maintain critical response capabilities during a pandemic rather than vaccinating the entire country. It is really this particular program with which PPV23 would be coupled, and it is these 20 million individuals who the working group wanted the committee to consider vaccinating with PPV23.

To better understand how great the problem might be during a pandemic, the working group took a relatively simple approach to estimate the burden of pandemic-associated pneumococcal pneumonia among these 20 million critical infrastructure personnel. The following method was used to make this estimation:

20 million personnel
X
influenza attack rate
X
secondary bacterial pneumonia
attack rate
X
% due to 23 pneumococcal serotypes
included in PPV23
=
expected cases of PPV23-type
pneumococcal pneumonia
attributable to influenza

This is a multiplicative rate-based model. The assumptions, which were many, were based whenever possible upon the published literature and the current pandemic plan. The working group considered "best case," "worst case," and "base case" scenarios that incorporate the lowest morbidity and mortality, the highest morbidity and mortality, and estimates in between these two extremes, respectively. Then they had to factor in the potential effects of several interventions that were not available during previous pandemics (e.g., antiviral prophylaxis and treatment, non-pharmaceutical interventions, pre-pandemic influenza vaccine, and reduced incidence of pneumococcal pneumonia as a result of routine childhood use of pneumococcal conjugate vaccine (PCV7). Some programmatic assumptions also had to be made. The first was that a pre-pandemic program will actually be implemented at the time a pandemic is declared. It was also assumed that this program would target 20 million critical infrastructure personnel (e.g., healthcare workers, water and electrical workers, and other individuals). Also assumed was that all 20 million of these individuals would be between the ages of 20 and 64 years, and that two doses of pre-pandemic influenza vaccine would be administered to all 20 million personnel.



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In addition, it was assumed that the program would allow for simultaneous administration of PPV23 to each of those individuals as they arrived for their first dose of pre-pandemic vaccine. Decisions also had to be made about the epidemiology of pandemic influenza, assuming that in the absence of any of the interventions available in the 20th Century that attack rates of influenza would be similar to that of previous pandemics. It was also assumed that attack rates of pandemic influenza may be reduced through the use of anti-viral prophylaxis, non-pharmaceutical interventions, and pre-pandemic influenza vaccine. Finally, the assumption was made that reductions in the influenza attack rates would be proportionate to the effectiveness of the interventions themselves and the proportion of the target population that actually receives them. That is, if a particular intervention is 50% effective for an individual and if 50% of the population receives that intervention, the population would experience a 25% reduction, in relative terms, in the influenza attack rate.

Virtually of the assumptions were derived from either the published literature or existing pandemic plans rather than expert opinion. Assumptions were made about the effectiveness of antiviral prophylaxis, coverage with antiviral prophylaxis, the effectiveness of pre-pandemic vaccine, and coverage with pre-pandemic vaccine. Assumptions also had to be made about secondary pneumococcal pneumonia during an influenza pandemic.

Thus, it was assumed that in the absence of interventions, attack rates of secondary pneumococcal pneumonia would be similar to those in previous pandemics. Also assumed was that attack rates of secondary pneumococcal pneumonia might be reduced through the use of antiviral treatment of persons who have pandemic influenza because it is known that people who are treated with antivirals and have seasonal influenza infection have a reduced risk of lower respiratory tract complications that require antibiotics. It was also assumed that attack rates of secondary pneumococcal pneumonia would be reduced proportionate to reductions in pneumococcal pneumonia observed since the introduction of 7-valent conjugate vaccine, and that the distribution of serotypes causing secondary pneumococcal pneumonia would be similar to the distribution of serotypes causing invasive pneumococcal pneumonia in 2007.

To estimate secondary bacterial pneumonia attack rates in the presence and absence of treatment with neuraminidase inhibitors for 20 million critical infrastructure personnel, for the base case it was assumed that 15% of individuals who develop pandemic influenza infection will go on to develop secondary bacterial pneumonia and about half of those cases will be caused by pneumococcus. Reductions were incorporated related to the introduction of PCV7 in children and herd effects in adults. Also assumed was that the proportion of PPV23 serotypes would be similar to that observed in 2007 (~78%).

The next step was to enter all of these assumptions into a software package that allowed them to do thousands of simulations of various combinations of the different assumptions to better understand what is really the most likely situation to occur given this very broad range of assumptions. Most of the estimates are below 100,000 cases. That is, it seems unlikely that there would be more than 100,000 cases of PPV23 type pneumonia during an influenza pandemic in the population of 20 million critical infrastructure personnel. The most likely estimate was approximately 35,000 cases of PPV23 type pneumococcal pneumonia in this population of 20 million critical infrastructure personnel. Beginning with that number of 35,000 cases, consideration was given to how much of that could actually be prevented with polysaccharide vaccine. This raised another tricky question with respect to what should be



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assumed about pneumococcal vaccine effectiveness in this population of young, healthy individuals who are exposed to pandemic influenza infection.

The working group reviewed the literature, finding that there really are no data on the effectiveness of this formulation of this vaccine for this population (e.g., young, healthy, but high-risk) during an influenza pandemic. Going back approximately 30 years, studies of PPV14 in South African gold miners suggest 76% efficacy against vaccine-type pneumonia. Studies of PPV23 in the elderly suggest 50-85% effectiveness against vaccine-type bacteremia, but not necessarily pneumonia. Thus, the working group decided to assume a very broad range of effectiveness from 20% to 80% and applied this to all vaccine type pneumococcal pneumonia (e.g., invasive and non-invasive); that is, they did not distinguish between bacteremic and non-bacteremic pneumococcal pneumonia.

With regard to the number of 20-64 year-olds needed to vaccinate to prevent a case of vaccine-type pneumococcal pneumonia is as follows:

| **Age Group, Years** | **Assumed PPV23 Vaccine Effectiveness** | | |
|---|---|---|---|
| | **20** | **50** | **80** |
| 20-49 | 3,749 | 1,499 | 937 |
| 50-64 | 5,644 | 2,258 | 1,411 |

This assumes base case model-derived estimates of 31,903 total cases of pneumococcal pneumonia, and that approximately 75% to 80% were caused by PPV23 types. Even with a low vaccine effectiveness of approximately 20%, approximately 3,000 to 6,000 individuals would need to be vaccinated to prevent a single case of PPV23 type pneumonia. Obviously, as vaccine effectiveness increases, the number needed to vaccinate decreases. Therefore, if this vaccine were 80% effective in this young, healthy population that is heavily exposed to influenza infection, the number needed to vaccinate would be approximately 1,000 to 1,500. This was somewhat of a surprise to the working group, as they were not so optimistic that the numbers needed to vaccinate were going to be so low. However, this may have to do with how this phenomenon of secondary pneumoccocal pneumonia is thought about. If beginning with a population that has a pandemic influenza attack rate of between 20% to 30%, even after incorporating all of the other interventions, the risk to this population of developing secondary pneumococcal pneumonia is sufficiently high that the numbers needed to vaccinate are actually lower than expected.

The working group went on to estimate the preventable burden of PPV23-type pneumonia in the absence of all influenza interventions (e.g., antiviral prophylaxis or treatment, non-pharmaceutical interventions, or pre-pandemic vaccine). Using the same range (20% to 80%), the working group estimated the number of individual cases that might be prevented (~5,000 to 20,000), hospitalizations that could be prevented (~700 to 3,000) and deaths that could be prevented (~300 to 1,100).

With respect to what is driving these estimates, the estimate of pre-pandemic influenza vaccine effectiveness is really the most important driver. As that effectiveness increases, the likely benefit of PPV23 decreases considerably. Similarly, if the secondary bacterial pneumonia attack rate is higher than the 15% estimated, an increased benefit of polysaccharide vaccine would be expected. If the proportion of those cases caused by pneumococcus is higher, a modestly increased benefit would be expected of polysaccharide vaccine. If the influenza attack



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rate is higher for any reason, that increases the benefit of PPV23. Somewhat to the working group's surprise pneumococcal polysaccharide vaccine effectiveness is not the most important driver.

With regard to whether there could be a role for PCV13, which is under development. Licensure is being sought for use in children, but it may be licensed for adults at some point as well. This same model can be used to estimate the burden of PCV13 type pneumonia.

In conclusion, the working group thinks that a rate-based model can be used to estimate the burden of pneumococcal pneumonia during an influenza pandemic. The group's best estimate is that about 35,000 cases of secondary pneumococcal pneumonia caused by these polysaccharide vaccine types could occur among 20 million critical infrastructure personnel during the next influenza pandemic. The use of polysaccharide vaccine during a pandemic really could have substantial public health benefits, especially if the influenza interventions are ineffective or if they are unavailable, and even with relatively low polysaccharide vaccine effectiveness.

## Discussion

Joel Ward (UCLA) pointed out that one important factor not discussed was that those individuals who have pneumonia and high fever presumed to be due to influenza with respect to what proportion of those will have received antibiotics, in which case a significant proportion of potential pneumoccocal disease will have been treated by antibiotic prophylaxis and will not occur.

Dr. Moore responded that this model has also been used to estimate the number and types of courses of anti-bacterials that may be necessary during an influenza pandemic. However, consideration has not been give to what would occur if everyone was simply treated with antibiotic versus being vaccinated.

Dr. Cieslak requested clarity on where the 50% for *Streptococcus pneumoniae* causing secondary bacterial pneumonia came from. Based on the table presented in the pre-conference materials, this appeared to be more in the range of 20%. In addition, he wondered about serotypes, because his understanding of the pathogenesis had something to do with specific receptors induced on respiratory epithelium and the possibility that there is strong serotype specificity. Serotypes I, II, III, and IV are mentioned, but he was trying to make a connection between the 23 in the vaccine.

Dr. Moore replied that this may have been with a different serotyping scheme with respect to the pathogenesis of individual serotypes being more likely to cause pneumonia than others. The currently available epidemiology was used on invasive pnumococcal pneumonia and assumed that it was not really the serotype that made a difference. However, it may be that the individual influenza strain makes a difference. There is some evidence that the neuraminidase activity in individual influenza strains may make a difference in terms of the likelihood of developing secondary bacterial pneumonia of any kind. One of the assumptions is that the strains that would cause secondary bacterial pneumonia in a pandemic setting are the same strains currently circulating in communities throughout the US. In terms of the determination to use 50% versus 20%, a judgment call had to be made in examining the different sources of information for the proportion of secondary bacterial pneumonia cases causes by pneumococcus, taking into consideration that some of the studies involved upper respiratory tract specimens only, some were from autopsy studies, and others were from sterile sites only.



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Dr. Duchin (NACCHO) inquired as to whether it was assumed that the vaccine would be equally protective against bacteremic and non-bacteremic pneumonia.

Dr. Moore responded that they assumed three point estimates for effectiveness against the combination of bacteremic and non-bactermic pneumonia. One way to think about that is that it is thought that roughly 30% of all pneumococcal pneumonia is bacteremic. If the vaccine effectiveness against that 30% is similar (~50% to 85% range) to that of PPV23 against bacteremia in the elderly, but there was essentially no effectiveness against non-bacteremic pneumonia, then the 80% effectiveness against 30% of diseases is essentially an overall effectiveness of 24%. Taking into account the broad range of 20% to 80% would account for the issue of bactermic versus non-bacteremic disease.

Regarding the estimation of *Streptococcus pneumoniae* (S. pneumoniae) as a cause of pneumonia following influenza, Dr. Englund pointed out that over the past few years there has been a major predominance of *Staphylococcus aureus* (S. aureus) as opposed to S. pneumoniae. This may be related to high rates of pneumococcal vaccine coverage in the young, which may impact the nasal coverage in older individuals (e.g., over 21 years of age). She expressed concern that the pnuemococcal causes were overestimated.

Dr. Moore responded that this was a legitimate concern that the group had discussed extensively. The problem is that there is no population-based data on the incidence of *Staphylococcus aureus* (*S. aureus*) pneumonia. There is great concern that methicillin-resistant (MRSA) *S. aureus* in particular is more common; however, the group used a very broad sensitivity analysis that incorporated pneumococcal estimates from as low as 10% to as high as 80%. It does not make that much of a difference, but when it comes to making planning decisions, especially with regard to anti-bacterials, careful thought has been given to the *S. aureus* situation.

Dr. Meissner noted that the efficacy of anti-viral therapy assumption used of 65% to 70% might not be characteristic of a pandemic strain. If the efficacy rate were lower, that would lead to greater benefit from the vaccine.

Dr. Moore responded that essentially anything that increases the risk of pandemic influenza increases the benefit of PPV23.

If there is high efficacy against the pandemic influenza strain in this population of 20 million such that they acquire very little influenza, Dr. Morse pointed out that use of the pneumococcal vaccine will not prevent very much disease because this population does not have to get influenza to have the secondary pneumonia. Knowing that, would this formula be used for another population who does not receive the pandemic influenza vaccine? While it is easier to administer both at the same time, it may be wasted in terms of preventing very much disease. He wondered whether the model took this into consideration.

Dr. Moore responded that this was approached from the standpoint of the objective of maintaining critical response functions early in a pandemic. Therefore, this group would not yet have had the opportunity to receive pandemic vaccine because it would not yet be available.

Dr. Cieslak asked what the vaccine efficacy was against pre-pandemic influenza. Dr. Moore responded that this was 75%.



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Dr. Duchin (NACCHO) noted that the terminology of "pandemic influenza" was based on a 1918-like scenario. He wondered whether this model would apply equally well to a 1957- or 1968-like pandemic or if these seemed to have difference propensity to be associated with secondary bacterial pneumonia.

Dr. Moore responded that the group essentially did not distinguish between the three pandemics. All of the data that could be found pertaining to all three pandemics were combined. The influenza attack rates, for example, are an amalgam of 1918, 1957, and 1968 with no particular weighting. The one area where this may come into play is that for a variety of reasons, there are actually more data from 1918 than for 1957 or 1968. It is true that the likelihood of secondary pneumonia varied in the three scenarios, which pertained to the issue of where all of the assumptions came from. To keep the meeting moving forward, he offered to go over these in more detail off-line with anyone interested.

Dr. Judson thought the major problem was that the assumptions used for the likelihood of an epidemic (e.g., which strain it would be, pathogenicity, secondary infections) keep changing / improving as knowledge improves. Originally everyone assumed that 1918 was the worst influenza virus anyone had ever observed; however, there is a fair amount of evidence to suggest that it was not necessarily a more pathogenic virus, spread more rapidly, and / or had a higher attack rate. Instead, there were no antibiotics and no one knew what was occurring. It appears that a large proportion of the deaths were later deaths owing to secondary bacterial infections. Over the course of the 20$^{th}$ Century, nature has shown that successful pandemics of influenza have become less fatal, with lower mortality rates. Everyone was completely thrown off by Swine Flu, which turned out not to be a pandemic at all. One reason for the lower pathogenicity or death rates in 1957 and 1968 could well have been that antibiotics were given as soon as someone presented with a febrile respiratory illness, which is continued currently to some extent. He did not believe that trying to equate H5N1 with 1918 was justified scientifically. In fact, that might be the least likely influenza virus to cause a pandemic because it has had 15 years to do so. Many of these assumptions are based on facts that have changed.

Dr. Moore responded that pandemic preparedness is a major priority for NCIRD and for CDC. The data referred to are not all from 1918. Some of it is from 1957 and 1968, while some of it is from as recently as the last few months in terms of analyzing autopsy specimens from those pandemics. He thought it was very important to make a decision about this vaccine, and this modeling was the way that they had tried to "tee up" the question for the full ACIP. Not only did they need to make a decision, a decision was going to be made regardless of whether it was based on data. While these are the data currently available, as data changes over time they can be incorporated into the model.

Dr. Judson pointed out that the ability to detect, type, and sequence new viruses had become far superior to what it had been in the past. If a real new threat evolved, there would likely be much more time to respond to it. Moreover, the vaccine development research has reduced the cycle and uncertainty for vaccine development from 6 to 8 months to approximately 2 weeks, which would also affect how secondary or indirect ways of preventing influenza mortality might be handled.



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## An Economic Analysis for Use of PPSV23 for Prevention of Pneumococcal Pneumonia during an Influenza Pandemic

**Mark L. Messonnier, PhD, MS**
**CDC / CCID / NCIRD / ISD**

Dr. Messonnier indicated that this presentation had gone through the process of review as put forth in the guidance for economic studies to be presented to the ACIP that was adopted in 2007 by the ACIP and implemented beginning in 2008. There were no conflicts of interest among any of the study participants.

The study question was: What is the cost-effectiveness of using 23-valent pneumococcal polysaccharide vaccine (PPV23) during an influenza pandemic to prevent secondary pneumococcal pneumonia (SPP) caused by PPV23 serotypes among members of priority target populations responsible for fulfilling critical pandemic functions in the United States? A direct medical cost perspective was taken in this review.

The intervention strategy was the use of PPV23 for prevention of PPV23-type SPP in adult target populations responsible for fulfilling critical functions during an influenza pandemic (N=20million). The intervention time frame was one year, a single pandemic occurrence. The analytic horizon included the remaining life expectancy of the people in the target populations. None of the effects of PPV23 beyond this pandemic year were included. Discounting all future outcomes was at a 3% rate. A cost-effectiveness analysis (CEA) was used, and as a summary measure, the cost-effectiveness ratios (CER) were used. The basic construction of the cost effectiveness ratio is the net cost divided by the outcomes of interest. In this case, this was as follows:

$$\frac{\text{(vaccine cost + administration cost) – (cost of illness averted by vaccination)}}{\text{number of outcomes of interest}}$$

Health outcomes included SPP health outcomes (e.g., cases, number of hospitalizations, deaths, life-years saved (LYS), and discounted LYS) all from the PPV23-type infections. The epidemiological model was calculated as follows:

Cases of SPP attributable to influenza by age in target populations
=
Target population by age
X
Age-specific influenza attack rate
X
Age-specific secondary bacterial pneumonia attack rate
X
Age-specific percent due to PPV23-type pneumococcus
X
Age-specific reductions attributable to currently recommended interventions
(antivirals, nonpharmaceutical interventions, influenza and pneumococcal vaccines)
[calculations to this point represent baseline strategy]
X
Age-specific reductions attributable to use of PPV23 in target populations
[these calculations represent intervention effects]



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The cost inputs used included hospitalization, outpatient, and program costs. These are taken from the published literature and publicly available resources, such as the DFC contract price list:

## Methods: Cost Inputs

| Cost Category | Age | Base | Lower[1] | Upper | Base Source |
|---|---|---|---|---|---|
| **Hospitalized pneumonia** | | | | | |
| | 15 to <45 | $ 9,148 | $ 7,319 | $ 10,978 | Ray, et al.[3] |
| | 45 to <65 | $ 10,389 | $ 8,311 | $ 12,467 | |
| **Outpatient[2]** | | | | | |
| | 20-64 yrs | $ 272 | $ 217 | $ 326 | Meltzer, et al.[4] |
| **Program cost** | | | | | |
| | Vaccine | $ 18 | $ 15 | $ 20 | CDC VFC Online Vaccine Price List[5] |
| | Administration | $ 12 | $ - | $ 20 | Zhou, et al.[6] |
| | Wastage | 0.05 | 0 | 0.1 | Assumed |

[1] Lower and upper bound on dollars values assumed to be 80% and 120% of base case, respectively
[2] Calculated using averages or "most likely" in Meltzer et al. Table 3; direct costs only
[3] Ray, et al., PIDJ, 25:6(June 2006) 494-501
[4] Meltzer, et al., EID 5:5 1999
[5] http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm; accessed 2/5/09
[6] Zhou et al., Pediatrics. 2002;110:653-661; J Infect Dis. 2004;189:S131-S145.

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Three types of sensitivity analyses are conducted on cost-effectiveness ratios: 1) a simulation to estimate the values of the cost-effectiveness ratios given the input variables used and distributions assumed for these; 2) a ranking of the variables that affect the cost-effectiveness ratio; and 3) estimation in the absence of any and the absence of all non-PPV23 interventions that are included in the model.

Health outcomes were as follows:

| Health Outcome | Outcome | 95% CL |
|---|---|---|
| PPV23-type Pneumococcal pneumonia cases prevented | 12,673 | (8,927-91,863) |
| Hospitalizations prevented | 1,827 | (842-8,745) |
| Deaths prevented | 700 | (327-3,323) |
| Years of Life saved | 27,280 | (11,862-133,675) |
| Discounted Years of Life saved | 15,773 | (8,273-82,927) |



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Cost outcomes included the following, based on base case values for input variables:

| Cost Outcomes | | Dollars |
|---|---|---|
| Cost of the Program | $ | 608,295,000 |
| Medical costs saved | $ | 19,657,861 |
| Net Cost | $ | 588,637,139 |

Summary measures included the following

| Health Outcome | | CE Ratio | 95% CL |
|---|---|---|---|
| PPV23-type Pneumococcal pneumonia cases prevented | $ | 46,449 | ($4,860 - $65,098) |
| Hospitalizations prevented | $ | 322,204 | ($51,301 - $685,553) |
| Deaths prevented | $ | 840,741 | ($135,875 - $1,771,196) |
| Years of Life saved | $ | 21,577 | ($3,376 - $47,758) |
| Discounted Years of Life saved | $ | 37,320 | ($5,865 - $80,359) |

Of the simulated cost-effectiveness ratios, 95% fall within a range of $6,000 to $80,000 per discounted life year saved. In terms of the relative magnitude effects of changing the input variables on the output variables (e.g., cost-effectiveness ratio), bacterial pneumonia attack rate (20-49), pre-pandemic vaccine effectiveness (20-49), and the PPV23-type infections (20-49) were the top three variables that had the most-effect on the estimated cost-effectiveness ratio.

In terms of zero effect for non-PPV23 interventions that are included as part of the model, if it assumed that there is zero effectiveness of prophylactic use of neuraminidase inhibitors, the result is $28,954 / Discounted LYS. Reduction in the influenza attack rate from non-pharmaceutical interventions is $28,954 / Discounted LYS. If pre-pandemic flu vaccine efficacy is zero, there is a greatly decreased Discounted LYS of $8,395. Reduction in SPP from treatment with neuraminidase inhibitors among those infected results in $24,593 / Discounted LYS. If all non-PPV23 are completely ineffective, the result is $2,396 / Discounted LYS. For comparison, which refers to the base case results, the result is $37,320 / Discounted LYS.

Limitations of the study are that only direct medical costs are included. Productivity losses averted, direct non-medical costs, and other indirect costs are not included. The effects of PPV23 beyond its effectiveness in a pandemic even are not included. Adverse events that may occur from vaccination are not included. The assumption of linkage to pre-pandemic influenza vaccination is also a limitation. In terms of the relation of this analysis to other studies, there are no other studies of cost-effectiveness of vaccine interventions in this population.

With respect to CDC peer-reviewers' comments, two peer reviewers found no substantive problems with the methods or results. It was suggested that some additional sensitivity analyses be conducted with respect to the impact of failure of other interventions. Also noted was that the cost of stockpiling is not included in the analysis. In addition, it was pointed out that the value of use changes. This may vary during a pandemic versus an ordinary season.



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## Discussion

It appeared to Dr. Chilton that this analysis was based on 700 deaths prevented out of 20 million people, or an incidence of death of 3.5 x $10^{-3}$ percent, which is pretty low. Thus, the sensitivity of the model in determination of the value of the 700 lives is fairly high. In addition, he wondered whether giving PPV23 to these healthy young people would be borrowing from children. If indeed there is a hyporesponsiveness induced by PPV23 for those who receive the vaccine, it may be less effective when they turn 65 and are supposed to receive it anyway.

Dr. Messonnier responded that the issue of hyporesponsiveness was one that the committee had discussed in the past. There are questions about exactly how relevant that issue is for routine vaccination. He thought vaccination of critical infrastructure personnel was a fundamentally different situation in that they were considering the vaccination of individuals who would be responsible for keeping society functioning during a pandemic versus thinking about whether to add additional indications for those under the age of 65.

Dr. Chilton wondered then whether they were considering the wrong end point. If the end point was really keeping important workers at work during a pandemic, perhaps they should be taking the value of that into consideration rather than the value of their lives.

Dr. Messonnier replied that this model did not incorporate those types of costs, but if this was done, it would actually reduce the cost-effectiveness ratio and make things look even more favorable than they already did.

In response to the hyporesponsiveness question, John Grabenstein (Merck Vaccines and Infectious Diseases) indicated that they had shown to the Pneumococcal Working Group a few months ago the responses to a third dose of PNEUMOVAX® 23 in 70- and 80-year old individuals. The responses to the third dose have been vigorous. He indicated that he would be happy to present numbers to the full ACIP at any time.

Dr. Paradiso (Wyeth) wondered whether consideration had been given to a situation in which the pre-pandemic vaccine was not available (e.g., cannot make it or cannot make enough); whereas pneumococcal vaccines are already available. With that in mind, he also wondered whether they modeled no influenza and just polysaccharide. The real value of vaccinating this group beyond just vaccinating them was the societal benefit that would be gained, which is a very important part of the economic analysis.

Dr. Messonnier responded that a broad sensitivity analysis was run with pre-pandemic vaccine. If pre-pandemic vaccine is simply not available or it is available but not effective, the cost-effectiveness ratios decrease and the burden of pnuemococcal disease increases.

Joel Ward (UCLA) stressed that the issue of antibiotic use was profound. In 1918 there were no antibiotics to be used. At best in 1957 approximately 10,000 units were given of various forms of antibiotics. If surveys were conducted currently, the findings would likely be that 90% of people are given broad spectrum antibiotics and that is probably an important reason for gram negative pathogens. The vaccine trials conducted that showed a reduction in pneumonia, primarily in children, were often conducted in populations where antibiotic use was not as profound as in developed societies. The benefit of the vaccine may be prolonged over 5 to 10 years, in which case there is a benefit to society by virtue of immunizing a large number of



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adults. The analysis being done is very difficult, given that the gain that they were attempting to measure was secondary versus primary.

Dr. Poland (ACP) wondered whether the economic analysis used the proportion of invasive pneumococcal infection.

Dr. Messonnier responded that it is known from recent studies in elderly populations who receive polysaccharide vaccine that effectiveness against bactermia caused by the serotypes included in the vaccine is between approximately 50% to 85%. If it is assumed that roughly 30% of pneumococcal pneumonias are bactermic, the 50% to 85% would apply to the 30% that are bactermic and could bring the overall effectiveness down to as low as roughly 20%. The estimates of vaccine effectiveness are against all vaccine type pneumococcal pneumonia whether bactermic or not.

Dr. Poland (ACP) noted that in earlier studies, in younger people in some unusual settings who received the vaccine there was prevention of non-bactermic pneumonia.

Dr. Messonnier replied that this was where the 80% came from.

Doug Campos-Outcalt (AAFP) inquired as to whether the working group considered and listed potential harms. For example, when people are vaccinated it sometimes alters their behavior. They might take fewer precautions than usual. There is a series of other potential harms that could occur and he wondered whether any consideration was given to this at all.

Dr. Messonnier responded that adverse events associated with vaccines were not included in this or in the calculations from the first presentation. This vaccine is believed to be very safe in young people. The goal was to estimate how great the problem might be during the next pandemic, and subsequently to bring the question to the full ACIP regarding whether it was worth using the existing licensed vaccine in attempt to prevent it.

Dr. Morse requested that Dr. Moore articulate the context in which the two questions were being posed to the ACIP and the timetable in which they were planning to bring this back to the group for a recommendation and vote.

Dr. Moore responded that the working group knew that this would be a lot of information to present in one session. It was not being brought to the ACIP during this meeting for a vote. At this point, the group merely wanted to determine whether the type of information presented would be beneficial to the ACIP in making recommendation decisions. If so, there would be a series of additional questions to address, such as: Should the vaccine be stockpiled? When should it be stockpiled, in what form, and at what cost? At this time, the group was merely seeking input from the full committee regarding what type of additional information they might be interested in receiving to have enough information to vote on the question.

Dr. Judson thought there were far too many unknowns, and too many current assumptions that were likely to change depending upon when the group anticipated a pandemic influenza occurring. In his 30 years in infectious diseases, the proportion of bacterial pneumonia that is pneumococcal from outside the hospitals as well as inside the hospitals where it has often become secondary to pulmonary edema, he would not be able to answer this question. He also wondered what was used for the assumption for the cross-protection from existing N1-containing vaccines.



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Dr. Moore responded that the assumption made for pre-pandemic vaccine effectiveness was 75% to a high of 85% and a minimum of zero. This range was chosen based on discussions with colleagues from the Influenza Division. The problem is that no one knows, nor will anyone ever know, what the vaccine effectiveness of pre-pandemic vaccine is until the pandemic actually occurs. The question the group is struggling with is whether to wait until the pandemic actually occurs to decide whether and how to use pneumococcal polysaccharide vaccine, or given this broad range of assumptions and a pretty favorable case for using this vaccine due to the relatively low numbers needed to vaccinate and the quite favorable cost-effectiveness analysis, to make a recommendation. He invited members to offer input regarding other critical information that the ACIP might need to make a decision.

Dr. Judson thought it was contradictory for society and ACIP to label pandemic influenza as somehow different from what the world experiences every year. Billions are being spent preparing for a hypothetical epidemic under circumstances that cannot be foreseen, although 36,000 deaths per year are accepted on normal pandemics that occur every year.

Harry F. Hull, MD (H.F. Hull & Associates, LLC) noted that there is a $600,000 cost for a stockpile of vaccine to prevent 35,000 cases. Although not all of the cases are going to be susceptible to antibiotics, it seemed important to know the comparison of stockpiling vaccine to that of stockpiling antibiotics, some of which will already be stockpiled. As a former ACIP member, he would want to see a comparison with antibiotic treatment.

Dr. Meissner requested information regarding the time factor. His understanding was that it would be a matter of months between the appearance of a pandemic strain, peak of activity, and winding down of pandemic influenza. He wondered if it was practical to administer 20 million doses to individuals within a relatively short period of time.

Dr. Gellin (NVPO) responded that a pandemic was very different from a seasonal epidemic. Part of the problem is that it is unknown what it would look like, and part of the planning is to deal with worst case scenarios. The mantra is “leave no stone unturned” in an effort to determine what is feasible to mitigate the otherwise unmitigated outcome of a pandemic. The question on the table is: Pneumococcal disease is a co-traveler with influenza. What if anything should the US do to try to prevent as much pneumococcal disease as possible in the setting of a pandemic? There is the issue of stockpiling and it is fair to consider how operational it is to conduct a “just in time” vaccination program. Another issue regards the pros and cons of whether people should be vaccinated now to create population immunity. This is not an academic exercise. It must lead to some decision by the government with respect to what to do. ACIP was silent on the matter in the last round of guidelines.

Rick Zimmerman (University of Pittsburgh) thought this was an exercise worth pursuing, particularly given the biologic tendency of influenza vaccine to predispose individuals to secondary bacterial infections, which may be even more common in pandemic. This is not yet well-understood. With respect to antibiotic speculation, he cautioned that there was no way to know what the resistance patterns would be to antibiotics in a pandemic, nor could they know how much would be available supply-wise.



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## Update on PCV13 Pediatric Phase 3 Trial Results

**Peter R. Paradiso, MD**
**Vice President, New Business and Scientific Affairs**

Dr. Paradiso presented an update on investigational 13-valent pneumococcal conjugate vaccine (PCV13). Prevnar® and PCV13 have 7 common serotype components (4, 6B, 9V, 14, 18C, 19F, 23F). Each of these 7 polysaccharides is conjugated to the same carrier protein, CRM197. The amount of conjugate per dose (2.2ug for each serotype except 4.4ug for serotype 6B) is identical for Prevnar® and PCV13. The 6 new serotypes include: 1, 3, 5, 6A, 7F, 19A. Each of these polysaccharides is also conjugated to CRM197 and the amount of each in a dose is 2.2ug. The conjugation chemistry used for the preparation of all 13 conjugates is the same. So, PCV13 uses a technology that has worked successfully with Prevnar®. The use of the CRM197 carrier protein in both Prevnar® and PCV13 will allow for the ability to transition between the two vaccines at any point in the vaccination schedule, as the 13-valent vaccine becomes available.

With regard to invasive pneumococcal disease (IPD) caused by PCV13 serotypes in the US in 2006, in children under 2 years of age, the 13-valent vaccine will cover approximately 64% of the disease and approximately 73% of the remaining disease in children 2 to 4 years of age. The types causes by the 7-valent are very low at 2% in children under the age of 2 and 4% in children 2 to 4 years of age after 7 years of use of that vaccine in the US. The rate of disease is 21 per 100,000 in children under 2 years of age and approximately 7.5 per 100,000 in 2 to 4 year olds [Matt Moore, Personal Communication, ABC Surveillance System]. Over 50% of IPD cases in children under the age of 5 are caused by serotype 19A. Serotype 19A has been increasing every year for the past several years, and becomes an increasing proportion of the total. It is also most likely to be antibiotic-resistant.

In terms of licensing a new vaccine that is actually a replacement for a currently available vaccine, given that Prevnar® is available, it is not possible to conduct placebo controlled efficacy trials. Thus, the basis of licensure for a new conjugate vaccine is a comparison to Prevnar®. Therefore, the pivotal trials compared PCV13 immune response to Prevnar® immune response, looking for non-inferiority by pre-established conditions of the immune response for the 7 common serotypes. For the 6 new serotypes, it was necessary to demonstrate that the immune response was comparable to the response of the original 7. This is done in a number of ways. The primary endpoints are the percentage of subjects who achieve a level of antibody of > 0.35 ug/ml, established by the WHO as a threshold to measure protection after 3 doses in infants; geometric mean antibody concentration (GMC) after 3 doses as well as after the booster; functionality of the antibody (opsonophagocytic activity); boostability in the second year of life; compatibility with concomitant vaccines; and safety.

Wyeth conducted a number of studies throughout the world that fall into a variety of categories. Numerous schedules were tested, given that various schedules are used around the world. Tests were conducted in infants as well as older children, and with a fairly broad variety of concomitant vaccines, to demonstrate that the 13-valent vaccine can be given as part of a routine immunization program with any schedule and almost every concomitant vaccine (Infanrix hexa, Pentavac, Pentaxim, Pediacel, DTwP, Priorix, Proquad, Meningitec, Neissvac C, Vaqta, Engerix B, and OPV). All of these programs provide information for the safety database.



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The pivotal non-inferiority trials were designed in a way to compare the 7-valent and 13-valent vaccines. To illustrate, Dr. Paradiso reported on a trial in Germany in which infants were randomized blindly to receive either PCV7 or PCV13 (n=603). Vaccinations were administered at 2, 3, and 4 months of age in the primary series, with serology one month later. Booster doses were administered at 11-12 months of age, with serology one month later. The endpoints included: Non-inferiority of %≥0.35 ug/ml after 3 doses for each serotype (within 10% of the 95% confidence interval of the difference)l; non-inferiority of the GMCs for each serotype (within 50% of the 95% confidence interval of the ratio PCV13/PCV7); and for new serotypes, the comparison was to the lowest Prevnar® type.

In the pivotal study, non-inferiority was achieved for every serotype except 6B. For 6B, the response was about 10% less but the lower bound of the confidence interval was around 16, so it failed. However, secondary outcomes that were agreed to with the regulatory agencies passed. These included passing the 2-fold non-inferiority test for GMC and demonstration of functional antibody response. In the US study, using the same lot at 2, 4, and 6 months of age, there was a better overall response to 6B as expected and the lower confidence of the difference was around 11%, barely failing. Another important point to focus on is the high percentage of responders for all of the new serotypes. The cross-reaction with serotype 19A in Prevnar® was non-functional in nature. With regard to GMC levels post-primary, each of the serotypes passed on inferiority that was preset for endpoints for these trials for regulatory purposes. All of the new serotypes were compared for non-inferiority against the lowest serotype in the Prevnar® types, and all of those passed as well.

For each of these groups in each serotype, functional antibody was measured, with good functional antibody demonstrated not only for the 7 serotypes that are common between Prevnar® and 13-valent, but also for the 6 new serotypes. For 19A, the GMT for Prevnar® was 6.70 compared to 442.48 in the PCV13 arm. While cross-reactive antibody is made from Prevnar® against 19A, that antibody does not have any functional activity. Ratios of OPA GMTs (PCV13 / PCV7) ranged from 0.64 to 1.02 for the 7 common serotypes, showing comparable functional activity. For the additional 6 serotypes, much higher PCV13 / PCV7 ratios of OPA GMTs were noted, ranging from 10 to 100. PCV7 recipients do have a significant OPA response to serotype 6A, but the GMT in the PCV13 recipients is 10-fold greater, suggesting the PCV13 might have increased efficacy against 6A. It is important to remember that the ELISA has been externally standardized, so comparisons can be made across serotypes. For the OPA, it is not standardized; therefore, comparison can be made only within a serotype, but not across serotypes.

Another way to look at this is to examine the correlation between the total antibody response and the functional antibody response. For common serotype 4, there is a good correlation for the total antibody to the functional antibody for both the 7-valent and 13-valent vaccines. PCV7 elicits binding antibody to the PS capsule of 19A; however, there is no functional activity to 19A in PCV7 recipients. There is no correlation between binding and functional antibody to 19A in PCV7 recipients. In contrast, there is a good correlation between binding and functional antibody in PCV13 recipients. This supports what has been observed in post-marketing surveillance for PCV7, where no protection was observed against 19A disease. Unlike PCV7, PCV13 has a substantial degree of PS binding antibody and also functional activity against 19A; thus, the expectation is that inclusion of 19A in PCV13 may have substantial clinical benefit. All of these considerations go into the assessment of the comparison between Prevnar® and 13-valent vaccines, and particularly the assessment of the value of 13-valent for the new serotypes, including 19A.



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Following the booster dose in children, there is a very high response of subjects achieving a pneumococcal IgG antibody concentration of greater than 0.35 μg/mL after the booster dose. Each one of those responses is functional as well.

With regard to the consistency lot trial conducted in the US, children were immunized at 2, 4, and 6 months of age. The antibody response and percent responders to each of the serotypes across the three lots of vaccine (Pilot Lot 1, Pilot Lot 2, Full Scale Manufacturing Lot) were examined. Each of the serotypes passed preset non-inferiority criteria to demonstrate consistency of manufacture.

These were the type of data that formed the basis for the immune correlate of protection and the non-inferiority of the immune response between Prevnar® and the 13-valent vaccine. There are more data from various studies, including non-inferiority trials in the US that have not yet been presented publicly. All of these support the conclusion that the 13-valent vaccine induces a response to all 13 types and can be expected to be non-inferior to Prevnar® for the 7 types and expand coverage for the new types. The trials included: Phase 1–2 (003) US; Pivotal Non-inferiority (006) Germany; Pivotal Non-inferiority (004) US; Safety, immuno & Convax (501) Spain; Safety, immuno & Convax (3007) Spain; Safety, immuno & Convax (008) France; Safety, immuno & Convax (500) Italy; Safety, immuno & Convax (007) UK; Safety, immuno & Convax (011) India; Polysorbate 80 Non-inferiority (009) Poland; Manufacturing scale trial (3000) Poland; and Clinical consistency (3005) US.

With regard to the safety database for the EU filing, the total number of infants in the database is over 7,000 with safety being assessed in all trials, in infants, toddlers, and after 6 months of follow-up. The total safety database includes data from 12 infant studies in which the safety and immunogenicity of PCV13 co-administered with other pediatric vaccines were evaluated. Most (9) of these studies included PCV7 as an active comparator. In the 3 remaining studies, different formulations or lots of PCV13 were assessed. Each of the 12 studies was conducted in a single country, and vaccination schedules varied across the studies, according to national recommendations. Various countries were selected to allow a thorough evaluation of different schedules.

Given the similarity of PCV13 to Prevnar®, the clinical development of PCV13 builds upon the record of safety that has been established for Prevnar®. The safety profile of Prevnar® is well-defined on the basis of the vaccine's pre-licensure clinical evaluation and extensive post-licensure experience, with more than 200 million doses having been distributed worldwide. Most of the clinical trials of PCV13 include Prevnar®, allowing a direct safety comparison between the two vaccines. The safety of PCV13 was evaluated on the basis of prompted (questions in an electronic diary relating to pre-specified symptoms or signs) adverse events (AEs), including local reactions and systemic events, as well as spontaneously reported AEs. Data on prompted AEs were recorded daily by the parent or legal guardian for a minimum of 4 days after each dose. Comparisons between PCV13 and PCV7 groups were made using a meta-analysis statistical procedure that could detect significant numeric differences between the two groups. This approach is a sensitive screening tool designed to identify any small differences that would not otherwise be detected in a single trial. Any such differences were then evaluated for potential clinical importance.



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The rates of local adverse events were comparable between PCV7 and PCV13. No clinically significant differences in spontaneous adverse events were seen during the infant series, between infant and toddler dose, or after the toddler dose. Serious adverse events (SAEs) incidence was comparable between the PCV7 and PCV13 groups during the vaccination period and follow-up. Overall, the safety profile of PCV13 was comparable to PCV7 Compatibility of PCV13 with concomitant vaccines was demonstrated many vaccine antigens including diphtheria, tetanus, pertussis, IPV, Hib, hep B, and MMR. Only the safety of concomitant administration of rotavirus vaccine and hepatitis A vaccines were tested and were found to be comparable between the PCV7 and PCV13 groups..

In terms of the transition from PCV7 to PCV13, the vaccination schedule for unvaccinated Children ≥7 Months of Age for Prevnar® is as follows:

| **Age at First Dose** | **Total Number of 0.5 mL Doses** |
|---|---|
| 7-11 months of age | 3* |
| 12-23 months of age | 2† |
| ≥24 months through 5 years of age (prior to the 6th birthday) | 1 |

*2 doses at least 4 weeks apart; third dose after the one-year birthday, separated from the second dose by at least 2 months.
† 2 doses at least 2 months apart.

A trial was conducted in Poland where children have not had Prevnar®, conducting the same experiment with the 13-valent vaccine. The conclusion was that the schedule in unvaccinated children will be the same for the 13-valent vaccine as it is for Prevnar®. This is not really an issue in the US where the vast majority of children have received or are in the process of receiving Prevnar®. However, in many countries where Prevnar® introduction has not yet occurred, this is important information to have. Indications being sought from the FDA for the transition from Prevnar® to PCV13 include the same age-appropriate schedules for unvaccinated children as Prevnar®; PCV13 can be substituted for PCV7 at any point in the immunization schedule (rationale: the seven Prevnar® types are common in the two vaccines; CRM is the carrier protein in the two vaccines); and a single dose of PCV13 in children >12 months olds will induce a response to the 6 new serotypes in over 90% of the children that is comparable to the response observed following the infant dosing. These were the criteria used to establish the catch-up schedule in unvaccinated children, and are the criteria that are now being applied to 13-valent vaccine.

The following chart helps to illustrate all of the possibilities that may be faced when Prevnar13® is introduced. For example, the top line is a child who receives a dose of 7-valent and subsequently receives two doses of 13-valent and booster dose of 13, and so forth:



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| Transition from PCV7 to PCV13 | | | | |
|---|---|---|---|---|
| Infant 2 mo | 4 mo | 6mo | ≥ 12 months | |
| 7v | 13v | 13v | 13v | -- |
| 7v | 7v | 13v | 13v | -- |
| 7v | 7v | 7v | 13v | -- |
| 7v | 7v | 7v | 7v | 13v |

The data to support this is really derived from several studies, but importantly the study conducted in France in which children were examined who received three doses of Prevnar® and one dose of Prevnar13®, found that for the 6 new serotypes there was a good response to one dose of the Prevnar13®, which was comparable to the response in infants following 3 doses. Based on those criteria, the goal for children who are previously immunized with Prevnar® is to recommend that they only need to have 1 dose of Prevnar13® if they are over 12 months of age.

Another very interesting trial underway is the Alaska Safety and Effectiveness Study with the 13-valent vaccine, which is being conducted in the YK Delta Region of Alaska. This study was initiated in January 2009. This region has experienced a great deal of disease caused by non-Prevnar® serotypes, particularly of 19A and 7F. In this study, the 13-valent vaccine has been introduced into the YK Delta Region population. This is the first location in which the vaccine is being introduced broadly into the population, with the Transition from PCV7 to PCV13 Schedule being applied. All children <5 years of age will receive PCV13. All children will be transitioned from PCV7 to PCV13. Those children who are fully immunized with PCV7 will receive an age-appropriate dosing of PCV13. In addition, the study will examine whether the disease occurring in this population can be reduced with the new serotypes in the PCV13.

The current status of PCV13 in the US is that the FDA has granted fast-track status for the pediatric indication based on unmet medical need. This means that Wyeth has been able to start the submission of the package in a phased manner. Rolling submission was initiated in September 2008, and Wyeth plans to complete the submission by the end of March 2009. The FDA will then decide whether they will conduct a priority review of that application. Key ACIP / AAP / AAFP considerations at the launch of PCV13 in the US include planning for the transition from PCV7 to PCV13 and catch-up recommendations. The first indication will be for children up to 5 years of age, but at the same time Wyeth has a Phase 3 trial on-going in adults over 50 years of age. That program is moving forward in the US and throughout the world, with trials based on immunogenicity, as well as a Phase 3 efficacy trial that is on-going in the Netherlands examining all-cause and pneumococcal pneumonia. The ultimate goal is to make this vaccine available for all ages.



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## Discussion

Dr. Morse noted that this presentation was part of continuing education as the ACIP moved closer to a vote.

Referring to the last line of the schedule to transition from PCV7 to PCV13 (e.g., 4 doses of Prevnar® and one of 13-valent), Dr. Baker inquired as to what the durability of a single conjugate dose would be and whether it would take a child through 5 years of age. She expressed concern that based on the bottom two lines, with a single dose of 13-valent, it was not clear that children would be protected through the period of risk for the 6 new serotypes. She wanted reassurance that these individuals lasted at least through 2 years, but stressed that they should last through 5 years.

Dr. Paradiso responded that they did not know the answer to this question, given that the durability of that dose has not been measured in over 12-month olds. At this point, only one month has been measured to show that it is as high as achieved in infants. The criteria used were the same as those used to determine the catch-up dosing schedule for Prevnar®. They found that, particularly in 12 to 18 months of age, certain serotypes of the original 7 after 1 dose of the 13-valent did not achieve a good response or a response that was comparable to the post-infant response. It took 2 doses in that age group. Since all 7 did not respond that way, they went to 2 doses. Above 24 months of age, the response was comparable to the response post-infant so the recommendation was for 1 dose. The response to the 6 new serotypes looks more like the response to the 7 types in above 24-month olds. Wyeth also has data with 2 doses in that age group.

Regarding the response to 6B, Dr. Meissner noted that in terms of the ELISA the IgG was 10% lower. However, in the functional assay, the GMT was still lower at 750 versus 1150. He wondered whether that was significant and whether this changed after a fourth dose.

Dr. Paradiso responded that following the booster dose, the responses were all comparable. Thus, they both boost very well. For all of the 7 types in the 13-valent, GMC is somewhat lower but not enough to fail non-inferiority for percent responders or even by GMC. These were the data in 2-, 3-, and 4-month olds. In 2-, 4-, 6-month olds (the way the US vaccinates) the response is somewhat better. In the consistency lot trial, the percent responders to serotype 6B were between 90% and 95% in that schedule compared to 77% in the 2-, 3-, 4-month old schedule. That difference becomes less with the 2-, 4-, 6-month old schedule. Wyeth does not believe that based on the reduction in percent responders that this will be clinically significant.

With respect to future ACIP recommendations, Joel Ward (UCLA) inquired as to whether Wyeth anticipated an increase in price of the 13-valent vaccine, whether they would continue to produce the 7-valent vaccine in addition to the 13-valent, and whether they would lower the price of the 7-valent vaccine. In addition, he thought there were interesting immune responses to some of the new antigens in the control group who did not receive 19A as if there was some cross-immunity from some of those antigens.

Dr. Paradiso replied that the global goal is for the 13-valent vaccine to replace the 7-valent vaccine. While at this time he did not have pricing information, this information would be presented as they moved closer to approval. With regard to the cross-reaction of the ELISA titers were most dramatically observed with 19A and were clearly vaccine-induced. Some of the other responses were perhaps due to some cross-reactivity, but also some natural immune



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responses occurred in some of the older children. Oftentimes, however, that was not mirrored in the functional response. It was more of an ELISA cross-reactivity without functionality.

## Use of Pneumococcal Vaccines: VFC Vote

**Dr. Jeanne Santoli**
**CDC / CCID / NCIRD, ISD**

Dr. Santoli presented an update on the VFC resolution for pneumococcal vaccines, which was last discussed during the October 2008 ACIP meeting. She reminded everyone that CDC wanted to simplify the VFC resolution by streamlining the text. Currently, VFC resolutions provide information about eligible groups, recommended schedule, dosage intervals, recommended dosage, and contraindications/precautions. Much of this information is detailed in the ACIP recommendations. CDC is working to identify ways to streamline the VFC resolutions, pointing to the ACIP recommendations and avoiding rewriting those recommendations to the extent possible. Whenever there are repetitions, there is potential for error. CDC would like to move to referring to published documents where these exist, and it is appropriate to do so.

When the update was made to the resolution in October 2008, the focus was on the pneumococcal polysaccharide component because that was where the changes in the recommendations were. What was posted had an updated pneumococcal polysaccharide component of the resolution. However, shortly after it was posted, a number of astute individuals submitted emails to point out at least two errors that were in the pneumococcal conjugate component of the VFC resolution. This underscores the need to avoid repetition of wording in more than one place.

With that in mind, she reviewed the places in which CDC wanted to streamline the resolution either because there was wording that did not add to the wording already there or because published documents could be referred to. With respect to the pneumoccocal conjugate component of the resolution that defines the eligible groups, Dr. Santoli explained that the VFC resolutions have five components: eligible groups, recommended schedule, dosage intervals, recommended dosage, contraindications and precautions. For the eligible group section, CDC found that one bullet is very inclusive, “All infants and children at least 6 weeks of age through 59 months of age . . .” Because of the time this recommendation was first made, there was discussion regarding high risk groups, those high risk groups are also listed. However, the first bullet is inclusive of all children who are eligible for the VFC resolution, so the proposal was to eliminate the second bullet because everyone in the second bullet was included in the first bullet. Looking at the other components, there are published documents that can be referred to regarding the vaccine schedule, the dosage interval, and the contraindications and precautions. These published documents include three ACIP recommendations. The first is the 2000 recommendations that detail out the schedule, dosage intervals, and contraindications and precautions. The second is the 2003 updated brief recommendation that covered children who were either indicated to have a cochlear transplant or who were cochlear transplant recipients. The third is another update to the recommendations published in 2008 regarding vaccinating older children for catch-up. By reference, the wording from the recommendations that the ACIP has made are incorporated.



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At this point, while there is a recommendation that is in the process of being published regarding the pneumococcal polysaccharide component, there is not a published document to which to refer, so the eligible groups would look exactly as they look in the statement. In fact, there was a decision to make the eligible groups for VFC somewhat broader than the recommendations. Therefore, this component would not change. However, the language for the vaccination schedule and the dosage intervals will soon be published in the ACIP statement.

Because CDC would like to be able to refer to the URL once it is available and to update the older URLs when they become available, there is a statement at the bottom of the resolutions that indicates that, "If an ACIP recommendation regarding the pnuemococcal vaccination is published within 12 months following this resolution, the relevant language above except for the eligible groups sections (which was specifically for the VFC resolution and not for the recommendation) will be replaced with language in the recommendations and incorporated by reference to the publication URL." The reason that this statement says "within the next 12 months" is that is not intended to cover all updates for future ACIP recommendations. CDC would want to bring those to ACIP to update the resolutions as the recommendations change.

**Motion: VFC Resolution**

Dr. Sawyer moved to approve the recommendations as presented. Dr. Cieslak seconded the motion. The motion carried with 15 affirmative votes, 0 abstentions, and 0 negative votes.

## Measles, Mumps, & Rubella Vaccine

### Introduction

**Dr. Jane Seward**
**CDC / CCID / NCIRD / DVD / OD**

Dr. Seward indicated that this session would address a proposed change in policy for vaccination of healthcare workers with measles, mumps, and rubella (MMR) vaccine. The context is the revision of the "HICPAC / ACIP Immunization Recommendations for Healthcare Workers" from 1997. This is a compilation of ACIP statements for specific vaccines that are endorsed by the Healthcare Infection Control Practices Advisory Committee (HICPAC). This work is being done in the context of the Adult Vaccine Working Group chaired by Dr. Ehresmann. Most of the vaccines being included in this statement were recently revised, such as varicella, Dtap, and yearly influenza. The "evidence of immunity" requirements for healthcare personnel are typically lifted and put into the statement. The MMR vaccine recommendations, in contrast, are a decade old. While the schedule is to be revised and updated across the board, the first topic under consideration is vaccination of healthcare workers.

The recommendations for healthcare workers for MMR vaccine are quite complicated, covering routine vaccination recommendations as well as vaccination during outbreaks. They are complicated by different language, footnotes, different strengths of recommendations for the routine and outbreaks, et cetera. CDC has received feedback that it would be beneficial to simplify these complicated recommendations. This is a new era of measles and rubella, having eliminated both of these diseases in the US since the general MMR recommendations were published in 1998. That might require a higher bar of immunity for the US population. The



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Division of Viral Diseases (DVD) has worked very closely with the Division of Healthcare Quality Promotion (DHQP) on the suggested recommendations.

## Proposed Changes in MMR Vaccine "Evidence of Immunity" Requirements for Healthcare Personnel

**Amy Parker, MSN, MPH, LCDR USPHS**
**CDC/CCID/NCIRD/DVD/EB**

LCDR Parker provided background on current MMR vaccine recommendations for healthcare personnel (HCP) routine vaccination and vaccination during outbreaks; and discussed the proposed changes and rationales.

The current MMR recommendations for healthcare personnel (HCP) that are being updated are from 1997 and 1998. During the national mumps outbreak in 2006, vaccine policy recommendations for children in high risk groups in the population, including HCP, were revised from 1 to 2 doses of mumps or MMR vaccine. At that time, the changes currently being proposed were raised in relationship to mumps prevention by some state and city public health officials. The decisions on these issues were deferred until the issues could be addressed for all three vaccines (e.g., measles, mumps, and rubella) simultaneously. Current ACIP MMR vaccine recommendations for HCP state that HCP without other evidence of immunity should receive 2 doses of MMR vaccine for measles and mumps and 1 dose of MMR vaccine for rubella. The recommendations stress the importance of vaccination to protect HCP and the responsibility HCP have to avoid transmitting these diseases and thereby causing harm to patients. The ACIP MMR vaccine recommendations include a permissive recommendation for 1 or 2 doses of MMR vaccine for unvaccinated workers born before 1957.

Currently, HCP are considered to have presumptive evidence of immunity if they have met one or more of the following four conditions:

1. Documentation of administration of appropriate vaccination against measles, mumps, and rubella (e.g., administration on or after the first birthday of 2 doses of live measles and mumps vaccine separated by greater than or equal to 28 days and one dose of live rubella vaccine);
2. Laboratory evidence of immunity;
3. Documentation of physician diagnosed disease (measles and mumps); or
4. Born before 1957, which may vary depending on current state or local requirements. That is, state or local areas may choose not to use this evidence of immunity criterion. Healthcare facilities should consider recommending a dose of MMR vaccine for unvaccinated workers born before 1957 who are at risk for occupational exposure to measles and who do not have a history of measles disease or laboratory evidence of measles immunity.

During outbreaks of measles and rubella, ACIP recommends that health-care facilities should strongly consider vaccinating HCP born before 1957 with a dose of MMR vaccine unless they have other evidence of immunity, such as serologic evidence of measles or rubella immunity or a history of measles disease [CDC. *MMWR* 1998;47{RR-8}:1-57]. During a mumps outbreak, healthcare facilities should strongly consider recommending 2 doses of a live mumps virus vaccine to unvaccinated workers born before 1957 who do not have evidence of mumps immunity [CDC. *MMWR* Notice to Readers. 2006;55(22):629-630].



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Since the last revision of the ACIP / HICPAC vaccine recommendations for HCP, the epidemiology of measles has changed considerably. The US declared elimination, meaning interruption of endemic disease transmission of measles, in 2000. However, there is an on-going risk of measles importation and indigenously acquired cases in the US. A single measles case anywhere in the US now results in an extensive response by local and state health departments to contain transmission. There is now a much higher expectation of maintaining high population immunity to measles and minimizing risk of transmission than a decade ago. Between 2001 and 2007, there was an average of 60 total reported measles cases per year. About half of the cases every year were importations. In 2008, there was a sharp increase in total number of cases with 140 and more spread from the imported cases compared to previous years.

Overall, population seroprevalence to measles, mumps, and rubella in the US is high according to National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2004. Although there is high population seropositivity to each of the three antigens, in persons born between 1967-1976 (now 30 to 40 years old), 15% to 20% of these adults do not have antibodies to one or more of the three diseases. Among adults born before 1957, approximately 3% to 8% lack antibodies to at least one of the three MMR antigens.

Measles is a well-described nosocomial problem. Due to the severity of measles, infected persons frequently seek medical care [Atkinson WL, Markowitz LE, Adams NC, Seastrom GR. Transmission of measles in medical settings—United States, 1985–1989. *Am J Med.* 1991;91:320S–4S; Davis R, Orenstein WA, Frank JA, et al. Transmission of measles in medical Settings.JAMA1986;255:1295–; and Atkinson WL. Measles and health care workers [editorial]. *Infect Control Hosp Epidemiol* 1994;15:5–7]. During a large US measles outbreak from 1989 to 1991, transmission of measles in hospitals and emergency departments was enough of a problem that triage tents were set up outside of hospitals. According to a 1996 study conducted in Washington State, HCP have a 19 times greater risk of being exposed to and acquiring measles than adults of similar age (RR 19, 95% CI 7.4, 45.4, $p < 0.01$). During 1985–1992, 643 measles cases were reported among healthcare workers (HCW) whose birth year was known, of whom 27% were born before 1957 [CDC. *MMWR. 1998;* 47{RR-8}:1-57].

With the decline in measles cases, fewer cases are occurring in HCP. However, the immunity profile for HCP born before 1957 is unlikely to have changed since the measles resurgence, and the potential exists for cases in this age group. Although the number of cases in healthcare settings is much lower currently than it was in the pre-elimination era, there were still 27 reported measles cases transmitted in healthcare settings, accounting for 5% of all reported US measles cases during 2001- 08 [*CDC, unpublished data*]. This percent more than doubled in 2008 when 15 (11%) of the 140 cases were transmitted in a healthcare setting. In the post-elimination era, there have been considerable economic costs to contain these cases and exposures, ranging from approximately $100,000 to more than $400,000.

In Arizona in 2008, the largest nosocomial US measles outbreak (N = 14 cases) occurred in 20 years. At hospital A, an adult infected with measles visiting the US from Switzerland was hospitalized with measles and pneumonia. This resulted in over 6,000 hospital contact investigations, including 4,269 hospital contacts and 1,872 HCP contacts. The hospital conducted a review of measles documentation of immunity of almost 2,000 HCP and did emergency serology and vaccination of 400 persons, many of whom were born before 1957. Since the records were not electronic, the review was time-consuming and challenging to implement quickly. One HCP with direct contact to one of the measles cases was vaccinated following this exposure; however, she developed measles, which resulted in some of the



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hospital contact exposures and investigations. The total cost to Hospital A was estimated to be more than $400,000.

There are several reasons why changes are being proposed to vaccination and immunity requirements for HCP. In the era of measles and rubella elimination, the tolerance for any cases or exposures has decreased. To maintain elimination, the goal is to have 100% immunity in high risk populations such as HCP. Proposed changes are driven primarily by measles, but are also relevant to rubella, another disease that has been eliminated in the US. Measles is highly contagious with the chance of spreading in unvaccinated subgroups. Importations into the US are continuing. Due to the high exposure risk, it is important to protect HCP preemptively. During outbreaks, it is disruptive and time-consuming to determine which staff are born before 1957, to find them, and to vaccinate them. This has occurred a number of times, as recently as 2008. Current permissive vaccine recommendations that allow healthcare facilities to consider vaccinations for HCP born before 1957 are not clear, and many facilities are already conducting routine serology screening for vaccination of this group.

Currently, healthcare personnel are considered to have evidence of immunity if they have one or more of the following, with the proposed changes underlined or stricken:

1) Appropriate vaccination against measles, mumps, and rubella (i.e., administration on or after the first birthday of two doses of live measles and mumps vaccine separated by greater than or equal to 28 days and at least one dose of live rubella vaccine)
2) Laboratory evidence of immunity <u>or laboratory-confirmation of disease</u>
3) ~~Documentation of physician diagnosed disease (measles & mumps)~~
4) ~~Born before 1957~~

The first proposed revision is the addition of laboratory confirmation of disease, as well as laboratory evidence of immunity. The second is for the elimination of documentation of physician-diagnosed disease for measles and mumps. The third proposed revision is for the elimination of birth before 1957 as acceptable evidence of immunity for HCP.

The rationale for including laboratory confirmation of disease in addition to laboratory evidence of immunity is for completeness. While cases of measles, mumps, and rubella are currently rare in the US, immunity from naturally acquired or wild virus measles, mumps, and rubella is considered to be robust and long-lasting. Although laboratory tests are not 100% sensitive and specific, for surveillance purposes and counting cases of measles, mumps, and rubella in the US, laboratory confirmation of disease is heavily relied upon, especially for measles and rubella. It is reasonable to conclude that persons who have laboratory evidence of disease are immune. In addition, as measles, mumps, and rubella "evidence of immunity" requirements are discussed, it is instructive to examine the updated ACIP recommendations for evidence of immunity for varicella published in 2007. Varicella already includes laboratory confirmation of disease [CDC. *Prevention of Varicella. Recommendations of ACIP. MMWR.* 2007;56{RR-4}:1-37].

There are several rationales for eliminating documentation of physician-diagnosed measles or mumps. A number of state health departments and health facilities have concerns that many potentially susceptible persons may be working in healthcare settings, because current "evidence of immunity" recommendations are not being adhered to as intended. Health departments and healthcare facilities report anecdotally that some employees have family or friends who are physicians sign off on the forms, even if they have no knowledge of the person's disease history. Thus, health departments do not trust the documentation that the HCP are



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immune. Additionally, it may not be feasible for persons to contact their childhood physicians to obtain verification of documentation of disease history; that is, the childhood physician may be retired or deceased. Finally, accuracy of clinical diagnosis has declined and vaccine-modified disease may make it especially difficult to determine if a person truly had disease history, especially with regard to mumps.

The rationale for eliminating "born before 1957" is because it is optimal to assure immunity through a preemptive vaccine policy. The current routine recommendations are already permissive and suggest that 1 dose of MMR vaccine "be considered" for this age group. Many facilities are already doing this. Current outbreak recommendations to "strongly consider" administering 1 dose for measles and rubella or 2 doses for mumps of MMR vaccine to all HCP born before 1957 are disruptive and challenging to implement in the midst of an outbreak response. The updated ACIP varicella vaccine recommendations do not include birth year as presumptive evidence of immunity for HCP. Many facilities already test for immunity of all HCP, regardless of birth year.

A survey of 450 hospitals conducted at the California Department of Health in the beginning of January 2009 shows that of the 56 that have responded to date, 95% of hospitals report performing serologic screening for vaccine preventable diseases (VPDs), 89% routinely screen employees born before 1957, and 75% screen new employees. Almost half screen employees even if they can provide proof of immunity, almost all (93% to 95%) report screening for measles and rubella, and 77% report screening for mumps [K. Harriman, CA Dept Health, personal communication].

In another non-randomized sample of occupational health practitioners (N = 38) who responded to a listserv survey, 10 (26%) of 38 facilities reported that they conduct serologic screening and / or vaccination on all employees regardless of age; that is, they only accepted documented vaccine doses and / or previous serologic titers and they did not accept physician diagnosed disease or birth before 1957 as adequate evidence of immunity. An additional 8 facilities reported that they serologically screen and / or vaccinate all new employees. Thus, a total of 18 (47%) of 38 facilities screen all new employees. Of the 37 facilities who responded to the question about whether they accept physician-diagnosed disease, 15 (41%) said they accept physician-diagnosed disease as acceptable evidence of immunity. Of the 28 facilities currently not screening and / or vaccinating all employees, 19 (68%) estimated how long it would take to implement the new policy: 3 (16%) reported that they would be able to implement the changes in <1 year; 10 (53%) in 1-2 years; 4 (21%) in 3-4 years; and 2 (11%) in ≥5 years.

Since 2007, all HCP should be tested for varicella immunity. Testing for measles, mumps, and rubella immunity for persons born before 1957 could be conducted concurrently with varicella immunity testing. In addition, many larger hospitals are already testing for immunity in all employees regardless of birth year. These policies could be implemented as new employees join the staff and / or with other annual routine disease-prevention measures (e.g., influenza vaccination or TB skin testing). Implementation could be started soon and phased in within a few years. The new requirements could be fulfilled either by testing for immunity and vaccinating those without serological evidence or by vaccinating with 2 doses of MMR vaccine. Whether screening prior to vaccination would be cost saving will depend on the cost of serology testing for measles, mumps, and rubella seroprevalence in the healthcare personnel being tested. Given that less than 10% are likely to lack antibodies, serology testing is expected to be cost-effective.



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In conclusion, evidence of immunity requirements for HCP for measles and rubella were established more than a decade ago. Since then, interruption of endemic transmission of both measles and rubella has occurred in the US. In an era of measles and rubella elimination, high standards for immunity to measles, mumps, and rubella are appropriate for HCP. HCP have a duty to protect themselves and their patients from diseases preventable by vaccination. The current permissive recommendations are confusing. It is optimal to have immunity through a preemptive vaccination policy prior to an outbreak occurring. From the experiences of state health departments during recent outbreaks, it was learned that determining who is presumed immune and providing vaccination to hundreds of HCP during a measles outbreak is costly and disruptive. The epidemiology of measles in 2008 reminds us that despite elimination, measles exposures and outbreaks are likely to continue in healthcare facilities. Some facilities are already implementing the proposed changes.

**Discussion**

Dr. Morse noted that the data on the percent of measles cases for those born before 1957 were from 1985-1992. He wondered how much disease there had been in people born before 1957 since 1992.

Dr. Gallagher added that she did not have data for that entire time period, 2 of the140 cases in 2008 were born before 1957. It is a small, but not zero percentage. These were US born individuals.

Given that someone pays the bills, Dr. Baker raised a question regarding the cost of determining immunity in those born before 1957 versus simply vaccination with MMR.

LCDR Parker responded that she contacted Quest Diagnostics and Focus Diagnostics to determine approximate screenings costs. One laboratory indicated that the cost for screening tests would range from $56 to $110 depending upon the antigen, while another laboratory could screen for measles, mumps, and rubella for approximately $150. The actual cost would depend upon whether a facility decided to serologically screen employees first or simply vaccinate, or how many employees actually have positive titers if they choose to screen.

Dr. Meissner agreed with the proposition, thought it made a great deal of sense, and thought it would be beneficial for the field to have backing from CDC. He wondered whether lack of antibody was a sufficient basis upon which to say a person is susceptible; that is, is there a role for cellular immunity in any of these diseases. He also wondered whether the threshold for mumps protective immunity was clearly defined and whether this would result in large numbers of indeterminate assays in people who do not need it. In addition, it was not clear whether the addition of laboratory confirmation of disease referred to the actual isolation of the virus. It is pretty infrequently that anyone isolates measles, mumps, or rubella. Therefore, the intention of this was not apparent.

LCDR Parker responded that they do not expect laboratory-confirmation of disease to arise very often, but because the definition is used for surveillance purposes, they thought this would add to completeness in the event that someone had that evidence.

Dr. Sawyer strongly supported the proposal to eliminate physician diagnosis, given continued “drive-by” reports of measles from physicians who are absolutely sure that they have observed measles, none of which has been confirmed. The current generation of physicians cannot make a diagnosis of measles.



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By usual cost-benefit measures, Dr. Judson did not think this would be favorable. As Dr. Baker pointed out, someone must pay for this. It appeared that a major change was being proposed based upon two small outbreaks. In his 30-year public health career in Denver, he never witnessed a case of measles in a healthcare worker from a hospital. He also did not believe mumps could reasonably stand the test of being a priority cost-beneficial goal. While measles is a bad disease, the issue regards what the recommendation will prevent and what it will cost. He did not believe ACIP could make a national recommendation based on a couple of expensive anecdotes.

LCDR Parker responded that measles was guiding the proposed recommendations, but many of these issues also arose during the 2006 mumps outbreak. Many state health departments raised these same issues. This was not addressed at that time because CDC wanted to include measles and rubella in any of the "evidence of immunity" requirements for HCW. The time has come to update the policy, which led them to raise the proposed changes.

Dr. Seward added that there are some very old studies describing mumps correlate of immunity, and there are data from serology studies using neutralizing antibody tests showing that there is some susceptibility in the US population. These are not the perfect measure, but it is very difficult to use any others. Regarding the cost issue, CDC agrees that on the basis of measles cases prevented in HCW, the economics are not favorable. However, when an outbreak occurs and it costs a facility $400,000 it would have been cost-effective to have vaccinated.
Dr. Plotkin said the measles picture is quite clear. There is an antibody level which absolutely correlates with protection. For rubella, the issue of B-cell memory may be more important because the incubation period is long; therefore there is time for a response.

Dr. Marcy wondered whether any direction should be offered with regard to which test should be used to avoid false positives. For example, there is a broad difference in varicella tests in terms of specificity and sensitivity.

Harry Keyseling (SHEA) indicated that pediatric facilities have a large volunteer population who are quite elderly, and there is rapid turnover (e.g., the Grandmother Program: Feeders and Rockers). If screened, there would likely be a large group born before 1920 to 1930 who are clearly immune but do not have antibody. He was concerned about safety and this being a deterrent to people volunteering. With that in mind, he wondered if there were any data on truly naïve people 80 years old who are given the MMR vaccine in terms of safety profiles, and whether ACIP would consider having an age implement on implementing the proposed policy.

LCDR Parker responded that she did not believe they had such data. Dr. Seward added that she had never seen anybody over 80 years old who did not have measles antibodies.

Dr. Katz (IDSA) indicated that many people were tested who had no demonstrable antibody but who were, indeed, immune to measles. Undoubtedly this was due to T-cells. The absence of antibody is not proof positive of susceptibility. Therefore, he tended to agree with Dr. Baker's approach that it is much cheaper for the hospital to vaccinate rather than conduct laboratory testing. With respect to giving MMR to adults, there is a significant incidence of arthritis in post-menarchal women who get rubella. The cost-effectiveness issue is a difficult one. If there is a case of measles in a community, this would be the time to check immunity. Whether this could / should be imposed on all hospitals, clinics, at cetera for all HCW is a difficult question to answer.



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Dr. Ehresmann thought a key point was that in an era of measles and rubella elimination, they were at a new point. The decisions to be made for the future need to focus on this issue to move forward.

Dr. Lett found the proposed clarifications very helpful from the public health standpoint because they harmonize what CDC recommends during cases or outbreaks in routine practice. It is difficult when there are cases or outbreaks to ratchet up the criteria, which often results in a great deal of disruption.

With respect to implementation in various settings, Dr. Campos-Outcalt expressed concern about how many HCW may have to be re-tested due to the addition of mumps to the proposal. In addition, he wondered what was known about the side-effects of mumps antigen in older adults.

Dr. Seward responded that evidence of immunity would be serologic evidence or vaccination. CDC will take all of the comments and discussion into account, and will discuss this in further detail with the Adult Working Group before additional presentations and a vote in either June or October.

Dr. Baker asked whether the wording would be “is recommended.”

Dr. Seward replied that this would depend upon these discussions and further discussions in the working group. She thought a range could be considered, although this is complex. For routine the language reads “should consider” and for outbreaks it is “should strongly consider.” It would be nice to simplify what is currently a complex set of recommendations if possible.

Richard Zimmerman (University of Pittsburgh) requested that opportunity cost issues be considered. While everyone is for disease elimination, among occupational health, the overwhelmingly predominant concerns pertain to influenza and pertussis. Given this time of national economic uncertainties and layoffs, even some of the financially fit hospitals have downsized. The question of priority arises in this setting. In his facility, the next $10,000 for occupational health would be allocated to influenza and pertussis. While this was not to speak against the importance of measles, he found the disease incidence, burden, and risk to patients and healthcare workers for influenza and pertussis to be much greater. While not within the purview of the ACIP, he thought it would be beneficial if the Occupational Safety and Health Administration (OSHA) made pertussis, influenza, and MMR vaccination of HCW mandatory, as is Hepatitis B vaccination.

LCDR Parker responded that CDC recognizes how difficult these decisions are within the current economic climate. Consideration has to be given to what the tolerance is for allowing potentially susceptible individuals to continue working in healthcare facilities. With respect to the global context of what is currently occurring with measles, it is known that it is now endemic in the UK and there have been major outbreaks in Switzerland and France. Thus, the US continues to get importations of disease and infected individuals will seek healthcare.

Dr. Morse wondered whether the same proposed recommendations were being considered for HCW in long-term care facilities.

LCDR Parker responded that this can be discussed with the Adult Working Group. It would be beneficial to have a unified recommendation for state and local health departments, given that they are working with various facilities in the context of importations and cases.



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Dr. Chilton agreed that the ACIP is not in the business of enforcing regulations or even recommendations that the committee makes; however, others do. There is a requirement of the Joint Commission that hospitals offer influenza vaccine to their HCW. No regulating body is feared more in most hospitals than the Joint Commission; however, the success of that effort has been only about 45%. He wondered if they thought they could do better than that with measles.

LCDR Parker replied that for this recommendation it would just be a one-time effort. Given the fact that facilities could be allowed several years to implement this recommendation, a higher success rate could be achieved.

With regard to attempting to harmonize evidence of immunity for measles with what is already being done for varicella, James Turner (ACHA) pointed out that according to the June 2007 *MMWR*, physician diagnosed disease is still accepted for varicella as evidence of immunity. This appeared to be inconsistent with one of slides that stated that "varicella already includes laboratory confirmation of disease." He wondered whether there was any intent to drop the physician diagnosis of varicella from the recommendation.

Dr. Seward responded that the vaccination program for varicella is at a very different stage than that for measles and rubella, although it is changing rapidly. The varicella program has only been in place for 10 years, so there is a lot more varicella circulation. Perhaps in two to three decades varicella history could be dropped. There are already problems with children in terms of varicella history. Dropping the recommendation for varicella evidence of immunity has not been specifically discussed with the ACIP Working Group; however, it could be raised for consideration. She thought they were drawing the analogy that no birth year level of immunity is allowed for HCW. A higher bar is required for varicella, so the same should be required for measles and rubella.

Stephen Foster (APhA) thought it would be much easier to find people born before 1957 compared to trying to find those who knew they had been screened or vaccinated. It was not clear how many HCW born before 1957 had been involved in these outbreaks, titers may not prove anything, and what the vaccine does to older individuals is unknown as this has not been studied. He thought far too many questions needed to be answered before making a general recommendation.

Dr. Katz (IDSA) noted that as discussed in the new *MMWR*, there were over 3,500 cases of measles in Europe in 2008. He wondered what data might be available with regard to nosocomial spread among HCW with the outbreaks in Switzerland, France, UK, and Italy.

Dr. Seward responded that she was not aware of such data. In terms of the experience during measles resurgence in 1989 to 1991, California had a lot of measles cases in HCW, including many in people born before 1957. She would expect that most people in Europe would have sought healthcare and thus they would have experienced a lot of these issues there. She will seek further information about this.

Dr. Cieslak was impressed by how low the numbers were (e.g., 27 reported cases of measles over an 8-year period in HCW). He would have a difficult time expanding the recommendation for measles vaccination, which this would effectively do, against a disease in which the current set of recommendations has resulted in the disease's elimination.



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## General Recommendations

### Overview

**Ciro Sumaya, MD, MPH**
**Chair, General Recommendations Working Group**

Dr. Sumaya reported that the General Recommendations Working Group publishes an *MMWR* at approximately 5-year intervals (although they are now working at a 3-year interval due to numerous upcoming changes in the general recommendations), addresses immunization issues relevant to all vaccines, and addresses topics ad hoc that cannot be attributed to a single vaccine. General recommendations on immunization are directed to providers who are giving many different vaccines every day. Providers come from variable backgrounds (e.g., physicians, nurse-practitioners, nurses, pharmacists, medical assistants). Text is accompanied by tables for quick reference.

Methods for recent general recommendations were to select a group of volunteers to review and revise storage and handling of imunobiologics recommendations. The working group has convened four teleconferences since the October 2008 ACIP meeting to discuss storage and handling and altered immunocompetence.

General recommendations that were recommended, brought forward, and completed through October 2008 included: Introduction, Timing and spacing of immunobiologics, Contraindications and precautions, Preventing and Managing Adverse Reactions (Benefit and Risk Communication), Reporting adverse events after vaccination, The National Vaccine Injury Compensation Program, and Vaccine administration. Added as of the February 2009 ACIP meeting were: Storage and handling of immunobiologics and altered immunocompetence. The group will continue to move forward on other sections of the document that have not yet been completed, and ultimately the entire document will be presented to the ACIP for a final vote, with publication projected for December 2009.

### Storage and Handling Immunobiologicals

**Andrew Kroger, MD, MPH**
**CDC / CCID / NCIRD / ISD / EIPB**

Dr. Kroger discussed the revision of a current section in the 2006 General Recommendations. The main focus of the 2006 section addresses various topics one of which is maintaining the cold chain through the proper selection of storage units, thermometers, and proper preparedness for what to do when the temperature deviates. The source material for the 2006 version of the General Recommendations was an *MMWR* published in 2003 that covered those topics [*MMWR* 2003;52:1023-5]. Information is also included in this section for recommended ranges for various vaccines, with its background in discussions which have been documented in the General Recommendations chapter of the then 4th Edition of the textbook “Vaccines” by Stanley Plotkin and Walter Orenstein. The specific topics in this section are: Introductory Statements, Storage Temperature (description and reference to a table that includes the actual temperature cutoffs), Storage Units, Temperature Monitoring (staffing considerations, selecting appropriate thermometers, et cetera), and Response to Out-of-Temperature-Range Storage. Topics considered as “vaccine handling” include: Expiration Dates and Windows and Multidose Vials (to state the importance of maintaining sterility and observing the labeled expiration dates).



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Limited revisions are being made to the storage and handling section. Many of the revisions are simply clarifications, the inclusion of new vaccines, and strengthening of the recommendation of proper storage units. Because there is an increasing number of vaccines, CDC has made some new recommendations, with which this document needs to align. The increasing number of vaccines means that financial risk of destroyed vaccine has increased and storage space is a concern. Due to these issues, the VFC program has now implemented an action plan to phase-out a particular type of combination unit known as a dorm-style unit. Illustrating with a photograph, Dr. Kroger pointed out that in these combination units, the evaporating plate in the upper right chamber creates a space that is cooler than the rest of the unit, basically meaning there are refrigerator and freezer spaces within the chamber. This type of unit is not sufficient for storing vaccines, given that they are typically small and cannot store all of the new vaccines, they have an uneven distribution of temperatures specifically in the refrigerator portion, and there can be deviations in the refrigerator having to do with the way units self-regulate their temperature. The primary problem that exists is that vaccine that should be kept at refrigerating temperature is freezing. Dr. Kroger also shared a photograph of a stand alone unit that contains only a single chamber. Use of these units is preferable because they are larger and will maintain temperature in a more uniform manner.

With respect to the specific language revisions that will be made to the Storage and Handling of Immunobiologics section is to strengthen the section in which the various types of units are described, "Such single-purpose units sold for home use are less expensive alternatives to medical specialty equipment (*100*) and are preferable to combination units " (Draft Page 2, Line 10).

Practical Considerations / Clarifications are also included, which are based on the expert opinion of the working group. These include the following statements:

> New units may need two or more days of operation to establish a stable operating temperature after being set up; vaccine should not be stored in the unit until the unit has settled upon an appropriate and stable storage temperature (Draft Page 2, Line 21).
>
> All office and clinical staff should be aware of vaccine vulnerability and storage requirements (Draft Page 3, Line 12). This statement is included in the Temperature and Monitoring section that includes accompanying language that still designates one person to be the champion of vaccine storage, along with having a back-up. The idea was to emphasize that everyone has something to gain from the proper storage of vaccine, and that this is a shared responsibility of all office staff.

Some language was changed to qualify or temper some of the absolute language in the previous document, with the emphasis on *it might be necessary* because the working group wanted to include qualifying language to emphasize the fact that whereas the previous language was very directive with regard to moving vaccine as quickly as possible, they wanted to recognize that there are certain occasions (e.g., power outages, fires, et cetera) that may make it dangerous for staff to enter the situation:



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It might be necessary to transfer vaccine to a pre-designated alternative emergency storage site if a temperature problem cannot be resolved immediately (i.e., unit unplugged or door left open) (Draft Page 4, Line 21)

- → "Weakened" revision reflects recognition that certain environments may be dangerous for staff to enter
- → External temperature monitoring may reduce the need for staff to enter the environment and open the door
- → Vaccine stability is enhanced if the door is NOT opened

Clarification on repeat dosing following administration of expired vaccine was also added, based upon expert opinion, "Inactivated vaccines should be repeated as soon as possible. Live vaccines should be repeated after a 28 day interval from the invalid dose. This is to allow waning of interfering (i.e., interfere with the replication of the second dose) antibodies that have been stimulated by residual antigen from previous doses" (Draft Page 6, Line 4). The point is to get across the idea that even if a vaccine has been administered and is considered expired, there still may be residual virus within that vaccine that may stimulate an antibody response. There was discussion within the working group with respect to what component of the immune system is actually responsible, so this language can be further revised. The idea was to document the concept of inactivated versus live vaccines in the context of expired vaccine that is administered.

Table 10, the Vaccine Storage Temperature Recommendations, which lists all of the vaccines in use and their storage temperature cutoffs, is straight from the 5th Edition of "Vaccines." The change was to reorder the categories by vaccine types, given the important considerations of whether the vaccine contains an aluminum adjuvant (which makes it freeze sensitive), whether the vaccine contains a varicella antigen (which makes it heat sensitive), and the route of administration. No changes have been made to the temperature range recommendations, with the exception of LAIV which now listed at 35º-46ºF. The table will include a list of the vaccines within each of the categories of: Non-lyophilized Aluminum Adjuvanted, Non-lyophilized Non-aluminum Adjuvanted, and Lyophilized Reconstituted Vaccine (non-varicella); the storage temperatures for the vaccine; the storage temperature for the diluent; and additional comments about the vaccine.

## Vaccination of People with Altered Immunocompetence

**Andrew Kroger, MD, MPH**
**CDC / CCID / NCIRD / ISD / EIPB**

The other section that the General Recommendations Working Group is revising is "Altered Immunocompetence." The working group does not want to make very many changes from the current 2006 General Recommendations. Much of the content in this section comes from the 1993 Altered Immunocompetence Standalone ACIP statement, which includes a great deal of useful information. The general topics in this section include: General Principles, Altered Immunocompetence as an Indication to Receive a Vaccine, Vaccination of Contacts of Persons with Altered Immunocompetence, Vaccination with Inactivated Vaccines, Vaccination with Live-attenuated Vaccines, Recipients of Hematopoietic Stem Cell Transplants, and Situations in Which Some Degree of Immunodeficiency May Be Present.



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There are safety issues with respect to live zoster vaccine in someone who is immunocompromised because it will be a replicating vaccine virus, perhaps not to the same degree as other live vaccines. This is a vaccine used in adults, and immunocompromized adults typically have antibodies to the vaccine virus due to a previous history of infection with varicella zoster virus. Zoster vaccine requires revision to several sections. All changes are imports of ACIP Zoster Recommendations (06/08).

The language for Vaccination with Live-attenuated Vaccines (Draft Page 13, Line 3), which is derived primarily from the package insert:

> "The incidence of zoster is increased in persons with altered immunocompetence. Adults with most types of altered immunocompetence are still expected to maintain residual immunity to varicella-zoster virus because of past infection that protects against primary varicella but offers incomplete protection against zoster. Zoster vaccine is contraindicated in individuals with primary or acquired immunodeficiency states (e.g. lymphoma, leukemia, tumors involving the bone marrow and patients receiving chemotherapy) and some AIDS patients. In some cases of altered immunocompetence such as AIDS patients with CD4+ lymphocyte counts greater than 200 cells/ul, there is no contraindication to zoster vaccine. "

Altered Immunocompetence Zos Language reads as follows:

> Persons with impaired humoral immunity can also receive zoster vaccine (Draft Page 14, Line 18).
>
> Many candidates for zoster vaccine are treated for other conditions with the drugs methotrexate (0.4 mg/kg/week or less) azathioprine (3 mg/kg/day or less or 6-mercaptopurine (1.5 mg/kg/day). Patients on these medications at these low doses can receive zoster vaccine (Draft Page 19, Line 3).

There are also some revisions to Table 12, Vaccination of Persons with Primary and Secondary Immunodeficiencies, which further categorizes primary immunodeficiencies into B-cell and T-cell deficiencies. In this table, there were some omissions from the 2006 version, so some corrections were made. This section will be harmonized with AAP Red Book. Severe B-cell deficiencies will now be included as a contraindication for yellow fever vaccine following discussions with yellow fever vaccine SMEs. T-cell deficiencies are also listed as a contraindication for yellow fever vaccine. Another correction is a listing of less severe B-cell deficiencies as a contraindication for bacterial vaccines. Severe B-cell and T-cell deficiencies are also listed as contraindication for bacterial vaccines. The footnote will be revised to indicate that OPV is no longer licensed in the US and not routinely recommended.

**Discussion**

Dr. Marcy strongly emphasized that using a standard fluid-filled thermometer was highly outdated. For example, there is no way to know based on this type of thermometer whether a power shortage has occurred. There are numerous thermometers on the market for reasonable prices that are much cheaper than wasting vaccine. The Fisher Scientific website now states that "CDC now recommends using continuous, certified, and calibrated chart recorders for vaccine storage monitoring." He suggested that CDC catch up with what Fisher Scientific says the agency does.



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As with many recommendations, Dr. Kroger indicated that the working group wants to use a common denominator in terms of the feasibility to be able to purchase these items. They were hesitant to make more specific recommendations without cost-effectiveness studies of the various products offset against the cost of vaccine losses. These types of studies are underway, but in the interim there is other practical guidance in the revised draft that addresses issues such as the potential cost-effectiveness of purchasing a new thermometer versus having it calibrated. However, no specific preference is stated.

With respect to corticosteroid, Dr. Marcy indicated that in 1993 the ACIP was asked where they acquired the data for 2 mg/kg and 20 mg of prednisone as being safe for live vaccines for less than two weeks. At that time, Dr. Orenstein indicated that he got this from the Red Book. The Red Book then said they got this from ACIP. With that in mind, Dr. Marcy pointed out that there are no data to validate those recommendations and he strongly encouraged someone to review this information.

Neal Halsey indicated that he was coordinating some of this issue, upon which considerable effort was spent. Some of the immunologists involved in the care of these children reviewed the guidelines. Therefore, while the recommendations were based largely upon expert opinion, it was not just the Red Book, but was also based on information from immunologists who use these drugs regularly. There is some evidence, although it is not as evidence-based as would be preferable.

Dr. Englund indicated that the Hematopoietic Stem Cell Transplants section needed to be updated. She is on the working group that has spent a lot of time on this issue, and reported that based on that work, there is good evidence-based medicine to suggest that immunization can be started early. This recommendation should be harmonized with the recommendations of that working group. Children 6 months of age are routinely immunized in a lot of centers. With that in mind, she did not believe ACIP should vote on the Immunocompetence Section at this time.

Dr. Sawyer thought the storage and handling recommendations were very good; however, they represented changes that would be lost on some practicing physicians who are not very familiar with the nuances of the temperature in their refrigerators and less familiar with the general recommendations. Thus, some effort to promote this information through CDC, AAP, AAFP, and other partners is imperative.

Dr. Judson indicated that a cheap alternative monitor is the double set back mercury u-tube thermometers at a cost of less than $20 that will lock in the high temperature and low temperature for a certain period.

Dr. Bell reported that CDC has a pilot project in a number of states in which refrigerators and continuous monitoring temperature equipment are being supplied to evaluate feasibility, impact, accessibility, et cetera.

Dr. Morse inquired as to whether there was a process of certifying refrigerators that meet basic criteria for vaccine storage. With the amount of funds being spent on vaccines, it seems that there should be some industry-wide standard. Recalling and revaccinating patients appears to be a major problem and burden that seems to be increasing.



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Dr. Santoli responded that CDC is also partnering with the National Institute for Standards and Technology (NIST) to develop a "Consumer Reports" type set of recommendations about equipment for storing, monitoring, and calibration.

Dr. Sumaya indicated that the Working Group realized that much remains unknown about how best to store and handle vaccines. There is also the reality check that whatever the storage unit, it must fit into the various settings where vaccines are kept (e.g., private offices, pharmacy areas, et cetera). All of this must be addressed.

Sandra Jo Hammer (Department of Public Health, California) pointed out that offices have a tendency to underestimate the value of the vaccines in their refrigerators. The California Department of Public Health has already sent out a letter indicating that facilities having more than 5000 doses a year must have a refrigerator only unit. The major problem is that many offices have equipment that has been recycled from elsewhere (e.g., the latest remodeling of a physician's home kitchen). There is no control over the temperature in such units. They receive calls asking them whether slush means that vaccine is frozen. Their VFC representatives have been equipped with temperature guns, who report different temperatures for different shelves within the same unit, yet vaccine get rearranged. To address this issue, perhaps ACIP could convene a special working group as Australia did to consider this complex problem.

**Motion: Storage and Handling Revisions**

Dr. Chilton moved to approve the Storage and Handling Section revisions. Dr. Baker seconded the motion. The motion carried with 14 affirmative votes, 0 abstentions, and 1 negative vote.

## HPV Vaccines

### Introduction

**Janet Englund, MD**
**Chair, ACIP HPV Vaccine Workgroup**

As discussed during the last few meetings, upcoming issues for ACIP consideration for HPV vaccine include: Bivalent HPV vaccine in females; quadrivalent HPV vaccine use in males; and quadrivalent HPV vaccine use in females greater than 26 years of age. Dr. Englund briefly reviewed the status of each of these topics.

As discussed during previous ACIP meetings, a supplementary Biologic License Application (BLA) with data for the quadrivalent HPV vaccine for females greater than 26 years of age was submitted to the FDA. This included data from the interim analysis of the efficacy trial in women 26 to 45 years. The workgroup considered and proposed some options to ACIP concerning possible recommendations for this age group. However, in December 2008 the FDA requested 48 month data from the trial. These data will be submitted in late 2009, so it is likely that this issue will not be considered by ACIP until 2010.

A supplementary BLA with data on the quadrivalent HPV vaccine in males was submitted to the FDA in December 2008. FDA action is expected to take up to 10 months. The workgroup is preparing for a potential ACIP vote in October 2009.



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For bivalent HPV vaccine in females, the BLA based on interim data from the Phase III trial was submitted to the FDA in 2007. Following feedback from the FDA, GSK decided to wait for end-of-study data. These data will be submitted during the first half of 2009. FDA action is expected to take up to 6 months. The ACIP workgroup is preparing for a vote in October 2009 or February 2010.

Based on the expected time frame for the upcoming decisions, the workgroup hopes to present data for these two decisions (e.g., quadrivalent HPV vaccine in males and bivalent HPV vaccine in females) over the next few ACIP meetings. The potential schedule for the HPV sessions during the ACIP meetings is as follows:

| Dates | Quadrivalent HPV Vaccine: Males | Bivalent HPV Vaccine: Females |
|---|---|---|
| February 2009 | Burden of disease in males<br>Phase III efficacy data | ASO4 adjuvant and meta-analysis |
| June 2009 | Cost effectiveness<br>Acceptability studies<br>Recommendation options | Phase III efficacy data<br>Cost effectiveness<br>Recommendation options |
| October 2009 | If FDA approval, vote | If FDA approval, vote |

The workgroup hopes to present cost-effectiveness analyses relevant to both of these decisions, as well as potential recommendation options during the June 2009 meeting. It is possible that there could be a vote on both of these decisions in October 2009.

The workgroup has continued to convene conference calls at least monthly, and has been reviewing data related to both of these decisions. For the bivalent vaccine, the workgroup has heard data on comparative bivalent / quadrivalent immunogenicity, ASO4 adjuvant mechanism of action, and meta-analysis of adverse events in Monophosphoryl Lipid A® (MPL®)-containing vaccines. The workgroup has also started to consider issues related to the quadrivalent HPV vaccine in males, reviewing efficacy data in males that were to be presented during this meeting and an overview of cost-effectiveness models published to date. Workgroup members have also reviewed data on HPV vaccine in pregnancy and vaccine safety.

## Update on Bivalent HPV Vaccine: AS04 Adjuvant Mechanisms of Action and Safety Meta-Analysis

**Thomas Verstraeten, MD, MSc**
**Head of Safety, GSK Biologicals**

Dr. Verstraeten explained that the reason for introducing the AS04 adjuvant was to have a better and more prolonged immune response, which is expected to lead to longer protection. During this presentation, he discussed the safety aspects of this novel adjuvant. Dr. Verstraeten reported on the mechanism of action of the adjuvant system AS04, the meta-analysis of the risk of Auto Immune Disease (AID) following AS04 adjuvanted vaccines, and the post-marketing experience. GSK does not believe this mechanism of action supports biological plausibility for induction of autoimmune disease.



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The novel adjuvant AS04 consists of two components: Alum and MPL®. MPL® is derived from lipopolysaccharide LPS (*Salmonella Minnesota*). MPL® basically has similar but reduced immune activity as LPS in that it acts via a TLR4 signaling pathway, and induces cytokines with a key role in the induction of humoral responses (IL-6 and TNFα); and does not induce IFNα, a cytokine associated with the precipitation of some autoimmune diseases [Baccala R et al,Nature medicine,vol13, N5, 543-551]. AS04 effect requires a temporal and spatial co-localization with antigen to function. AS04 acts at the earliest step of the immune response on antigen presenting cells (APC) only through TLR4 pathway and has no direct, non-specific activation of T and B effector cells.

To evidence that the AS04 effect requires temporal and spatial co-localization with the antigen, GSK investigators injected a group of mice first on one side with AS04 by itself and later with the VLP separately. This was done at several time intervals. The immune response decreased with the longer interval between the two administrations. From co-administration to one hour, there is little difference and it is not significant. However, after one day there is already a significant decrease in the response, and after three days the response has further decreased. A second experiment involved administering the AS04 on one side and then later administering the VLP on a different site. It made little difference whether this was done simultaneously or at different time intervals. The immune response was always highly inferior compared to the co-localization in time and space. This means that the adjuvant needs to be injected at the same place as the antigen, and needs to be injected simultaneously or at least within one day. This supports previous observations that the adjuvant is only present for about one day at the injection site. With respect to the relevance to autoimmune disease, in general the concern about this new adjuvant's relationship to autoimmune disease is that many people have a perception that these adjuvants are extremely potent and have prolonged and generalized stimulus of the immune system. This experiment shows that this is actually not the case. Instead, the immune stimulation is quite localized, it is targeted to a specific antigen, and there is limited time and space for the stimulation even though the actual immune response is quite long-lasting.

With regard to the clinical data, GSK performed a meta-analysis to examine the risk of autoimmune disease following the HPV vaccine and other AS04 adjuvanted vaccines. This safety evaluation was done in support of the HPV BLA in the US at CBER's request. Although there have been more updates of these analyses with more recent data, Dr. Verstraeten focused on that data that has been published. This evaluation included over 68,000 subjects from 42 studies, including on-going studies. All except two of these studies were completely sponsored by GSK. Two studies were co-implemented by GSK and other institutions. The data presented during this meeting were the analyses and interpretation of GSK only. The methodology for this analysis was pre-specified and agreed to with CBER [Analysis of adverse events of potential autoimmune aetiology in a large integrated safety database of AS04 adjuvanted vaccines. Verstraeten et al, Vaccine 2008, 26: 6630–6638].

This analysis was conducted at two different levels. The first level was the HPV vaccine alone, which is AS04 adjuvanted. This analysis included over 39,000 subjects in clinical trials. The second level is that added to this first group were the Herpes Simplex 2 Virus vaccine (HSV) clinical development program and a Hepatitis B Adjuvanted vaccine (licensed in Europe under the name Fendrix™) development program. The second level of analysis added an additional 30,000 subjects for a total of more than 68,000 subjects in this analysis.



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The list of events included in this analysis were: Neuroinflammatory (e.g., optic neuritis, multiple sclerosis, demyelinating disease, myasthenia gravis, transverse myelitis, myelitis, encephalitis, and Guillain-Barre syndrome); Musculoskeletal (e.g., systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, juvenile rheumatoid arthritis, arthritis, reactive arthritis, and scleroderma); Gastrointestinal (e.g., inflammatory bowel disease, Crohn's disease, ulcerative colitis, ulcerative proctitis, and Coeliac disease); Thyroid (e.g., Graves' disease, thyroiditis, hyperthyroidism, hypothyroidism, and goiter); Skin (e.g., cutaneous lupus, dermatomyositis, vitiligo, erythema nodosum, psoriasis, psoriatic arthropathy, Stevens-Johnson syndrome, and Raynaud's phenomenon); and Others (e.g., autoimmune haemolytic anaemia, antiphospholipid syndrome, IDDM, idiopathic thrombocytopenic purpura (ITP), autoimmune hepatitis, nephritis, autoimmune glomerulonephritis, uveitis, sarcoidosis, Addison's disease, and vasculitis).

Regarding the primary results of the AS04 safety meta-analysis of autoimmune disorders, Dr. Verstraeten described the relative risks observed when comparing the subsets who received AS04-containing vaccines compared to the group that received control vaccine without AS04. In the comparison of subjects who experienced any events, there were 96 diagnoses in the AS04 group compared to 104 in the control group, with a relative risk of 0.92 and relatively narrow confidence intervals of 0.70 to 1.22. The relative risks for systems (e.g., gastrointestinal, musculoskeletal, neuroinflammatory, skin disorders, thyroid disease, and others) do not differ much from 1.0 and the confidence intervals, as would be expected, are dependent upon the number of cases that go into the analysis. The majority of the cases came from the group of thyroid diseases, as would be expected in this female age group. Much fewer events were observed in the group of neuroimflammatory disorders. In terms of the second level of analysis (e.g., HPV vaccines combined with HSV-adjuvanted and Hepatitis B vaccines) overall the relative risk is not very much different, the confidence intervals become somewhat more narrow, and the relative risks change very little from category to category (all are fairly close to 1.00). None of the confidence intervals exclude 1.00.

In a comparison of observed and expected incidence rates (per 100,000 person years) for neuroinflammatory events among the subjects in the meta-analysis (e.g., Level 2, pooled controlled and uncontrolled studies), investigators estimated the incidence rates in the AS04 group and compared that to rates expected given the background rates and rates as they were observed in Northern California Kaiser in a similar gender and age group. The observed incidence rates fall pretty well within the expected incidence rates, which is reassuring in two ways: there does not seem to be an increase; and it supports that GSK did capture these cases in their clinical trials:

| | **Observed Rate In the MPL Group (+ 95 % CIs)** | **Range of background rates** |
|---|---|---|
| Guillain-Barré Sy | 1.3 (0.0, 7.4) | 0.4 – 3.5 |
| Multiple sclerosis | 5.3 (1.4, 13.6) | 3.1 – 15.9 |
| Myasthenia gravis | 1.3 (0.0, 7.4) | 0.1 – 2.0 |
| Optic neuritis | 4.0 (0.8, 11.7) | 5.7 – 8.2 |
| Transverse Myelitis | 0.0 (0.0, 6.4) | 0.1 – 3.2 |

There are some limitations to these analyses. The first is that there is a lack of validation of the diagnoses. The analyses as shown are based on the diagnosis as reported to GSK by the investigators. Given that these are randomized trials, there is no reason to expect that the validity of the diagnoses would differ between the AS04 and control groups. Further sub-analyses are on-going, including adjudication of selected events of interest. Another limitation is



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the variability between studies in the collection of adverse event data. The HPV studies collected more extensive and complete safety information, including non-serious adverse events throughout the study periods. The results are consistent between HPV only and extended analyses.

Regarding the post-marketing experience to date, GSK's vaccine is now licensed in 93 countries. The largest use of the vaccine currently is in the UK, given that this vaccine has been chosen to be used for universal mass vaccination of females 12 years of age. This universal program began in September 2008. At this time, Over 80% have received at least one dose [www.immunisation.nhs.uk/vaccines/hpv]. Catch-up vaccination in those up to 18 years of age using GSK's vaccine has begun. Intense safety monitoring is being conducted by the Medicines and Healthcare products Regulatory Agency (MHRA) and GSK. No safety concerns have arisen thus far.

In conclusion, the MPL® mode of action does not suggest a biologically plausible mechanism for induction or exacerbation of AID. A meta-analysis of clinical studies showed no indications of any causal association between GSK's HPV or other AS04 adjuvanted vaccines and the development of autoimmune disease, given that the proportion of subjects in whom autoimmune diseases occurred was comparable between the AS04 and control groups, and that the distribution of the autoimmune diseases reported corresponds to the distribution expected. The observed incidence rates for neuroinflammatory events are within the expected ranges. Post-marketing surveillance has indicated no safety concerns on GSK's HPV vaccine thus far.

## Burden of HPV Related Disease in Males

**Mona Saraiya, MD, MPH**
**CDC / NCCDPHP / DCPC**

Dr. Saraiya discussed HPV and its causal role in various male diseases, and the burden of HPV-associated male disease with respect to anal cancer, penile cancer, oropharyngeal cancer, and genital warts. For the sake of comparison, she provided disease burden information about women as well.

The International Agency for Research on Cancer (IARC) released a second report in 2007 assessing the causal role that HPV plays in cancers. They found that 13 HPV types, including HPV 16 and 18, cause cervical cancer. In addition, they concluded that HPV 16 causes several other anogenital and oropharyngeal cancers. However, the report concluded that there was insufficient evidence that HPV 16 definitely causes laryngeal or that HPV 18 causes other anogenital or oral cancers [International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 90 (2007) Human Papillomaviruses].

With regard to HPV-associated cancers and the attributable fraction due to HPV, 90% of anal cancers are thought to be due to HPV. Of those, approximately 92% are thought to be due to HPV 16 or 18. That is, approximately 80% are due to HPV 16 and 18. This percentage is fairly conservative for some cancers and it is important to know that this percentage can vary depending on when the study took place, type of HPV assay used, where and when the study was conducted, how the anatomic site was sampled, and what kind of histology the study was limited to. More recent studies do show that the percentage of HPV prevalence may be higher in vaginal and oral cavity and oropharynx cancers.



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The status of US registries today is such that 100% of the US population is covered. Having such a large amount of coverage is ideal for monitoring rare cancers and having the ability to look at specific histology or racial / ethnic groups for a shorter period of time. Cancer registries collect data on all types of invasive cancers and all in situ cancers, except cervical carcinoma in situ. Generally, the Surveillance, Epidemiology and End Results (SEER) cancer registries have been in existence much longer; therefore, they are able to provide trend data. Traditionally, cases are diagnosed by providers in hospital-based registries. Registries have expanded over the years to also register cases diagnosed in non-hospital settings (e.g., physician offices, non-hospital based pathology labs, radiation treatment centers, and surgery centers). All cases are registered by certified tumor registrars and reported to state-based central cancer registries, also known as population-based registries, either through direct reporting or via regional registries. These data are transmitted to federal agencies to compile a national database of cancer incidence and mortality. Throughout the remainder of her presentation, Dr. Saraiya used SEER data to described trends because they go back to the 1970s, and she used the combined cancer registries to illustrate the current burden of disease.

With regard to the average annual counts and rates of HPV-associated cancers among women and men from 1998-2003, 39 cancer registries met the criteria for high quality data so the coverage is limited to 83% of the US population. Since cancer registries do not collect data on HPV positivity, the way HPV-associated was defined was by limiting cancers to the epithelial types, and in certain instances limiting it to certain anatomic sites that are considered to have higher HPV DNA prevalence. Not taken into consideration was the fraction of those cancers attributed to HPV, given the caveats described earlier. Among women, cervical cancers represent the largest proportion of all HPV-associated female cancers for a total of 17,350 HPV–associated cancers in women compared to 7,568 in men. Of those 7,568 in men, the number of oropharyngeal cancers are by far the larger proportion of all HPV-associated cancers (n=5,658).

Trends for anal cancer have been increasing over the past 30 years, with approximately 1000 cases a year, the rate being 1.0 per 100,000. Females have higher rates than men. Risk factors in men include lifetime number of sexual partners, receptive anal intercourse, and immunosuppression. High risk populations include men who have sex with men (MSM), those who are HIV+, and African Americans. Routine screening using anal cytology is not recommended, although certain experts do advocate screening in high risk populations, such as MSM and HIV+ populations.

The incidence of invasive anal cancers has been increasing over the past 30 years, from 0.6 in 1973 to 1.3 in 2003. The increase occurred in both males and females, but the gap between women and men persisted over time [Data source: SEER 9 Regs Limited-Use, Nov 2005 Sub (1973-2003), covering 9% of US population]. The incidence increases with age and peaks somewhat earlier for males than females. The median age of diagnosis for males is 57 versus 62 for females [Adapted from Joseph D et al. Understanding the Burden of Human Papillomavirus-associated Anal Cancers in the US, *Cancer* 2008. Data Source: National Program of Cancer Registries and SEER, covering 83% of US population].

Penile cancer rates have also been decreasing in the US for the past 30 years. It accounts for less than 1% of all cancers in men, with 829 cases of invasive cancer per year, withy a rate of 0.8 per 100,000. Risk factors include lack of circumcision, chronic penile inflammation, immunosuppression, and cigarette smoking. High risk populations include Hispanic men partially due to lower circumcision rates. Routine screening is not recommended. The incidence of penile caner actually has declined over the past 30 years from 1.0 per 100,000 in



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1973 to 0.6 per 100,000 in 2003 [SEER 9 Regs Limited-Use, Nov 2005 Sub (1973-2003), covering 9% of US population]. Like most cancers, penile cancers increase with age. The median age of diagnoses is 68 [Adapted from Hernandez B et al. Burden of Invasive Squamous Cell Carcinoma of the Penis in the United States, 1998-2003. *Cancer* 2008. Data source: National Program of Cancer Registries and SEER covering 83% of US population].

Twenty to 35% of oropharyngeal and oral cavity cancers have had HPV DNA presence. However, even with that group, a certain subset has higher HPV positivity. Anatomic sites used as surrogates of potentially HPV-associated cancers include the base of the tongue, Waldeyer Ring, lingual and palatine tonsil, and oropharynx. The rest of the head and neck cancers are considered less HPV-associated, are grouped together for comparison, and are called HPV-unrelated sites. The trend for oropharyngeal and oral cavity cancers has been increasing specifically in men. There are approximately 5,658 cases per year, with a rate of 5.2 per 100,000. Risk factors include tobacco use, alcohol use, and lifetime number of sexual partners. High risk populations include African American. Routine screening not recommended by the USPSTF as screening has not been shown to reduce mortality, but certain experts do recommend screening as part of a routine checkup.

From 1973-2003, the incidence of invasive HPV-associated oropharyngeal and oral cavity cancers increased from 3.2 to 4.9 among men, with an annual percent change of 0.8 per year. The rate for women went down every year [SEER 9 Regs Limited-Use, Nov 2005 Sub (1973-2003), covering 9% of US population]. The trend has decreased for non-HPV-associated oropharyngeal and oral cavity cancers in both men and women. The age-specific incidence curves show that the peak for men is curvilinear and rises steeper compared to women. The median age of diagnosis for men is 58 versus 64 for women [Adapted from Ryerson B, et al. Burden of Potentially Human-Papillomavirus-associated Cancers of the Oropharynx and Oral Cavity in the US, 1998-2003. *Cancer* 2008; Data source: National Program of Cancer Registries and SEER covering 83% of US population].

An important HPV disease in men is genital, with HPV 6 and 11 causing 90% of genital warts. The incidence is estimated at 250,000 cases per year, although these are imprecise estimates given that there is no systematic surveillance of genital warts. The prevalence is higher in men than women in most studies. Risk factors include lifetime numbers of sexual partners and being immunocompromised. Genital warts impact quality of life, are often recurrent, and can require extensive treatment. Administrative claims data on the prevalence of genital warts show that the rate peaks earlier by five years for women in their early 20s compared to men in their late 20s to early 30s [Insigna R et al. The health and economic burden of genital warts in a set of private health plans in the United States; Clin Infect Dis 2003. Data Source: Medstat]. In contrast to other studies that show prevalence is higher in men and women, in an NHANES nationally representative sample of 18-59 year olds from 1999-2004, sexually active men and women were asked, “Has a doctor or health care provider ever told you that you had genital warts?” Based on this survey, the cumulative prevalence of genital wart diagnosis in women was 7.2% and in men was 4% [Dinh TH et al. Genital warts among 18- to 59-year-olds in the United States, National Health and Nutrition Examination Survey, 1999-2004; Sex Trans Dis 2008].



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In summary, there is a higher burden of HPV-associated cancers in females compared with males. Oral cavity / oropharyngeal cancers are the largest proportion of HPV-associated cancers among males and the incidence is increasing. There is a low incidence of anogenital cancers in men, although anal cancers are increasing and certain populations are at higher risk. No screening is recommended for anal, penile, or oral cavity / oropharyngeal cancers. Genital warts are common.

**Update on Quadrivalent HPV Vaccine: Efficacy Data in Males**

**Richard M. Haupt, MD, MPH**
**Clinical Research**
**Infectious Diseases & Vaccines**
**Merck Research Laboratories**

Dr. Haupt reported on Merck's male efficacy and safety study, known as Protocol 020, in 16 to 26 year old males (N = ~4000 men). Merck conceptualizes the benefit of male vaccinations is in terms of the benefit of GARDASIL® in two populations: (1) boys and men themselves, and (2) in addition, the broader population, including females. There is an intrinsic benefit to boys and men, given the overall disease burden of cancers and genital warts in men. There is also an overall public health benefit in that vaccine coverage in girls is likely to be incomplete. Vaccinating men offers the opportunity for herd immunity. Transmission of HPV occurs efficiently between sexual partners. The value of a gender-neutral vaccination is that it extends vaccination coverage, eliminates gender inequities, reduces viral transmission, decreases circulation of virus in the population, and broadens the population and public health benefit.

With respect to background, Protocols 16 and 18 were immunogenicity and safety studies in adolescent males and females between 9 and 15 years of age. These studies were conducted several years ago, have already been published, and were submitted to the FDA with the original Biologic License Application (BLA) in Fall 2005. In December 2008, the data from Protocol 020 (male safety and efficacy study) were submitted to the FDA.

As with all of Merck's GARDASIL® efficacy trials, Protocol 020 is a randomized (1:1), double-blind, placebo-controlled trial. Males received GARDASIL® or placebo at 0, 2, and 6 months. Anyone who received three doses within a year would have been counted in the per-protocol efficacy analysis. This study is designed to be 36 months in total follow-up, while the women's studies were designed to be 48 months. The data to date in the men's study are based on approximately 30 months of follow-up and is based largely on the heterosexual male component of the study. Enrolled subjects include heterosexual men (HM) 16-23 years old (N = 3463) and men having sex with men (MSM) 16-26 years old (N = 602). The enrollment for MSM lagged behind enrollment for HM; therefore, the majority of the HM population is completing this study while the MSM are approximately a year and half behind. This is important because it affected the endpoints Dr. Haupt was able to review during this presentation.

The primary endpoints in Protocol 020 included safety and efficacy. The primary efficacy endpoint is the combined incidence of HPV 6/11/16/18-related external genital lesions. Both the HM and MSM study participants contribute to that endpoint. External genital lesions includes external genital warts; penile / perianal / perineal intraepithelial neoplasia (PIN); and penile, perianal, or perineal cancer. There is also a sub-study in the MSM in which anal intraepithelial neoplasia (AIN) and anal cancer are the primary endpoints; however, because the MSM population is behind in enrollment, the pre-specified event cases have not been reached to conduct the formal analysis for this endpoint. Therefore, Dr. Haupt presented no data on the



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AIN sub-study at this time. Also examined was immunogenicity in terms of GMTs and seroconversion rates. The secondary efficacy endpoints included incidence of persistent HPV 6/11/16/18 infection, and incidence of HPV 6/11/16/18 DNA detection at one or more visits. Persistent infection is defined as two consecutive swabs or biopsies (defined as six months apart) positive for a vaccine type. The any type DNA means that they were looking for efficacy against any type of DNA detection, one time or more, of a vaccine HPV type in a swab or biopsy.

Baseline demographics, are as follows:

| | GARDASIL™ (N = 2,032) | Placebo (N = 2,033) | Total (N = 4,065) |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| **Age (years)** | | | |
| Mean +/- SD | 20.5 +/- 2.0 | 20.5 +/- 2.0 | 20.5 +/- 2.0 |
| Median (range) | 20 (15-26) | 20 (16-27) | 20 (15-27) |
| **Race/Ethnicity** | | | |
| Asian | 201 (10) | 205 (10) | 406 (10) |
| Black | 412 (20) | 393 (19) | 805 (20) |
| Hispanic American | 388 (19) | 447 (22) | 835 (21) |
| Native American | 2 (0.1) | 1 (0.0) | 3 (0.1) |
| White | 734 (36) | 697 (34) | 1,431 (35) |
| Other | 292 (14) | 293 (14) | 585 (14) |
| **Circumcision** | | | |
| Yes | 794 (39) | 749 (37) | 1,543 (38) |
| No | 1,232 (61) | 1,286 (63) | 2,518 (62) |
| Missing or Unknown | 3 (0.1) | 1 (0.0) | 4 (0.1) |

There was a greater participation of black males in Protocol 020 than in the studies with women, given that one of the sites was in South Africa. The circumcision rates were also captured, although these are more typical of rates observed globally than in the US alone.

While he did not have AIN efficacy data for MSM, Dr. Haupt was able to share Day 1 baseline PCR and serology information that includes both MSM and heterosexual males. 14 HPV types were tested for on Day 1, the four types in the vaccine (6, 11, 16, and 18) and 10 other high risk types. 25.2% of men were positive for one or more of the tested types. The day 1 HPV DNA positivity rate for one or more of the 14 tested HPV types was 20.9% in the HM population and 48.1% in the MSM population. The exclusion criteria were the same for heterosexual men and MSM, in that both groups were supposed to have had five or fewer lifetime sexual partners. This represents a relatively lower risk MSM population. 12.2% of the subjects were HPV DNA positive by PCR to at least 1 of the 4 vaccine types. The day 1 HPV DNA positivity rate for one or more vaccine HPV types was 8.8% in the HM population and 30.5% in the MSM population. 87.8% of all subjects were naïve to all 4 types. In terms of seropositivity on day 1 to vaccine HPV types, 7.6% of all study participants were seropositive to at least 1 of the 4 vaccine HPV types. Stratified results based on sexual orientation showed that 5.0% of the HM population were seropositive to one or more vaccine HPV types at day 1 while 22.8% of the MSM population were seropositive. Overall, 82.7% of male subjects in the Protocol 020 male efficacy study were naïve by PCR and serology to all 4 HPV vaccine types. Most men who were



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infected were infected to only one vaccine type, which is very similar to the women's study. Hence, the vast majority of men would benefit from protection to at least 3, if not 4, of the vaccine types from vaccination with Gardasil.

There was a very high vaccine efficacy of approximately 90% against external genital lesions, with 3 cases in the GARDASIL® group (n = 1,397), all of which were genital warts. There were 31 cases in the Placebo Group (n = 1,408). Persistent infection efficacy was approximately 86%, with 45% efficacy against any type DNA detection over the course of the study. The efficacy across the different types is very similar. The differences in efficacy depend more on the number of endpoints. Some of these infections are more common for types 6 or 16. Generally, there is high efficacy across all 4 of the vaccine types. In terms of GMTs and seroconversion in males, very similar to what was observed in women, virtually all men seroconverted to this vaccine who were naïve to the relevant type at baseline. The GMTs are high across all 4 types. The GMTs in men, compared to women, are somewhat lower, although it is not clear what this means at this point. Adverse events in men were similar to those in women, with the most common adverse event being local injection site reaction. Very few serious adverse events occurred, and there was no imbalance in any of the adverse events across the placebo or GARDASIL® groups. In the women's trials, the injection site reactions were in the 80% range, while these are in the 60% range in the men's trial. Merck is in the process of conducting more analyses from the placebo arm of the trial assessing natural history. Early analyses of the placebo subjects demonstrates a high rate of infection with vaccine HPV types in sexually active men who were previously uninfected.

In summary, sexually active men are at high risk for acquiring genital HPV infections. Genital HPV infections lead to a significant burden of disease in men. HPV 16 and 18 are important cancer-causing HPV types in men, responsible for the majority of HPV-related penile, anal, and oropharyngeal cancers and their associated pre-cancers. HPV types 6 and 11 cause over 90% of genital warts and RRP. GARDASIL® is highly efficacious against HPV 6/11/16/18-related persistent infections and genital warts in men. This efficacy may also translate to reduced transmission of vaccine type HPV strains between sexual partners. GARDASIL® was generally well-tolerated in 9-26 year-old boys and men. The value of vaccination of boys and men is the direct impact in preventing HPV 6/11/16/18-related diseases in boys and men, as well as the contribution to an additional public health benefit of GARDASIL®.

## Discussion

Dr. Ehresmann noted that in his summary Dr. Haupt mentioned that GARDASIL® is generally well-tolerated in males 9-26 years old; however, the study design was in 16 to 26 year olds.

Dr. Haupt responded that for the sake of time, he did not present data from the 9- to 15-year old population. Studies were conducted in the younger age groups several years ago and those data were presented to the ACIP in the past. The adverse event profile is very similar across the age groups between 9 and 26.

Recalling that in the immunogenicity studies, the group the younger women had higher immune responses Dr. Neuzil inquired as to whether the same was true for males. It appeared as if the younger ages of both genders have better immune responses than the older age groups.

Dr. Haupt responded that the 9 to 15 year old boys had higher GMTs than the 9 to 15 year old girls. In the adult population (16-26 year-olds), women are somewhat higher than men. It is known that there are gender differences in immune responses, and reports with other vaccines



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and other immune response to natural infection have demonstrated that. That may explain the difference in adult women 16 to 26 years of age. Merck believes that the difference in the 9- to 15-year old age group in terms of GMTs is that many of the 9- to 15-year old adolescent girls have gone through puberty versus the boys in that age group (who are predominantly pre-pubertal). It is known that there is developmental impact that is related to immune response. Without question the younger ages of both genders have better immune responses than the older age groups.

Dr. Neuzil's recollection of prior presentations was that a high level is achieved, which quickly comes down to baseline, and then the baseline is fairly consistent. She wondered if there was an additional time point in Protocol 020 (e.g., blood draws between 7-months and 12-months).

Based on the antibody kinetics observed with women, Dr. Haupt indicated that that they did not believe the 12-month antibody level to be very valuable. Thus, they do not do a blood draw between 7-months and 12-months for the males. Indeed a peak response has been observed, followed by a tapering of antibody level, and a what appears to be a plateau by about 24 months where they have stayed five years out. The Protocol 020 men will have another blood draw at month 36.

Referring to the 9- to -15-year olds, Dr. Meissner noted that this is very analogous to what was done with females; that is, rather than efficacy data, these are bridging studies and presumably approximately the same number of males (25%) are sexually active by 15 or 16 years of age.

Dr. Haupt responded that the 9- to 15-year old immunogenicity data bridging data was used in the original application for approval or 9- to 15-year old girls in the original bridge. Protocol 18 is an adolescent study that was extended up to month 36, which is now being extended as an effectiveness study for boys and girls for the next 10 years to evaluate vaccine effectiveness over time if, and when, the study participants become sexually active.

Dr. Meissner pointed out that Dr. Haupt was very careful in the way he phrased the effect of immunization on transmission. He wondered whether there were any data or Dr. Haupt could address this question at all; that is, is a vaccinated male less like to transmit HPV to his contacts than an unvaccinated male. Thinking of the inactivated polio vaccine, for example, such a vaccinee can still transmit polio virus.

Dr. Haupt responded that while they do not have data to support this, Merck has had internal discussions about conducting formal studies to examine the interruption of transmission. It certainly makes sense that if men and women are not becoming infected, especially persistently, and especially if they are not getting disease, transmission is very likely to be reduced. Merck is aware of data are being generated in Australia where the coverage rates are very high (80% to 90%) in which they are examining disease outcomes to determine whether there is already a reduction. In addition, they are looking at disease reductions in males to determine whether there is an impact on transmission.
An audience member inquired as to whether Dr. Saraiya had any estimates on the impact of vaccinating women according to the current vaccination recommendations on the burden of disease.

Dr. Saraiya replied that at this time, such information was not available.

Dr. Katz (IDSA) was under the impression that dentist screened for oropharyngeal cancers.



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Dr. Saraiya responded that she was going by the recommendations of the US Preventive Services Task Force, which does not recommend routine screening in general. While screening is conducted for oral cavity cancers, the kinds of cancers she addressed occur further back, so there is no recommended screening.

It was not clear to Dr. Chilton that all of the oropharyngeal and oral cavity cancers are caused by HPV 16 and 18. He wondered if there was an attributable risk for those.

Dr. Saraiya responded that the way that CDC defined the sub-set of oropharyngeal and oral cavity cancers that were HPV-associated for cancer registry purposes was to look at the anatomic sites that have been shown by studies to have high HPV prevalence (e.g., base of tongue, Waldeyer Ring, lingual and palatine tonsil). Systematic studies have been conducted that show that approximately 25% of oral cavity cancers have HPV identified in them, as do 35% of all oropharyngeal cancers.

With that in mind, Dr. Chilton wondered what percentage would be used to calculate the risk-benefit ratio and the cost-benefit ratio of GARDASIL®.

Dr. Saraiya replied that the modeling studies will take into consideration the percentage that are HPV associated. She did not present any in situ cancers, but these will also be of significant burden, especially in anal and penile cancers and these should be taken into account as well.

Dr. Plotkin asked Dr. Haupt to compare and contrast the male efficacy data with what was achieved in females, given the difference by gender that was observed in the herpes simplex virus (HSV) vaccine efficacy results. His impression was that there was somewhat less efficacy in men than women with respect to genital warts.

Dr. Haupt indicated that the efficacy observed for genital warts in the young adult women was approximately 99%. There were 2 cases in the GARDASIL® group and approximately 156 cases at the end of study. The point estimate was 99% and the confidence intervals were very narrow (96% to 100%). There may be a slight difference between efficacy in women and men, but certainly it is very high in men as well, and very different from what was observed with the HSV vaccine. Perhaps the size of the study and the robustness of the data is driving the point estimate somewhat lower on the male side. The any kind DNA detection was not a pre-specified analysis in the women's trial.

Georges Peter (Brookline, Massachusetts) understood that the value of the AS04 adjuvant is that it leads to more prolonged antibody responses. He wondered if Dr. Verstraeten had data to demonstrate this particular point with GSK's HPV vaccine, and wondered whether it would lead to an argument for a 2-dose schedule for this vaccine versus a 3-dose schedule.

Gary Dubin (GSK) responded that all of the efficacy data have been generated with vaccine given on a 3-dose schedule. They have observed efficacy that has now been demonstrated for up to 6.4 years, which is the longest follow-up to date. They have shown that antibody titers plateau at approximately 18 months and are sustained for that entire period of time. Modeling has been done to show that the plateau level of antibodies is likely to be sustained for at least 20 years from the time of vaccination. Given that they do not have efficacy data beyond 6.4 years, the question about 2-dose vaccination is difficult to answer. In theory a 2-dose regimen might be possible, but the studies have not been conducted to evaluate a 2-dose schedule. Studies conducted to evaluate 3 doses have shown a significant boost (approximately 5-fold) in antibody response upon receiving the third dose. Therefore, it may be the three doses are



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required for long-term protection. Dr. Haupt agreed, adding that it is not known what minimum level of antibody is needed for protection. A 2-dose vaccine study may demonstrate comparable GMTs at month 7 to a 3-dose schedule. However, it is unknown what this translates to in terms of long-term protection. The prime boost is probably very important for this vaccine in terms of its durability of immune response.

Georges Peter (Brookline, Massachusetts) inquired of Dr. Haupt whether there were differences in the incidence of genital disease geographically.

Dr. Haupt responded that while many countries are involved and surveillance is limited in some countries in terms of their disease states, there are some rate differences in terms of genital wart development across the various countries. The efficacy did not different no differ by country. Efficacy was high across all populations, all racial / ethnic groups, and all countries in which the studies were conducted.

Regarding genital warts, Dr. Judson wondered whether there was any good evidence for same type re-infection or relapse.

Dr. Haupt replied that this is a difficult question to answer. The concept of whether one has long-term natural immunity versus whether there is a latent stage with HPV that can reactivate over time is a question that has yet to be answered. There are varying expert opinions in the field with respect to this issue.

## Vaccination of Immigrants & Refugees

**Martin Cetron, MD, Division Director**
**CDC / CCID / NCPDCOD / DGMQ**

Dr. Cetron noted that the purpose of this session was to give ACIP an informational update on the topic of vaccination of immigrants and refugees, and to set forth the proposed language. With respect to background, in 1996 the Immunization and Nationality Act was amended by Congress to require “Proof of vaccination against at least mumps, measles, rubella, polio, tetanus and diphtheria toxoids, pertussis, *Haemophilus influenzae* type B and hepatitis B, and any other vaccinations against vaccine-preventable diseases recommended by ACIP.”

Given that 13 years have passed since this amendment, there has been some discussion with respect to whether the original intent is still in place or whether it needs to be revised—not as vaccines recommended for public health purposes, but vaccines specifically that would be required in time and place as a pre-requisite for immigration.

With that in mind, an internal committee at CDC has been convened with representation across the agency to consider proposing some criteria by which the original amendment would be interpreted in a more contemporary context. Clearly, the portfolio of vaccines that are available and the purposes for which vaccines are being used have evolved significantly over time. The proposed criteria for identifying ACIP-recommended vaccines as immunization requirements for immigrants: “The vaccine must be an age-appropriate vaccine as recommended by ACIP for the general U.S. population and at least one or more of the following: 1) The vaccine must protect against a disease that has the potential to cause an outbreak; and 2) The vaccine must protect against a disease that has been eliminated in the United States, or is in the process for



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elimination in the United States." An outbreak is defined as the occurrence of more cases of disease than expected in a given area or among a specific group of people over a particular period of time.

This is language believed to reflect more clearly the Congressional intent of having an immunization requirement for the purposes of immigration. The proposed language more directly addresses the sub-set of vaccines for diseases that have epidemic potential and for which introduction of those diseases through importation may cause significant propagation, versus the broader pallet of vaccines that ACIP actively considers. Another important consideration is that from a regulatory framework, vaccine mandates in the U.S. are in the jurisdiction of the states. The federal oversight for vaccine mandates for immigrants is part of the regulatory framework in the Division of Global Migration and Quarantine (DGMQ). ACIP serves as an advisory board for vaccine recommendations. DGMQ is proposing a set of criteria that would be used (in consultation with the respective disease/vaccine experts at CDC) to determine which vaccines would be required at the time and place of the medical exam for immigration. The application of the criteria with the required list of vaccines would be put forth in "Technical Instructions" for panel physicians and civil surgeons performing the medical exam. The Technical Instructions generally outline recommendations within the regulatory framework and are submitted to the Department of Homeland Security, the Department of State, and the implementing partners that conduct medical assessments for immigration applicants. The process DGMQ was proposing would include ACIP's weigh in on the criteria, provisions for public comments, and potential annual revision of the Technical Instructions based on the criteria ultimately determined.

**Discussion**

Drs. Baker, Beck, and Judson expressed their support for the language shown on the slide, particularly with respect to its simplicity in cutting across a number of complex issues.

Indicating that she had been following this issue since 1996, Sandra Jo Hammer (California) suggested that yearly requirement changes were too often. This is an adjudication process, so people may have been in the United States for 4, 10, to 15 years. This is when they actually receive their Green Card, not when they enter the United States. The Civil Surgeon makes the assessment of the vaccines, which are then submitted to the Adjudication Officer who ensures that the form is filled in correctly. Given that changes in requirements every year will involve numerous processes, she suggested a two- to three-year change. With regard to vaccines being required to protect against diseases with potential for outbreak, ZOSTAVAX™ is currently recommended for people over the age of 60, which includes adjudicated aliens who are 60 years of age and older. This means that a grandmother who has been in the United States for 20 years must suddenly obtain ZOSTAVAX™ and influenza vaccines before she can acquire her Green Card. Varicella is an outbreak type of disease, so perhaps the language should be revised with the idea that ZOSTAVAX™ may not be appropriate as a requirement.

Dr. Cetron clarified that the application process for lawful permanent residence applies overseas to incoming applicants (approximately n=400,000 per year) through Panel Physicians of whom there are approximately 600, and the Civil Surgeons of whom there are approximately 3,000 in the United States for applicants for adjustment of status (approximately n=600,000 per year). The Vaccine Technical instructions apply in both frameworks.



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## Public Comments Day 1

No public comments were offered during the first day of the meeting.

**February 26, 2009**

## Pediatric Haemophilus

**Invasive *Haemophilus Influenzae* Type B (Hib) Disease Minnesota 2008**

**Kristen Ehresmann, RN, MPH**
**Minnesota Department of Health**

During this session, Ms. Ehresmann reported on Minnesota's experience with five cases of *Haemophilus Influenzae* b (Hib) that occurred in 2008 and how they responded to this outbreak. To frame this in the current context of Hib vaccine, she reminded everyone that in December 2007, Merck announced a voluntary recall of 10 lots of Hib vaccines and the suspension of Hib vaccine production. In October 2008, Merck announced a continued delay. At this point, the return of the Merck product is expected no earlier than mid-2009, leaving a single manufacturer of Hib vaccine. The interim Hib recommendations during this vaccine shortage have been that the Hib vaccine supply is sufficient to ensure completion of primary series for all children. Providers have been instructed to continue the primary series; temporarily defer the booster dose except for children at high risk; and to prioritize polysaccharide polyribosomal phosphate outer membrane protein (PRP-OMP)-containing Hib vaccines for American Indian / Alaska Native (AI / AN) children.

The Minnesota Department of Health (MDH) conducts surveillance for invasive *H. influenzae* as part of the Active Bacterial Core surveillance system of CDC's Emerging Infections Program. A case of Hib is defined as isolation of *H. influenzae* type b from a normally sterile site. There was a Hib cluster in Minnesota in 2008. During that time five Hib cases were reported, which is the highest number observed there since 1992. The cases were in children ages 5 months to 3 years old. There was one death in a 7-month-old, prior to which the last death due to Hib reported in Minnesota was in 1991. Clearly, this was a departure from surveillance in recent years. In 1983, Minnesota had approximately 250 cases of Hib. With the licensure and introduction of the polysaccharide vaccine, the cases decreased to approximately 200. Upon licensure of the conjugate vaccine >18 month olds the number of cases dropped below 200. With the licensure of the conjugate vaccine for infants the number of cases declined to approximately 120 and steadily declined from there until 2008.

With respect to the characteristics of 2008 Hib cases in Minnesota, three of the five children were unvaccinated due to parent refusal. All of the children were from different counties, although they were clustered in a central band across the state. Pulsed-field gel electrophoresis (PFGE) data results showed that there were three different strains, so there was no commonality in terms of the fingerprinting. The cases had no known relationship with each other, and none of children were enrolled in group child care:



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| Illness onset | Age | Clinical syndrome | Outcome | Hib vaccination status |
|---|---|---|---|---|
| January | 15 mos | Meningitis | Survived | 2 doses, 2 and 5 mos |
| February | 3 yrs | Pneumonia | Survived | 0 doses |
| November | 7 mos | Meningitis | Died | 0 doses |
| November | 5 mos | Meningitis | Survived | 2 doses, 2 and 4 mos |
| December | 20 mos | Epiglottis | Survived | 0 doses |

The 15-month old had received the Merck product and was up to date in terms of the two doses of their primary series. At age 15 months when diagnosed, further medical work-up indicated that this child had an immune deficiency that was unrecognized prior to that time. Therefore, it is likely that the child may not have had a good response to the vaccine. The 5-month old was on schedule for the three-dose series, but contracted the disease.

Based on Minnesota Immunization Information Connection (MIIC) registry data, MDH evaluated immunization data for children born between November 2007 and March 2008 to include children who would have been receiving vaccine after the shortage had begun. Due to limitation in the data, they were unable to determine whether use of the Merck product was a factor in reduced coverage rates. There was a difference in coverage rates by dose and antigen. Other states have reported similar data. As 2008 progressed, the number of doses attributable to Merck was reduced considerably.

In a comparison of the three-dose series, MDH studied PCV7 and Hib. For the first dose these two vaccines are given at 2 months and they very much correlated. The second dose and PCV7 is very close. However, a very large difference was observed with the third dose. Therefore, it appeared that children were being taken to clinics but were not receiving the third dose of vaccine [Administration of Hib Vaccines by Brand and Month of Vaccination, Minnesota, 2008]. Data presented in the *MMWR* article highlight that difference. Children were receiving DTaP and PCV by age 7 months, but the third Hib dose was much lower than would have been expected for the other two antigens [Centers for Disease Control and Prevention. Invasive Haemophilus influenzae Type B Disease in Five Young Children — Minnesota, 2008. *MMWR* 2009;58:58-60].

Rates for 2007 were compared with rates for 2008. It does not appear that there was a difference in terms of the third dose of the Hib vaccine. However, in examining the data MDH discovered that the coding for Hib is very complicated due to different schedules for different products and because coding is probably not a providers' highest priority. It appears that many providers are still coding for use of the Merck product, although it was not the product they were actually using. While it appears that there has been a reduction of the third dose of Hib, the registry data and coding need further scrutiny.



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Regarding Minnesota's public health response, MDH has engaged in a considerable amount of communications. The *MMWR* article was published in conjunction with CDC. MDH also engaged in a joint press conference with CDC. In advance of the publication of the MMWR and the press conference, conference calls were convened with state AAP and AAFP affiliates and local public health representatives. A statewide HAN was also issued. In addition, MDH collaborated with CDC on coordination of the allocation of more Hib vaccine to Minnesota so that there were adequate doses once providers became aware of the situation. MDH is planning to expedite resumption of the booster dose once the vaccine supply resolves. Significantly, an extensive evaluation is underway to determine Hib carriage and understand reasons why some children are not vaccinated. The plan is to swab 2000 children across the state and conduct surveys with their parents to examine Hib carriage in Minnesota.

In terms of some of the challenges, with the vaccine shortage Pentacel® has become available; however, there has been a provider reluctance to switch inventory and schedules. There are also concerns about proper use of vaccine (e.g., mixing liquid and powder). In addition, there are catch-up issues in terms of determining differences between primary and booster doses, as well as over-vaccination. Providers and parents have expressed concerns about over-vaccination when a third dose is needed and Pentacel® is the only vaccine available. It has been wonderful to receive the CDC guidance that will now be included in all of the packages for providers that re-emphasizes that using Pentacel® is appropriate, even if it may result in additional antigens for the children.

Ms. Ehresmann concluded that Minnesota had reached a "Perfect Storm" situation due to parental refusal, the vaccine shortage, and reduced herd immunity. A very important message out of this situation was that three of the five children's parents had refused vaccine. This included the child who died. In addition, it is clear that heightened disease surveillance during vaccine shortages is highly important. Moreover, parental concerns about vaccine safety must be addressed to reassure parents.

**CDC's Response**

**Dr. Jeanne Santoli**
**CDC / CCID / NCIRD / ISD**

Dr. Santoli reported on CDC's response with respect to the Minnesota issue, as well as issues pertaining to the nation. Regarding the third dose, CDC examined registry data from CDC sentinel site projects which have well-populated registries with very good data to determine whether the phenomenon was occurring in states other than Minnesota. At this point, CDC continues to struggle with analyzing Hib coverage due to the complexities (e.g., different products with different schedules, coding issues in terms of what product was actually used, et cetera). CDC conducted a re-analysis to study product type and did find that across all of the sites there appear to be some limitations with regard to the third dose coverage. This is of great concern and needs to be better understood to protect children with at least the primary series at this point. CDC is also working with states that do not have registries and are not sentinel sites, but may have other registries and want to use similar analyses to study the coverage of children within their jurisdictions. For the states that do not have the registries needed to conduct their own analyses, CDC is providing tools such as sampling strategies for use with provider practices, sometimes through their vaccine coverage assessment data, to get a sense of whether a problem is occurring in their jurisdictions.



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CDC has a number of other activities underway as well. Work is being done to enhance Hib surveillance nationally, disease modeling is being done to help understand how the shortage might impact what could be expected in terms of the incidence of this disease, and carriage studies are begin conducted as well. A provider survey was conducted in 2008, which identified very high awareness of the recommendations. However, there was some reported non-compliance with the recommendations that led to increased messaging at that time. CDC is considering conducting another survey to better understand if providers are unable to comply with the recommendations, why that is and what the barriers are. Consideration is being given to whether such a survey should be conducted nationally or targeted to areas where third dose coverage appears to be lower. Communications are very important. CDC has made an effort to reach providers directly through provider organizations. In addition, due to a centralized distributor in the VFC program, CDC has the opportunity to include a letter in every box of vaccine shipment that goes out to providers. The letter emphasizes that there is sufficient Hib-containing product to vaccinate children with the primary series, and that the issue of giving children antigens that they do not need is an important consideration, but when not contraindicated for other reasons, it is recommended that the combination Pentacel® vaccine be used so that children have Hib protection even if they repeat some of their antigens.

Based on all Hib-containing products available, the current vaccine supply is sufficient to support a three-dose schedule for non-high risk children and a full schedule for children who are at increased risk of Hib disease. In 2008, sanofi pasteur distributed approximately 13.5 million doses of this vaccine. From the stockpile for AI / AN children in residential settings, CDC distributed approximately 250,000 doses in addition to the 13.5 million. The distribution of anything is not 100% efficient, so CDC recognizes that there are challenges and that sometimes provider experiences in their offices may differ from what is observed at the national level. However, CDC feels assured with the current distribution scheme that there is a sufficient number of doses to meet the recommendation currently in place. Merck communicated to CDC that their return to market which had been predicted for mid-2009 may be further delayed until later in 2009. At the same time, sanofi pasteur has developed a supply plan that supports reinstatement of the booster dose in the US in summer 2009 using both ActHIB® and Pentacel®. CDC is working closely with sanofi pasteur to understand supply more precisely so that options regarding catch-up can be defined.

## Discussion

Dr. Leonard Friedland (GSK) reported that GSK had been working closely with CDC and FDA for the past several months on a plan to assist during the shortage and to ensure adequate supply of a monovalent Hib vaccine for the booster dose. GSK has engaged in several meetings with the FDA to discuss a licensing application for Hiberix®, a monovalent Hib vaccine currently registered in nearly 100 countries. GSK has submitted the initial data to the FDA, and is currently preparing a BLA. In addition, GSK has deployed resources to begin manufacturing for the supply of Hiberix® in the US. Although the timing is not currently known, GSK is committed to continued collaboration with CDC and FDA to bring an additional Hib vaccine to the market in the US to help protect children.

Dr. Sawyer wondered whether providers were confused about the difference between the two-dose and three-dose schedule such that if they were in the habit of using the two-dose vaccine and had now shifted to the three-dose vaccine, some of their staff are not remembering that the third dose is required.



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Ms. Ehresmann replied that this is a possibility; however, providers have also indicated that they are concerned about not receiving an adequate supply of vaccine for the third dose.

Joel Ward (UCLA) found this to be an onerous report, given that this is such a preventable disease. There were as many as 20,000 to 40,000 cases per year in the US as late as 1989. To return to that by any means is not necessary. With respect to the three of the five cases that refused, he thought an investigation was to illustrate the health risk of refusing to immunize for any vaccine in terms of impact so that this part of the story is told. There was a preventable, fatal outcome. Carriage is typically at an older age between 18 months and 5 years (e.g., daycare center range). Therefore, a markedly increased carriage rate could be observed in that age group as compared to what it would have likely been when immunizations are low. When there is a shortage and people are not receiving their booster doses at 18 months, there may be a carriage rate increase in that pool, which is where the younger children are being exposed. With that in mind, he suggested investigating the five Minnesota cases to determine how much contact they had with daycare or other siblings in the household who were in the age range between 18 to 20 months. *H. influenzae* conjugate vaccine is now available almost globally, so the US should not be experiencing shortages. Those involved in the causes of the shortage should question the consequences of doses not meeting perfect expiration dates, not having a back-up supply, switching manufacturers, et cetera.

Dr. Ehresmann clarified that these children were not in childcare settings. As mentioned in her presentation, Minnesota is conducting a carriage study of *H. influenzae* in 2000 children under the age of 5 years in Minnesota. In addition, parents will be surveyed regarding vaccination and their views on vaccination.

Dr. Paul Offit (Children's Hospital, Philadelphia) wondered whether there had been a concomitant increased incidence of invasive Hib disease across the US, and if not, he wondered why. If they were arguing that absent a booster dose, carriage was being increased in older children and thereby increasing risk for parents choosing not to vaccinate or those with compromised immune systems, a national increase would be expected. If a national increase was not observed, then they must take into consideration whether there was something unique about Minnesota.

CDC's active bacterial core surveillance, for which CDC receives every isolate and is able to confirm the serotype for 10% of the population, detected no national increase reflected in Hib disease in any age group. No increase has been noted transnationally either. Modeling suggests that for a while after deferring the booster dose, there is a cushion of protection that protects everyone which, over time, begins to wane. As the booster is increasingly deferred and as third-dose coverage is imperfect, the cushion of protection may not be waning universally across the US. It is early and this is all occurring rapidly. Thus far, Minnesota's clustering experience has not been observed elsewhere in the nation.

It was not clear to Dr. Offit why there would be pockets of waning immunity, assuming that the shortage occurred for all areas of the US simultaneously.

It was noted by CDC that this does not pertain to pockets of waning immunity, but to pockets of introduction of Hib. Even if immunity is similar nationally, perhaps Minnesota had the unfortunate luck to experience introduction of Hib strains at the wrong moment in time, resulting in localized increased transmission in Minnesota. Unfortunately, perhaps these five cases were simply at higher risk for disease because of underlying illness or lower immunization, it was simply a conglomeration of those events.



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With regard to timing, Dr. Ehresmann noted that if they had not had the cases in November (n=1) and December (n=2), the year was relatively normal.

Phil Hosbach (sanofi pasteur) reported that of the 13.5 million doses of Hib-containing vaccine supplied by sanofi pasteur in 2008, approximately 62% of that went into the VFC program. Given that this was higher than would normally have gone into that program from this resource, there was adequate vaccine from sanofi pasteur's perspective. If immunizing 100% of the cohort with three doses, only 12 million doses total should be required. Knowing that 100% of the cohort is not immunized, it was not clear to him where the doses were. Whilst there were distribution issues, there were other confounding factors that were not mentioned. For example, not only did providers hesitate to utilize Pentacel® to supplement their Hib usage, but also there was hesitancy on the state and local levels to allow it to be made available to their providers. In fact, a couple of states are still doing this. There was a communication from CDC about how to code for Pentacel®, which may also have confused providers and resulted in incorrect coding. Thus, the number of children who did not receive a third dose may be overestimated.

Dr. Ehresmann responded that Minnesota began promoting Pentacel® in August 2008 before they even had the ability to order it.

While a great deal of discussion had centered around supply, shortage, and forumations, Dr. Schuchat stressed that three of the five cases refused vaccines. CDC observes clusterings of hesitant parents or vaccine refusals due to social, cultural, and other factors. Perhaps it is similar to the measles situation in which there is fairly good measles coverage throughout the country, but there are areas (e.g., communities, states, towns) in which many people are unvaccinated. Hence, Minnesota has rightly focused on the issue that three of five cases occurred that were not vaccinated despite the availability of vaccine. It is known that approximately 400,000 deaths from Hib occur every year throughout the world despite increasing Hib coverage. One action item is to remind people that this is a tragic, preventable disease. Parents must understand that vaccine for this disease is truly lifesaving.

Ms. Stinchfield (Children's Hospital and Clinics in Minnesota) commented that a great deal of information is expected to result from the carriage study with respect to the age group of 5 years and under in terms of whether they are in childcare, what their parents vaccine beliefs are, what their antibiotic use has been, et cetera. She has been highly impressed with the state health department's rapid response due to their excellent surveillance capabilities. Moreover, parents have been extremely willing to offer up their children's throats and have been very concerned about this. Kindergarten surveys do reflect that the number of conscientious objectors has increased throughout the years from 1% to 3%. The 15-month old with immune deficiency was cared for at Children's Hospital and Clinics in Minnesota and this mother is very interested in telling her story, explaining what it was like to wait for her child fighting for her life with meningitis when she had had all of the precautions possible. Ms. Stinchfield also underscored that Pentacel® is causing confusion amongst practitioners.

Dr. Baker reminded everyone that children 6 to 24 months of age who have disease do not make a protective immune response and should be immunized following their illness.



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## Agency Updates

### Centers for Disease Control and Prevention

Dr. Bell reported that in December 2008, the Measles Initiative using an updated estimation procedure reported a 74% drop in measles mortality globally since 2000. That represents 197,000 deaths in 2007. The Measles Initiative is a partnership that includes American Red Cross, CDC, UN Foundation, WHO, and UNICEF. The goal is 90% reduction in measles mortality globally by 2010. She also noted that the final version of the stimulus package includes $300,000 million to CDC for the 317 Immunization Program as part of the $1 billion Wellness Initiative. CDC is working in the context of an HHS process to determine how these funds will be allocated. The vast majority of these funds will be utilized to purchase vaccines for states through the 317 program. Dr. Bell also mentioned that the National Immunization Conference will be convened in Dallas, Texas March 30 through April 2, 2009.

### Center for Medicare and Medicaid Services (CMS)

Dr. Linda Murphy indicated that the items that will be published in the new *Federal Register* notice have been agreed upon. The previous Acting Director approved the notice to begin the regulatory process. The anticipated date to have this published is July 2009 so that it can be completed and acted upon before school is back in session.

### Department of Defense (DoD)

Wayne Hatchey indicated that the DoD was looking forward to the FDA licensure of the new Japanese encephalitis (JE) vaccine and adenovirus vaccine, both of which represent components of the DoD's overall protection portfolio. With regard to influenza vaccines, the 2009 DoD influenza policy included the expanded pediatric age groups without the "if feasible" clause and universal recommendations, with mandatory immunization for all those in uniform. Current DoD immunization rates exceed 95% of all uniformed personnel. DoD also has a policy making it mandatory for all healthcare workers providing direct patient care with the services being required to report immunization compliance beginning with the next influenza season. DoD is also in the process of improving its immunization tracking system to begin capturing dependents and retirees across all services. Some of the services do capture that data currently; however, others do not. The goal is to have one system that meets the services needs in terms of readiness, but also includes an accurate account of what is occurring throughout the entire beneficiary population. CDC issued their guidance pertaining to antiviral resistance, DoD issued a policy making it mandatory for DoD installations and the policy was placed on DoD's influenza website as an information piece in the medical health system blog, and was disseminated through DoD's listserv, a flash email, and DoD pharmacies and immunization clinics as a flash alert.



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## Department of Veterans Affairs (DVA)

Linda Kinsinger indicated that while they were not yet mandating influenza vaccine for all employees who engage in direct patient care, DVA does track this. In 2008, they had a 65% vaccination rate of all employees in the Veteran's Health Administration (VHA). That was up from 55% in 2007. The target set for 2009 is 70% and facilities are required to track and monitor this. A feature of their electronic medical record (EMR) system is a clinical reminder window that pops up for each patient that reflects their recommended services due. DVA recently revised a comprehensive list of all ICD-9 and CPT codes that would trigger a clinical reminder for patients with any codes for influenza and pnuemococcal vaccines. Everyone over 50 years of age would be targeted, but having a list of high risk patients helps facilities determine which patients with high risk codes have not been immunized to be able to engage in an outreach effort to get to them. This represents another way of increasing the targeting of influenza and pnuemococcal vaccine delivery to those patients. In addition, DVA is in the process of developing a set of clinical preventive services guidance statements that would cover all recommended preventive services for all eligible patients. Immunizations will be included in this guidance statement that will follow ACIP guidelines.

## Food and Drug Administration (FDA)

Dr. Norman Baylor indicated that the FDA convened a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting the week prior to the ACIP meeting, which included three parts related to influenza. The first part was deciding the strains for the 2009-2010 influenza season. The strains agreed upon are 1) A/Brisbane/59/2007 (H1N1)-like virus (same as 2008-2009); 2) A/Brisbane/10/2007 (H3N2)-like virus (same as 2008-2009); and 3) B/Brisbane/60/2008-like virus (new; this is the Victoria lineage virus which is different from the Yamagata virus that is currently in the vaccine). Also discussed was the feasibility of a quadrivalent influenza vaccine. CDC presented data during this meeting on the modeling of epidemiology and discussed whether there was a public health need for adding a second B strain to the current TIV. Although discussions are in the early stages, the FDA will be revisiting this issue. Based on the outcome of the meeting, FDA believes they should move forward to work with the manufacturers to develop a regulator pathway for the possibility of developing a quadrivalent influenza vaccine. How that will be implemented into the routine schedule, how it will be licensed, et cetera is yet to be determined. FDA will also engage in discussions with WHO, given that they are involved in the process of reviewing surveillance data to make recommendations to national regulatory authorities. Also discussed during the VRBPAC meeting was whether there is a need to continue pediatric studies for pandemic influenza vaccine candidates. Although the committee members were not asked to vote, it was clear that that the committee overwhelmingly agreed that such studies should continue to move forward. This issue is somewhat complicated due to regulation of Subpart D, which addresses specific pediatric trials and the prospect of the benefits. FDA will move forward to develop a regulatory pathway for the requirements for clinical studies in pediatric populations with pandemic influenza vaccine candidates other than H5N1.

## Heath Resources and Services Administration (HRSA)

Dr. Geoffrey Evans indicated that he had distributed the 20-year history of the program statistics versus just the vaccines. Overall, nearly 13,000 claims have been filed of which 5,500 are autism claims. Of the 5,500 claims over5,100 are pending. Awards are just over $1.8 billion total and the trust fund currently stands at $3 billion with annual revenues against outlays of approximately $180 million per year. Interest alone is over a third of that annually. That is, the



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trust fund stands in very good stead. Another handout he provided regarded the omnibus autism proceeding. To the US Court of Claims credit, it did a very nice job of outlining the procedural history, the current status, what is expected in terms of the appeals schedule, et cetera. This is available on the court's website as well. The decisions that received so much publicity on February 12, 2009 reflected the outcomes in three test cases that originally were supposed to have been the combination theory of MMR and thimerosol. However, because there was no separate MMR vaccine only proceedings, it is covering both theories: combination of MMR and thimerosal as well as MMR vaccine alone. The 670 pages of decisions are daunting to read, but include a great deal of scientific information. The remaining theory (thimerosal-only) is still being briefed. The briefing period is expected to end in summer 2009. These were based on hearings in 2008. It is unknown when the court will issue decisions in those three test cases. There has been publicity on a case that was decided by the US Court of Federal Claims that was tried individually and was defended by HHS. The specifics of the ruling, procedural history, et cetera can be accessed on the court's website. He will forward the URL to Dr. Jean Smith. As reported during the last ACIP meeting, HRSA has contracted with the Institute of Medicine (IOM) to conduct a two-year evaluation of the medical and scientific literature on four vaccines: Hepatitis B, influenza, varicella, and HPV. The first organization meeting is expected to take place in April 2009.

**Immunization Safety Office (ISO)**

Melinda Wharton announced that ISO has been working very closely with NVPO and with all of the other HHS operating divisions to update the *National Vaccine Plan*. The IOM is hosting a stakeholders meeting on the vaccine safety goal of the *National Vaccine Plan* on April 14, 2009 in Washington, DC. This is part of an on-going review of the priorities of the National Vaccine Plan.

**National Institutes of Health (NIH)**

Barbara Mulach noted that the question she had been receiving the most often regarded what NIH planned to do with the stimulus money it would be receiving. NIH has been engaged in numerous discussions pertaining to the best way to move forward with this in the most effective, transparent, and quick use of the funds. The agency has taken to heart the true goal of the funds which is to stimulate the economy and what can be done within NIH's purview to allocate the funds to do so. They have a couple of things in mind, the first being an NIH accelerated program known as the Challenge Grants Program, which would request applications in focus areas that would be reviewed and funded in a very short turnaround. R01s are also being considered that are highly meritorious but could not have been funded normally, which are for basic research grants. Some of the funding is allotted for construction, alterations, and repairs. The Director's page of the NIH website has a short summary and updates will be provided, and updates will also be reported on www.recovery.gov.

**National Vaccine Program Office (NVPO) / National Vaccine Advisory Committee (NVAC)**

Given that Dr. Gus Birkhead was unable to attend, Dr. Bruce Gellin presented updates for both NVPO and NVAC. During the February 2009 NVAC meeting, there was a discussion of a document that was developed by NVAC titled, "State of the National Vaccine Program." This was developed to be put forth to the Assistant Secretary for Health and the new administration as a transition document. A major activity was the late November 2008 release of the updated draft of the *National Vaccine Plan*. The previous *National Vaccine Plan* was written and released in 1994. The plan includes five broad goals: 1) new and improved vaccines, 2)



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vaccine safety, 3) education, communication, and informed decision-making, 4) supply and use of current vaccines, and 5) global vaccination. The comment period was scheduled to be open through the end of March 2009. NVAC welcomed comments from non-federal stakeholders on their views of what should be included in the plan, particularly with respect to the state goals, objectives, and indicators and the role of non-federal stakeholders in the development of a national and not just a federal plan. They have struggled with whether such a national plan should be achievable or aspirational.

The Vaccine Safety Working Group is currently addressing two charges that were made for them, which are to: 1) review the ISO's research agenda to determine gaps and help prioritize the research the ISO conducts; and 2) examine the broader vaccine safety infrastructure. The working group has been engaged in the process of collecting input from a variety of stakeholders. A stakeholders meeting was planned for March 16, 2009 during which they hoped to hear from the broader community with an interest in this area. Documents were to be available approximately a week prior to that meeting to help focus the discussions. This meeting is designed to address the specific task currently before the working group to examine CDC's ISO research agenda. Safety is one of the goals of the *National Vaccine Plan*, which is where NVAC expects to have synergy with IOM's activities. The IOM's April 2009 meeting is being convened regarding the *National Vaccine Safety Plan,* and will address safety more broadly. Due to many discussions regarding vaccine financing, several years ago NVAC established a Vaccine Financing Working Group that Dr. Birkhead leads. A series of recommendations pertaining to vaccine financing were voted upon that are now working their way through the system.

Beyond NVPO and NVAC, the National Biodefense Science Board (NBSB) was created under the authority of the Pandemic and All-Hazards Preparedness Act signed into law on December 19, 2006 to provide expert advice and guidance to the Secretary of the HHS. This group is examining the current policy pertaining to the use of stockpiled H5N1 vaccine with respect to: 1) timing and whether it should be used before a pandemic is eminent, which is the current policy; 2) broader population use; the current policy is 20 million people made up primarily of first responders, but new adjuvants allow the potential for a greatly expanded stockpile if adjuvants are applied to the existing antigen. The Office of the Biomedical Advance Research and Development Authority (BARDA), an authority within HHS, is tasked with developing products that essentially do not have commercial use. Dr. Gellin suggested that ACIP hear a briefing on what BARDA has in the Emergency Use Authorization (EUA) pathway pipeline to have some awareness of what vaccines are in development for use in emergencies.

## Indian Health Services (IHS)

James Cheek indicated that over the last few months IHS has been working on the Assistant Secretary's Initiative to Improve Vaccine Coverage of Healthcare Workers. During the first year, IHS managed to reach 71% influenza vaccination coverage among IHS healthcare workers throughout the country.

## Discussion

Noting that the rates of vaccines being given to pregnant women are increasing, Dr. Baker asked Dr. Baylor what FDA's plans were for studies during pregnancy and in infants. Dr. Baylor responded that these discussions are occurring with respect to pandemic influenza vaccine, although no firm decisions had been made thus far. There is also a paucity of data for seasonal



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influenza vaccine in pregnant women. The question does need to be addressed across the board.

Dr. Neuzil requested that Dr. Gellin clarify the role of ACIP in addressing the two pandemic vaccine questions. She thought they would have to be very careful to coordinate this issue, reminding everyone that during the first day of the February ACIP meeting they heard a discussion about ACIP weighing in on using PPV23 in a pre-pandemic. ACIP has an Influenza Work Group that routinely makes recommendations for seasonal influenza vaccine, but it seemed to her that these recommendations should be made together and not by separate committees.

Dr. Gellin responded that part of the reason that this evolved as it did was that ACIP's purview is to deal with licensed vaccines. The vaccines under consideration by NBSB may not be licensed and may be used under an EUA, which falls under its purview as a broad policy question. NBSB will wrestle primarily with the question: Should the vaccine be used prior to a pandemic and if so, for what reasons? Given that the current policy was created before there was enhanced production capacity and adjuvants, it was set at 20 million people who would keep society going while a pandemic vaccine is being developed. Given that there is a potential for that number to now be expanded beyond 20 million people, NBSB is reviewing this policy. Who in the population should receive it would certainly fall under the purview of ACIP. He concurred that the two committees should ensure that their recommendations are congruous to avoid having cross purposes or finding themselves in conflict. NBSB will receive input from a range of other existing federal advisory committees, not just those pertaining to vaccines, but also those that have access to this in other places. For example, DHS has a Critical Infrastructure Advisory Committee (CIAC) which will also be a liaison. Without having to convene this meeting in a stadium, the idea was to have the appropriate components of the government and external advisory committees be included as part of these discussions, which regard broad policy versus specific individual use.

Dr. Neuzil suggested that an ACIP member should serve as an ex officio member of the NBSB committee to facilitate clear communication between the two committees.

Dr. Bell indicated that CDC will be addressing this issue further to ensure that ACIP does not take up an issue which may be duplicative.

## Meningococcal Vaccines

### Update: Meningococcal Work Group

**Carol J. Baker, MD**
**Chair, Meningococcal Work Group**

Dr. Baker reported on recent and future activities of the Meningococcal Work Group, as well as adolescent vaccine considerations with respect to new vaccines on the horizon in addition to MCV4. With regard to meningococcal disease incidence from 1970-2007, importantly there have been cycles of meningococcal vaccine incidence every five to seven years until recently. The downturn is for all serogroups, including B which is not included in the adolescent vaccine program. Unfortunately, what accounts for the downturn is unclear [1970-1996 uses National



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Notifiable Diseases Surveillance System (NNDSS) data; 1997-2007 uses ABCs data projected to US population].

In terms of recommendations from 2005 to the present, in May 2005 following the ACIP vote an *MMWR* was published regarding the prevention and control of meningococcal disease. Shortly after the summer use of this vaccine, the first Guillain-Barré Syndrome (GBS) report was published. In 2006, a second report was published. There was then the problem of reduced supply, along with the problem of inadvertent administration in that the polysaccharide was to be administered subcutaneously and the conjugate intramuscularly. This was followed by a third GBS update approximately midway into 2006. Improved supply by the end of 2006 was followed by a recommendation of MCV4 for all adolescents 11 through 18 years of age. Recommendations were then made for MCV4 for children 2 through 10 years of age at high-risk, but routine vaccination was recommended with MCV4 for children 2 through 10 years of age based on disease burden, et cetera.

With regard to the projected licensure of new meningococcal vaccines (2009-2012), it is difficult to project precisely for a variety of reasons. However, the manufacturers have worked with the group to determine a projected timeline. There is now a second conjugate vaccine for ACYW-135 (MenACYW-CRM) anticipated to be licensed in 2009 for 11 to 55 year olds, the same age group for the first conjugate. A revision of the 2005 ACIP statement is anticipated that would include all of the interval recommendations. The first statement was for three cohorts of adolescents, so this statement needs to be brought more up to date. At the beginning of 2010, licensure is anticipated for a conjugate for 9 to 12 month olds and infants.

In terms of considerations for adolescent MCV4 meningococcal vaccination, vaccine effectiveness and duration of protection are very important. Safety and reactogenicity continue to be under surveillance, with updated data that are very reassuring. As noted, the new meningococcal conjugate vaccines, MenACYW-CRM, is anticipated to be licensed for 11 through 55 year-olds in 2009.

Regarding the estimated number of cases of meningococcal disease per year in 10 to 21 year olds due to vaccine-containing strains (A,C,Y,W-135), Dr. Baker reminded everyone that the reason for the three cohorts for the adolescent platform to be utilized was to immunize those entering high school or 15-year olds (whichever came first) was due to the peak between 15-18 year olds and the special risk group of college freshman who would be living in dormitories. The 2005 meningococcal vaccination recommendations focused on two age cohorts in the setting of the limited vaccine supply: 11-12 year-olds, 14-15 year-olds (high school entry), and others at increased risk for disease (college freshmen) based on the amount of supply available. The assumption was that the vaccine would protect for 10 years. The hope was that those immunized at 11-12 years of age would be protected through age 21. The 2007 revised recommendation stated that there should be “Routine vaccination of all persons aged 11-18 years with 1 dose of MCV4 at the earliest opportunity” and that “The ACIP goal is routine vaccination of all adolescents with MCV4 beginning at age 11 years. ACIP and partner organizations . . . recommend a health-care visit for children aged 11-12 years to receive recommended vaccinations and indicated preventive services. This visit is the optimal time for adolescents to receive MCV4.” Thus, a strong statement was made in the 2007 recommendations to strengthen the adolescent platform.

In terms of MCV4 coverage among 13-17 year-olds based on NIS-Teen data for 2006 and 2007, there were fairly low coverage rates across the age groups in 2006 and approximately 30% coverage across the age groups in 2007. In 2009, four years after the initial MCV4



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recommendation, 11-12 year-olds are now 15-16 years-old and 14-15 year-olds are now entering college. The work group has been discussing whether there should be a recommendation for revaccination with the conjugate. The prior recommendations for revaccination with meningococcal polysaccharide vaccine (MPSV4) was 3 to 5 years. More recently, there was a five-year interval recommended. The most recent *Red Book* will recommend a three-year interval.

With respect to the duration of protection, the correlate of protection is serum bactericidal activity (SBA). SBA diminishes over time with the conjugate and the polysaccharide, and this correlate alone may underestimate protection. Immunologic memory alone may not be sufficient to protect against meningococcal disease. Not all conjugate vaccines are created the same. Meningococcal conjugate vaccines are unlikely to provide life-long protection. Dr. Baker's own opinion of why the Hib conjugate vaccines are so effective is because there was a routine immunization for all infants, so there was an incredible herd effect. This is also a limited disease in terms of invasive disease versus a 10-year period of risk for healthy children.

In terms of monitoring the safety of MCV4, in place are the VAERS and VSD systems as well as a post-licensure case-control study of Guillian-Barré Syndrome (GBS) after MCV4. The goal of the post-licensure case control study for monitoring of GBS after immunization with MCV4, funded by sanofi pasteur, was to design and conduct a study with adequate power to answer the question of increased risk of GBS following MCV4 vaccination. The challenges are the low prevalence of GBS (1/100,000 PY), and the MCV4 vaccination within specific 6-week time windows (0.614% estimate). The study requires the combined efforts of several large health plans with active health research divisions. This is a multi-site retrospective cohort study. It is a nested case-control study examining the period from March 2005 through August 2008. This is a collaboration between Harvard Coordinating Center and the research arms of five US health plans. Cases are being identified through claims data, confirmed through medical chart review, and adjudicated by neurologist panel [*Registered at ClinicalTrials.gov (NCT00575653)*]. Pertaining to the interim GBS study results, 4.5 million 11 to 18 year-olds were identified for the primary study population (5.9 million total, over 7 million person years). The MCV4 immunization level overall was 7.6% through May 2007, with 20% among 17 to 18 year olds (n=387,491 total vaccinations). Of the 240 potential GBS cases identified in claims, 100 had sufficient information to determine case status, 29 met the primary study endpoint definition, 26 during study period (21 from primary / 5 secondary), and 0 cases were exposed to MCV4 or other vaccinations within 42 days of an interval. This is very encouraging data that suggest that GBS is not occurring in any greater a frequency in vaccinated versus unvaccinated adolescents.

The new vaccine, MenACWY-CRM, is being reviewed for licensure in 11 to 55 year-olds. The expected licensure in summer 2009. Immunogenicity data will be presented by the company to ACIP in June 2009. There will be no VFC or ACIP vote required because this is another conjugate vaccine just like the Hib conjugate. MenACWY-CRM will protect against the same groups as the first meningococcal conjugate (serogroups A, C, Y, W-135). Conjugation is somewhat different in that there is sizing of oligosaccharides before conjugation with CRM-197.

In summary of the adolescent meningococcal immunization considerations, early adolescent immunization may not maximize protection through late adolescence. The work group is evaluating all available data. MCV4 safety continues to be monitored, and safety to date appears very good. With the MCV4 conjugate vaccine on the market, no changes are expected to the recommendations.



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With regard to revision of the 2005 ACIP meningococcal vaccine statement, the work group plans to update the full ACIP in Fall 2009 with new data and recommendations for the current 2 to 10 year-olds and 11 to 18 year- old adolescent recommendations. Safety data to be presented will include GBS monitoring. MenACYW-CRM vaccine information will be added, and hopefully data will be presented regarding the duration of protection. A new statement for infant vaccination recommendations will need to be made for 2010 to 2011, for which data presentations to ACIP are not expected to begin until in October 2009.

**Discussion**

Dr. Katz requested further information about the potential for a group B vaccine. It seemed to him that if ACIP was going to move forward with an infant and toddler program, it would be beneficial if the vaccine was pentavalent rather than quadrivalent.

Dr. Baker indicated that when the work group asked this question, they were told about the ACYW-135 vaccine.

Dr. Decker (sanofi pasteur) responded that sanofi pasteur is hard at work on a group B vaccine, but that ACIP recommendations should not be held up and the ACYW vaccine based on this.

Dr. Friedland (GSK) indicated that GSK also continues to work on the development of meningococcal serogroup B vaccine, and that they hoped to report to ACIP in the future on the results of these development plans.

Dr. Stoddard (Novartis Vaccines) replied that Novartis is also actively engaged in serogroup B meningococcal vaccine development. They too hope to update the panel in the near future.

Laura York (Wyeth Vaccines) reported that Wyeth has a bivalent recombinant conserved protein program that, based on preclinical work, appears to have broad coverage in some early work with clinical sera. This program is currently in Phase II.

**Guillain-Barré Syndrome (GBS) Among Recipients of Meningococcal Conjugate Vaccine (MCV4, Menactra®)**

**Angela Calugar, MD, MPH**
**CDC / OD / OCSO**

MCV4 was licensed on January 17, 2005. Over 22,181,400 doses were distributed in the US through December 31, 2008. Data about doses administered nationwide is not available, however. As noted, the ACIP recommendations in June 2007 are for "…routine vaccination of all persons aged 11-18 years with 1 dose of MCV4 at the earliest opportunity," and "…routine vaccination for persons aged 19-55 years who are at increased risk for meningococcal disease…including college freshmen living in dormitories."

Several updates were made by ACIP regarding GBS following MCV4. In an *MMWR* update in October 2006, it was indicated that, "Data suggest a small increased risk for GBS after MCV4 vaccination, the inherent limitations of VAERS and the uncertainty regarding background incidence rates for GBS require that these findings be viewed with caution . . . Because of the risk for meningococcal disease and the associated morbidity and mortality, CDC continues to



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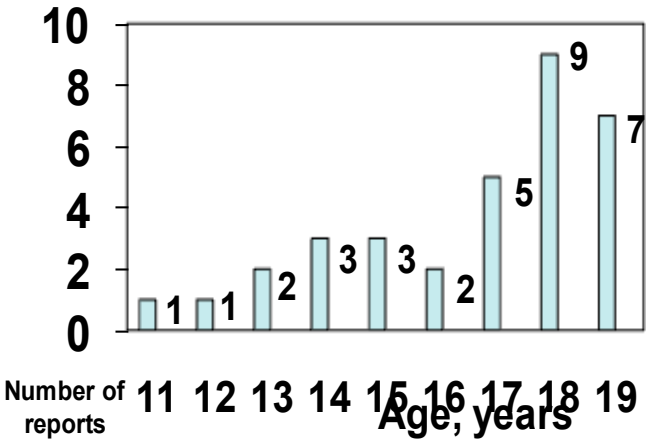
recommend routine vaccination with MCV4 for adolescents, college freshmen living in dormitories, and other populations…" An update in the *MMWR* in December 2007 read, "Persons with a history of GBS might be at increased risk for GBS after MCV4 vaccination; therefore, a history of GBS is a precaution to administering MCV4."

Based on post-licensure findings, changes were incorporated into the package insert in its contraindications and warnings sections. Product approval information for Menactra® states under Contraindication: "known history of GBS is a contraindication to vaccine administration" and under Warnings: "GBS has been reported in temporal relationship following administration of Menactra vaccine. An evaluation of post-marketing events suggests a potential for an increased risk of GBS following Menactra vaccination."

GBS is an immune-mediated rapidly evolving polyradiculoneuropathy generally manifested as a symmetric motor paralysis. Certain infections may cause this condition. Some cases are vaccine-associated. A study of GBS following A/NJ/1976 "swine flu" vaccine confirmed a risk window within six weeks following vaccination, or 42 days. That is, attributable risk was within six weeks after vaccination with 4.9 to 11.7 cases per million in the 42-day risk window. This is a rare condition. The estimated incidence rate of GBS is 1 to 2 cases per 100,000 person years.

Methods used for post-licensure surveillance of GBS after MCV4 vaccination include VAERS, which is a national post-licensure passive surveillance system. MedDRA coding may capture all possible cases, and this system allows for the generation of hypotheses for further studies, but does not show causality. The VSD is a collaboration between CDC and eight managed care organizations. Data from 8.8 million members is captured annually, which represents 2.9% of the US population. The Clinical Immunization Safety Assessment (CISA) Network includes six medical research centers and individual consultants.

In terms of the VAERS data, all reports of GBS and with symptoms of suspected GBS were carefully reviewed using the Brighton case definition. Additional medical information was obtained during the follow-up process, when possible. Of the total of 61 reports to VAERS, there were 37 confirmed cases for all ages, which had onset within 42 days following immunization. Of the 37 confirmed cases, 33 were in the age group of interest, 11 to 19 year olds. Dr. Calugar focused the remainder of her presentation on the 33 confirmed cases. Importantly, there were no cases with onset on day 0. Some cases were excluded from the final count for various reasons. The reports broken down by age group are as follows:



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The onset interval from MCV4 administration to the adverse event ranged between 2 to 37 days, with a mean of 19.2 days, a median of 15–days, and temporal scan cluster of 10 to 15 days (p=.002). To better understand VAERS data, the background rate is of interest. To that end, a comparison was made of observed GBS cases in VAERS to the background rates in the Healthcare Cost and Utilization Project (HCUP) data from 2000 to 2004 (prior to the licensure of the vaccine). Based on VSD data, investigators assumed that 45% of doses were administered in the sub-group of 15 to 19 years. In the 11 to 19 year old age group, the 33 reports is a lower number than the expected rate of 36.17% in HCUP. Of the 33 total reports, 26 occurred in the 15 to 19 year old age range, which is a higher number than the expected 19.78% in HCUP data. However, the confidence interval of .87 to 1.90 indicates that there is no statistically significant difference between the observed and expected number of cases of GBS reports based on the background rate calculation using HCUP data. Dr. Calugar acknowledged that background rates in VSD were similar to HCUP background rates.

Regarding monitoring GBS following MCV4 through the VSD Rapid Cycle Analysis (RCA) Study is an on-going project from April 2006 through February 2009. The case definition for GBS for signal detection is an ICD 9 code 357.0 (acute infective polyneuritis). An exposure window of 1 to 42 days was used. Hospitalization, outpatient, and emergency department visit records were used to find diagnoses of GBS. The first event of GBS had to be within the 42-day risk window. Diagnosis is confirmed with chart review. RCA results reflect that 642,493 doses were administered at eight study sites. Five GBS cases $\leq$ 42 days after MCV4 were found in the automated data. Three GBS cases received a chart review. Of the three cases, one was pre-existing GBS, one had a related diagnosis that was not GBS, and one had “rule out GBS” and a different subsequent diagnosis. A fourth case had onset of symptoms on day 0, which is not within the formal risk window. A fifth case is pending medical record review. For comparison, if the fifth case proves to be GBS, this will mean that there is one observed case.

In summery, more than 22 million doses were distributed in the US from January 2005 through December 2008, including 642,493 doses administered in the VSD population. Reported GBS within 42 days of vaccination among MCV4 recipients continues to be of concern. VAERS data identified 33 confirmed cases of GBS identified following MCV4. Current data do not suggest an overall increased risk for GBS in ages 11 to 19 years; however, there is a possible risk in the subgroup of 15-19 year olds. VSD RCA data identified five cases following MCV4, of which four were ruled out from the final count after chart review, and one is pending review. There is no safety signal.

Surveillance data limitations for surveillance of GBS following MCV4 vaccination are that the completeness of reporting to VAERS is unknown. Thus, there is a risk of underreporting or stimulated reporting. The system includes incomplete data, lacks a direct and unbiased comparison group, and lack of data for doses administered. VSD has limited capability to detect very rare AE following immunization (1 per 100,000) in minimal time periods for minimal risk ratios. VAERS and VSD continue to monitor for GBS reports following MCV4 vaccine. Harvard Medical School / Harvard Pilgrim Health Care are conducting a consortium study to assess the relationship between immunization with MCV4 and GBS.



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## Discussion

Dr. Temte noted that over time there had been a consistent pattern than under the age of 14, little activity is observed. With that in mind, he wondered whether any analyses had been conducted for just the subgroup of 17 to 19 year olds.

Dr. Weintraub replied that they had not done so, partly due to the limited power. Somewhat ironic with regard to the five automated cases that have been found from computerized records in VSD, only one was in the 15 to 19 year old age range.

Dr. Baker reminded everyone that former ACIP member Dr. Allos used to point out that the disease peak is between 15 to 19 years of age for GBS incidence. Individuals 18 to 19 years of age going to college had the highest uptake in the first year of immunization, with a summertime predominance. *Campylobacter* is the most common preceding event before GBS, yet data have not been able to be teased out due to insufficient numbers to determine whether this is the same season association-wise with the peak incidence of *Campylobacter* and GBS.

Referring to the ACIP recommendations and the package insert, Dr. Chilton noted that there was a discrepancy regarding whether MCV4 was a precaution or contraindicated in previous GBS sufferers, and wondered where ACIP stood on this currently.

Dr. Calugar replied that the manufacturers decided that a known history of GBS was a contraindication to vaccine administration. However, based on *MMWR* updates, this is a precaution. With respect to the ACIP recommendations, it was left up to providers to address specific patient situations.

Dr. Iskander reminded everyone that the data point used in support of listing prior GBS as a precaution rather than a contraindication was that among the initial case series of five reports, one young woman had experienced three episodes of post-vaccination GBS all following diphtheria toxoid-containing vaccines.

Sandra Jo Hammer reported that when she took her two nephews for their camp physicals, amongst the eight forms to be completed, several required meningococcal vaccine for overnight camps. Of those, two had the incorrect meningococcal vaccine requirement (e.g., the polysaccharide vaccine). She assumed that this was because they were using an old form that was duplicated; however, if there was a case of GBS in a camp setting, this could delay investigation of the disease, a determination of who might be susceptible, et cetera. With that in mind, she suggested some type of communication to camp associations, Boy Scouts, Girl Scouts, et cetera to update their forms.

Dr. Baker responded that some states and some camps have overnight requirements; however, that was never an ACIP recommendation for the polysaccharide vaccine or the quadrivalent conjugate vaccine except in someone who was not immunized between 11 and 18 years of age. There are no data to suggest that there is sufficient risk in a camp situation.



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## Herpes Zoster Vaccine

### Update: Herpes Zoster Shingles Vaccine

**Rafael Harpaz, MD MPH**
**CDC / CCID / NCIRD / CDC**

Dr. Harpaz noted that it had been approximately two years since ACIP voted to recommend the herpes zoster vaccine (HZV). Thus, CDC thought it would be beneficial at the beginning of this session to present an update on the status of the vaccine program.

With regard to the background of herpes zoster (HZ) and post-herpetic neuralgia (PHN), there are approximately 1 million cases of HZ annually. The primary known risk factors include age and immunosuppression. The risk of HZ increases with age and the risk of PHN increases even more dramatically with age. Approximately 30% of all persons develop HZ in the course of a lifetime. Immunosuppression explains only a small portion of that 30%. It is not clear what other risk factors may exist or what distinguishes the 30% who get HZ from the 70% who do not. HZV is 51% effective at preventing HZ. However, efficacy declines with age and varies from youngest to oldest vaccinees by a factor of 3 to 4. Other than age, risk factors for vaccine failure are plausible but have not been well-characterized. The vaccine is 67% efficacious at preventing PHN.

With respect to HZV cost and reimbursement, this is an expensive vaccine. The catalogue price of the vaccine is approximately $150, while in 2008 the average wholesale price was $194 and the retail price was variable. At Dr. Harpaz's pharmacy the price was $250. The vaccine is covered by Medicare Part D primarily for persons ages 65 and over. For persons aged 60-64, commercial insurance is the typical coverage. Other payor mechanisms include VA, Medigap Medicare supplemental insurance, Medicare Advantage, Medicaid, and health departments. With regard to Medicare Part D reimbursement, the relationship of drug plans is with pharmacies rather than physicians. Therefore, vaccination by physicians usually entails filing a claim (e.g., paying full price up front), referring the patient to a pharmacy for vaccination, or referring the patient to the pharmacy to purchase HZV for transport and vaccination at the doctor's office. This practice is known as "brown-bagging." Given that this is a freezer-required vaccine, this is not a good practice. Non-reimbursable costs include deductibles, co-pays, and the coverage gap / "donut hole." Co-pays alone are approximately $20 to $60. For commercial insurance for persons 60-64 years old, deductibles and co-pays also apply.

With regard to the HZV target population, there is marked heterogeneity in the senior population as compared to pediatric or adolescent populations. Dr. Harpaz would argue that the heterogeneity is many times greater. This has an important bearing on the unknown risk factors in terms of vaccine uptake, immunogenicity, risk of zoster itself, vaccine efficacy, vaccine safety, et cetera. All of those unknown risk factors can translate to unmeasured confounding, and make it very difficult to interpret data regarding the impact of the vaccine program .

The challenges to enabling vaccinations is that there have been HZV supply shortages, although these have been largely resolved. Provider barriers include awareness, up front cost, complexity of reimbursement, and storage / handling issues. Patient barriers include awareness, financial burden, and finding HZV. A shared barrier is that the system does not accommodate adult vaccines very well. Activities and plans through NCIRD to enable vaccinations include promotional and informational activities; provider training and education; a



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provider survey on practices and barriers (completed), and a patient survey that is being developed to characterize barriers from their perspective.

Given the barriers to HZV vaccination, timely and thorough monitoring of uptake is needed to determine whether corrective measures are necessary. Due to the heterogeneity in the target population, it is important to know who is / is not being vaccinated to be able to interpret vaccine performance. No routine state-level data are available on HZV uptake such as those which exists for pediatric vaccines (e.g., NIS). With regard to NCIRD activities and plans regarding these issues, an adult National Immunization Survey (NIS) module was conducted in the summer of 2007. That survey found that uptake in the target population was just under 2%. There are no plans to repeat that survey. Instead, NCIRD is working with the University of Michigan on the Health & Retirement Study, which is a biennial survey of 22,000 adults ≥50 years on a variety of issues (e.g., health, insurance, et cetera. Results are expected in July 2009 on HZ rates and HZV uptake. NCIRD is also working with the National Health Immunization Survey (NHIS), which is an annual survey, from which data are expected in July 2009 on HZV uptake from approximately 6,200 adults ≥60 years. The Behavioral Risk Factor Surveillance System (BRFSS) annual survey would typically provide state-level data on HZV uptake; however, it is not clear whether any states are going to adopt the HZV module. Biologic surveillance data are collected semiannually from the manufacturer on the number of doses distributed. Medicare Part D claims data provides a theoretical mechanisms to acquire data on uptake, but that will be delayed. State registries also provide a theoretical source of information; however, to date only one state collects comprehensive information on HZV vaccination.

There are considerable challenges with respect to safety. This is the first live (i.e. not inactive) vaccine targeted for seniors. Distinguishing cause and coincidence among the elderly who have high rates of medical events will be very challenging. Safety may vary by co-morbidities, medications, and frailty in this heterogeneous population. Adult providers may be less experienced at reporting to VAERS. The ISO and FDA are conducting VAERS surveillance, with the two-year review currently in preparation. A Vaccine Safety Datalink (VSD) protocol is in development to assess safety.

The challenges are also considerable with respect to impact. It is difficult to make HZ reportable; therefore, accordingly, CSTE did not express an interest in such measures. It is difficult to monitor the outcomes of greatest interest (e.g., severity and duration of pain). Age-specific HZ rates appear to be increasing over time without any recognized cause. Thus, it is challenging to interpret HZV impact when it is not clear how rates would change in its absence. The unique risk factors in most of the 30% of persons who develop HZ are unknown. It is challenging to interpret HZV impact without knowing the risk factors. Studies are underway to better define long-term HZ trends (e.g., Olmsted County, Medstat, Medicare, Harvard). Studies are also underway to better define HZ risk factors (e.g., Medstat, Marshfield, Medicare). NCIRD and its partners at Harvard are developing and validating methods to conduct HZ and PHN case findings using claims data. Prospective HZ and PHN surveillance has also been established (e.g., Medicare, Medstat, HRS, Varicella Active Surveillance Project).

In terms of challenges to monitoring performance of the HZ vaccine program, no surrogates exist for vaccine protection. Greater understanding of baseline HZ trends, risk factors for HZ, characteristics of elderly who receive HZV is critical for designing studies to monitor HZV performance and duration of protection. Current and planned HZ studies should provide data needed to inform the design of studies to measure HZV performance.

**Provider Attitudes and Practices Regarding**



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## Herpes Zoster Vaccine and Perceived Barriers

**Allison Kempe, MD, MPH**
**Professor, Pediatrics**
**University of Colorado Denver**

Dr. Kempe noted that she viewed her job as representing the interests of the primary care providers who were kind enough to share their attitudes and thoughts with the University of Colorado and to assist ACIP with its deliberations. With that in mind, she reported on provider attitudes and practices regarding HZV and perceived barriers to its use.

HZV is the first vaccine to be reimbursed through Medicare Part D. It is the most expensive vaccine recommended for older adults (≥ 60). The vaccine requires freezer storage at an average temperature of ≤5°F (≤-15°C). The NIS 2007 found a low rate of uptake at 1.9% six months after recommendations [Lu et al. *Vaccine* 2009 (in press)], although these data did proceed the *MMWR* publication. Nevertheless, this low uptake number raised concerns about why use was so low.

The objectives of the study were to assess, in a nationally representative sample of family medicine physicians (FM) and general internists (GIM), current vaccination practices, barriers to vaccination, knowledge and practice regarding reimbursement for vaccine, and characteristics associated with stocking and administering HZV. This study was conducted just over two years after HZV was licensed in the US in an existing sentinel physician network recruited from random samples of AAFP and ACP. Quota sampling was done to ensure that networks were similar to overall AAFP and ACP memberships. A previous study demonstrated this method produced comparable results to the most commonly used method of randomly sampling the AMA membership with respect to physician demographics, practice characteristics, and responses on surveys regarding vaccine-related issues [Crane LA, *Eval & Health Prof*, 2008]. The survey period was from July through September of 2008 (26 months post-licensure, 21 months post-provisional recommendations, and 1 month post-publication of the recommendations). Providers were surveyed by internet or mail based on their preference. The internet group received a pre-letter and up to 8 e-mail reminders with links to the survey, while the mail group received pre-letter and up to 3 surveys.

Dr. Kempe noted that she would be presenting FM and GIM results together with any differences highlighted, given that the results were generally similar. She presented separate multivariate models predicting routinely stocking and administering zoster vaccine for each specialty, given that these differed somewhat. There was an overall 72% response rate: FM: 72% (301 / 417) and GIM: 72% (297 / 411). Respondents were not significantly different from non-respondents with respect to region, practice location, and practice setting. With regard to the most common vaccine delivery methods for this vaccine, 51% of physicians stock and administer vaccine in their offices; 39% refer patients to the pharmacy to purchase vaccine and administer the vaccine in the office (e.g., brown bagging); 33% refer patients to the pharmacy to purchase and have the vaccine administered at the pharmacy; 23% refer patients to the public health department to purchase and have vaccine administered at the public health department; and 9% refer patients to another clinic or office to purchase vaccine and the vaccine is administered at that clinic or office. Some physicians use more than one delivery method. Among both FM and GIM physicians, 93% reported using at least one delivery method. Of these physicians, 62% used one delivery method, while 38% used two or more delivery methods.



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With respect to the estimated number of patients to whom providers administered HZ vaccine in the past year, 49% of FMs and 47% of GIMs reported delivering the vaccine to less than 10 patients in a year; 45% of FMs and 35% of GIMs to 10 to 49 patients; and 6% of FMs and 16% of GIMs to over 50 patients.

In terms of the strength of the recommendation for HZV compared with other vaccines, rates of strongly recommending pnuemococcal (94%) and influenza vaccine (96%) are almost universal, and 76% strongly recommend tetanus and diphtheria. However, only 41% are strongly recommending HZV. It is important to note that when the strongly recommend and recommend categories are added, 88% are doing either. Thus, there is a shift rather than a real difference in direction. With regard to the reported percentage of time patients decline HZV after provider recommendation, approximately 50% of providers in both specialties report that the vaccine is declined less than a quarter of the time; 25% of FM and 29% of GIM report that the vaccine is declined a quarter to half of the time; and 25% of Fm and 17% of GIM report that the vaccine is declined more than half of the times they recommend it.

Regarding the perceived barriers to delivery of HZV, of the combined FM / GIM (n= 598), 53% said that cost concerns for patients was a major barrier, while 30% said cost was somewhat of a barrier. Reimbursement problems for physicians' practices were a major barrier for 52% of providers and somewhat of a barrier for 25% of providers. Up-front cost to purchase the vaccine was a major barrier for 43% of practitioners, while this was somewhat of a barrier for 30% of practitioners. The need to pick up zoster vaccine at a pharmacy was a major barrier to 23% and somewhat of a barrier to 25% of providers, while the need to store the vaccine in the freezer was a major barrier to 16% and somewhat of a barrier to 20% of providers. More pressing medical issues taking precedence was a major barrier to 12% and somewhat of a barrier to 23% of providers, with difficulty obtaining vaccine posing a major barrier to 12% and somewhat of a barrier to 14% of providers. Barriers reported as major less than 10% of the time include provider / patient concerns about safety of the vaccine; provider / patient concerns about effectiveness of the vaccine; perceived low incidence of HZ and PHN; perceived lack of serious sequelae of HZ and PHN; provider feeling the vaccine is not important; patients feeling the vaccine is not important; provider discomfort with administering vaccine that the patient brought back from a pharmacy; and provider concern that he / she will inadvertently administer vaccine to an immunocompromised patient.

Pertaining to knowledge of HZV reimbursement of the combined FM / GIM (n= 598), only 45% knew that this vaccine is reimbursed through Medicare Part D, 3% thought it was through Medicare Part B,13% thought it was not covered by Medicare, and 39% did not know or were not sure. In terms of knowledge of HZV administration reimbursement, only 13% knew this was reimbursed through Medicare Part D, 31% thought it was reimbursed through Medicare Part B, 9% thought administration was not covered by Medicare, and 48% did not know or were not sure. The eDispense™ Vaccine Manager is a web portal through which physicians can electronically submit claims for reimbursement for HZV. This was launched in August 2007 in the hope that this would simplify the process for physicians. Unfortunately, only 7% of respondents were aware of eDispense and only 1% reported being members.



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In terms of strategies to evaluate coverage for HZV. The most commonly used strategies were generally similar for the two insurance types (e.g., Medicare Part D; Private Insurance), with the exception of the most common reported strategy of asking the patient to check with their plan regarding coverage. This strategy was more commonly used for private insurance (69%) than with Medicare Part D (57%). Asking the patient to pay for vaccine and pursue reimbursement on his / her own was done 27% of the time for those with private insurance and 33% of the time with Medicare Part D. Office staff contacted the patient's plan to identify coverage 24% of the time for private insurance and 20% of the time for Medicare Part D. Practitioners later billed the patient if administration of the vaccine was subsequently not covered 19% for private insurance and 18% for Medicare Part D. The strategy of assuming the vaccine would be reimbursed by the patient's plan was used 15% of the time with private insurances and 20% of the time with Medicare Part D. Responses were not mutually exclusive.

Focusing down specifically on major barriers to reimbursement for HZV when dealing with Medicare Part D or private insurance, 43% reported that the level of complexity of the reimbursement process was a major barrier for Medicare Part D, while 33% reported complexity as a major barrier for private insurance. Other major barriers were similar for the two insurance types and included the time and effort required to assess insurance coverage (44%, 39%), lack of inadequate reimbursement for purchasing the vaccine (40%, 37%), and the lack of or inadequate reimbursement for administering the vaccine (24%, 23%).

Multivariate associations with not stocking and administering HZV, included perceiving the up-front cost of vaccine as major barrier with an odds ratio of 5 for FM and almost 14 for GIM; perceiving freezer storage as a major barrier with an odds ratio of 4.3 for FM and 49 for GIM (although the confidence intervals are very wide for that estimate); perceiving reimbursement as a major barrier with and odds ratio of 2 for FM; having a low volume of patients with private insurance; and being in a rural location. The only factor that was associate with stocking and administering the vaccine among the items checked were having knowledge of the claims submission and reimbursement process with an odds ratio of 2 for both specialties, which is likely to be a circular issue as they are likely to know about if they are doing it. Also tested but not found to be significant in these models were a variety physician demographic issues (e.g., age, gender, demographic issues, graduation year) and practice characteristics (e.g., region, type, urbanicity). In terms of the likelihood that physicians would provide HZV if covered under Medicare Part B, 49% of practitioners said they would be much more likely to provide the vaccine, 27% said they would be somewhat more likely to provide it, and 24% said it would not change their practice.

There are some important strengths and limitations to these studies. With regard to the strengths of this study, this represented the first survey to assess physician perceptions of the HZV post-licensure and the response rate was high. However, the limitations are that respondents may have differed from non-respondents, sentinel physicians may differ from physicians overall (although previous data do not suggest that these differences are significant), analytic associations do not imply causality, and probably most importantly the survey results represent reported practice—actual practice was not observed in this study.

In terms of the summary of findings, although roughly half of physicians report stocking and administering the vaccine, the number of patients to whom they administer is generally small. Multiple delivery methods are being used, some of which may jeopardize the integrity of the vaccine and compromise vaccine delivery in the medical home. Although most physicians felt that the vaccine was safe, effective, and important, the reported strength of recommendation



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compared to other routine adult vaccines thus far is low. Only 45% of providers knew that HZV is reimbursed through Medicare Part D. Providers appear to be turning to their patients to determine coverage and rarely report taking responsibility for that aspect, and reported that the reimbursement process for Medicare Part D was more complicated than for private insurance. The most frequently reported barriers to vaccination were financial. However, in multivariate analyses controlling for physician and practice characteristics, those who identified the need for freezer storage and the up-front costs of the vaccine as major barriers were the least likely to stock and administer the vaccine.

Thus, barriers to optimal adoption of HZV may include lack of uniform support from physicians; lack of knowledge regarding reimbursement; perception that the reimbursement process through Medicare Part D is complicated; reliance on patients to determine coverage; and physicians' concerns regarding upfront cost, reimbursement problems, and freezer storage. Approaches to optimizing HZ vaccine delivery should include education regarding appropriate delivery methods and a focus on solutions to financial and billing problems, such as the inclusion of HZV coverage under Medicare Part B; promotion of provider use of eDispense™, simplification of the claims process under Medicare Part D; and increased reimbursement for vaccine and administration.

**Discussion**

Given the previous day's discussion pertaining to refrigeration and freezers in pediatrician and family medicine practices, Dr. Morse wondered what kind of obstacles this posed for internists with respect to storage and types of freezers used.

Dr. Kempe responded that the survey basically shows that internists are more concerned than family medicine doctors about the freezer issue. It is a major barrier. However, the survey did not specifically inquire about the type of storage the practices have.

Dr. Marcy asked whether the investigators examined what was occurring at Kaiser in Denver and Northern and Southern California where there are no financial barriers to speak of, freezers are not an issue, and claims are not of concern.

Dr. Kempe responded that they had not, although she supported the idea. Their particular database does not include a large number of HMOs because it is sampled in the same way as the organizations. While they could certainly examine the HMO population, it would probably be better to go directly to the HMOs.

Dr. Temte was struck within his own patient population of the knowledge of seniors about this vaccine. Overwhelmingly, most of his patients have heard about it and want it. However, he had to create a phrase in his EMR that can be entered easily for this vaccine, which is "economic deferral." This is a vaccine that he is not providing to patients because they cannot afford it. Increasing numbers of his patients lack the resources to afford this vaccine. This is a crucial issue because this is the one vaccine of those he provides that he provides in a very inequitable manner.

Dr. Neuzil stressed that this is a horrible disease for which there is a safe and effective vaccine. This illustrates that the adult immunization system is broken. The Shingles Prevention Study was conducted as a VA cooperative study. The VA has an electronic medical record and cost is removed as a financial barrier, so it would be a wonderful place to also examine some of these



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same attitudes. She expressed her hope that the results presented by Dr. Kempe would be published and in the public domain very quickly.

Dr. Hahn had heard from providers that they are aware that efficacy declines with age; therefore, the comfort level is greater for a strong recommendation for someone 60 years old than 80 years old. She wondered whether this was considered.

Dr. Kempe responded that they did consider strength of recommendation for certain sub-groups, but did not find any major differences for the perception of effectiveness for those over 80 years of age.

Dr. Harpaz highlighted how important it is to vaccinate the oldest of the old because not only are they are the ones who disproportionately bear the longer duration and more severe disease, but also they have less resources, are more frail, are less able to tolerate the disease, are less able to tolerate the medications used to treat post-herpetic neuralgia, et cetera.

With regard to the efficacy of the vaccine, Dr. Plotkin pointed out that the CD-4 T-cell response is a probable surrogate as shown in the VA study. In addition, a good deal is known about immunosenescence and the immune response profile; that is, distinguishing the elderly who can or cannot respond immunologically. This is crucial with respect to the economics, given that if it makes no sense to vaccinate a frail elderly individual at 75, this should be known. Therefore, it is very important to conduct studies regarding the response in different classes of elderly using the immunologic tests that are known to correlate with immune response in the elderly so that response to the HZV can be predicted to tailor the recommendations more carefully. While not against the vaccination itself, when making a choice about who should be vaccinated, a correlation should be made with immune status.

Dr. Harpaz responded that of the different correlates studied, none really performed very well. Although the efficacy against zoster per se in persons 80 years and older was not very good (18%), considering the very high burden of post-herpetic neuralgia amongst that 18% and the fact that they are not able to tolerate disease or perhaps seek medical attention or tolerate the medications as easily, in terms of population and the burden of disease, in the broadest sense, prevented, he would argue that those 80 and over should be the first ones targeted.

Florian Schodel (Merck) agreed that the efficacy against the severe consequences of zoster is fairly high in the elderly; whereas, the efficacy against herpes zoster is less high in terms of the simple incidence of herpes zoster. Given that proportionally the severe cases increase with age, the net effect is still pretty good. It is true that there is a correlation of immune response, but it is better for antibodies than for T-cell responses. While that may be a function of T-cell response, it is easier to measure which may be the reason it is easier to find. That is true for placebo and vaccine recipients. That is, if someone has a high antibody titer initially, they will have a lower likelihood of becoming a case than if they do not have a high titer. Unfortunately, there is not a cutoff so there is no test that could be administered to people to determine whether they would benefit from the vaccine.

Dr. Schmader indicated that his own institution decided not to stock this vaccine for all of the reasons Dr. Kempe mentioned and are referring people to a local community pharmacy. The Medicare Improvements for Patients and Providers Act (MIPPA) has extended benefits for a number of items, potentially vaccines. He wondered if that would perhaps provide a mechanism for adding HZV to Medicare Part B.



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Dr. Harpaz responded that CDC is aware of the MIPPA legislation and is in the process of exploring the implications and whether it would change the payment for the HZV from Medicare Part D to Part B.

Dr. Foster reported that one of the greatest problems was the "donut hole" in co-pays because not only with vaccines in this particular case, but also with all prescription medication, prescription volume in most pharmacies is decreasing significantly because patients are not taking their medications due to the payments they are having to make. Pharmacists who go through this program probably have as much if not more training in giving vaccines and vaccinology than probably any other healthcare professionals. In 49 states, pharmacists are approved to administer vaccines, and are required to take approximately 20 additional hours of CE credit before they can qualify to do so. Pharmacists also do not experience too many difficulties with supply or storage issues. The cost is not an issue because there are far more prescriptions that cost much more. Their greatest problem is getting the physicians to understand that pharmacies are working with them rather than in competition. There are areas in the country in which physicians will not sign standing orders for pharmacists to administer vaccines. Pharmacists do not administer vaccines without a prescription or standing orders. Another mechanism that can be used is for physicians to write a prescription for their patients to have their vaccine administered by the pharmacist. As an organization and in teaching, APhA highly discourages "brown bagging." Their pharmacists are told that it is appropriate if they have a delivery system through which they can deliver a frozen prescription to the physician's office; however, they discourage giving a vaccine to a patient to take to a physician to be administered. He agreed with Dr. Temte that patients do want this vaccine, but when they realize the barriers, they defer.

While Dr. Harpaz agreed that while most pharmacists were likely opposed to the practice of "brown bagging," this was not universal.

Dr. Kempe added that most of the physicians referring to a pharmacy were generally writing prescriptions. Based on what physicians were telling the investigators, "brown bagging" is occurring frequently.

Dr. Lett thought what was presented was an accurate representation of what was being observed at the state level when visiting providers' offices. Massachusetts has a strong partnership with pharmacists and has several pilot programs. She stressed that pharmacists are excellent partners for administering this vaccine because they have the knowledge and skills to do so. One thing she thought would facilitate vaccination outside the medical home in pharmacies, public health clinics, and mass vaccination settings would be standardized protocols for screening patients (e.g., to determine who may be immunocomprised, et cetera). Perhaps some standing orders and screening forms would be beneficial with respect to operationalizing the administration of this vaccine.

Dr. Judson thought it was fair to present this to older patients as them having approximately a 1 in 6 chance of benefiting from the vaccine, with 50% efficacy and 30% risk. As others had implied, the greatest challenge in using this expensive vaccine with maximum cost-benefit impact was to learn more about why 30% obtain it and 70% do not. He declined to take the vaccine, which was offered to him free through Kaiser, because the 30 people in his family who made it into their 80s never had zoster. While he did not know what that meant genetically or immunologically, he typically looked to his ancestors to get some idea of what is in store for him.



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With regard to the economic issue, John Grabenstein (Merck) reported that Zostavax® is one component of Merck Vaccine's patient assistance program. That has been rolled out to private practices first, and have several projects in place using public clinics as well. Merck is at the point of shipping its 4 millionth dose, which when administered would bring the coverage of the indicated populations to approximately the 9% level. Merck is currently filling orders from the second half of January and should be caught up by summer. He agreed that "brown bagging" was not appropriate, and Merck councils against this practice. He encouraged everyone else to do the same.

Dr. Neuzil clarified that 50% efficacy was against the rash, which was not what they were trying to prevent. Instead, they were trying to prevent post-herpetic neuralgia, which is closer to 70% efficacy, which is better maintained with age.

## Vaccine Supply

**Dr. Jeanne Santoli**
**CDC / CCID / NCIRD / ISD**

Dr. Santoli presented vaccine updates for hepatitis B vaccines (pediatric and adult); hepatitis A vaccines; varicella-containing vaccines; and measles, mumps, and rubella vaccines.

In February 2009, both US manufacturers experienced an inability to fill orders for pediatric hepatitis B vaccine, resulting in backorders. CDC has released doses from its monovalent pediatric hepatitis B vaccine stockpiles to each manufacturer to support private and public sector vaccine usage through March 2009. Merck expects supplies of pediatric RecombivaxHB® to be limited during 2009 and does not expect to return to full supply until some time in 2010. Additional vaccine may be available in the second quarter of 2009. GSK expects to be able to meet the US market demand for monovalent hepatitis B vaccine through the end of May 2009, and is working closely with CDC to determine how much additional monovalent hepatitis B product can be supplied for the US market for the second half of the year should the shortage persist. Their combination product that contains hepatitis B, Pediarix™, is another option for hepatitis B vaccination. Based on current supply projections, there is no change in the recommendations for the use of pediatric hepatitis B vaccine at this time. Obviously, it will be imperative to work closely with the vaccine manufacturers, the ACIP, and other stakeholders should the situation change.

In December 2008, Merck communicated with CDC that it expected to deplete available supplies of the adult and dialysis formulations of RECOMBIVAX HB® in the first quarter of 2009. Merck does not expect to return to full supply of the adult and dialysis formulations of RECOMBIVAX HB® until some time in 2010. The supply of GSK's adult hepatitis B vaccine (Adult Engerix-B®) and adult hepatitis A/hepatitis B combination vaccine (Twinrix®) is sufficient to meet US market demand for usage of this vaccine, including routine use and CDC's on-going High Risk Adult Hepatitis B Initiative in state and local health departments. Based on current supply projections, there is no change in the recommendations for the use of adult hepatitis B vaccine.

With respect to hepatitis A vaccines, Merck's pediatric formulation of Vaqta® became available again in December of 2008. Merck's adult formulation is currently not being distributed, but may be available in the second half of 2009. GSK's production and supply of adult hepatitis A vaccines (Adult Havrix®) and adult hepatitis A / hepatitis B combination vaccine (Twinrix®) are



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currently in good supply to meet demand. Based on current supply projections, there is no change in the recommendations for the use of hepatitis A vaccine.

The current and projected supply of single antigen varicella vaccine is sufficient for anticipated demand in 2009, including the second dose catch-up. Distribution delays for zoster vaccine have become shorter, and Merck expects to clear backorders during the first quarter of 2009 and return to normal shipping times in mid-2009. MMR-V vaccine will not be available during 2009.

In December 2008, Merck communicated with CDC that it would not be producing or taking orders for its monovalent measles, mumps, or rubella vaccines. Merck is currently prioritizing the production of M-M-R® II over the monovalent components of the vaccine, and has not yet made a decision about the future availability of these monovalent vaccines.

**Discussion**

Dr. Pickering pointed out that CDC's vaccine shortage link is updated in real-time. When there is knowledge about a shortage, it is immediately entered. This section also includes links to any interim recommendations that have been made while shortages are in effect. The URL for the shortage page is http://www.cdc.gov/vaccines/vac-gen/shortages/default.htm.

Dr. Moore (Tennessee Department of Health) pointed out that the issue with the single antigen hepatitis B vaccine for children is being exacerbated by the need to use Pentacel® due to the Hib shortage. That is, the use of single antigen hepatitis B is having to be increased to pair that with Pentacel®, so Pediarix™ does not work due to having to deal with Hib. This is a practical issue faced at the local and state level.

Dr. Santoli agreed that the use of combination products changes the use of single antigens, and sometimes not completely in sync as providers are determining exactly how much they need of each of the components. CDC realizes that the situation is confusing, especially when there are multiple combinations that have some overlap. This is why they have been focusing on the monovalent supply and doing what they can to release doses of CDC's stockpile to make monovalent vaccines available. GSK is explicating considering the issue of monovalent vaccine because they know that this is what CDC has requested, given that the agency believes this would minimize the confusion that already exists.

Dr. Whitley-Williams requested that Dr. Santoli comment on the use of monovalent mumps and rubella, particularly given that some parents are choosing not to have their children immunized with measles vaccine. She wondered if requests for monovalent antigens by some parents were affecting the supply.

Dr. Santoli responded CDC has engaged in discussions with Merck about the use of monovalents, which is fairly modest. The issue around that decision is not that demand has increased dramatically for those products, but rather is that it is much more efficient to make the combination. Even making a small amount of monovalent impacts how much combination product can be made. Her sense was that this was the reason the focus was on the combination.



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Dr. Feinberg (Merck) replied that use of monovalent products is very limited, and these have gone in and out of stock over the past few years. Therefore, it has not been a reliably available product on the market. Indeed, production of monovalents mitigates against the maximized production of the combination M-M-R® II vaccine. Given the importance of ensuring the supply of M-M-R® II in the US as well as the growing global demand for combination M-M-R® II vaccines, Merck prioritized M-M-R® II. A final decision about bringing monovalent vaccines back to the market has not yet been made. Merck is in the process of seeking extensive stakeholder feedback about that. To the best of Merck's understanding, there is no independent public health rationale for use of monovalents; however, it remains an important question to address.

Dr. Morse wondered whether CDC was easily able to replenish the stockpile financially when it is tapped, and whether consideration was being given to expanding the stockpile with stimulus funding.

Dr. Santoli replied that typically the stockpile loans the doses to the manufacturers so they can use them to fill orders—CDC's orders as well as private sector orders. Manufacturers repay the doses when they are able to do so. It does not mean that additional doses must be purchased. For short-term problems, CDC receives the vaccine back quickly. For the Hib shortage, the stockpile will not be rebuilt until there is enough vaccine on the market to meet the demands for vaccination. With regard to the stimulus funding, CDC's stockpile funding is a VFC-supported program, while stimulus funding is a different source of funding. At this point, consideration for the stimulus funds is directed more toward routine use. The stockpile does have other options within the VFC program, which supports the building up of stockpiles.

Dr. Marcy pointed out that the shortage appeared to be primarily related to shortages of Merck products.

Dr. Feinberg (Merck) responded that Merck sincerely regretted any supply issues for which they were responsible. The issues being cited are all valid concerns, although they each were independent episodes with independent issues. Merck is making significant investments to ensure the capacity and stability of its vaccine manufacturing processes. They take this very seriously and regret any public health issues and inconveniences that have accrued as a result of these shortages. They are doing their best to bring all of these vaccines back to the market in a stable and reliable manner.

Dr. Lett expressed concern about issues occurring with not giving hepatitis B and people not being able to switch back to Pediarix™. Of Massachusetts providers, 80% are using Pentacel® and 20% are using Pediarix™. Their vaccine unit said that it was like "turning a battleship on a dime" to prevent any Hib shortage in the state. To ask providers to switch back will be difficult. She anticipated children not receiving doses of hepatitis B just like children are currently not receiving Hib doses.

Dr. Santoli responded that this is why CDC has requested that manufacturers look at the monovalent supply that could be brought in. Given the situation, that is probably the vaccine needed to ensure that children are fully protected moving forward. She said she mentioned Pediarix™ because it does contain hepatitis B, but manufacturers are currently considering how much monovalent they can bring to the market.



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# MMRV Vaccine Safety

## Introduction

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

Dr. Temte introduced the ACIP Vaccine Safety session. Since forming last summer, the MMRV ACIP Vaccine Safety Working Group has been meeting on an every two week basis. This working group has had a very ambitious schedule, and has received a great deal of excellent input from numerous consultants. The group hopes by June 2009 to have a comprehensive product to present to the full ACIP with regard to policy options for MMRV vaccine use.

## Update on Work Group Activities for Developing Policy Options for MMRV Vaccine Use

**Mona Marin, MD**
**CDC / CCID / NCIRD / DVD**

Dr. Marin provided a brief background regarding the MMRV Vaccine Safety Working Group. Pre-licensure MMRV data indicated significantly more fever after MMRV vaccine than after MMR and varicella vaccine administered at the same visit–0-42 days post-vaccination (22% versus 15%) usually within 5-12 days post-vaccination. Two post-licensure studies were initiated to assess the risk for febrile seizures, which included a Vaccine Safety Datalink (VSD) study and a Merck-sponsored study. In February 2008, preliminary information from both studies suggested an increased risk for febrile seizures during the first through second weeks after the first dose of MMRV vaccine among children aged 12 to 23 months. Based on these findings, 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 MMRV Vaccine Safety Working Group terms of reference were to conduct a risk assessment, on which CDC / ISO is the lead, to evaluate post-licensure safety data on risk for febrile seizures after MMRV vaccine, identify data gaps, and propose additional analyses or studies; to review encephalitis cases reported after MMRV vaccine; and to communicate vaccine safety findings related to MMRV vaccine with ACIP and the public in a clear and transparent manner. The activities for this term of reference are in progress. An interim synthesis of evidence for febrile seizure risk after MMRV vaccine was presented during the October 2008 ACIP meeting. The working group was also tasked with addressing risk management, on which CDC / DVD is taking the lead, to formulate policy options for use of MMRV vaccine for ACIP, considering benefit of vaccination and risks of vaccine adverse events; and identify and reconcile potential inconsistencies in ACIP statements related to measles, mumps, rubella, and varicella vaccination and febrile seizure prevention. Activities for this term of reference have begun in November 2008. MMRV vaccine is not currently being distributed in the US and is not expected to be available in 2009.



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As presented during the ACIP meeting in October 2008, for the first term of reference to assess the evidence for febrile seizure risk, the working group developed an evidence framework that incorporated criteria using other frameworks, and which considers three separate lines of evidence for risk: clinical importance of the event (febrile seizures), population-based risk, and biological plausibility. The clinical importance of the event was to be assessed after the October 2008 ACIP meeting; requires consideration of medical impact and perceived severity of adverse event following immunization (AEFI). To address the population-based risk, the epidemiologic evidence was assessed regarding a possible causal relationship between vaccine exposure and the AEFI. The biological plausibility of the association between the immunization and the AEFI should be explicable biologically according to known facts in the natural history and biology of the disease, antigen, and / or host response [This framework was adapted from criteria used by the IOM, WHO, and draft guidance from the ACIP Evidence Based Recommendations Working Group].

The table summarizing the core epidemiologic data presented as part of the interim synthesis at the October ACIP meeting was discussed. VSD and Merck-sponsored studies compared the rates for confirmed febrile seizures after Dose 1 of MMRV versus rates after separate MMR and varicella vaccines administered simultaneously (MMR+V). VSD found a statistical significant increased risk for febrile seizures within 7 to 10 days post-vaccination with an odds ratio of 2.3 and attributable risk of 5.2 per 10,000 doses. VSD did not conduct chart reviews to confirm febrile seizures during the later period after vaccination (weeks 3-4). The Merck-sponsored study had similar findings for 5 to 12 days post-vaccination, with a statistically significant increased risk for febrile seizure with a relative risk of 2.2 and an attributable risk of 3.8 per 10,000 vaccinations. Merck did confirm febrile seizures in the later period, and found non-significant decreased risk during the 13 to 30 days following vaccination in the MMRV group compared to the MMR+V group, and found no statistically significant difference in the risk for the overall 0 to 30 post-vaccination between the two groups.

After reviewing the epidemiologic evidence, as well as the biological plausibility line of evidence, the working group made two interim conclusions regarding the risk for febrile seizure after Dose 1 of MMRV vaccine. Compared with separate Dose 1 injections of MMR and varicella vaccines administered at the same visit, the evidence supports a causal relationship between receipt of Dose 1 MMRV vaccine and increased risk for febrile seizures during the 5 to 12 days after vaccination. The magnitude of the risk is approximately two-fold. During the 5 to 12 days after MMRV vaccine, 1 additional febrile seizure is expected to occur per approximately 1,900 to 2,600 children vaccinated. Compared with separate Dose 1 injections of MMR and varicella vaccines administered at the same visit, the evidence is insufficient to accept or reject a conclusion that Dose 1 MMRV vaccine is associated with a decreased risk for febrile seizures during the 13 to 30 days after vaccination. Therefore, the evidence is also insufficient to accept or reject a conclusion that children receiving Dose 1 MMRV vaccine have no overall increased risk for febrile seizures during the 0 to 30 days after vaccination.

With respect to activities performed following the October 2008 ACIP meeting, VSD has expanded its study to conduct a cohort study to assess risk for confirmed febrile seizures after Dose 1 MMRV vaccine in the 0-42 day post-vaccination period. The initial VSD study only confirmed febrile seizures during the 7-10 day post-vaccination period. The study population includes the more recently vaccinated children aged 12–23 months who received MMRV or MMR+V during the same visit. MMRV is a contemporary cohort of children vaccinated between January 2006 and October 2008, while the MMR+V group continues to be a largely historical cohort with children vaccinated from January 2000 to October 2008. The study is for Dose 1 only [Information provided by Dr. N. Klein, Principal Investigator VSD study].



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The methods for the VSD expanded MMRV epidemiologic study are identical to what was previously presented to the committee. Febrile seizure identification will be made by using seizure codes in automated data during the 42 days after MMRV or MMR+V. The ICD-9 codes include: 345.* (epilepsy) and 780.3* (convulsions, febrile convulsions, other convulsions). The study is limited to an emergency department or a hospital visit, and to children with no seizure diagnosis of any etiology in any setting in the previous 42 days. The case definition for the study is a diagnosis of febrile seizure in the chart. For confirmation of febrile seizures, chart review will be performed for all seizures occurring 0 to 42 days following MMRV, all seizures occurring 7 to 10 days following MMR+V, and a random sample of seizures occurring 0 to 6 and 11 to 42 days following MMR+V. Analyses will compare the risk for febrile seizures after MMRV with that after MMR+V during different post-vaccination time windows comparable to the Merck-sponsored study to allow for comparison of data. The post-vaccination windows include: 7-10, 13-30, 0-30, and 0-42 days. [Information provided by Dr. N. Klein, Principal Investigator VSD study]. The working group plans to present the results of this study during the June 2009 ACIP meeting.

Another update on risk assessment refers to assessing the risk for febrile seizures after Dose 2 of MMRV versus MMR+V vaccines. The risk after Dose 2 was not an initial objective of either VSD or Merck-sponsored studies, and only automated data were available. They include codes for seizure and epilepsy. Very few seizures were reported in either study. As presented during the October 2008 ACIP meeting, the rates between the MMRV and MMR+V groups were not statistically different. In addition, febrile seizures are less common in children 4 to 6 years of age compared with children aged 12 to 23 months. The working group is currently assessing the risk for febrile seizure after Dose 2 MMRV, with several updates since October 2008. There are now data from 7 VSD sites as of October 2008. During the 7-10 days after dose 2 vaccination, the following was observed: 4 seizures were identified among 84,653 MMRV recipients; the same number of seizures as previously reported but with an increase of approximately 50% in the number of doses administered; and 0 seizures were identified among 61,489 MMR+V recipients, an increase of approximately 40% in the number of doses administered. Of the 4 seizures reported after MMRV, a review of charts showed that three were not febrile seizures [Information provided by Dr. N. Klein, Principal Investigator VSD study].

The working group has several other safety activities underway to finalize the safety assessment according to the evidence framework, including discussions of the clinical importance of febrile seizure in consultation with experts, with medical and psychosocial impact considered; assessing the population-based risk for each relevant age group and the biological plausibility of febrile seizure patterns after MMRV and MMR+V. A review of the two encephalitis cases reported in VSD after MMRV vaccine is underway and is being performed by two independent pediatric neurologists using the Brighton Collaboration case definition [SejvarJJ et al. Vaccine. 2007].

Regarding the working group's second term of reference, risk management, the group developed an analytic framework for policy discussions that includes: 1) vaccine safety (febrile seizures and other important events); 2) burden of disease to prevent, including influence of vaccine coverage for measles, mumps, rubella, and varicella burden of disease; 3) efficacy / effectiveness and immunogenicity; 4) program implementation (e.g., storage conditions, number of injections); 5) social expectations / perceptions (current context of parent and provider perceptions regarding general safety issues and febrile seizure, which has some overlap with



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risk assessment); 6) equity in access to vaccine and use of public funds; and 7) recommendations of other groups (e.g., AAP, AAFP). The working group welcomed suggestions from the committee for additional elements to consider for the analytic framework.

In terms of the process for arriving at a working group decision, the first priority will be to discuss policy options separately for MMRV vaccine for Dose 1 and Dose 2 at routinely recommended ages because both the data available and the epidemiology of febrile seizures is different at the routinely recommended ages for Dose 1 and Dose 2. The recommended age for Dose 1 is 12 to15 months and for Dose 2 is 4 to 6 years. The working group will formulate policy options for the general population of children. The second priority will be to discuss policy options for MMRV vaccine for Dose 1 and Dose 2 separately, but at ages other than those routinely recommended, and to discuss special considerations for MMRV vaccine use for children at higher risk for febrile seizures (e.g., those who have had previous seizures, family history of seizures, and other situations identified by the working group). For each of these scenarios, the working group will assess the evidence for each element of the framework, discussing the evidence for MMRV and for separate MMR and varicella vaccines. The working group will attempt to assess the quality of evidence for each element, the difference in benefit or risk of MMRV versus separate MMR and varicella vaccines [Assessment based on guidelines of the ACIP Evidence-Based Recommendations Working Group and US Preventive Services Task Force], and assess and synthesize the evidence across the entire analytic framework. The conclusion will be a value judgment of the working group rather than a sum of each element assessment. Based on that, the working group will make recommendations for policy options for MMRV vaccine use to be considered by ACIP for a vote.

The policy options currently under consideration by the working group are separate policy options for Dose 1 and Dose 2 MMRV vaccine include (presented in no particular order): 1) No preference for MMRV versus separate injections of MMR and varicella vaccines (the current recommendation [CDC. Update: Recommendations from the Advisory Committee on Immunization Practices (ACIP) Regarding Administration of Combination MMRV Vaccine. *MMWR*. 57(10);258-260]; 2) Preference for MMRV versus separate injections of MMR and varicella vaccines; 3) Preference for separate injections of MMR and varicella vaccines versus MMRV use; and 4) MMRV not recommended; separate injections of MMR and varicella vaccines recommended.

The current ACIP recommendations for MMRV vaccine use voted on in February 2008 state, "Combination MMRV vaccine is approved for use among healthy children aged 12 months-12 years. MMRV vaccine is indicated for simultaneous vaccination against measles, mumps, rubella, and varicella. ACIP does not express a preference for use of MMRV vaccine over separate injections of equivalent component vaccines (i.e., MMR vaccine and varicella vaccine)" [Update: Recommendations from the Advisory Committee on Immunization Practices (ACIP) Regarding Administration of Combination MMRV Vaccine. *MMWR*. 57(10);258-260].

In regard to the proposed timeline for working group activities, during the June 2009 ACIP meeting, the group expects to present the following: results from the VSD Dose 1 expanded epidemiologic study; a final safety evidence assessment; a synthesis of evidence for the policy framework; and the working group's recommendations for policy options for MMRV vaccine use for a proposed ACIP vote.



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## Discussion

Having been in private practice during at least two brief shortages of varicella-zoster virus-containing vaccine within the past year (varicella vaccine and zoster vaccine), and realizing how difficult shortages are in a practice that is required to recall patients, Dr. Chilton wondered whether it was justifiable to put more varicella virus into an MMRV vaccine when there is a shortage of varicella-zoster virus-containing vaccines.

Mark Feinberg (Merck) responded that to be clear, there is not a shortage of the monovalent varicella vaccine. There is an adequate supply to meet the current ACIP recommendations for Doses 1, 2, and catch-up immunization. The reason that Merck has made certain decisions to prioritize the monovalent varicella at the expense of ProQuad® (MMRV) or Zostavax® (zoster vaccine) was due to the public health priority for varicella prevention. The issues regarding how to proceed will be determined by what the best public health recommendations that arise from the ACIP and the best way for Merck to allocate the supply of varicella-zoster virus-containing products are to ensure that the range of medical needs that are addressed by these vaccines is met. Merck has made significant efforts to ensure the availability of varicella-zoster virus-containing vaccines to meet the childhood immunization recommendations.

Regarding the framework for policy decisions, Dr. Englund pointed out that public relations and publicity were not included, although these are important activities. Many outbreaks are due to parental refusal rather than shortage issues.

Dr. Temte thought under social expectations and perceptions this was very clear. From the outset, safety and risk have been elevated in this working group by the very nature of the group. Formulation of policy should be done in a clear and transparent manner not only to help partners in clinics, but also to provide reassurance to the population. An internal AAFP survey found that one leading barrier for appropriate immunization was the concern that patients and parents have for the safety of the vaccine.

Dr. Marin added that the discussions regarding social expectations and perceptions pertained to better understanding of trends in vaccine exemptors and reasons for choosing exemption from vaccination.

Dr. Seward indicated that for the first dose the risk was an extra febrile seizure for every 2000 doses MMRV administered compared with MMR+V. For the second dose, there is likely no risk..

Tamara Lewis (AHIP) noted that in the current recommendations, according to the footnote, providers are allowed to give Dose 2 three months following Dose 1. The providers in her area have elected that choice with the increase in measles and varicella circulation to cover children earlier and achieve higher rates. Consideration is being given to giving Dose 2 along with hepatitis A at its Dose 2 visit, which would be 18 to 24 months. With that in mind, she requested that the working group take this age group into consideration as well for Dose 1 and 2.

Dr. Marin responded that they would consider this, but the three-month interval for Dose 2 MMRV is driven by the interval between the two varicella doses. In the varicella statement, the emphasis is to give the second varicella dose at 4 to 6 months with a permissive language to give it three months after the first dose. The recommendations will reflect that. The age routinely recommended will not be changed.



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Dr. Temte added that this would be a consideration, but not an evidence-based one given that there is not sufficient data that would inform the working group either way in terms of the risk for a second dose at an earlier interval.

Dr. Marin indicated that there may be some data from clinical trials on febrile seizures from Dose 2 given at 15 to 26 months of age, but the numbers will be small.

Florian Schodel (Merck) reported that Merck has extensive second dose data for fever, which are available and some of which are published. If not published, Merck can supply these data. If this is at all linked to fever, the second dose should not pose the same risk because there is no risk of fever.

Dr. Temte indicated that along that line, the working group had the privilege of reviewing data also from the VSD with regard to fever specifically following a second dose. The working group found that to be very reassuring as well.

Dr. Broder indicated that she was not aware of data that would specifically address the issue of second dose use in the younger age group under age 2.

It appeared to Dr. Judson that there was no difference. The numerators are obviously small to be slicing them into 5- or 7-day or other intervals. In the 0- to 30-day period, there is no difference. Thus, it could be speculated that if there really is a difference in the first 5 to 12 days, the few people who are prone or susceptible to febrile seizures might have been triggered early in the period and therefore were not available later in the period for other causes of febrile seizure. Perhaps one could argue for a compensatory decrease during the second two or three weeks. At any rate, the differences are trivial over a 30-day period.

Dr. Marin clarified that they have data from only one study examining 0 to 30 days. The working group is waiting for results from the VSD study to make a final conclusion about 0 to 30 days in general.

Dr. Katz (IDSA) disagreed with Dr. Judson, pointing out that during the 5 to 12 days after MMRV vaccine, 1 additional febrile seizure is expected to occur per approximately 1,900 to 2,600 children vaccinated. If 3 million children are receiving this vaccine, this translates to 1,500 children having febrile seizures nationally. That is significant, not miniscule.

Dr. Judson noted that with the Merck side, there was a statistically significant under-representation with regard to the 30-day period.

Dr. Temte interjected that the Merck study was not significant, and the conclusion of the working group was that there was not sufficient evidence for or against making a statement of a compensatory decline.

To keep this in some perspective, Dr. Marcy pointed out that the incidence of febrile seizures in children is 3% to 5%; that is, 3 to 5 out of every 100 children will at some time in the first five to six years of life have a febrile seizure. While he was not questioning that there is a relationship temporally, he thought they should keep this in mind.

Dr. Judson stressed that his point was that the background is high.



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Florian Schodel (Merck) indicated that in clinical studies more febrile seizures are observed than in observational studies. In the randomized blinded studies they did not have enough power to exclude an increase in febrile seizures, but they saw equal distribution between MMRV and MMR+V.

## Provider Survey Regarding Opinions on the Use Of MMRV Vaccine

**Allison Kempe, MD, MPH**
**Professor, Pediatrics**
**University of Colorado Denver**

Dr. Kempe explained that the study objectives for the survey regarding provider opinions pertaining to MMRV vaccine were to determine, in nationally representative samples of family medicine (FM) and pediatric (Peds) physicians, 1) knowledge regarding increased risk of febrile seizures with use of MMRV vaccine and ACIP's removal of preference for administering MMRV over separate MMR and Varicella (MMR+V) vaccines; 2) perceptions regarding severity of febrile seizures; 3) intended practice regarding recommending MMRV versus separate MMR+V vaccines in light of data regarding post-vaccination seizures; and 4) barriers and important factors in the decision to use MMRV vs. MMR+V vaccines.

The study population included family medicine and pediatric physicians who were part of existing sentinel networks, recruited from random samples from AAFP and AAP. Quota sampling was done to ensure that the networks were similar to overall AAFP and AAP memberships. A previous study compared the sentinel networks to randomly selected physicians sampled from AMA (most commonly used survey method) and found results comparable with respect to physician demographics, practice characteristics, and responses on surveys regarding vaccine-related issues [Crane LA, Eval& Health Prof, 2008]. Respondents practicing less than 50% in primary care practice were excluded. The survey was pilot-tested in a community advisory panel including 6 pediatricians and 6 family medicine physicians from throughout the US. The survey period was from October 2008 to January 2009.

With regard to survey administration, physicians were sent a survey based on their preferred method (e.g., mail or internet-based). Those who preferred mail received an initial mailing and up to two mail reminders, while those who preferred internet-based received an initial e-mail and up to eight e-mail reminders, with a final mailing to non-respondents by e-mail. In the survey instrument, physicians were provided with informational paragraphs about the post-licensure studies showing an increased risk of febrile seizures 5 to 12 days after MMRV compared to MMR+V in 12- to 15-month old children; ACIP's removal of the preference for MMRV combination vaccine because of these data; and the fact that no data were available regarding risk of seizures following MMRV in 4- to 6-year old children. Physicians were first asked their baseline knowledge of risk of febrile seizures related to MMRV or MMR+V and of ACIP's removal of preferences for MMRV prior to reading the provided information. Physicians were then asked to respond to all questions regarding vaccination practices with the assumption of adequate supply of MMRV, MMR, and varicella vaccines.

There was a 73% response rate overall, with 71% for FM (299 of 424) and 76% for pediatricians (321 of 425). The pediatrician respondents were not significantly different from non-respondents with respect to gender, birth year, urban / rural location, region, and type. Compared to non-respondents, FM respondents were more likely to be female, more likely to be from rural locations, and less likely to be from the South. Of the respondents, 43% of FM and 74% of pediatricians reported offering the MMRV vaccine in the past two years. With regard to



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the awareness of increased febrile seizure risk after MMRV, 26% of FM and 71% of pediatricians among all MDs and 30% of FM and 74% of pediatricians among MDs who offered MMRV were aware of the increased risk. Among all MDs, 18% of FM and 65% of pediatricians were aware of ACIP's removal of the preference for MMRV, while 26% of FM and 67% of pediatricians among MDs who offered MMRV were aware of this removal.

In terms of intended practice in healthy 12 to 15 month old children, given the data provided to them regarding risk for febrile seizures, of FMs 43% reported that they would definitely recommend separate MMR+V, 24% reported that they would probably recommended separate injections; together 67% of FM indicated that they either probably or definitely would recommend separate injections given this data. Another 24% would allow the parents to decide, while 9% would either definitely or probably recommend the MMRV vaccine. Among pediatricians, 35% reported that they would definitely recommend a separate MMR+V, and 24% would probably recommend separate MMR+V. Together 59% would definitely or probably recommend MMR+V, 20% would let parents decide, and 21% would either definitely or probably recommend MMRV.

Regarding intended practice in 12 to 15 month old children with a history of febrile seizures, much higher percentages among FM and pediatricians would definitely recommend MMR+V separately (79% of FM, 71% of pediatricians); 15% of FM and 20% of pediatricians would probably recommend separate injections. In terms of intended practice in 12 to 15 month old children with known or suspected seizure disorder, 83% of FM and 72% of pediatricians would definitely recommend MMR+V. With respect to intended practice in healthy 4 to 6 year old children, given the lack of data, among FM 36% would definitely recommend MMR+V separately, 19% probably would, together 55% would definitely or probably use MMR+V, 25% would let parents decide, and 20% would definitely or probably recommend MMRV. Among pediatricians, 23% would definitely recommend MMR+V, 18% would probably recommend separate injections for a total of 41% in these categories, 21% would let parents decide, and 38% would definitely or probably recommend MMRV.

With respect to physician perceptions about the severity of febrile seizures, there are fairly notable distinctions between the specialties. Among FM physicians, 22% perceive febrile seizure to be a moderately serious event, 1% find it to be a very serious invent. In contrast, only 8% of pediatricians consider a febrile seizure to be a moderate or serious event. A little over half of both specialties (57% of FM and 53% of pediatricians) consider febrile seizure to be mildly serious, while 20% of FM versus 39% of pediatricians consider this event to be not at all serious. Regarding physicians' perception of parent attitudes of severity of febrile seizures, there is substantial agreement between the specialties that the vast majority of parents view a febrile seizure to be a very serious event (76% of FM, 56% of pediatricians). The preponderance of people who do not think it's very serious think it is moderately serious (22% of FM, 36% of pediatricians). In terms of factors reported as very important to physicians in their decision to give MMRV versus MMR+V in 12 to 15 month old children, the percentages are substantially similar between the specialties, with only one significant difference between the two. The top most important factor was ACIP, AAFP, and AAP recommendations regarding this issue. Second were parental concerns for the risk of febrile seizures. Third was the amount of reimbursement for vaccine administration, which did differ between the specialties with 45% of pediatricians compared to 36% of family medicine physicians ranking this as a very important factor. These were followed by the cost of the vaccine to the practice, physician concerns for risk of febrile seizures, parent preference for fewer injections, the potential to improve varicella up-to-date rates, and the time spent discussing with parents safety issues related to MMR-containing vaccines.



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Regarding the results of a multivariate analysis the factors associated with recommending the MMRV vaccine to healthy 12-15 month olds were: potential to improve varicella up-to-date rates with an odds ratio of 4.46 (95% CI 2.41-8.28); parent preference for fewer injections, odds ratio of 3.75 (95% CI 2.02-6.97); and physician specialty of pediatrics, odds ratio of 3.33 (95% CI 1.70-6.55); variables tested and found not significant included: physician gender and age, practice setting and location, physician and parent perception of febrile seizures, vaccine cost, and amount of vaccine administration reimbursement. Factors associated with recommending separate MMR+V to healthy 12 to 15 month old children included physician concern for febrile seizures associated with an odds ratio of 8.73 (95% CI 5.07-15.04); and the importance of AAP / AAFP / ACIP recommendations in decision-making regarding MMRV versus MMR+V was associated with an odds ratio of 1.93 (95% CI 1.19-3.14). Variables tested and not significant included: physician gender and age, practice setting, location, and region, physician and parent perception of febrile seizures, vaccine cost, and amount of vaccine administration reimbursement.

In summary, most FM physicians were unaware of the increased risk of febrile seizures associated with MMRV and the change in ACIP recommendations. Most pediatricians were aware of both of these. FM physicians were more likely than pediatricians to feel that febrile seizures are very or moderately serious medical events (23% versus 8%). However, the majority (>90%) of both FM and pediatricians thought that parents perceive febrile seizures as either very or moderately serious events. Given the data provided regarding febrile seizures risk after MMRV, only 9% of FM and 21% of pediatricians reported that they would give MMRV to healthy 12 to 15 month olds. Despite the lack of data, only 20% of FM and 38% of pediatricians would give MMRV to healthy 4 to 6 year olds. Factors correlated with the intended use of MMRV vaccine in healthy 12 to15 month olds included the potential to improve varicella up-to-date rates and parent preference for fewer injections. Factors correlated with intended use of separate MMR+V vaccines in 12 to 15 month olds included increased physician concern for febrile seizures and the importance of AAP / AAFP / ACIP recommendations.

There are important limitations to these data. No MMRV vaccine was available at the time of the survey; therefore, some responses are theoretical. Information provided in the survey may have resulted in reporting bias, although reported rates of not being aware were quite high, so it is not clear that this case can be made. Respondents may have differed from non-respondents, although the response rate is high. Sentinel physicians may differ from physicians overall, although previous data do not suggest this. Most important, these survey results represent intended practice, some of which was based on new information, so actual practice may differ. Actual practice was not observed.

In conclusion with respect to Dose 1 for children 12 to 15 months old, the majority of physicians report they would recommend MMR+V separately in this age group even if adequate supplies of MMRV were available. Concern about febrile seizure risk was the most important predictor of this behavior. With regard to Dose 2 for children 4 to 6 years of age, despite having no data on febrile seizure risk for this age group, more physicians would recommend MMR+V separately than MMRV vaccine.



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## Discussion

Dr. Seward noted that data on the second dose had become available since this survey was conducted and are reassuring with regard to there being no detectable risk of febrile seizure due to Dose 2. The risk of febrile seizures in that age group is much lower as well.

Regarding the intended use, given that more than half of FM and about a quarter of the pediatricians had not used this vaccine at all in the previous two years, Dr. Sawyer pointed out that it appeared they had already decided not to recommend it presumably for a variety of reasons not just febrile seizure, since it is a more recently identified problem. With that in mind, he wondered if the investigators had examined the sub-set who had previously used the vaccine and if so whether they observed the same distribution of intended use.

Dr. Kempe's guess was that many physicians who had not used the vaccine simply did not have any supply of it. It was not necessarily a conscious choice not to use it. They have not broken the results down by those who previously used the vaccine versus those who had not.

Dr. Sumaya noted that a single febrile seizure has a great deal of impact on physicians and families. It could cause a major disruption in seeking additional immunizations on the part of those who have been afflicted with this. Therefore, it is important to amass as much quantitative information as possible.

Dr. Marcy pointed out that one of the take-home messages may be that family physicians are simply not well-informed regarding vaccine problems such as this.

Dr. Temte replied that on the flipside, the spectrum of care is very different. For example, within the context of febrile seizures in children, it is a rare event since most of the children seen by family physicians are healthy. Parents are also being seen by family practitioners in the aftermath for sleep problems. The dynamic of the family may change for months following a febrile seizure. These things weigh into this as well.

Harry Keyseling (SHEA) observed that it would be interesting to distinguish why physicians choose not to give the second dose. Two possible reasons would be increased inventory control and the possibility of making a mistake. Even if there is no increased safety risk for the second dose, there are other consideration that might be worthwhile to understand.

Dr. Temte indicated that the working group had the opportunity to hear the results of a provider survey conducted by Merck.

# Polio Vaccine

## Update on the Global Polio Eradication Initiative

**Steven Wassilak, MD**
**CDC / CCID / NCIRD / GID**

During this session, Dr. Wassilak reported on the current status of progress toward polio eradication to inform the ACIP discussion on polio vaccination policy in the US, and discussed the challenges and the way forward.



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The Global Polio Eradication Initiative was established in 1988, after the Global Health Assembly voted to eradicate polio from the globe. The Global Polio Eradication Initiative employs four key strategies, which include routine immunization, Supplemental Immunization Activities (SIAs), surveillance, and mop-ups in areas of high risk. Fecal specimens are collected from children who have paralysis and are tested in the laboratory. The Acute Flaccid Paralysis Surveillance is the system used. If a virus is found, it can be characterized and sequenced. Among the many families of viruses circulating in Nigeria from 2007 and 2008, three were selected to illustrate to ACIP where these are. Basically, families can be tracked to determine whether they are newly moving into an area, or if they have been in an area before, and how well they are promulgating. In 1988, there were 350,000 cases of paralytic polio in more than 125 endemic countries. In 2008, there were 1655 laboratory-confirmed cases. Four endemic countries remain, including India, which borders Bangladesh.

Since the resolution in 1988, there has been great progress with only four countries in which transmission has not been interrupted for Type 1and Type 3 poliovirus. Type 2 was interrupted successfully in 1999. From these four countries, however, there have been re-seedings into countries that had previously stopped transmission. There have been problems in up to 14 countries in 2008, some of which have had very persistent transmission. In common for all countries with persistent transmission is weak health infrastructure and therefore poor routine immunization and limited other health structures to support supplementary immunization. With respect to a reduction in the number of polio-affected districts relative to the prior year, at the end of 2007, there was an overall reduction of 24%. The number of districts worldwide affected with Type 1 poliovirus dropped 59%. The status at the end of 2008 was an overall increase of 36%. The number of districts worldwide affected with type 1 poliovirus increased 112%. Regarding the level of immunity against polio among children aged 6-35 months in affected districts, the status by the end of 2007 was that 2 of the 4 endemic countries achieved or are close to achieving at least the level in polio-free districts. By the end of 2008, 2 of the 4 endemic countries had achieved or were close to achieving at least the level in polio-free districts. By the end of 2007, outbreaks were stopped in 10 of 13 countries (31 of 35 separate importations stopped), but new outbreak countries and previously undetected circulation were identified. At the end of 2008, there were 32 importation events in 13 countries.

With regard to current areas of active transmission, polio is endemic with transmission never having been interrupted in India, Nigeria, Pakistan and Afghanistan. Outbreaks following importations in previously polio-free areas have included Angola / DRC, Chad / Central African Republic, and Sudan / Ethiopia. Recently, with the seedings from the four endemic countries into other countries, there have been large outbreaks and the number of cases has been substantial relative to these seedings. The good news is that even with continued seedings, it has been better and more quickly recognized due to laboratory advances and better control. Therefore, the number of cases tends to be lower. In the last six months (August 11, 2008 through February 10, 2009), the number of cases and number of districts affected have gone up.

In terms of the background on how CDC considers progress, Dr. Wassilak introduced the tool of looking at a surrogate of population immunity through the AFP surveillance system. The immunization histories in children who present with acute flaccid paralysis at 6 to 35 months of age who were not found to have polio virus in their stools are used as a surrogate of the history for the background community. Referring to data regarding the OPV status of children from 2003 to 2008, Dr. Wassilak indicated that by the time a child is 6 months of age, he or she should have reached seven doses. In reality, this is found to be true in India. Even in high risk states, the immunization history of the background population is high. The problem is that the



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cases also have the same type of immunization history. The vaccine is failing to protect in the Indian environment for reasons of virus load, malnutrition, diarrheal disease, et cetera. Somewhat of the same problem is occurring in Pakistan because there are still pockets in which immunization efforts are not as strong. Within Afghanistan, there is a specific problem within an area of the country where there are security issues, which have been increasing. In Nigeria, there is a massive failure to reach children with vaccine.

The cases within India are located within Uttar Pardesh and Bhar historically. Over time, in 2005 there was an introduction of monovalent vaccine which is basically more effective against Type 1 polio than the trivalent dose for dose—about three times more effect. Despite that introduction, there was a recrudescence of disease. Basically, by increasing the number of rounds, there was better control of Type 1. With the emphasis on Type 1, because it is found throughout the world more frequently, there has been an increase in Type 3. However, even that is complicated because it is based on how the vaccines were used and where they were used. The pocket of all disease was Western Uttar Pardesh. That is the location where Type 3 had been at the beginning of the time period from January 2006 to September 2007. They were focusing on Type 3 vaccine use intermittently with the other vaccines in that area. Bihar was poorly covered by Type 3 vaccines and in the process of the virus marching across from Western Uttar Pardesh, to Eastern Uttar Pardesh, to Bihar a massive outbreak occurred long before there could be a response. After three effective rounds, there was better control, at least before the high season began.

In 2006 the focus was still in Western Uttar Pardesh. At the beginning of 2007, over time, very few of these genetic families are found. Basically, by the end of 2007, there were no more cases occurring in Uttar Pradesh; however, the virus that had been circulating in Uttar Pradesh moved to Bihar, and then returned to Delhi and to the high risk area again, leading to expansion of disease. The good news is that polio transmission can be stopped. The bad news is this has not been possible everywhere at the same time in India.

With regard to Nigeria, the disease is centered in the Northern states where routine immunization has been the worst and where there also was a problem in trust of vaccine. In 2003-2004, for various reasons vaccine was being considered a sterilizing agent and some leaders of the communities voiced opinions against vaccination, and four states stopped vaccinations. Even with a restart of the program because of a continual effort of community and leader education, uptake remained weak and health workers were complacent and were not necessarily delivering the vaccine they said they were. Beginning in 2006, the monovalent type 1 vaccine was introduced, which was thought to be more effective. They also introduced an integrated program, adding multiple antigens plus other health interventions such as antipyretics or de-worming. There was improved uptake and immunity levels improved, but the program was never implemented the way it should have been. Health interventions have been poorly delivered and with the continued birth cohort, there was a build-up of a susceptible population in the outbreak of 2008. Routine immunization in particular has been weak, and seems to have worsened between 2007 and 2008. In addition, the data over-represent the truth. Coverage is actually lower than what is reported. There are some halos of good news within Nigeria. Certain states have actually understood the message and have attempted to supply the logistics, supervision, and political will to improve the supplementary campaigns.



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In terms of Pakistan and Afghanistan, there have been two zones of circulation primarily compounded by the fact that security and access are major problems on the borders both in the Northern Zone that includes the Northwest Frontier Province and in the Southern Zone that includes high risk areas on both sides. This also included a zone where immunization should not have been a problem as there are no security issues in most of Balochistan and Sindh. However, in 2008 increases in these two zones led to an outbreak in Punjab State where routine coverage is not strong and supplementary immunization has been weak. Fortunately, since this has occurred, the highest levels of health authorities and politicians have become involved such that there has been some effort shown to improve delivery in Sindh and Punjab. In fact, there have been no Type 1 cases in Sindh since August 2008. However, security issues cannot be ignored. Between 2005 and 2008 children could not be reached. The UN staff could not go in to supervise and the local staff have been hindered in their movement. Even when there have been agreements with anti-government forces, those agreements have not always been honored, so coverage and security have deteriorated.

Seeding is traced with molecular epidemiology and the sources for multiple outbreaks have been India and Nigeria. From 2003 to 2005 when there was suspension of vaccination in Nigeria, there were movements East and West of the polio virus. Much of this movement is frequent, with many viruses moving around. From Northern India to Angola, there have been three importations—two Type 1 and one Type 3 that have not been abated. With regard to the immunization histories among those children, basically the immunity level was poor when these problems first occurred from 2003 to 2005. Due to additional supplementary immunization, the overall immunity of surrounding countries has improved.

In conclusion, the threat of long-distance importations of wild poliovirus in the US continues into 2009. In India, Type 1 wild poliovirus transmission is at its lowest level, with potential for interruption in 2009. Type 3 interruption is to follow. Conflict and security issues continue to plague polio eradication operations in Afghanistan and Pakistan. There are potential signs of improvement in the non-secure areas of Pakistan with better implementation. Poor vaccine delivery and inadequate political commitment impede success in Nigeria, with uncertain outcome from recent political “commitments.” Chronic problems remain to be mitigated in reaching children in Angola, Chad, Sudan (less so in the Democratic Republic of Congo), albeit with low level of transmission. The worst situation is that this is compounded by weak surveillance, so in addition to having persistent transmission, there are times when virus is not found in a given area, but it is a false negative. In fact, for approximately three years virus was not found to be circulating in Sudan when, in fact, it was. There have been recent importations traveling further into Uganda and Kenya from Sudan. These are relatively low transmission issues, but they are chronic. Other options are being considered for other vaccinations, including inactivated polio vaccine and other ways of using oral polio vaccine. If successful, the focus will be placed back on eliminating polio entirely, which means interrupting Type 3 as well with the monovalent Type 3 vaccine. For the other problem countries, there are areas of promise.



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## Discussion

William Schaffner (NFID) inquired as to where consideration was being given to using inactivated polio vaccine rather than the continued reliance on oral polio vaccine in the problematic areas.

Dr. Wassilak responded that among the people who worry about polio eradication, there has been a great deal of discussion. It has only been discussed in seriousness for India because that is where vaccine delivery is not the problem. In the other countries the issue is more a failure to vaccinate. While discussions have been serious for the last two years, beyond a very small clinical trial, there is no testing planned at this time. Realistically, none of these contingencies will be considered until later in the year due to elections. IPV is not off the table, but the Indian government is not leaning in that direction. They are trying to make a link to their strengthening of routine immunization in general and would like to use a combination vaccine with IPV, which would complicate how to deliver the vaccine and how to follow up.

Neal Halsey stated that he had a conflict of interest in this arena in that he had conducted studies for many years with IPV and OPV, some of which was supported by sanofi pasteur. He also participated in the workshop held by NIH that was published in *The Lancet* recently, which comes down strong on the need to use IPV much more extensively not just for India, but also for some of the other areas as well and in the transition to sometimes stopping OPV. Most people who have been involved in this arena believe that this will be necessary. No doubt there are major cost and delivery issues, but there should be a much more open discussion of this issue in the WHO presentations. Also not mentioned was the very problematic issue of the continuing outbreak in Nigeria of the vaccine-derived polio and the multiple outbreaks that have occurred and continue to occur. That should be a part of the presentation on the elimination of paralytic disease due to polio viruses.

Dr. Wassilak agreed that those two issues were incredibly important. With respect to vaccine-derived polio virus, at least 12 outbreaks have been recognized, with 150 cases in Nigeria that is on-going despite four rounds of Type 2-containing vaccine over several years. Many are in agreement that to stop oral polio vaccination is absolute, but to do it without some reliance on IPV is perhaps reckless. Even among WHO colleagues, there is an understanding that IPV will provide an important role if not in interrupting wild polio virus perhaps in transitioning to the cessation of oral polio vaccine use. While this point is valid, he did not address it during this session due to time constraints. The other aspect is that despite the non-immediate intention of the use of IPV within the next several months, an incredible amount of research is underway to examine how to make it affordable for the vast part of the world. That includes dose reduction, intradermal vaccination, less expensive and safer production, et cetera.

Stanley Grogg (AOA) was recently in Afghanistan where he inquired as to what the problem was with getting the polio and rotavirus vaccines to refugee areas, outside of security issues. The response was that they do not have refrigeration.

Dr. Wassilak noted that OPV can be used even without a cold box in some situations because it has temperature thermal indicators on it to see how well the vaccine is holding up to heat stress. There can be barriers to doing the right thing, but given the right preparation it can be done correctly. The funding for the program is 85% secure for the next two years thanks to the generosity of the Gates Foundation, Rotary International, the German and UK governments most recently, and others. The US government also provides a substantial amount of money for the program.



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## Domestic Poliovirus Vaccine Issues

**Gregory S Wallace, MD, MS, MPH**
**CDC / CCID / NCIRD / DVD**

Dr. Wallace presented on the history of poliovirus and poliovirus vaccine in the US and inactivated poliovirus vaccine (IPV) schedule issues including minimum intervals and accelerated schedules, and optimal schedules including timing of boosters.

With regard to the history of poliovirus vaccine in the US, IPV was introduced in 1955 and OPV was introduced from 1961 to 1964. Enhanced Potency eIPV was licensed in 1987. The Americas were certified polio free as a region in 1994, with the last indigenous case in the US occurring in 1979. With the transition from routine OPV, to sequential IPV-OPV schedule, to an all-IPV schedule came the elimination of VAPP cases with the exception of an imported case in a young adult who had traveled to Central and South America. No OPV has been distributed since 2000. More recently, there has been a transition to a use of more IPV-containing combination vaccines with DTaP-HepB-IPV licensed in 2003 and DTaP-IPV/Hib and DTaP-IPV licensed in 2008.

In terms of the evolution of IPV schedule in US, when the enhanced potency IPV was licensed in 1987, while it was not the routine vaccine at the time, it was indicated for certain high risk groups. The ACIP recommendation for eIPV for Dose 1-2 to have a preferred 8 week interval, but a 4-week interval was acceptable. Dose 2-3 had a minimum interval of 6 months, with 12 months being preferred. A booster dose was to be administered after the 4$^{th}$ birthday. This is really two priming doses, a booster dose, and an additional booster dose prior to school. With the transition from IPV to a routine OPV schedule there were priming doses of IPV at 2 and 4 months of age, with OPV being given in the second year of life, and at age 4 or over. There was some language about accelerated schedules if starting late. At that point, the package insert for eIPV was amended to allow the third dose to be administered as early as 6 months of age. Prior to that, the minimum age for the third dose was 12 months of age.

With the evolution to an all-IPV schedule in the US in 1997, the ACIP recommendation for transition to IPV was IPV at age 2 and 4 months, OPV at 12-18 months and 4-6 years, and an accelerated schedule for IPV if starting at >6 months of age. The minimum interval was 4 weeks between doses 1 and 2 and 6 months preferred between Doses 2 and 3, and a 4$^{th}$ dose at age 4-6 years. IPV PI was amended to allow a 3$^{rd}$ IPV dose as early as age 6 months in an all-IPV schedule. With the evolution of the IPV schedule in the US in 1999 / 2000, the ACIP recommendation for routine use of IPV was at 2, 4, 6-18 months and 4-6 years, with a minimum interval of 4 weeks between doses, and 2 months preferred between Doses 2 and 3.

The 2009 recommended routine schedule is 2, 4, the window of 6-18 months, and 4 to 6 years. With the other routine schedules and the use of combination vaccines, a lot of IPV is being given at 6 months of age. The catch-up schedule for those who are late, for those under 7 years of age, is 4 weeks between all doses and is the same for older children as well.

Studies have shown that a 2, 4, 6 month priming schedule induces higher GMTs than a 2, 3, 4 months or a 6, 10, 14 weeks schedule. Starting later and / or having longer intervals does induce higher GMTs. Maternal antibodies can have an impact on the first dose, especially if given early. However, this does not affect subsequent responses to doses administered later. Longer intervals are optimal for memory response for GMT and duration of immunity. At least



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4-6 month intervals prior to the dose in the second year of life are optimal for memory cell maturation. Essentially everybody, regardless of their priming schedule, will have detectable antibodies in a booster given in the second year of life. With respect to how long that lasts, there are some data but it is incomplete. There are also anecdotal reasons to think that this is long-lasting, but there are no specific data to show exactly how long the duration of immunity would persist.

The current minimum intervals and minimum age are 4 weeks between each IPV dose, starting at least at 6 weeks of age for the first dose. The statements from package inserts, depending upon the vaccine preparation is used may include a "preferred" interval of 6 or 8 weeks, with a longer interval "preferred" between the 2nd and 3rd dose and / or the 3rd and 4th dose. For routine scheduling, current ACIP recommendations include a booster dose at age 4 to 6 years, but with the advent of Pentacel®, the package insert allows a 2, 4, 6, and 15-18 month schedule with all doses counting as valid. Accelerated schedules with minimum intervals can result in shorter intervals and younger ages, with technically 4 doses in the first year of life.

**Examples of IPV Schedules in Various Countries**

| COUNTRY | DOSE 1 | DOSE 2 | DOSE 3 | DOSE 4 | DOSE 5 |
|---|---|---|---|---|---|
| USA | 2 mos | 4 mos | 6-18 mos | 4-6 yrs | --- |
| Canada | 2 mos | 4 mos | 6 mos | 18 mos | 4-6 yrs |
| Sweden | 3 mos | 5 mos | 12 mos | 5-6 yrs | --- |
| United Kingdom | 2 mos | 3 mos | 4 mos | 3.3-5 yrs | 13-18 yrs |
| Spain | 2 mos | 4 mos | 6 mos | 15-18 mos | --- |

In summary of the different IPV schedules used worldwide, the variations are either 2 or 3 doses in the first year of life followed by later booster doses. The vast majority of recommended IPV schedules include 1 or more doses after the 2nd year of life. Spain has utilized a 2, 4, 6, 18 month schedule using IPV-containing combination vaccines since 2004.

Potential policy questions include the following:

1. Minimum Intervals and Accelerated Schedules:
    - Are Minimum Intervals with lower GMTs okay in the first year of life?
    - Should Minimum Intervals be extended for boosters?
    - Is more specific guidance on accelerated and catch-up schedules needed?

2. Timing of IPV-containing Vaccine Doses for Routine Schedule:
    - What are the optimal intervals for each dose?
    - Should the current schedule for the 3rd and 4th dose be changed?
    - Should a booster dose at ≥4 years of age be maintained? (which may require one additional IPV-containing dose in some circumstances)



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## Discussion

Dr. Morse requested information about forming the group and submitting recommendations to the full ACIP.

Dr. Wallace responded that they anticipated the general recommendations possibly being approved in June 2009, with a publication possibly later in the year. Ideally they would like to take on the minimum interval issue by the June 2009 meeting, and certainly by the October 2009 meeting.

It appeared to Dr. Marcy that the UK had one-month intervals between doses and to his knowledge were not having a problem. It seemed that ACIP was being asked to fix something that was perhaps not broken.

Dr. Wallace responded that it was only broken because people were confused and there are recommendations that could be interpreted as being in conflict with each other. There are two issues, the timing of the booster dose and the accelerated schedule issue. They probably do not have the same types of problems with that in the UK.

Dr. Seward added that CDC has data that show a minimal interval on the catch-up schedule produces inferior immune response. That is fairly new data from a study CDC conducted. The first question regards whether it is acceptable to have an accelerated 6, 10, 14 week schedule or whether those minimum intervals need to be changed. Combination vaccines are being used increasingly on an accelerated schedule, which is pushing that to become routine. There must be clear guidance. The UK is starting later, and they have an accelerated schedule within a schedule of five overall doses.

Dr. Wallace interjected that 4 months to 3.3 years raised his eyebrow to some extent, but the US schedule compared to others is somewhat of a hybrid. Even if not accelerated, the schedule could be 2, 4, 6 and nothing until 4 to 6 years. However, that is not the way the studies have been conducted. There are two issues. The minimum interval issue informs the routine issue to some extent, but the minimum interval issue needs to be communicated more clearly. Spain and Slovenia are the only countries known to be routinely stopping with a booster in the second year of life. UK is the outlier waiting a while to give their booster. There have been some discussions about whether that is ideal or not. Also at issue is how clinically relevant a higher GMT is to a lower one with a vaccine that protects everybody eventually.

Dr. Sawyer noted that in his short tenure with ACIP, this was not the first time he had heard questions raised about minimum intervals in general. He encouraged the effort to examine the minimum intervals carefully as stated to ensure that they are appropriate. If they are, then they need to be minimum intervals and it needs to be acceptable to give the vaccine at those minimum intervals.

Dr. Wallace added the caveat that the appropriateness of a minimum interval can change depending upon how old someone is at the time, the disease, and the vaccine. For an adult who has never been vaccinated, who is going to go to Afghanistan, a 4-week interval for the first two doses and a slightly longer interval to the third dose is all they really need for optimum protection.



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## Yellow Fever Vaccine

**Carol J. Baker, MD, Chair**
**ACIP Yellow Fever Working Group**

Dr. Baker indicated that the ACIP Yellow Fever Working Group's charge was to update and revise the 2002 ACIP Yellow Fever Vaccine Recommendations, as necessary, based on new information.

Yellow Fever Working Group meetings have included the following:

- September 16, 2008
  - → Welcome and Group Introduction
  - → Background of yellow fever disease and vaccine

- November 10, 2008
  - → Vaccine presentation, dose and booster
  - → Simultaneous administration of other vaccines

- December 9, 2008
  - → General Safety
  - → Requirements for vaccination before international travel
  - → Upcoming changes to yellow fever risk areas

- January 12, 2009
  - → Hypersensitivity
  - → Yellow fever vaccine-associated viscerotropic disease

- February 9, 2009
  - → Thymic disease and use of vaccine
  - → Yellow fever vaccine-associated neurotropic disease

Regarding the proposed timeline, monthly meetings are planned from February to May 2009 to review topics pertinent to yellow fever vaccine use. Draft recommendations are expected to be developed to present to ACIP to obtain feedback before the final recommendations are presented. Final recommendations are expected to be presented for an ACIP vote in October 2009. The final document will be submitted to the *MMWR* in November 2009.

Anticipated revisions to the 2009 document include updating the epidemiology of yellow fever disease, including an updated risk map and recent epizootic activity (South America); including information on updated International Health Regulations (2005); updating vaccine safety information, including new incidence rates and additional information on serious adverse events (e.g., viscerotropic disease, neurotropic disease); strengthening the wording related to vaccine precautions and contraindications based on new data; and outlining research priorities.



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## Public Comments Day 2

No public comments were offered during the second day of the meeting.

## Certification

I hereby certify that to the best of my knowledge, the foregoing Minutes of the February 27-28, 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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## List of Attendees

| | |
|---|---|
| Abraham | Brian |
| Abramson | Allison |
| ALLAVOINE | Thierry |
| Allred | Stephen |
| Ambrose | Karita |
| ANI | GEORGE |
| Arnhart | Tom |
| Ault | Kevin |
| Bahta | Lynn |
| Baker | Carol J. |
| Banach | Stephanie |
| Bandell | Allyn |
| Baylor | Norman |
| Beck | Robert L. |
| Benning | Eric Benning |
| Benning | Eric |
| Billings | Pamela |
| Blazek | Nicole |
| Bocchini, Jr. | Joseph |
| Bowman | Pepe |
| Brooks | Dennis |
| Buehler | James |
| Calhoun | Eve |
| Campos-Outcalt | Doug |
| Cary | Donna |
| Chamberlain | Allison |
| Chaney | Mike |
| Cheek | James |
| Chilton | Lance |
| Cieslak | Paul |
| Cipriano | Michael |
| Colwell | Chris |
| Conner | Penny |
| Counard | Catherine |
| Curlin | George |
| Cyrus | Jobin |
| Dalrymple | Donald "Dack" |
| Deal | Carolyn |
| DeBlois Buchanan | Anna |
| Decker | Michael |
| Denovchek | Bradley |
| Dhankhar | Praveen |
| Dinovitz | Richard |
| Dosanjh | Jag |
| Dougherty | Kelley |



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| | |
|---|---|
| Douglas | John |
| Dubin | Gary |
| Dubischar-Kastner | Katrin Luise |
| Duchin | Jeffrey |
| Duffy | Colleen |
| Dzubin | Shannon |
| EBULE SAMMEH | ELVIS |
| Ehresmann | Kristen |
| Englund | Janet |
| Evans | Geoffrey |
| Feinberg | Mark |
| Feng | Zijian |
| Feng | Luzhao |
| Fitzgerald | Bernadette |
| Florez | Jorge |
| Foster | Stephan |
| Friedland | Leonard |
| Frutos | Sylvina |
| fryhofer | sandra |
| Gaffoglio | Diane |
| Gall | Stanley A |
| Garrett | William Matthew |
| Gaskins | Diana |
| Geddes | Cathy |
| Gellin | Bruce |
| Gershon | Barry |
| Gonda | Mike |
| Grabenstein | John |
| Greenberg | David |
| Grogg | Stanley |
| Grogg | Barbara |
| Gurunathan | Sanjay |
| Hachey | Wayne |
| Hahn | Christine |
| Halsey | Neal |
| HALSTROM | ERIK |
| Hammer | Sandra |
| Hammes | Mary |
| Haupt | Richard |
| Hosbach | Philip |
| Huber | Helen |
| Hull | Harry |
| Humphrey-Franklin | Donelle |
| Iacuzio | Dominick |
| Ismail (nee Virani) | Shainoor |
| Jackson | Melonie |



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|---|---|
| JAMES ANUEKATOA | PETER |
| Johnson | David |
| Joice | Melodie |
| Judson | Frank |
| Kaplan | Susan |
| Katz | Samuel |
| Kempe | Allison |
| Keyserling | Harry |
| Kimberlin | David |
| Kinsinger | Linda |
| Koinis | Thomas |
| Kroger | Andrew |
| Krull | Andrea |
| Kruzikas | Denise |
| Kuter | Barbara |
| L | OKESADE |
| Laird | Susan |
| Lake | Tom |
| Lammers | Peter |
| Lane | Barbara |
| Langley | Joane |
| Lease | Christian |
| Lee | Lucia |
| Leger | Marie-Michele |
| Lett | Susan |
| Lewin | Clement |
| Lewis | Tamara |
| Lievano | Fabio |
| Lovell | Ethan |
| Lukus | Lori |
| Malik | Manzoor |
| Malone | Jill |
| Malone | Robert |
| Mansoura | Monique |
| Manzoor | Malik |
| Marcellous Agendia | Nkengacha |
| MARCY | S(tephan) Michael |
| Martinez | Laura |
| Mascarenas | Cesar |
| Mason | Dean |
| Mazur | Marie |
| McGriff-Lee | Nayahmka |
| McLoughlin | Sean |
| McMullin | David |
| Meigs | Wendy |
| Meissner | Cody |
| Middleman | Amy |
| Miller | Elaine |
| Milley | Frankie |



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| | |
|---|---|
| Mina | Vivian |
| Moore | Kelly |
| Morse | Dale |
| Mulach | Barbara |
| Murphy | linda |
| Naumoff | Nicole |
| Neuzil | Kathleen |
| Obara | Timothy |
| Offit | Paul |
| Omer | Saad |
| omer | hamza |
| O"Neill | Kevin |
| Oriol | Valérie |
| Otoo | Drew |
| Papa | Thomas |
| Paradiso | Peter |
| Parikh | Shefali |
| Pei | Xuesong |
| Penrod | Deborah |
| Peter | Georges |
| Peters | Martin |
| Peterson | Diane |
| Pisani | Amy |
| Plotkin | Stanley |
| Poland | Gregory |
| PQIDJohn | PQIDJohn |
| Pugh | Pearl |
| Quinn | Jane |
| Rall | Kristen |
| Randall | Lisa |
| Ransom | James |
| RANTI | OKESADE |
| Ray | Jill |
| Rennels | Margaret |
| Richards | Steve |
| Richardson | Vesta |
| Ross | David J. |
| Rousculp | Matthew |
| Saddier | Patricia |
| Sammons | David |
| Saslow | Debbie |
| Sawyer | Mark |
| Schaffner | William |
| Schechter | David |
| Schmader | Kenneth |
| Schodel | Florian |
| Schott | Chris |
| Schutt | Robert |
| SEARFOORCE | AMY |
| Sever | Perica |



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| | |
|---|---|
| Sherner | James |
| Shin | Tom |
| Shindman | Judith |
| SIEVERT | ALAN |
| Silverstein | Leonard |
| Skjeveland | Eric |
| Smith | Parker |
| Smith | Stephen |
| Southall | Jennifer |
| Spencer | Yvonne |
| Stinchfield | Patsy |
| Stobbe | Mike |
| Strutton | David |
| Stuerke | Stacy |
| Sumaya | Ciro |
| Swain | Christopher |
| Sylvester | Gregg |
| Tan | Litjen |
| Temte | Jonathan |
| Thomas | Lonnie |
| Tucker | Miriam E. |
| Turner | James |
| Tursi | James |
| Uduman | Sayenna |
| Verstraeten | Thomas |
| Ward | Joel |
| Wassil | James |
| Waytes | Tom |
| Wexler | Deborah |
| Wheatley | Lisa |
| Whitley-Willimas | Patricia |
| Wible | Sharon |
| Wighton | Timothy |
| Wiskind | Robert |
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| Yamauchi | Terry |
| York | Laura |
| Zimmerman | Richard |
| Zink | Thomas |



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