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

Advisory Committee on Immunization Practices (ACIP)

Summary Report
February 27-28, 2008
Atlanta, Georgia

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Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
AIM	Association of Immunization Managers
AIS	Adenocarcinoma *In Situ*
ALA	American Lung Association
BLA	Biologics License Application
BOI	Burden of Illness
CAIS	Childhood / Adolescent Immunization Schedule
CAIV-T	Cold-Adapted Influenza Vaccine
CCID	Coordinating Center for Infectious Diseases
CDC	Centers for Disease Control and Prevention
CIN	Cervical Intraephithelial Neoplasia
C. jejuni	*Campylobacter jejuni*
CMS	Centers for Medicare and Medicaid Services
DBD	Division of Bacterial Diseases (of NCIRD)
DoD	Department of Defense
DSMBs	Data Safety Monitoring Boards
DVA	Department of Veterans Affairs
DVBID	Division of Vector-Borne Infectious Diseases
DVD	Division of Viral Diseases (of NCIRD)
DVH	Division of Viral Hepatitis (of NCIRD)
DVRD	Division of Viral and Rickettsial Diseases
FDA	Food and Drug Administration
FFF	Families Fighting Flu
FQHCs	Federally Qualified Health Centers
GBS	Guillain Barré Syndrome
GMP	Good Manufacturing Practice
GSK	GlaxoSmithKline
HDCV	Human Diploid Cell Vaccine
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
HUI	Health Utility Index
HZ	Herpes Zoster
IC	Immunocompromised
ID	Influenza Division (of NCIRD)
IDSA	Infectious Disease Society of America
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHS	Indian Health Services
ILI	Influenza-Like Illness
IOM	Institute of Medicine
ISD	Immunization Services Division (of NCIRD)
ISO	Immunization Safety Office (of CDC/OD/Office of the Chief Science Officer)
MCO	Managed Care Organization

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MCV4	Meningococcal Conjugate Vaccine
MMRV	Measles, Mumps, Rubella, Varicella
MMWR	*Morbidity and Mortality Weekly Report*
mOPV1	Monovalent Polio Vaccine Type 1
MSW	Medically Significant Wheezing
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
NCVIA	National Childhood Vaccine Injury Act
NCZVED	National Center for Zoonotic, Vector-Borne, and Enteric Diseases (of CDC/CCID)
NIH	National Institutes of Health
NIS	National Immunization Survey
NSFG	National Survey of Family Growth
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
OD	Office of the Director (of CDC)
P&I	Pneumonia and Influenza
PCECV	Purified Chick Embryo Cell Vaccine
PCV	Pneumococcal Conjugate Vaccine
PEP	Postexposure Prophylaxis
PhRMA	Pharmaceutical Research Manufacturers of America
PSC	Protein Sciences Corporation
QALMs	Quality-Adjusted Life Months
QALYs	Quality-Adjusted Life Years
RCA	Rapid Cycle Analysis
RHCs	Rural Health Centers
sBLA	Supplemental Biologics License Application
SMEs	Subject Matter Experts
SPG	Sucrose Phosphate Glutamate
SPS	Shingles Prevention Study
TIV	Trivalent Inactivated Vaccine
VAERS	Vaccine Adverse Event Reporting System
VFC	Vaccines for Children
VICP	National Vaccine Injury Compensation Program
VNAs	Virus Neutralizing Antibodies
VSD	Vaccine Safety Datalink
VZV	Varicella-Zoster Virus
WHA	World Health Assembly
WHO	World Health Organization

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

February 27-28, 2008
Atlanta, Georgia

Summary Report

The Department of Health and Human Services (HHS), Centers for Disease Control and Prevention (CDC), National Center for Immunization and Respiratory Diseases (NCIRD) convened a meeting of the Advisory Committee on Immunization Practices (ACIP) on February 27-28, 2008 at CDC's Global Communications Center in Atlanta, Georgia. The following represents a summary of the proceedings.

Wednesday, February 27

Welcome & Introductions

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

Dr. Dale Morse, ACIP Chair, welcomed those present and called the meeting to order at 8:07 a.m.

Dr. Larry Pickering, ACIP Executive Secretary; CDC, pointed out several individuals who were to be present throughout the meeting to assist with meeting functions, following which he reviewed housekeeping issues. In addition, he referred participants to the ACIP website (www.cdc.gov/vaccines/recs/acip), noting that copies of the handouts distributed to ACIP members were available on the table outside the meeting room for members of the public, that slides used during the meeting would be posted on this site where they would be available approximately one week following the meeting, and that the minutes of the meeting would be posted within approximately 90 days following the meeting. ACIP recommendations and other information related to immunization and ACIP activities also can be found on this site. Members of the press interested in conducting interviews with ACIP members were instructed to contact Curtis Allen to arrange those interviews. To avoid interruptions during the meeting, Dr. Pickering requested that all business not directly related to discussions of the ACIP be conducted in the hallway outside of the meeting room and that all electronic devices placed on vibrate or turned off.

Dr. Pickering recognized two visitors from Japan who were in attendance to observe the United States' immunization policy development process. This was in follow-up to the visit by several Japanese colleagues during the October 2007 meeting. Dr. Okabe Nobuhiko is Director of the Infectious Disease Surveillance Center at the National

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Institute of Infectious Diseases in Tokyo, Japan. For many years, Dr. Nobuhiko has been a leader in the Japanese Pediatric Society and has played a key role in the leadership and development of immunization policy in Japan. Dr. Chiaki Miyazaki is a Pediatrician who is the Director General of the Fukuoka-West Rehabilitation Center for Children in Japan. Dr. Pickering stressed how honored ACIP was to be joined by Drs. Nobuhiko and Miyazaki. He also recognized another distinguished visitor, Dr. Carla Odio, Professor of Pediatrics and Pediatric Infectious Diseases at the University of Costa Rica and the University Health Science Center in San Jose, Costa Rica.

Dr. Pickering announced the appointment of two new ACIP members: 1) Dr. Jonathan Temte, an Associate Professor of Family Medicine at the University of Wisconsin in Madison, Wisconsin. Dr. Temte currently serves as one of the two liaison representatives from the American Academy of Family Practice (AAFP). He will be appointed to fill the vacant position that was previously held by Dr. Harry Hull, who resigned in 2007; and 2) Dr. Mark Sawyer, Professor of Clinical Pediatrics in the Department of Pediatrics at the University of California in San Diego, who will be appointed to fill the vacant position that was held by Dr. Allan Craig, who is assuming an international position with the Centers for Disease Control and Prevention (CDC). The terms of Drs. Temte and Sawyer will begin in March 2008 upon completion of the appropriate paperwork. Both will attend the June 2008 ACIP meeting as voting members.

Those unable to attend the February 2008 ACIP meeting included: Dr. James Cheek, Indian Health Services (IHS); Dr. Stanley Gall, American College of Obstetrics and Gynecology (ACOG); Dr. Paul McKinney, Association of Preventive Teach and Research (APTR), with Dr. Rick Clover attending on his behalf; Dr. David Salisbury from the United Kingdom Department of Health (UK DOH); and Dr. Damien Braga, Pharmaceutical Research Manufacturers of America (PhRMA), with Dr. David Johnson attending on his behalf. Given that two members of the ACIP were unable to attend, Dr. Pickering stressed the importance of all members remaining throughout the meeting to maintain a quorum. He explained that the ACIP charter gives the Executive Secretary, or his or her designee, the authority to temporarily designate ex officio members as voting members. This would occur only if there were fewer than eight appointed members available or qualified because of conflicts of interest. The ex officio members, if needed, would be formally requested to vote when necessary, and would also be required to declare any conflicts of interest.

Dr. Pickering explained that topics presented at the ACIP meeting include open discussion, with time reserved for public comment on each day. In certain circumstances, a formal comment period may be scheduled during the specific deliberation of an agenda item. Comments from the public may be received during open discussions depending upon the amount of time and at the discretion of Dr. Morse. Individuals planning to make public comments were instructed to sign-in at the registration table at the rear of the auditorium. Those who registered prior to the meeting were instructed to check the sign-in roster to ensure that they were included. Microphones were located at either end of the committee tables for comments from the

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audience. Those making comments were instructed to identify themselves and their organizations prior to making their comments. Both CDC and members of the public believe in a transparent process for information gathering and decision making. To ensure such transparency during the public comment session, CDC believes that it is important to understand the context of an individual's comments. With that in mind, CDC encourages people at the beginning of their comments to advise the committee of any financial relationship that they may have with any company or organization that is likely to be impacted by the topic being discussed. For example, such financial information may include the company's or organization's payment of travel, lodging, or other expenses in connection with attending this specific meeting. Although encouraged, choosing not to address the 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. CDC has launched a new vaccine safety website (www.cdc.gov.vaccinesafety/).

With respect to disclosures, Dr. Pickering explained that the goal in appointing members to the ACIP is 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 CDC 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 all discussions with the proviso that he or she abstains on all votes related to vaccines of that company. ACIP members who may have a potential financial conflict of interest should make this conflict known by disclosing all of their vaccine-related financial interests and related activities.

Dr. Morse added his welcome to new members, as well as his gratitude to departing members for all of the service they provided to this committee. Prior to beginning the first session, he requested that ACIP state any conflicts of interest. Dr. Janet Englund indicated that she has research support from sanofi pasteur and MedImmune. All other ACIP members present declared no conflicts.

Influenza Vaccines

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Surveillance Update

Anthony Fiore, MD, MPH
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National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Fiore described the structure of the meeting, including the objectives. The agenda for this session included presentations on: Influenza surveillance, Influenza vaccine strain selections 2008-09; Oseltamivir-resistant influenza A (H1N1); Influenza vaccine effectiveness among 6-23 month old children, 2005-6 and 2006-7 seasons; Expanding influenza vaccination recommendations to include all 5-18 year old children; Influenza Vaccine Workgroup Report: Key issues regarding expansion; and Influenza vaccination recommendations, 2008 (Vote and VFC Vote).

With regard to the influenza activity so far this season, Dr. Fiore reported data which were current through February 16, 2008, the most recent reporting interval. Based on estimates of influenza activity which CDC receives from the State and Territorial Epidemiologists, as of the end of October 2007 the season was fairly quiet, with only two states reporting local activity. The season remained fairly quiet around Thanksgiving, with only four states reporting local activity. The first regional activity was reported on December 22, 2007, with the first widespread activity reported on January 5, 2008. By January 26, 2008, approximately 10 states reported widespread activity. Most states reported widespread activity by February 9, 2008. By February 16, 2008, Florida was the only state not reporting widespread activity.

This is also reflected in CDC's viral surveillance data from collaborating laboratories in the United States that participate in the World Health Organization / National Respiratory and Enteric Virus Surveillance System (US WHO / NREVSS), with over 100,000 specimens tested. The percentage of specimens that tested positive for influenza virus steadily increased over the course of the influenza season, with the most recent reporting week being at approximately 34%. As usual, Influenza A predominates over Influenza B. With regard to influenza A, early in the season it was an H1N1 year. However, over the past few weeks much more influenza A H3N2 has been observed and is now the predominant strain for this season. These findings are also reflected in the percentage of visits for influenza-like illness and acute respiratory illness that are seen in the Sentinel Providers networks and in the BioSense Outpatient Facilities data. The percentage of visits to Sentinel Providers due to influenza-like illness has gone well over the baseline. Similar data are reflected for the BioSense data, which also reflect an increase over baseline. Based on the 122 cities mortality reporting system, Pneumonia and Influenza Mortality were well above the epidemic threshold. The 2003-04 and 2004-05 seasons were relatively mild, with limited activity above the epidemic threshold. However, this season has well-exceeded the epidemic threshold for at least the last six to seven weeks.

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The New Vaccine Surveillance Network (NVSN), a population-based cumulative hospitalization system which monitors hospitalizations among 0-4 year olds, reflects that the 2007-08 season is tracking similarly to the last two seasons. These systems lag somewhat behind the others, so this can be expected to increase in the next few weeks. The Emerging Infections Program Laboratory, another population-based surveillance system that tracks cumulative hospitalizations for children aged 0-4 and 5-17 years, reflects increases as of Week 5. This system also lags behind somewhat, so continued increases in cumulative hospitalizations will likely be observed in this system as well.

Surveillance for pediatric deaths began in the 2003-2004 season. As of February 23, 2008, CDC has received 24 reports of influenza-associated deaths among children <18 years old. Of these, 10 were 5 years old or older. The median range has been 4.2 years, but ranges from infancy to adolescence. Of the 24 reported, 18 were tested for bacterial co-infections. Of those 18, 9 had *S. aureus* invasive infection, 5 of which were MRSA. Dr. Fiore reminded members that there had been continued concern over the past several years with the increasing proportion of *S. aureus* invasive co-infection. Only 1 of these children was vaccinated. To put this into context, 153 deaths were reported in 2003-2004; 46 in 2004-2005; 47 in 2005-2006; and 73 in 2006-07.

Vaccine Strain Selection and Antiviral Resistance

Alexander Klimov, Ph.D.
Virus Surveillance and Diagnosis Branch
Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Klimov reported on the composition of the Northern Hemisphere Influenza Vaccine for the upcoming 2008-2009 season and about antiviral resistance seen in the United States (US) in the past season. This information was presented to the Food and Drug Administration (FDA) on February 21, 2008 and the decision was made about the vaccine strains. In most countries, Influenza A (H1N1) viruses predominated until recently, causing outbreaks in some countries. Many of the viruses were closely related to the A/Solomon Islands/3/2006 strain, which is the strain that was in the 2007-2008 influenza season. Over the course of the season, the virus surveillance group has observed an increasing proportion that were antigenically distinct from the A/Solomon Islands/3/2006 and were similar to a strain called A/Brisbane/59/2007. There is an increasing proportion of the H1N1s that have a neuraminidase resistance gene, an Oseltamivir-resistance gene called H274Y. Interestingly, Oseltamivir-sensitive and Oseltamivir-resistant viruses were antigenically similar. That is, they have a single mutation that is different, although the antigenic characteristics are the same.

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H3N2 influenza has been distributed sporadically in many countries and outbreaks have been reported in the US. H3N2 activity in the US is currently increasing. Some H3N2 viruses were antigenically similar to A/Wisconsin/67/2005 vaccine virus, which is in the vaccine used for this season. However, the majority were closely related to the more recently recommended vaccine virus, A/Brisbane/10/2007. Phylogenetically, the majority of recent H3N2 viruses fall into the HA clade represented by A/Brisbane/10/2007. At the beginning of the season, there were several clades, but currently the majority of viruses are represented in this genetic clade. Post-infection ferret antisera against A/Brisbane/10/2007 virus reacted well with the majority of recent H3N2 viruses. Influenza B viruses circulated in many countries and outbreaks were reported in China and the US. Viruses of both B/Victoria/2/87 and B/Yamagata/16/88 lineages continued to co-circulate in many countries. B/Yamagata-like viruses predominated. B/Yamagata/16/88 lineage viruses were antigenically closely related to the B/Florida/4/2006 reference strain.

There are several possible vaccine candidates:

- a A/Brisbane/59/2007; A/South Dakota/06/2007
- b A/Brisbane/10/2007; A/Uruguay/716/2007
- c B/Florida/4/2006; B/Brisbane/3/2007

Based on this data, on February 14, 2008 the World Health Organization (WHO) recommended the following 2008–2009 trivalent vaccine virus strains:

- A/Brisbane/59/2007 (H1N1)-like virus
- A/Brisbane/10/2007 (H3N2)-like virus
- B/Florida/4/2006-like virus

On February 21, 2008, VRBPAC / FDA confirmed the WHO recommendations. Dr. Klimov stressed that only the H1N1 component, A/Brisbane/59/2007, is a new component for manufacturers because Bisbane/10 and Florida/4 were recommended for vaccine production for countries of the Southern Hemisphere.

With regard to resistance to adamantanes, based on data from October 1, 2007 through February 2, 2008, the proportion of total Influenza A viruses with resistance to adamantanes is still fairly high (31.2%). It is especially high for H3N2 (98.6% US). The proportion of viruses that show resistance is rising among H1N1 viruses (7.2%), not as much in the US compared to some other countries, but still higher than in the previous seasons. In previous seasons, approximately 3% of H1N1 viruses were resistant to Adamantanes. Globally, there is 38.4% resistance among Influenza A viruses, with 99% resistance among H3N2 viruses in particular.

Pertaining to resistance to neuraminidase inhibitors, resistance has been observed in the sample of Influenza A viruses to Oseltamivir (5.7% in the US; 2.3% in foreign isolates; 4.5% globally). In H1N1 viruses in the US, resistance to oseltamivir was 8.7%

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as of February 2, 2008. All of these H1N1 viruses have a specific nuclotide substitution in the neuraminidase molecule. All of these are sensitive to another neuraminidase inhibitor, zanamivir. According to the WHO data, different countries have different proportions of resistant H1N1 viruses, which vary from 0% in some countries to 60% in Norway. There is no satisfactory explanation for why Norway has such a high percentage of resistant influenza A H1N1 viruses. France has about 20%. Some other countries have greater than 10% resistance currently. Dr. Klimov stressed that globally there is less than 5% resistance.

Vaccine Effectiveness among 6-23 Month Old Children

David K. Shay, MD, MPH
Epidemiology Branch
Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Shay reported on a multi-state case-control study of the effectiveness of influenza vaccine in preventing laboratory-confirmed influenza hospitalizations among children aged 6-23 months during the 2005-06 and 2006-07 seasons. This study was conducted within the Emerging Infections Program (EIP), which is a network of state health departments currently conducting surveillance for lab-confirmed influenza hospitalizations. He reminded everyone that ACIP recommended annual influenza vaccine for all children aged 6-23 months beginning with the 2004-05 season. This was motivated by the burden of disease in this age group. Specifically, hospitalization rates in this age group were shown to be similar to those observed among the elderly for many years. However, no past studies of effectiveness of trivalent inactivated vaccine (TIV) have been conducted in preventing lab-confirmed influenza requiring hospitalization for this age group.

The objective of this study was to estimate the effectiveness of TIV in preventing hospitalizations among children aged 6-23 months over several influenza seasons. With regard to the methods, cases were children who were hospitalized with lab-confirmed influenza infection in areas of 8 states. Influenza was diagnosed by direct fluorescence antibody (DFA), viral culture, RT-PCR, or a rapid diagnostic test. For each case, attempts were made to enroll 4 age- and zip code-matched controls using birth records. This was tightly matched on age, plus or minus 2 weeks of the case patient's date of birth. Case and control families were interviewed and providers were contacted to obtain information on vaccination status and other important covariates. Conditional logistic regression was used to estimate the effectiveness of partial and full immunization in preventing influenza-associated hospitalization.

The EIP sites which participated in the 2005-06 and 2005-07 study included: Atlanta, Denver, Nashville, Oregon, New Haven, and San Francisco. Those joining the study in 2006-07 included: Minneapolis-St. Paul and New Mexico. Based on the 2000 Census, 277,365 children aged 6-23 months reside in these sites, or 4.8% of all US children.

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With respect to the definition of "immunization" that was used in this study, children were considered immunized 14 days after receipt of each dose of vaccine. However, the definition of "fully immunized" changed during the planned three seasons of the study such that the 2007 ACIP recommendations were more stringent than the 2006 recommendations and were brought in line with the AAP recommendation. The 2007 ACIP definition of "fully immunized" was used here, which was two doses in the current season if it was the first season being immunized, or if the child had one dose in last season; or one dose in the current season if the child had two doses in a single prior season (or if the child had one dose in two or more prior seasons), which was not the case for many of these relatively young children.

Regarding the results, 93 (49%) of 191 eligible cases and 334 controls (mean of 3.6 per case) were enrolled in the first two seasons. Influenza was diagnosed by rapid test in 52%, by DFA in 35%, by viral culture in 8%, RT-PCR in 1%, and by multiple tests in 4%. When divided by the Influenza type, 85% were Influenza A; 12% were Influenza B; and 3% were unknown based on children who were diagnosed with just a rapid test.

Pertaining to characteristics, of the cases 56% were males, 72% were white, 40% were aged 6-11 months, 38% were aged 12-17 months, 23% were aged 18-23 months. Of the controls, 52% were males, 80% were white, and the age groups were similar to those among the cases.

In terms of immunization status by season and by case / control status, overall 23% of the children who participated in the study were characterized as fully immunized, 27% partially immunized, and 51% were not immunized. Immunization rates did increase during the two seasons of the study. Among controls, 20% were fully immunized in 2005-06 and 32% were fully immunized in 2006-07, while 25% of controls were partially immunized in 2005-06 and 30% were partially immunized in 2006-07. Those not immunized decreased from 55% in the first season to 38% in the second season. Concerning the proportion of children who were fully immunized among cases versus controls, there appears to be effectiveness in both the 2005-06 and 2006-07 seasons. Regarding TIV effectiveness in preventing hospitalization, crude vaccine effectiveness by immunization status in those fully vaccinated was 74% protective with a 95% confidence interval of 44% to 88%. Partial protection was significantly lower at 39% and was not statistically significant as the confidence interval includes zero (-10% to 66%). When these estimates were adjusted for the presence of a high-risk conditions, very low birth weight (VLBW), and insurance status (e.g., not having a private source of insurance), the adjusted vaccine effectiveness estimate was similar at 76% with a 95% confidence interval of 41% to 91%. Partial protection decreased somewhat to 27% and was not statistically significant (-39% to 62%) for these first two seasons.

In summary, the investigators were able to provide estimates of TIV effectiveness in preventing lab-confirmed influenza hospitalizations in US children. Full immunization was ~75% effective in preventing hospitalizations. Partial immunization was less effective and not significantly protective based on two seasons of data from a planned

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three-season study. Based on these findings, Dr. Shay thought it was critical to ensure that children aged 6-23 months are fully immunized to prevent influenza-associated hospitalizations among children. The next steps for this study are to complete enrollment among children aged 6-23 months during the 2007-08 season, and to examine effectiveness among children aged 24-59 months for 2006-07 and 2007-08 seasons.

Discussion

- Dr. Neuzil congratulated Dr. Shay and his colleagues on a well-conducted study, stressing that these are critically important data. As noted, there was not previously a randomized control trial with an outcome of hospitalization; however, the ACIP made the recommendation because of the high burden of illness and because the committee did not believe they could wait any longer. To her, the effectiveness estimates seemed amazing and were actually higher than what was used in most of the cost-effectiveness models when ACIP made this decision. She expressed her hope that this would emphasize the point that children absolutely need two doses, and that with two doses hospitalization can be prevented even in very young children.

- Dr. Morse requested that Dr. Fiore further discuss worldwide surveillance.

- Dr. Fiore responded that based on epidemiologic surveillance data from around the world, it is known from the Southern Hemisphere data (where winter occurs during the US summer) that they also had a lot of H3N2 in several countries (most prominently in Australia and Argentina) and had a similar sharp spike in influenza across their country similar to what has been observed with H3N2 in the US. The strain is also similar (e.g., the H/Brisbane strain). A somewhat drifted strain from what was in the vaccine is being observed, which is what they were concerned they would see.

- Dr. Grogg said it had come to his attention that clinicians were depending heavily on rapid tests, although he was aware of data that show that the sensitivity and specificity of those tests are not extremely high. He wondered what CDC's opinion was and how it related to the reporting of influenza cases.

- Dr. Fiore responded that many influenza diagnoses are made with rapid tests, which work quite well for both positive and negative predictive value in children, who shed lots of virus. They work somewhat less well in adults, who shed less virus. The general CDC view on this has been that a positive test is a somewhat useful piece of information in an adult who has an influenza-like illness with the absence of any other potential cause for this illness. In a situation where a lot of influenza is circulating in a community, it makes sense that it is influenza. A negative test is somewhat less useful. If there is a lot of influenza circulating in a community at the time of a negative test, it is justifiable to continue with further diagnostics and, if the

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timing is right, provide treatment for a patient who is at risk for complications and has a negative rapid test, but appears to have influenza.

- Dr. Lett requested a summary of the overall strain drift across the three strains and how it compared to previous years when there was more of a mismatch.

- Dr. Fiore replied that in previous years in which the circulating strains differ somewhat from the vaccine strains, some protection with vaccination is still observed, particularly protection against more severe outcomes such as hospitalizations. This occurred in 2003-04 when there was a somewhat similar situation. It appears that the match between H1N1 strains in the community and the vaccine were somewhat good. For the B strains this was less so in the sense that the lineage circulating is in large part different from the lineage represented in the vaccine.

- Dr. Klimov added that every year is different. Sometimes, for example, an H1N1 component was in the vaccine which was A/New Caledonia/20/99 for eight years in a row. Antigenically, H1N1 has not been changed for a while. During the last two seasons, global data were accumulated which indicated that H1N1 vaccine components should be changed twice during the last two years. This is based on the data about the antigenic profile in the use of tests with ferrets. It is based also on the so-called "human serology" data when sera from people, including children, immunized with the last year's vaccine formulation are tested against some representatives of more recent viruses plus genetic data. All this can be used as the basis for recommendations to change or not change vaccine strains. The major point is that even when there is no absolute match between the circulating virus and vaccine strains, there is still some level of protection with the sub-types. The H3 virus circulating in the population currently is antigentically quite different from the vaccine H3. Nevertheless, there is some protection.

- Regarding Tamiflu® resistance, Dr. Morita said that anecdotally she had the sense that clinicians are not judiciously using Tamiflu®. With that in mind, she wondered if CDC was examining Tamiflu® use by physicians in the US as a contributor to the resistance being observed currently.

- Dr. Klimov responded that after observing an increase in the proportion of resistant viruses, CDC began to request all H1N1 viruses and a reasonably good subset of H3 B viruses to be tested for drug resistance. CDC is using several techniques in addition to neuraminidase inhibition test. Probably most importantly, CDC very quickly developed a sequencing technique that allows for partial sequencing of the material from the original clinical sample, which allows them to be sure that the resistance observed in viral isolates from patients was not the result of mutations in the vaccine virus. These data are updated on a weekly basis and are posted in the FLUVIEW and are sent to WHO. The WHO website includes weekly updates by country about the situation with resistance to Oseltamivir. Dr. Klimov stressed that to date, all oseltamivir-resistant viruses are sensitive to zanamivir.

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- Dr. Schuchat agreed the vaccine effectiveness studies had been incredibly useful to have. In addition to the EIP, the Marshfield populations, and the NVSN, CDC has a commitment to both track vaccine effectiveness each year and to try to increase the timeliness of the availability of information to get estimates during the season. However, they do understand that only so much can be predicted about the drift and the importance of the change in the strains from the viral surveillance. CDC is trying to understand the protection that occurs, and does believe there is partial protection against the H3N2 strain that is circulating currently. With regard to the Tamiflu® use, CDC is also committed to try to evaluate trends in antiviral use over time. Thus far, there are no ecologic data supporting inappropriate use as the cause of the oseltamivir-associated resistance being observed. Data are primarily from Japan where they have very high use and they are not experiencing the resistance observed elsewhere.

- In answer to Dr. Lett's question regarding vaccine effectiveness, Dr. Turner indicated that the University of Virginia has a fairly closed population of 19,000 students, so they know who is vaccinated and who is infected with the flu. They have had a fairly robust outbreak on this campus this year, with about 515 cases among those 19,000 students as of February 23, 2008. The University of Virginia has conducted a sensitivity analysis, based upon which it appears that students who have been vaccinated have a 41% reduction in disease incidence with statistically significance confidence intervals. A sensitivity analysis was conducted 2003-04, the data from which were presented to ACIP, and at which time the University of Virginia was at 69% effectiveness. Preliminarily, it appears that there is at least some effectiveness from the vaccine.

- Dr. Duchin (NACCHO) inquired as to whether Dr. Shay could characterize the hospitalizations in terms of whether they were all for respiratory complications, and whether there was anything done to enhance the diagnosis in the EIP study. Data were presented to ACIP recently indicating that influenza is frequently under-diagnosed; therefore, he wondered how this was accounted for in the EIP study.

- Dr. Shay replied that the EIP cases were based on clinical tests as ordered by the healthcare provider. Most of these children are hospitalized for bronchiolitis or other respiratory complications, and sometimes fever or not feeling well in the younger age group of children. The investigators do not ascertain every case in these EIP sites. They do not accept a rapid test if it precedes the onset of influenza in the local community. A local definition of flu season is considered in this process, and investigators think these children are representative of those children who are hospitalized with influenza during each particular season, but by no means is every child representative.

- In follow up to Dr. Schuchat's comments, Dr. Duchin (NACCHO) thought that making this type of data available was extremely useful; however, there are two edges to this because a lot of the public did perceive that the vaccine may not be beneficial.

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The emphasis in previous seasons on vaccinating throughout the season dwindled to some extent. Thus, consideration must be given to communication to the public. Given that this season presents a very good opportunity to study the comparative effectiveness of live attenuated and trivalent activated vaccines, Dr. Duchin wondered whether CDC planned to present data on that topic.

- Dr. Shay indicated that in many communities, uptake of live attenuated vaccine has not been great. For instance, CDC has conducted a study for several seasons with the Marshfield Clinic. Preliminary estimates of vaccine effectiveness for Marshfield this season are similar to what has been observed at the University of Virginia. However, in the Marshfield health plan, live attenuated vaccine is not widely used and that is a constraint. As the use of that particular product increases over time, CDC should be able to make estimates of its effectiveness as well.

- Dr. Raymond Strikas (NVPO) said that while it has been noted that two of the strains for the forthcoming fall for the Northern Hemisphere are the same as those targeted for Southern Hemisphere production, his understanding was that there have been difficulties with growth characteristic. He requested that the vaccine companies manufacturing seasonal vaccines which were present comment on their views of prospects for supply in a timely / abundant manner for 2008-09 in the US.

- Mr. Phil Hosbach (sanofi pasteur) stressed that changing all three strains is unprecedented. Introducing a new strain carries the risk of lower yields and potential delays. From sanofi pasteur's perspective, the intent is to manufacture 50 million doses and distribute it as soon as possible. They have 40 years experience in this process, which they believe serves them well.

- Mary Mazur (CSL Biotherapies) indicated that for many years, CSL has been the laboratory for Southern Hemisphere strains. They have 40 years of experience in 17 strains. In addition, they have a fair amount of experience in the current three strains and are confident that they can deliver the strains and the product early in the season. The plan is to deliver approximately 6 million pre-filled syringes beginning in August 2008.

- A representative from MedImmune reported that they had already begun working with all three of the strains in anticipation of the changes now recommended by WHO and VRBPAC. The plan is to manufacture approximately 12 million doses of FluMist® this year, which is a Thimerosal-free formulation. While there are always variables, Medimmune currently expects to be on target to manufacture all three strains in time for the vaccination season.

- Ted Tsai (Novartis Vaccines) indicated that their technical operations group is projecting to produce approximately 40 million doses, a proportion of which will be delivered by the end of the third quarter. While these are estimates, Novartis should be able to provide more precision around these estimates as they gain more experience in working with the strains.

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- Dr. Baker stressed that every group present should continue to work diligently on the message that two doses are necessary. Unfortunately, a culture has been created of stopping vaccination in late November to early December. The same thing happened in Houston this year. This mentality must change, so anything that can be done through physician education or media should be.

2008 Vaccine Recommendations

Anthony Fiore, MD, MPH
Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Given that the major topic for discussion during this influenza session pertained to expanding the existing ACIP recommendations for influenza to other age groups, Dr. Fiore recapped the proposed time-frame for modifying influenza vaccination recommendations presented during ACIP meetings in 2006-07:

- 2007-2008: Consider expanding recommendations to include school-age children

- 2010-2011: Consider expansion of recommendations to include household contacts and caregivers of school-age children

- 2012-2013: Consider expansion to universal vaccination

To consider the underlying evidence for expanding influenza vaccine recommendation to the school-age population and to help them think through the issues, the Influenza Division of the Centers for Disease Control and Prevention and the Council of State and Territorial Epidemiologists (CSTE) convened a consultation on Influenza Vaccine Recommendations for School-Age (5-18 Year Old) Children on September 10-11, 2007. Critical factors considered included vaccine supply, vaccine safety, cost-effectiveness, disease burden, vaccine effectiveness, and feasibility of sustained implementation. Dr. Fiore briefly recapped the findings of this consultation, reminding everyone that the conclusions were presented in more detail during the October 2007 ACIP meeting.

The vaccine supply appears to be adequate and is improving, with many more companies making vaccine. However, planning at local vaccine clinics remains somewhat problematic due to continuing local distribution issues. Vaccine safety appears to be established with a good safety record year after year, but there is a need for continued vigilance and long-term studies to establish safety when vaccines are given in a multi-year period of time. While there are some early data, continued collection is important. Cost-effectiveness is higher than many currently recommended vaccines; however, economic models have been criticized in that they do not fully account for potential indirect effects amongst school-age children. Cost-effectiveness is about equivalent to several of the most currently recommended vaccines.

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Pertaining to disease burden, Dr. Fiore illustrated influenza infection rates by age groups from two different multi-year community-based studies conducted in Houston and Tecumseh Michigan, which showed that the highest rates of influenza-associated illness occur among children and lower rates occur among adults. These studies were conducted in the late 1960s and 1970s in the US. With a higher proportion of children in daycare, it is likely that one may see higher influenza illness rates in children <5 years of age than were observed in these two studies. The discussion during the consultation was led by Kathy Edwards, who summarized that amongst school-age children there are few deaths and hospitalizations compared to younger children, elderly, or chronically ill. What is seen are 5-7 outpatient visits per 100 children annually, many of whom receive antibiotics because they present with a febrile illness. There are as many as 10-30 illnesses per 100 children that are frequently associated with school absenteeism and its resulting economic burden with parents staying home from work and children missing their education. Thus, with regard to disease burden, the highest rates of influenza are in this age group. However, the severe outcomes are less common than in older or younger age groups.

Concerning vaccine effectiveness in this age group, established effectiveness is estimated to be 50-90% in reducing influenza illness. A number of studies have resulted in this range. Meta-analyses have estimated approximately 65-70%, which falls in the middle of the estimated range. There is also the potential for indirect effects of vaccinating school-age children. There is a growing literature on reductions in illness among contacts of school-age vaccinees in community demonstration projects, often with fairly modest coverage levels among children that typically have not exceeded 50%. There is also evidence for reductions in school or work absenteeism in some studies. These studies have not demonstrated reductions in severe outcomes among contacts of vaccines, although this could simply be the result of limited study sample sizes. Nevertheless, there is evidence of established effectiveness in reducing influenza illness and increasing evidence for indirect effects. Dr. Fiore pointed out that while the consultants in the CDC / CSTE Consultation were intrigued by the idea of indirect effects, many of them believed that the established benefit for school-age children would be sufficient in itself to move forward with the recommendation.

The topic that probably received the most discussion during the CDC / CSTE Consultation was the feasibility of sustained implementation. A number of themes emerged during the consultation. For example, low expectations will probably be required for coverage during the first few years of implementation. That is based on experience with other new influenza vaccine recommendations. There continues to be quite low coverage in 6-23 months olds and 24-59 month olds, with fully vaccinated coverage at approximately 20%. Another theme was that vaccinating all school-age children increases the number of annual recommended vaccinations by ~50%, which will burden immunization programs. The medical home does not have the capacity to deliver influenza vaccinations to all school-age children. Therefore, immunization programs and providers must maintain focus on children at higher risk for influenza complications, such as children with chronic illness and those less than age 5, and

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particularly those less than age 2. Implementation strategies will vary according to local capacity, but are not likely to be planned until the recommendations are made. Assessment of impact will be a major challenge and will require planning and additional resources. While uncertain, the comprehensive efforts to vaccinate this large cohort are not likely to be established until a recommendation is made.

Taking into consideration the CDC / CSTE Consultation information, as well as information from the various discussions the over the past two years, the ACIP Influenza Vaccine Workgroup proposes putting forward a recommendation to vaccinate all children ages 6 months through 18 years annually. However, largely in deference to the difficult implementation issues, the recommendation should take effect in 2009-10 season.

ACIP Influenza Vaccine Workgroup Recommendations

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

Dr. Neuzil reported on the Influenza Vaccine Workgroup discussions that had ensued since October 2007. During the October ACIP meeting, the question was raised regarding what they were waiting for if they waited to make a recommendation. They acknowledged that there were really no critical data gaps, and that there was no indication that data would be available in the near future on feasibility or indirect protection. In addition, there was no indication that steps would be taken to prepare for the feasibility and the infrastructure in the absence of a recommendation. It was proposed that waiting to expand might be helpful because they had heard from the CDC / CSTE Consultation that practitioners had been dealing with an unprecedented number of new vaccine recommendations in the last two to three years, that education would be important, and that this would also allow some time to harmonize with other organizations.

Three options have been discussed by the workgroup since October: 1) No change in the current recommendation; 2) Recommend influenza vaccine for all children through 18 years of age, beginning in 2008-09 season; or 3) Recommend influenza vaccine for all children through 18 years of age, beginning in 2009-2010 season. Most workgroup members favored Option 3 (expand recommendations to include all children through 18 years of age, beginning with the 2009-10 influenza season). The reasoning behind the support for this recommendation was that while indirect effects may be an added benefit of universal expansion to this age group, evidence for the direct benefit to vaccinated children is sufficient to recommend a change to a universal childhood recommendations. Vaccination providers who want to begin vaccinating all children in 2008-09 can do so using the current VFC “any child who wants it” indication, and these pilot efforts should be encouraged. This allows for implementation and assessment planning, ordering vaccine, and harmonizing the message with other professional societies. Dr. Neuzil acknowledged that a few workgroup members favored expansion beginning with the upcoming influenza season (Option 2), pointing out that

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implementation issues will not be solved regardless of the start date, and it is anticipated that the vaccine supply will be sufficient.

With respect to the rationale, the recommendation to expand routine influenza vaccination to include school-age children and adolescents is based on: 1) evidence that influenza vaccine is effective and safe for school-age children; 2) evidence that influenza has substantial adverse impacts among school age children and their contacts (e.g., school absenteeism, increased antibiotic use, medical care visits, parental work loss); 3) the expectation that a simple age-based influenza vaccine recommendation will improve current low vaccine coverage levels among the approximately 50% of school-age children who already had a risk-based or contact-based indication for annual influenza vaccination; and 4) the expectation that reducing influenza transmission among children will reduce influenza among their household contacts and within the community.

The working group strong endorsed the need for an improved impact assessment of any change in recommendation. For school-age children, this would need to include the ability to assess less severe effects (e.g., clinic visits) and indirect effects, and the ability to look at laboratory-confirmed influenza infections in this age group. The working group acknowledged that several factors will challenge the ability to demonstrate indirect effects, including anticipated low coverage rates in the early years of implementation, the variability in influenza epidemiology and vaccine effectiveness, and the small number of large population-based studies among adults with laboratory-confirmed outcomes. to show indirect benefits in adults, surveillance capacity for laboratory-confirmed outcomes in adults must be improved. Dr. Neuzil stressed that they had just heard very powerful evidence in the 6 to 23 month old children what this kind of testing / study can provide, and the educational messages which can be derived from the feedback obtained by these programmatic assessments.

There is a discrepancy between the 75% effectiveness shown by Dr. Shay and the dramatically low coverage observed of fully immunized 6-23 month old children. From 2002 through the 2005-06 season, fully vaccinated children in the 6-23 month old age group is only 20%. Over time, coverage levels have shown a slow to no increase in the last three years. Thus, it is important as changes are made in the program that impact in terms of coverage rates and effectiveness of the program are considered. The message that two doses are needed cannot be overemphasized. This vaccine works in 6-23 month old children, and this point must be impressed upon practitioners who are administering this vaccine.

The workgroup also discussed expansion to all adults. The current recommendation states that anyone who wants to protect themselves against influenza should be vaccinated. There was a lot of discussion and some disagreement about the definite timelines for a universal vaccination recommendation to all age groups. The workgroup will continue to evaluate evidence for a universal recommendation in this age group. There was some thought that by taking the incremental step of universal vaccination up to the age of 18 would allow for evaluation of indirect effects, which may influence a

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later universal recommendation. Other variables that may influence this decision include licensure of a better vaccine, indirect effects from vaccinating all school-age children, additional seasonal vaccine effectiveness studies, and public engagement on vaccination opinions.

Discussion

- Dr. Baker said she had supported implementation of vaccination in the younger age group first, subsequently moving to the older children. While the argument was made that practitioners needed time to prepare, they have now had three years to do so for the 6-23 month old recommendation. Moreover, there is an evaluation infrastructure in place for the 6-23 month old age group. Nevertheless, coverage of this age group remains at 20%. With this in mind, she inquired as to whether implementation continued to be the major barrier for the workgroup with respect to waiting.

- Dr. Neuzil responded that in terms of the evaluation, it was important to note that this was the first time Dr. Shay's data had been presented publicly. This is a message that they did not have previously, but now they must deliver to practitioners. Previously, they could only tell practitioners that effectiveness was *assumed* against hospitalization. With regard to implementation, she said the workgroup's viewpoint was congruous with Dr. Baker's, which was why they were putting out a vote during this meeting for universal recommendation. The hesitation regarding whether to recommend implementation this season or next pertained to the potential for putting practitioners in a bind, given that many have already placed orders. With Option 3, the statement and rationale would clearly be made now, anyone who could implement immediately would be encouraged to do so, but the effect date would be in 2009.

- Dr. Chilton expressed concern with the implementation component based on the data from Knoxville, which appeared to have been a highly resource-intensive effort. Substantial hours were required on the part of school and public health personal, suggesting that implementation in a larger community or in the country as a whole may be problematic. He inquired as to whether CDC planned to promote and fund efforts to implement vaccination with fewer hours and more efficiency than appeared to have been the case in Knoxville.

- Dr. Fiore responded that CDC will certainly want to examine the demonstration projects to glean the lessons learned, and potentially provide communities with some of the methods and strategies that have been most successful in accomplishing large-scale clinic vaccinations.

- Dr. Jeanne Santoli (NCIRD) indicated that two Requests for Proposals (RFPs) are out to support examination of school-based vaccination of adolescents, particularly of influenza in school-age children, in ways that are sustainable. This will address the point that amazing efforts can be carried out, but must be sustainable over time.

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These awards will support partnerships between public health and community vaccinators, given that the ability to bill is a critical component in building sustainable efforts. CDC is hopeful that they will learn important information this year through these demonstration projects.

- Mr. Hosbach (sanofi pasteur) said he was aware that approximately $20 million was appropriated to the Department of Health and Human Services (HHS) specifically for CDC targeted at flu education outreach. While he assumed that was what some of the funding was being spent on, he requested that CDC representatives comment on that appropriation.

- Dr. Schuchat responded that the appropriation was for the purpose of increasing seasonal demand. The vast majority of the resources will be awarded to the states through the cooperative agreements. The states are applying for funding from this appropriation as a supplement to their grants. While there is flexibility with respect to the methods that they choose to use, this funding is more about increasing the demand than the logistics of delivering vaccines.

- Dr. Cieslak said he was aware of the cost-effectiveness data that suggest that $70,000 to $120,000 per quality adjusted life year (QALY); however, he did not recall whether those estimates were based on cost in a medical setting. If the recommendation were to be expanded, his understanding was that a lot of the vaccine would be given outside the medical care setting. Thus, he wondered how the cost of administering vaccine per child in a school setting was comparable to that in a medical setting in terms of how that would change the equation.

- Dr. Fiore confirmed that those cost-estimates were done with vaccination in medical settings.

- Dr. Lieu added that she was involved in the study to which Dr. Cieslak referred. It is known from other studies in adults that administering influenza vaccine in other settings, rather than traditional medical offices, tends to be far less expensive than administering in medical settings. There are efficiencies of scale when administered in workplaces, pharmacies, et cetera. There are some data on school settings, but they are relatively sparse. Nevertheless, she expected that school settings would be more cost-effective (e.g., less expensive).

- Dr. Judson indicated that he had extensive experience attempting to administer vaccines in the school system. If anything, this is becoming more challenging and less sustainable as school nurses, school health programs, and infrastructure are cut back. Moreover, standardized tests are dominating the curriculum and time in school. He would not want to approach Denver Public Schools, which has a 40% dropout rate at least for a year between early adolescence and graduation, to request that they implement vaccination in 65 different schools. Schools have always been a logical idea because all of the children are there; however, attempting

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to pay for and sustain such an effort competently, and to connect the records, is difficult.

- Dr. Englund thanked the CDC for helping to publicize the impact of *Staphylococcus aureus*-associated pneumonia, particularly in influenza patients. Clinicians must realize that there are changes on-going in the epidemiology of Staph, particularly with MRSA in hospitals. All of the cost and hospital estimates were done before MRSA was as endemic. Necrotizing pneumonia incidence is increasing. This must be taken into account when making recommendations. There is no good treatment for Methicillin-resistant staphylococcus infection, which is what is being seen in hospitals. Her institution has multiple children on the ventilator at one time for weeks this year, although they did not see this two years ago. These cost estimates should improve the potential cost-benefit of flu vaccine.

- Regarding whether private providers would be prepared this season or thereafter, Dr. Stinchfield reported that the clinicians at Children's Hospitals and Clinics in Minnesota, which has two large hospital-based pediatric clinics, already offer the flu vaccine to everyone and they do not feel fearful of a new implementation program. They have already ordered their vaccine and typically throw vaccine away at the end of every season. She thought the critical piece regarded whether providers would be nimble and flexible enough at the local level to request more vaccine mid-season and plan major clinics. Schools, public health, and private providers must be collaborative in the vaccination effort. This goes beyond the traditional medical model of making an appointment, having a well child check, and receiving a vaccine. They must be creative with flu vaccine delivery in the medical home.

- Dr. Baker reported that this is the only vaccine that pediatricians in her community do not want to have to give to children, given that it is complicated for a number of reasons. She stressed that they must not forget the recommendations already in place for those less than 6 months of age, as well as those for pregnancy, household, and daycare contacts of less than 6 months old. This is difficult to diagnose in this age group, given that they present with apnea and intussusception-type pictures. It is also the age group in which hospitalization is almost uniform, death occurs, and it is not necessarily being measured. Thus, the message must be extremely powerful.

- Dr. Poland (ACP) pointed out that there may be an error in Dr. Shay's and Dr. Neuzil's presentations. He reviewed the ACIP minutes from two years ago, which reflect that ACIP affirmatively voted signaling its intent to move to universal influenza immunization. In June 2006, ACIP affirmatively voted on a timeline that would allow that to occur by 2013. Thus, they need to clarify this. This also reflects the value of a verbatim transcript. Dr. Poland expressed his personal support of moving toward this recommendation and his belief that doing so was in the best interest of the ACP, given that the data available suggest indirect benefit to adults at risk. Nevertheless, he also expressed concern about how the decision was being made. He thought the credibility of this committee was strained as an unbiased interpreter of the data in

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making flu vaccine policy when they made discrepant decisions based on the same data with respect to children versus adults. There was nothing in the presentations they just heard that would not be equally as true if adults were substituted for children in the data. In February 2006, Dr. Poland moved that ACIP adopt the universal influenza vaccination recommendation. There was a great deal of discussion regarding this, but ACIP did signal their intent to do so. However, multiple issues were raised by ACIP that resulted in the conclusion that they could not move to this for another seven years in 2013. During the February 2006 meeting, Ben Schwartz reported on behalf of NVPO on the October 2005 meeting workshop on the notion of universal flu immunization. The participants there raised issues that were believed to be sufficient to prohibit a universal recommendation, including: 1) incomplete data on the indirect benefits of vaccinating school children to reduce disease burden among other groups; 2) incomplete data on effectiveness and safety of repeated vaccination; and 3) lack of cost-effectiveness. All of these concerns were endorsed by ACIP members, resulting in the recommendation to delay until 2013 pending the development of an infrastructure to do so. During the June 2006 meeting, Dr. Poland again raised this issue arguing that a universal recommendation would serve to expand the supply and force the creation of infrastructure. For no other public health measure do they insist upon this. If everyone decided to obtain a colonoscopy, pap smear, and a mammogram, it could not be done, but that does not prohibit making a recommendation that is in the best interest of the public's health. Nevertheless, ACIP members felt strongly that first the influenza vaccine supply had to be expanded before such a recommendation could be made. The expressed fear of this committee was that otherwise, chaos would result from adults suddenly demanding vaccines. Since June 2006, little new data exist to counter ACIP's original concerns about vaccine effectiveness, safety, supply, and cost-effectiveness. These same issues were acknowledged during today's discussions. The cost-effectiveness studies indicate a cost of up to $120,000 for each 15- to 17-year old. There are unclear mechanisms for how this is going to be accomplished, and substantial concern persists about diversion of resources necessary to devise these programs. Distribution of vaccine remains problematic. Financing and payment of such a recommendation are problematic. Most surprising to Dr. Poland was point 24 on page 18 of their briefing documents was the question, "Should infrastructure and resources be in place before recommendations are advanced?" followed by the answer, "No. The recommendation must be in place for the infrastructure to be built." This is the same reason ACIP rejected expanding this recommendation to adults. Dr. Poland stressed that the major issues related to a universal influenza immunization program, whether for children or adults, were the same. Remarkably, the issues thought by ACIP to prevent such a recommendation that would include adults disappeared with respect to such a recommendation that would include children. Whether a 17-year old high school student, a 35-year old office worker, or a 50-year old frequent flyer brings flu into the home, the consequences are the same. Dr. Poland implored the ACIP to use science to make these decisions. The effects of influenza are no less severe in a 30-year old than a 17-year old. He thought they had to consider a public health leadership position and implement a universal

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recommendation in one step, given that a chasm cannot be crossed with two leaps. Dr. Poland's belief was that the approach of creeping incrementalism continued to foster confusion among their colleagues and patients. Moreover, in the near future there may be levels of neuraminidase inhibitor resistance such that vaccination will be the only cost-effective measure for preventing the substantial burden of illness due to influenza in the US. Last year, CDC estimated that it costs the US well over $80 billion a year. Dr. Poland concluded that in retrospect, others would marvel that given the data available, ACIP hesitated to move to a universal recommendation, waiting at least seven years to get there.

- Returning to the issue of schools, which constantly arises in the context of implementation of the recommendation up to age 18, Dr. Duchin encouraged CDC to fully engage at every level with their partners in the education system to truly understand whether this is acceptable to them, what the barriers are in various communities, and whether it is realistic to consider schools as a major delivery venue for influenza vaccine for that wide age spectrum. In his community, commercial vaccinators were not at all interested in the RFA, given that the reimbursement is not high enough, they do not want to vaccinate small children, et cetera. While commercial vaccinators may be willing to do this in some communities, it was not clear to Dr. Duchin that this would be an answer in the overall implementation effort. While pharmacies are eager to do this, they also do not wish to vaccinate small children.

- Dr. Morse pointed out that with 36,000 deaths and 100 to 200 deaths in children each year, everyone had come to realize the importance of the common goal of trying to reduce that burden through universal immunization, and a desire to reach that goal as quickly as possible. However, he has struggled with the timeframe and ability to implement an effort successfully. Dr. Morse reflected upon President John F. Kennedy's declaration of the intent to go to the moon, not by the next day, but by the end of the decade with careful, phased-in flights and an approach that was necessary for ultimate success. Based on that analogy and the desire to use evidenced-based and carefully reviewed information, Dr. Morse has tried to temper his urge to move forward as *quickly* as possible with that of moving forward as *successfully* as possible. With that in mind, he supported moving ahead with children using a phased-in approach.

- Dr. Judson clarified that he agreed with Dr. Poland that changing immunization policy and practices in the US begins with a recommendation, following FDA approval. His earlier point was a narrow point regarding the extent to which the US school systems currently can play a role in implementation, especially in inner cities.

- Dr. Schaffner (NFID) noted that their AAP and AAFP colleagues had not spoken thus far, and expressed interest in hearing their opinions.

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- Dr. Temte (AAFP) responded that a common theme he heard across many of the comments pertained to the lack of education of clinicians and the public, which he thought was paramount to any discussion on expansion. There is a clear recommendation for pregnancy, with 13-14% of pregnant women receiving vaccine. In his clinic where he is dealing with residents, they are probably vaccinating 80-90% of pregnant women. These patients are presenting routinely for care. Clinicians do not think about this or they think there are reasons not to immunize. A poor job is being done in immunizing children with asthma, which is a much higher risk group, as well as in 6-23 month old children. Clearly, education is key. He commended the working group on the current proposed recommendation to phase this in, not because this is not needed immediately, but because there must be time to get the clinicians on-board. With respect to the AAFP membership, they are dealing with such a vast array of new vaccines, he expressed great concern about losing the fight in terms of practitioners believing this is a necessary vaccine. Therefore, while being proactive, they also must be cautious. His opinion was that a recommendation should be made in a manner which would allow practitioners to order stocks. Most AAFP members have ordered their vaccine for the 2008-09 season, which must be kept in mind. He inquired as to whether there was any background or any basis from theoretical models to suggest the percentage of a population that must be immunized to shut down influenza. His guess was in about the 45% range.

- Dr. Fiore replied that there have been indirect effects, including reductions in medically-attended respiratory illness in some of the community projects, with rates of coverage fairly low, even in the 30-40% range. It is likely that to achieve a substantial impact, the coverage rates would have to be much higher. He had seen ranges required in models of 70% or more coverage amongst all children to begin to observe measurable impact on reductions in laboratory-confirmed influenza in adults who are not vaccinated.

- Dr. Grogg (AOA) indicated that he and AOA highly supported the recommendation to vaccinate through 18 years of age. There is a principle in pediatrics, “Keep it simple.” He stressed that it was easier for pediatricians to remember 6 months to 18 years of age than it was to move along incrementally. He thought if the recommendation was mandated, it would occur immediately. If not, the process would flow the way it had been. He also believed that getting children into the office for their flu vaccinations would increase rates for other immunizations.

- Dr. Bocchini (AAP) complimented the workgroup and Drs. Shay and Neuzil for working through a significant series of issues to develop what appeared to be very reasonable recommendations. AAP certainly favors expansion to 18 years of age, but also believes that there are some significant implementation issues (e.g., effect on the medical home, delivery in schools and other venues, and other issues). There is no question that influenza poses unique issues, given that annual immunizations are necessary during a limited timeframe. Despite the fact that there is already an age recommendation for children, that is not being met very well. The

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major emphasis should be on physician and family buy-in so that everyone understands the importance of the recommendation. Dr. Bocchini said he thought it would take a number of years to reach the ultimate goal, but that he thought the workgroup's recommendation was a good start.

- Dr. Nichol (DVA) urged the members of the ACIP not to lose sight of adults 18-49 who were not being considered during this meeting according to the workgroup recommendations. She stressed that everyone is affected by influenza and everyone stands to befit from vaccination. Data regarding where adults 18-49 are immunized in the US reflect that about half or more are immunized at the worksite, while the remainder are immunized at the medical home and other venues. For school-age children, the same will likely occur. The most feasible settings will differ in each community; therefore, each community will have to decide the best methods. Dr. Nichol suggested that they think in terms of "school-located" rather than "school-based" vaccination. School nurses cannot deliver immunizations, but the school building can provide the location. In many communities, other vaccinators can be brought in. That is the worksite-based vaccination model. At most worksites, the employer does not have a nurse on staff who is immunizing. Instead, they partner with a VNA or other organization to administer the immunizations at the worksite. If there are charges for the vaccination, at some worksites the immunizer also deals with the money. This is the model which is used in grocery stores and pharmacies as well.

- Dr. Middleman (SAM) indicated that SAM definitely supports the recommendation for immunizing school-age children. Certainly, SAM supports all preventive healthcare measures that will help protect the health of adolescents in the US. There is also a great deal of evidence to show that universal recommendations are more beneficial than targeted recommendations. She agreed with Dr. Nichol's suggestion about "school-located vaccination." An important message that schools are invested in and excited about is that schools are the site for the education of children, and there is no more important measure than the ability to protect one's own health throughout the lifespan. She has observed that schools are incredibly excited about sending that message to their children, having their children immunized, and having children healthy to attend school and receive all of the other important messages that take place there.

- Andrew Eisenberg (Texas Medical Association) echoed Dr. Poland's point that ACIP must gives practitioners the tools they need to say that flu vaccination is important. What the public believes currently is that flu vaccines do not work, which is what he hears from his own patients. Age does not predicate whether someone with be infected with influenza or spread it to someone else. Neither does one's risk category predict what their actual response will be. He has had plenty of patients who were in no risk categories who died or whose family members died that could not have been predicted. Therefore, to deny access to the vaccine to anyone for any reason is the wrong message. He assured the ACIP that if they made the recommendation for universal influenza immunization, the provider community would

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develop plenty of mechanisms at various sites to deliver the vaccine. However, without a clear go-ahead, they could not do so.

- Stephen Allred (getaflushot.com) expressed his gratitude to Dr. Neuzil and the working group for their excellent work, and offered his support for the adoption of the recommendations as an interim step to universal recommendations. He reminded everyone that there is a large anti-vaccine movement in this country that uses the presence of the preservative thimerosal, which has never been shown by any scientific evidence to pose any harm to anyone, as a rallying point to pass laws across the US limiting the ability to give vaccinations. He wondered whether the workgroup had given any thought to taking a stronger stance toward educating the population in general, as well as the legislative branches, which are passing such laws.

- Dr. Neuzil responded that as individuals, many members of the working group have been involved in their local and state areas helping to educate the legislatures about some of these laws. As a working group, they have not taken this on. However, the working group's position is that there are clear benefits to the vaccine. They have discussed the risk-benefit ratios and continue to strongly endorse the current flu vaccines for pregnant women, young children, and all age groups.

- Gary Stein (Families Fighting Flu) said that his daughter, Jessica, died six years ago from the flu. She was not vaccinated. It was amazing to Mr. Stein that if she were alive today she would still run the same risk because she would not be in the recommended age group. While he understood all of the implementation issues that had been discussed and he appreciated all of the progress that had been made, demand and awareness remained major challenges to protecting society, and this could not be resolved without a recommendation from ACIP. C.S. Mott Children's Hospital in Michigan found that on the heels of the recommendation to expand up to 5 years old, half of the parents who were vaccinating their children in that age group had never vaccinated before. The Visiting Nurses Association found that half of mothers who do not protect their children today do not do so because they believe it is unimportant. Mr. Stein stressed that the public needs ACIP's guidance and he strongly urged the committee to move forward as soon as possible. As a parent, as much as he appreciated this committee, he would be confused with a delayed implementation to 2009-10. Families Fighting Flu is trying to spread awareness and appreciates ACIP's help and support with that.

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2008 VFC Vote

Anthony Fiore, MD, MPH
Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

In preparation for a vote, Dr. Fiore reviewed the current recommendations for vaccinating school-age children against influenza, and discussed the rationale that was the basis for these recommendations:

2008 Prevention and Control of Influenza: Recommendations of the ACIP Updates and Changes (1), included the following:

- Persons and organizations that provide influenza vaccination to children should begin planning for implementation of annual vaccination for all children aged 6 months to18 years

- Annual vaccination for all children aged 6 months to 18 years should begin in the 2009-2010 influenza season

- Immunization providers should begin efforts to offer influenza vaccination to all children aged 6 months to 18 years in the 2008-2009 influenza season if feasible, consistent with the current recommendation that all persons who want to reduce the risk of becoming ill with influenza or of transmitting influenza to others should be vaccinated.

The last point was to ensure that efforts already underway are not undercut. Some practitioners and programs are already offering vaccines to everyone, so they would be encouraged to continue their implementation planning and to continue their offering of vaccines to all persons.

With this delayed implementation, the box which describes the risks, ages, and contact-based indications will stay the same. However, a note will be added to the box, which will read:

> Note: Beginning in the 2009-10 influenza season, all children aged 6 months-18 years will be recommended for annual vaccination. Providers and programs should develop plans to implement this recommendation during the 2008-09 influenza season, and can begin vaccinating all children aged 6 months-18 years during the 2008-09 influenza season if feasible.

Dr. Fiore reviewed the rationale for the proposed recommendation to expand routine influenza vaccination to include school-age children and adolescents, which Dr. Neuzil presented earlier. This will occur in the text along with language to describe some of

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the challenges that might be faced and language pertaining to immediate implementation where feasible, as follows:

> Achieving community-level reductions in influenza will require mobilization of community resources and development of sustainable annual immunization campaigns to assist healthcare providers and immunization programs in providing influenza vaccination services to children of all ages. In many areas, innovative community-based efforts, which might include mass vaccination programs in school or other community settings, will be needed to supplement vaccination services provided in healthcare practitioners' offices or public health clinics.
>
> Routine vaccination of all school-age children can begin immediately where feasible. However, because many communities will require considerable planning for implementation of influenza vaccination programs for all children, the ACIP recommends that immunization programs and providers prepare for implementation beginning with the 2009-2010 influenza season. Delaying full implementation until 2009-10 will also allow physicians, other health care providers, and immunization programs more time to identify systems and plan studies capable of evaluating the impact of vaccinating school-age children on influenza epidemiology.

Dr. Fiore noted that there were some other changes in this year's recommendations. There was a licensure change in the age indication for the LAIV in September 2007. As a result, in October 2007 ACIP voted to extend the age down to 2. Previously 5 years was the lower age limit for LIAV. ACIP also voted at that time to include recommendations for screening children aged 2-4 years for asthma or wheezing due to some safety signals observed in some of the studies conducted in that age group. While this language was voted upon in October 2007, it will appear for the first time in this recommendation. The 2008–2009 trivalent vaccine virus strains are all new for this season: An A/Brisbane/59/2007 (H1N1)-like virus; An A/Brisbane/10/2007 (H3N2)-like virus; A B/Florida/4/2006-like virus. These will also be listed in the recommendations. Information will also be provided on oseltamivir-resistant influenza A (H1N1) strains in the US. Updated information will be provided on antiviral effectiveness, safety, and usage, including citation of recent recommendations from the Infectious Diseases Society of America, the American Thoracic Society, and the American Academy of Pediatrics pertaining to patients who may benefit from treatment with antiviral medications.

Motion

Dr. Baker made a motion that beginning in the 2008-2009 season, annual influenza immunization is recommended for all children ages 6 months to 18 years. Dr. Stinchfield seconded the motion. This motion was not voted upon, given that further discussion ensued.

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Discussion

- Dr. Morse clarified that the motion on the floor differed from the recommendation in that the motion was to begin in the 2008-09 season, while the recommendation was to begin in the 2009-10 season.

- Dr. Judson suggested separating the evidence-based recommendations from the concerns of practical implementation and the payer. If they expected efforts to move beyond where they already were, based on his experience, for school-age children mandatory school entry laws typically are required to ensure that children get vaccinated. For adults, the recommendation must become standard of care. Once school entry laws and the standard of care are in place, usually a provider will materialize. However, without changing those key aspects, Dr. Judson believed these recommendations would result in limited movement forward. He stressed that this was not in opposition to the motion.

- Dr. Lett complemented the workgroup on the way they phrased the recommendation, in that it reflected that ACIP wanted this effort to be successful and that timing should be staged to maximize that. While she heard the urgency in everyone's voices, she thought the workgroup balanced the language and captured the ideals for success. Therefore, she disagreed with the motion to begin in the 2008-09 season.

- Dr. Beck indicated that he intended to change his position in support of Dr. Baker's motion to begin in the 2008-09 season. They seemed to be trapped in a debate between two strategic concepts: top-down or bottom-up. Top-down would mandate that which has been decided as comfortable from a safety and efficacious standpoint in using a vaccine that has all of the indications of being successful, with no way to successfully implement it. The bottom-up approach has been used for some time, yet implementation remains low. He did not believe a 50% coverage factor at this stage was a successful indication. Perhaps they need to change their approach. Dr. Beck reflected on the approach toward polio worldwide. At the start of polio, while there was the benefit of an oral vaccine, there was no infrastructure in place. Yet a worldwide program was implemented to eradicate polio and a tremendous impact was made with no infrastructure. With polio, an infrastructure was built with volunteers. Dr. Beck drew a distinction between marketing and education, pointing out that education by its etymology requires that the student be open and reach out to become educated. He did not believe that was the case and that instead they were talking about marketing. They must show the benefits of this product to the market and get them to buy into it. What has been done to date with influenza vaccine has shown no adverse effects and has shown some tremendous benefits. Therefore, Dr. Beck was willing to change his position and support Dr. Baker's motion to recommend in the 2008-09 season. While ACIP was attempting to be cautious and to do the right thing, he thought they needed a new approach. Otherwise, people would remain at risk.

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- Dr. Chilton indicated that he would vote against Dr. Baker's motion, given his belief that a year was needed to try a variety of approaches to implement the strategy of giving influenza vaccine to all school children. He thought that all school children could receive the vaccine according to the current recommendation. He also expressed concern about the effect of an immediate recommendation on the supply for people at higher risk than those between ages 5-18, despite the fact that the companies have said they will producing an adequate supply this year. This recommendation will add 70 million doses that could be given with full implementation. In addition, Dr. Chilton said he had carefully read the information sent to him by Families Fighting Flu. While he appreciated their concerns and offered his sympathy for their losses, he expressed his hope that Families Fighting Flu would help in the interim year proposed by the working group to develop implementation methods that would make this a successful campaign in 2009-10.

- Dr. Englund said she would favor the Influenza Working Group statement as written. In her setting, flu vaccine was ordered in January and nurses have been hired. It will take her institution, private practitioners, and pediatricians in her county time to deal with this. In representing them, the recommendation felt like yet another burden for which they would receive very little money and spend an enormous amount of time. While Dr. Englund was very much in favor of universal immunization, as written by the working group it would assist those who are actually doing the work.

- To clarify, Dr. Neuzil said she was hearing strong support for a universal recommendation up to the age of 18, and that the only disagreement pertained to the year in which this should begin.

- Dr. Morita said she was in favor of what was proposed by the working group because she did believe that from the local public health perspective, a year of planning would be beneficial. The AAP and AAFP also seemed to strongly support the additional year of planning from the provider perspective.

- Dr. Baker agreed that if the year was an issue, certainly they should vote for the recommendation to expand. Most children who are 5-18 years of age can be immunized at the grocery store or pharmacy. They do not have to go to a heath care provider, at least in the State of Texas.

- Dr. Stinchfield said that she did not second Dr. Baker's motion lightly. She is on the working group and will have to deal with the barriers in her own institution, so she was clear about what she was bringing upon herself. However, there is only 20% implementation with the 6-23 month olds, despite the amount of time that has been spent on that. In addition, there is essentially already a universal vaccination policy that is allowable. Therefore, she did not believe that Dr. Baker's motion was that great of a leap. She suggested either splitting the vote, or adapting the time period implementation allowing communities, states, public health venues who are rigorous

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and ready to go an opportunity to do so as early as possible with language such as, "as soon as feasible, but no later than 2009-10."

Modified Motion

Dr. Baker modified the motion on the floor to recommend annual influenza immunization for all children ages 6 months to 18 years. Dr. Stinchfield seconded the modified motion. The motion carried with 11 affirmative votes and 1 abstention.

Motion

Dr. Stinchfield made a motion that the recommendation for annual influenza immunization for all children ages 6 months to 18 years should be implemented as soon as feasible, but no later than the 2009-2010 season. Dr. Beck seconded the motion. The motion carried with 10 affirmative votes and 2 abstentions.

Discussion

- Dr. Lieu liked the wording of the motion regarding implementation, given that it left open the idea that people should start vaccinating this year if feasible. She said she would lean toward the working group's interpretation of this, partly because she thought that ACIP should be up front and be making in general top-down recommendations; however, they must not be so far out in front that they are perceived as unrealistic or as ignoring the implementation concerns.

- Dr. Judson pointed out that as an advisory committee, they do not mandate, pay for, or directly implement anything. Therefore, their recommendations are important to begin the process of change on policy and practices and are based on considerations of risks, benefits, and costs. Beyond that, he did not believe they should ever hold back on a recommendation that the evidence supports based on risks, benefits, and costs because they do not think that somewhere downstream somebody will be able to implement the recommendations.

- Dr. Stinchfield inquired as to whether Dr. Judson was proposing silence on the implementation component.

- Dr. Judson replied that he was proposing silence on the implementation component. Having been on the implementation side for the last 30 years, he would not look to these recommendations to tell him how to pay for the vaccine or deliver it. Those are the implementers' responsibilities. Therefore, it was his preference for the specifics of implementation to be left out of the recommendations.

- Dr. Schuchat clarified that as a federal advisory committee, among the factors that ACIP is supposed to consider beyond immune response, effectiveness, and safety, are cost-effectiveness and programmatic concerns. An effort has been made to

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ensure that the ACIP includes members with strong program expertise. Even if only the evidence-based information is being considered, very confusing recommendations have come out when the programmatic expertise is not considered. Hence, CDC views the programmatic expertise and considerations as part of what the agency wants ACIP to take into account.

- Dr. Judson thought the cost-effectiveness component was key.

- Pointing out that while in terms of VFC there is already assurance that there will be coverage, Dr. Baker inquired as to whether there were any concerns that the term "as feasible" may influence reimbursement for vaccines.

- Tamara Lewis (AHIP) responded that the recommendation as it currently stood already had opened up the concept of coverage. Given that it is already recommended for those who wish to be immunized, it is and has been considered by the insurance industry as a universal recommendation. She cautioned ACIP that terms such as "as feasible" could give some individuals an out.

- Dr. Lett pointed out that previous feedback from clinicians indicated that terms such as "feasible" and "consider" caused confusion. The working group took this into consideration in their effort to come to suitable wording and a staged approach. She preferred the working group's original wording and was concerned that terms such as "feasible" tended to raise medical liability questions.

- In an effort to represent the working group's perspective, Dr. Neuzil was not as troubled by the term "feasible," noting that it was used in a different place and that the working group felt comfortable with the term.

- Dr. Pickering pointed out that this was just one component of the whole set of influenza recommendations. There are a few other issues that must be voted upon that will be included in the new recommendations, which the full committee would see before they were finalized.

- Dr. Fiore clarified that the only other component requiring a vote would be the recommendation of LAIV down to age 2, which was done in October 2007. It was simply appearing in these recommendations for the first time.

- Dr. Schuchat pointed out that the wordsmithing of the second motion would get worked out later; however, she did not believe they should say "6 months to 18 years as soon as feasible," given that 6 months to 59 months" had already been recommended. For example, the recommendation might written as, "Expanding the age group should be implemented as soon as feasible, but no later than the 2009-2010 season."

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Motion

Dr. Baker moved that ACIP accept the changes as listed for TIV or LAIV. Dr. Neuzil seconded the motion. The motion carried with 11 affirmative votes and 1 abstention.

Vaccines for Children (VFC) Vote

Dr. Greg Wallace
(CDC / NCIRD / ISD)

Dr. Wallace indicated that the current ACIP recommendations have a permissive recommendation, which is reflected in the Vaccines for Children (VFC) resolution. Children 5 to 18 years can be covered by the VFC resolution without any changes. He explained that with the implementation of a full universal recommendation, the intent of this vote was to unify that and simplify the VFC resolution. There was no need to have a different date from that which appeared in the recommendation. It currently reads that all children 6 to 18 years of age are eligible for VFC vaccine, but includes the caveat that when supplies are limited, vaccination should be limited to those who are in the current high risk groups that ACIP was voting to change. Similarly, for LAIV the language currently reads that those ages 2 to 18 years are eligible, with the caveats on supply, which would also be removed. With respect to the influenza schedule for those who need two doses, some wordsmithing has been done to clarify, "All children ages 6 months to <9 years who receive influenza vaccine for the first time should be given two doses. Children who receive only one dose of vaccination in the first influenza season they receive vaccine, should receive two doses, rather than one, in the following influenza season." The adopted date would be February 27, 2008 and the effective date would be July 1, 2009. This is to unify the language and will not restrict anybody from having access based on payment with the VFC resolution as it currently stands.

Discussion

- Dr. Schuchat inquired as to whether Dr. Wallace meant July 1, 2008.

- Dr. Wallace responded that the intent was 2009. The vote for the ACIP resolution was as soon as feasible but no later than 2009. The way the current VFC resolution reads, those children are already entitled and this is simply to clean up the extra language and to unify the two dates to avoid confusion.

- Dr. Cieslak thought the recommendation pertaining to the two-dose requirement was confusing and it seemed wordy to him. He asked whether he correctly understood that if a child received fewer than two doses in all previous seasons, they would now need two doses if they were under age 9.

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- Dr. Wallace responded that this was not correct. If a child did not receive two doses in the first year, there was a split in which ACIP recommended only receiving one dose in the second year and AAP recommended two doses in the second year. Currently, children who do not receive two doses during their first flu season, should receive two doses in their second season and one dose thereafter.

- Dr. Cieslak suggested that an easier way to state this would be that in the third season, children who did not receive two doses in previous years, should receive one dose.

- Dr. Schuchat pointed out that it was not necessarily the VFC language that needed to be cleaned up for that, so much as it was the educational materials.

- Dr. Lett inquired as to whether the amount of potential funding that could be available would differ based on the effective date.

- Dr. Wallace replied that there are regular meetings with OMB and funding is based on what the uptake is predicted to be, so he did not believe the language in the VFC would affect what ACIP was able to do or what CDC was able to contract for.

- Dr. Schuchat added that CDC makes estimates to OMB about the VFC purchase needs every year, with a mid-year update. If the mid-year update is not sufficient, CDC can go back to OMB in between. She thought the committee should decide upon whether it would be simpler to make the effective date 2008 rather than 2009 and have the full language clarified.

Motion

Dr. Neuzil made a motion that ACIP vote on the VFC as presented by Dr. Wallace, with a change in the effective date to July 1, 2008. Dr. Beck seconded the motion. The motion carried with 11 affirmative votes and 1 abstention.

Discussion

- Dr. Morse commented that now that the ACIP had passed recommendations for universal flu immunization for children, expanding the age range to 6 months to 18 years with the added age groups, and done so mainly on the basis of risk for children without depending on a potential added benefit to the community through decreased transmission, he thought they needed to reconsider the timeframe for voting on recommendations for ages 19 to 49. Given that the cost benefit for that age group is comparable to that for ages 5 to 18, he saw no reason to delay that decision out to 2013 or even into the next decade. He urged the workgroup to continue discussions and bring back recommendations for a vote within one year so that the phased-in approach for universal vaccine, which began in early 2000 can be accomplished within this decade, similar to the US's previous success in reaching the moon.

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- Speaking personally, Dr. Schaffner (NFID) congratulated the ACIP and supported Dr. Morse's sentiments about recommendations for ages 19 to 49. In addition, he reported that the NFID has been working on the immunization of healthcare workers, on which he requested ACIP's support. NFID is also very interested in adolescent immunization and its initiatives. For information on both health care workers and adolescent immunization, he referred the committee to NFID's materials located in the back of the room.

- Dr. Kenneth Schmader (American Geriatrics Society) indicated that the American Geriatrics Society strongly supports the recommendation of the Influenza Working Group that all children aged 6 months to 18 years old receive influenza vaccination. The American Geriatric Society also strongly supports universal influenza vaccination.

Meningococcal Conjugate Vaccine (MCV4)

Overview & Working Group Update

Carol J. Baker, MD
Advisory Committee on Immunization Practices

Dr. Baker reminded those present that Meningococcal Conjugate Vaccine (MCV4) was licensed for 2–10 year olds in October 2007 in addition to initial licensure for 11-55 year olds. The October 2007 ACIP recommendation stated that 2-10 year olds at increased risk of meningococcal disease should be immunized with MCV4 in preference to the MPSV4. The objective of the Meningococcal Session was to hear a presentation on the general use of MCV4 in 2–10 year olds. Dr. Baker indicated that the working group does not recommend routine vaccination against meningococcal disease in 2-10 year-olds at this time. In the future, the 2005 ACIP statement will require revision. The potential for meningococcal conjugate vaccines to be licensed in younger age groups is coming in the near future, with several products for children younger than age 2 in the pipeline. There is also potential for meningococcal vaccines that include serogroup B.

Burden of Meningococcal Disease among Infants and Children

Amanda Cohn, MD
LCDR, USPHS
(CDC / NCIRD / DBD)

Dr. Cohn acknowledged Dr. Ismael Ortega-Sanchez, who wrote a portion of the presentation she delivered. She then offered an overview of the meningococcal vaccine working group's discussions over the last six months regarding routine use of meningococcal conjugate vaccine among children aged 2-10 years. Dr. Cohn explained that meningococcal disease prevention in the United States (US) has been an evolving strategy. There is now a single conjugate vaccine, MCV4, available for use in 2-55

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year-olds, which provides protection against serogroups A,C,Y, and W-135. There are several meningococcal conjugate vaccines in development and in pre-licensure clinical trials targeting infants, young toddlers, and adolescents. Moreover, vaccines are being developed to cover all serogroups of meningococcal disease, including serogroup B for which there is currently no available vaccine in the United States. Every case of meningococcal disease is devastating, and the long-term goal of the working group is to prevent all cases of meningococcal disease with vaccination, including cases caused by serogroup B.

Currently, ACIP recommends routine vaccination with MCV4 in adolescents aged 11-18 years and persons aged 2-55 years at increased risk of meningococcal disease. The question the working group has been asking over the last several months is, “Should ACIP recommend routine MCV4 vaccination in the 2-10 year-old age group?” The working group agreed early that vaccination in this age group would have the greatest impact if given at 2 years-old. For that reason, Dr. Cohn provided a framework for the working group’s considerations of the question regarding whether ACIP should recommend routine MCV4 vaccination at 2 years-old. Aspects related to burden of disease, population impact, the economic cost-effectiveness analysis, vaccine safety, immune response to the vaccine, and programmatic implications influenced the working group’s position.

Consideration was given to whether routine vaccination of 2 year-olds makes sense in the US during a time in which there is an historic low in meningococcal disease incidence. Referring to the National Electronic Telecommunications System for Surveillance (NETSS) national surveillance data to show rates of meningococcal disease from 1970-2005, Dr. Cohn reported that rates of disease have declined or remained stable each of the last ten years. Generally, meningococcal disease cycles up and down over 8-10 years. It is unknown whether rates will remain this low or will start to rise over the next few years, but being at this nadir of disease incidence did impact the working group’s discussions. Even at this historic low, an estimated 900 cases of meningococcal disease occurred in 2006. The case fatality ratio is high at 10-15% even with proper treatment. Of those who survive, there is substantial morbidity and 10-20% of survivors have permanent sequelae such as limb loss, neurologic disability, or hearing loss.

Dr. Cohn explained that ABCs is an active, laboratory- and population-based surveillance system composed of 10 geographically disperse sites. ABCs data are relied upon in particular for serogroup and additional clinical information on cases. Data from ABCs by Dr. Cohn was presented as projected to 49 states using ABCs cases, excluding Oregon, and then adding Oregon’s cases back in for a projection to the 50 states. This is because of a serogroup B outbreak which elevated rates of disease from Oregon compared to other states. With respect to trends of serogroup-specific disease rates from 1997-2006 as reflected in ABCs data, serogroups B,C, and Y each account for approximately a third of meningococcal disease in the US, with disease caused by other serogroups and non-groupable organisms accounting for a small proportion. Rates of all three serogroups have decreased from 1997-2006; however, until 2006,

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more of the decrease was a result of C and Y; whereas, in 2006 more of the decrease was in B disease and C and Y remained stable. The adolescent MCV4 recommendation was implemented in 2005 and coverage during 2005 and 2006 was too low to expect it to have an impact on disease rates. However, it is unknown how the adolescent recommendation will impact future rates of meningococcal disease.

Referring to 2003-2006 NETTS data for average annual rates of meningococcal disease caused by all serogroups by single year of life, Dr. Cohn pointed out that while rates of meningococcal disease are as high among 2-3 year olds as they are in late adolescence, a vaccination strategy targeting 2 year-olds would be catching the downslope of disease incidence, as opposed to the adolescent strategy that aimed to achieve high coverage in adolescents before the increase in disease incidence in late adolescence.

When evaluating burden of disease in 2-10 year-olds, the working group looked closely at how much disease is caused by serogroups contained in MCV4. Based on 1996-2005 ABCs data regarding the proportion of disease caused by serogroups A,C,Y, and W-135, Dr. Cohn indicated that these serogroups are responsible for 75% of disease in adolescents compared with 59% of disease in the 2-10 year-old age group. Regarding the rate of meningococcal disease by serogroup, by age group, ABCs cases from 1997-2006 show that in 2-10 year-olds, Serogroups B and C occur at a similar rate, while serogroup Y is less common. Among adolescents, B occurs less frequently than C and Y. Thus, most disease that would be covered by MCV4 in 2-10 year-olds is serogroup C. Rates of disease are much higher in children less than 2 years old for all serogroups. Given that there is currently no licensed vaccine in this age group, the burden of disease in infants is substantial. Although estimates are based on small numbers, approximately 18 deaths occur in 2-10 year-olds annually, 13 of which are caused by serogroup C. In terms of the estimated annual number of case of serogroup A,C,Y, or W-135 disease by single year of life, among 2-10 year-olds, the burden of disease from these serogroups is highest among 2 year-olds and then decreases with increasing age before rates increase again in adolescence. Thus, among children aged 2-10 years, there are an estimated 160 cases of A,C,Y, and W-135 disease annually, of which 25% occurs in 2 year-olds and 50% occurs among 2-4 year olds. The burden of disease is about 1/3 less than in adolescents 11-19 years-old, in whom there are approximately 250 cases of A,C,Y, or W-135 annually. Clearly, cases of meningococcal disease and deaths occur in 2-10 years olds. The working group concluded that the burden of potentially-vaccine preventable disease is relatively lower and is primarily in the younger children in this age group.

The working group considered the potential impact vaccination of 2-10 year-olds would have in the general population. An advantage of meningococcal conjugate vaccines is that they may reduce pharyngeal carriage of serogroups of Neisseria meningitidis in the vaccine, reducing transmission to persons who are not immunized, leading to herd immunity. In most studies, young children have a low prevalence of carriage, and adolescents are generally considered the reservoir of carriage.

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Caugant et al published a paper in 1994 of asymptomatic carriage *of* Neisseria meningitidis in a random population of Norway ["Asymptomatic Carriage of Neisseria meningitidis in a randomly selected population. *J. Clin Micro*. 1994;32;323-330]. Studies conducted in the US have shown a similar pattern, but these studies have not been repeated in recent years. As shown by the Norway study, rates of carriage of all serogroups are highest in late adolescents and young adults, but are lowest among young children. The current state of carriage is unknown and it may be different. However, the working group concluded that the potential for a routine recommendation in 2-10 year-olds to decrease disease in other age groups through reduction in carriage is low.

The working group reviewed an economic analysis of meningococcal vaccination strategies, which Dr. Ortega-Sanchez completed in a short time-period. Dr. Cohn presented a portion of this analysis that focuses on the 2 year-old vaccination strategy, and compared this strategy to a vaccination strategy in 11 year-olds. The adolescent strategy in 11 year-olds has been updated from what was presented to ACIP in 2005. A Monte Carlo analysis was performed in which multiple parameters were varied. The economic costs and benefits of vaccinating a hypothetical population of a 4 million birth cohort and a 4 million 11 year-old cohort was evaluated. The study followed the cohort for 22 years using an age-specific life expectancy and a discount rate of 3%. ABCs data from 1991-2005 were used to calculate age- and serogroup-specific incidence rates and case-fatality rates. Vaccine efficacy was based on MCV4 efficacy data for serogroup C, which for 2 years-old was 87% and for 11 year-olds was 93%. Data on the proportion of survivors with sequelae by condition was obtained from previous studies. A key assumption in this analysis is that duration of protection is 10 years for both 2 year-olds and 11 year-olds. It is unknown whether MCV4 given to a 2 year-old will protect for as long as it does for 11 year-olds. Another key assumption that impacts this analysis is coverage. Using infant and adolescent coverage from other vaccines, coverage among toddlers was assumed to be 91% and coverage among adolescents was assumed to be 70%; however, there is not an ideal vaccine comparison to determine what coverage in these age groups will be. Importantly, the analysis assumes that coverage is achieved at 24 months as opposed to over the whole course of the third year of life, which would be extremely difficult to achieve.

At baseline, with no vaccination, there would be 468 cases in the 11 year-old cohort followed until 32 years old and 788 cases in a birth cohort followed through 22 years old. Focusing just on the birth cohort, if MCV4 were given at 24 months, 205 cases and 14 deaths would be prevented. By adding a booster dose at 11 years-old to that cohort, a total of 407 cases and 35 deaths would be prevented in this cohort. Six hundred eighty nine life-years would be saved by vaccinating at 24 months and 1496 life-years would be saved with a booster dose on top of that 2 year-old dose. Two thousand twenty eight quality adjusted life years (QALY) would be saved with a 24 month strategy and 4688 QALYs would be saved with a 24 month and booster strategy. A 24 month vaccination strategy would cost $453,000 per life year and $160,000 per QALY. This strategy with a booster would cost $376,000 per life-year saved and $120,000 per QALY saved. Comparing these 2 toddler strategies, with and without a booster, to an

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updated analysis of an 11 year-old strategy and previously published costs of other vaccination strategies, a 24-month vaccination strategy is more expensive at $160,000 per QALY saved compared to an adolescent 11 year strategy at $90,000 per QALY saved. This is assuming the same duration of protection in both age groups. In sensitivity analyses, incidence has the highest correlation with the output. As incidence decreases, such as during the current nadir, the cost of a vaccination program increases. Cost also has a high correlation with output in the opposite direction, as the cost of the vaccine increases, as does the cost of the program. As are most meningococcal vaccination strategies in the US, a 2 year-old routine vaccination program would be expensive.

Dr. Cohn noted that much of the data she was presenting on vaccine safety and immunogenicity were from the pre-licensure clinical trial, which was a comparative, modified double-blind study comparing MCV4 in 2-10 year-old subjects with Meningococcal polysaccharide vaccine, or MPSV4, in 2-10 year-old subjects. All subjects had previously received 4 doses of DTaP. Six hundred ninety six subjects received a single dose of either MCV4 or MPSV4. MCV4 was tested for non-inferiority to MPSV4 both in safety and immunogenicity. The working group evaluated the pre-licensure safety data. There were no serious adverse events in either group. The majority of the reactions were mild or moderate, and all reactions resolved without sequelae. MCV4 recipients experienced more severe local reactions than MPSV4 recipients. While reports of any local reaction were similar between the two groups, swelling and induration within 7 days of vaccination were reported more frequently among the MCV4 group. Most of these reactions resolved within 3 days of vaccination. The working group concluded there is sufficient evidence that MCV4 is safe in 2-10 year-olds.

The working group spent a considerable amount of time evaluating available data to understand the immunogenicity of MCV4 in 2-10 year-olds, and in particular 2, 3, and 4 year olds. Dr. Cohn discussed serum bactericidal antibody titers, or SBA, which is generally considered a correlate of protection. She explained that seroconversion is considered a marker for short-term protection against meningococcal disease. In terms of subjects with no detectable serum bactericidal antibody (<8) at Day 0 who seroconverted (Titer≥32) by Day 28, the proportion of seroconverters with MCV4 exceeded the proportion of seroconverters with MPSV4 for all four serogroups, with p-values of less than 0.02 for all serogroups. When looking at immunogenicity by serogroup, Dr. Cohn focused on serogroup C, given that most of the disease that would be prevented by this vaccine in 2-10 year-olds is serogroup C. Pertaining to the SBA geometric mean titers, or GMTs, generated by MCV4, at day 28 and 6 months post-vaccination, GMTs with MCV4 were significantly greater than GMTs produced by MPSV4 [Pichichero et al. *PIDJ.* 2005:24;57-62]. These data met criteria for non-inferiority and the working group concluded that MCV4 is immunogenic in 2-10 year-olds.

While MCV4 was compared with MPSV4 in pre-licensure trials because MPSV4 was the only vaccine available for MCV4 to be compared to, this is what was used in the

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pre-licensure clinical trials. There is evidence that MPSV4 does not produce as robust an immune response in young children and does not provide long-lasting protection. Conjugate vaccines should provide longer lasting protection than polysaccharide vaccines. Although there is no correlate of long-term protection, high SBA titers post-vaccination is considered by some experts to be a marker for long-term protection. Evidence suggests that antibody levels alone are not sufficient for protection. Because the disease is so rapid, the immune system does not have time to mount a response from memory B-cells. Therefore, maintaining SBA titers is critical for protection.

Referring to age-dependent serogroup C SBA - MPSV4 data Dr. Cohn offered an example of SBA titers generated by polysaccharide vaccine in three age groups [Mitchell, L, Ochnio, J, and Glover, C. Analysis of Meningococcal Serogroup C-Specific Antibody Levels in British Columbian Children and Adolescents. *J Infect Dis* 1996;173:1009-1013]. She pointed out that the immune response to MPSV4 in 2-6 year-olds is not as robust as in older age groups. Secondly, in both 2-6 year olds and 9-12 year-olds in this study had no detectable SBA 1 year after vaccination and adolescents had only a small amount. This is one of the reasons MPSV4 was not recommended for routine use by ACIP.

With respect to the SBA GMTs for three different age groups from pre-licensure clinical trials, similar to MPSV4, there is a more robust response to MCV4 in adolescents and adults compared to children 2-10 years [Pichichero et al. *PIDJ.* 2005:24;57-62; CDC. MMWR. 2005;54(RR 7). A small subset of subjects from the clinical trial who were vaccinated with MCV4 at 2-3 years old were followed for 24-36 months and SBA titers were measured at that time, before they were tested for a booster response. So, there was a group of children who received MCV4 2-3 years prior and a group of 4-5 year olds who did not receive either vaccine. At 2-3 years after vaccination, SBA GMTs for serogroup C are 59, and cross the confidence intervals of SBA GMTs produced by children who did not receive any vaccine, which the working group considered to be low. Regarding SBA titers to serogroup C by single year of life in 2-10 year olds, consistent with maturation of the immune system, the immune response is more robust as children get older, and the immune response to MCV4 in the 2 and 3 year-old subjects is not very different than with polysaccharide vaccine. SBA titers generated by MCV4 in two year olds is similar to the other conjugate vaccines in toddlers, such as some of the meningococcal C vaccines licensed in the United Kingdom (UK). A single dose of conjugate vaccine in this age group may not be sufficient in toddlers to produce a robust immune response. The working group concluded that MCV4 is immunogenic in 2-10 year-olds, but there was insufficient evidence to conclude that a single dose of conjugate vaccine in 2 year-olds would protect a child through late adolescence and college entry.

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Regarding programmatic considerations, MCV4 might not be readily incorporated into the routine infant and early childhood schedule because there is currently no vaccine recommended at the 2 year-old well child visit. Additionally, the working group recognizes the potential that meningococcal vaccines may be licensed for infants and young toddlers in the near future. The only example of a routine vaccination at the 2 year-old well-child visit was the 1999 ACIP recommendation for routine hepatitis A vaccination in the 11 states where there was a high burden of hepatitis A. Five years later in 2004, 1-dose coverage among 24-35 month olds was only 54.4% with a range of 8.6-74.4% by state. This coverage should not be considered in relation to coverage of other vaccines because they are evaluation children at 24-36 months rather than waiting for the entire year to be complete before assessing coverage. However, this is an important aspect of MCV4 vaccination because of the cases of meningococcal disease that occur in 2 year-olds, 75% happen before the child turns two and a half. That is a total of 20% of all cases in this age group. To prevent these cases, coverage with MCV4 would have to be high early in the third year of life. The hepatitis A vaccine recommendation was changed to be a routine vaccination for all children at 12 months when the licensure age was lowered.

Children 2-10 years old would be protected, however, against meningococcal disease with an infant or young toddler vaccine. A recently published study of a MenACWY vaccine in infants shows promise [Snape et al. *JAMA*. 2008:299;173-184]. In infants who received MenACWY at 2, 4, and 6 months, more than 98% of infants seroconverted for serogroups C,Y, and W-135. A second dose produces a robust response. The working group concluded that programmatically, implementing a routine vaccination at 2 years-old would be difficult and vaccines may be licensed for younger ages that would be more feasible to implement in the near future. Putting all of these considerations together, and recognizing that the working group's eventual goal is to prevent all cases of meningococcal disease, the working group agreed that it does not endorse routine vaccination in this age group at this time. The working group revisited the decision to vaccinate 11 year olds using these same considerations and determined that vaccinating 11 year-olds looks different than vaccinating 2 year-olds.

The working group proposed that ACIP take the position that it does not recommend routine vaccination against meningococcal disease in children aged 2-10 years at this time, except for children at increased risk of disease. If providers or parents choose to vaccinate against meningococcal disease in this age group, MCV4 is preferred to MPSV4.

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Discussion

- Dr. Morse asked what the timeframe was for the new vaccines on the horizon for younger age groups and for adding serotype B.

- Dr. Cohn responded that they hope the timeframe for conjugate vaccines, not serogroup B vaccines, is in the near future within the next couple of years. She requested that manufacturing companies respond.

- Dr. Hosbach (sanofi pasteur) responded that it could be a few years. It is difficult for them to project trial completion, review of results, and back and forth with FDA. He also pointed out that another reason for not making a decision now for 2-10 years old is that sanofi pasteur is unsure of supply at this time. The 11-18 year old broad recommendation made by the ACIP in 2007 has had significant impact. There has been great uptake in adolescents, about which sanofi pasteur is very pleased. Of the cumulative effect for the past three years, nearly 40% of all adolescents have been immunized with Manactra®. Last year, based on a review of claims data, MCV4 immunization surpassed TDaP immunization in 11-18 year olds. Thus, ACIP has had a great impact. sanofi pasteur is supplying the vaccine at a great rate, but is unsure as to how high the peak will be in the summer. They expect a strong summer season, having observed a strong uptake late last year and continued strong uptake early in the year, which is different from previous years. Therefore, supply is unsure in terms of being able to take on a routine recommendation at any age at this point. However, sanofi pasteur could handle a permissible recommendation as described by the working group.

- Dr. Martin Myers (University of Texas) pointed out that a cost-effectiveness analysis would become very important with respect to vaccines for infants. In the re-analysis of the adolescents, two major impacts changed the cost-effectiveness analysis. The first regarded whether it included a catch-up analysis and the second regarded whether it included the expected herd immunity that was found in the UK. Dr. Cohn did not mention this in the analysis, but he thought it would have a profound impact on the cost-effectiveness estimates.

- Dr. Cohn replied that the cost-effectiveness analysis she described did not include catch-up vaccination. It was vaccination of only 11-year olds. Therefore, impact from herd immunity was not included in this analysis.

- Barbara Mahon (Novartis) indicated that Novartis's ACYW-135 conjugate vaccine is expected to be filed later this year. Serogroup B meningococcal vaccines are going into Phase 3 and are expected to be available within several years.

- Jacqueline Miller (GlaxoSmithKline Biologicals) responded that GlaxoSmithKline Biologicals has a bivalent serogroup C and Y infant vaccine in development designed to be given at 2, 4, 6, and 12-15 months of age. Their thinking was that this prioritizes the vast majority of ACWY disease that is combined with Hib to ease

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implementation into the vaccination schedule. GSK Biologicals presented data at the Infectious Disease Society of America (IDSA) meeting in late 2007 demonstrating immunogenicity as early as 5 months of age and demonstrating the immunogenicity of a booster dose. They are in late Phase 3 of development.

- With regard to cost-effectiveness, Dr. Cieslak inquired as to whether the societal cost for QALY on the toddler 24 months plus the boost at 11 years was a marginal cost per QALY saved over the vaccination of adolescents at 11 years of age alone, or if it was all comers mixed together. He pointed out that there is already vaccination at 11 years old, for which a certain amount of lives are saved and a certain price is paid.

- Dr. Ortega-Sanchez replied that vaccinating 24-month old toddlers included the booster dose at 11 years old, following the cohort from 0 to 22 years and considering the specific incidence rates and the case fatality ratio in each of the specific years. The toddler 24 months plus the boost at 11 years is not a marginal cost per QALY saved over the vaccination of adolescents at 11 years of age alone because in this case, data were used from after 2005, which was the time at which the vaccine was recommended for adolescents. There is no assumption of impact of the 11 year-old recommendation in the analysis.

- Dr. Baker reminded everyone that this cost-estimate assumed that all toddlers would be immunized instantly at two years of age and that there would be a 91% efficacy, which she thought was generous, as well as an unknown duration of protection.

- Dr. Lieu noted that most of the vaccines recommended by ACIP in the past three years had actually fallen in the range of $20,000 to $30,000 per QALY saved. Meningococcal vaccination of adolescents was on the high side. At the time ACIP discussed the recommendation a few years ago, members were aware that there were some unmeasured societal effects of being able to prevent outcry when there are outbreaks in college dormitories. In reality, most vaccines are far more cost-effective than the meningococcal vaccine modeled.

- Dr. Chilton wondered if vaccines needed to be held to the $20,000 to $30,000 range, or whether consideration should be given to the $100,000 range, which people discuss with respect to other measures.

- Dr. Lieu noted that according to a recent paper in the *New England Journal of Medicine,* most treatment and preventive measures are in the $0 to $100,000 range. While they could all cite examples of tertiary care that costs much more, beyond $100,000 really is on the high side.

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Meningococcal Conjugate Vaccine (MCV4) Vote

Amanda Cohn, MD
LCDR, USPHS
(CDC / NCIRD / DBD)

Dr. Cohn presented the language the working group proposed for use of MCV4 in children aged 2-10 years, indicating that the ACIP's position on the use of MCV4 in this age group would be published as a Notice to Readers in the *Morbidity and Mortality Weekly Report* (*MMWR*), with the intention of the working group to revise the entire meningococcal vaccination ACIP statement in the next year. She pointed out that ACIP members had a draft of this notice in their binders. The Notice to Readers would review the burden of disease, cost-effectiveness analysis, safety and immongenicity data of MCV4, and the programmatic implications as outlined previously. The ACIP recommendation and future directions for meningococcal prevention would complete the Notice to Readers. The Meningococcal Working Group does plan to revise the statement within the next year, but preferred to get something out soon, followed by a total meningococcal disease prevention recommendation in 2-55 year olds to include all adolescent revised recommendations as well. In the meantime, the proposed ACIP recommendation presented for a vote was as following:

- ACIP does not recommend routine vaccination against meningococcal disease in children aged 2-10 years at this time.

- Children aged 2-10 years at increased risk of meningococcal disease should be vaccinated with MCV4 according to the previously published recommendations [CDC. Notice to Readers. *MMWR*. 2007:56 (48);1265-1266].

- If healthcare providers or parents elect to provide meningococcal vaccination to children in this age group, as for children at increased risk for meningococcal disease, MCV4 is preferred to MPSV4.

Dr. Cohn pointed out that new to the recommendation was the third bullet beginning with, "If healthcare providers or parents elect to provide meningococcal vaccination to children in this age group . . ."

In response to inquiries regarding whether a vote was actually needed, Dr. Schuchat added that this actually was a recommendation to not use this vaccination routinely. In addition, there was some miscommunication following last fall's vote for high-risk children in that some of the communication media or provider organizations misstated that as being for all 2-10 year olds. Therefore, a vote would be clarifying.

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Motion

Dr. Chilton made a motion to approve the ACIP position as stated by the working group. Dr. Baker seconded the motion. The motion carried with 11 affirmative votes and 1 abstention.

Discussion

- Clarification was requested regarding what was being recommended for a booster at age 11 if a child receives the vaccine at 2-10. Based on the current state of knowledge, it seemed that there should be some language indicating that a booster is needed at age 11.

- Dr. Cohn responded that the working group discussed this issue. There is not enough data at this time to make a statement about when a booster should be recommended. However, they do expect to receive more data over the next couple of years to further consider this issue. She thought they had at least 3-5 years to gather data and make a determination about whether these children should be boosted. Also not clear is if children receive the vaccine at 9 years old whether they should receive it again 10 years later at 19 years old.

- Dr. Schaffner (NFID) reported that the NFID has a Stop Meningitis program on its website, which provides educational materials for laypersons and professionals.

- Peter Paradiso (Wyeth) commented that there is a lot of data in Europe on the effectiveness of the meningococcal group C vaccine that was given in one dose to children 2-10 years of age. A fairly massive campaign for this vaccine was begun several years ago. 11 year olds who were vaccinated in 1999-2000 are now 18-19 years old, so there may be some data available there.

- Dr. Hasbach (sanofi pasteur) said that the European data are confounded by the fact that they have vaccinated all of their children and there may be a herd effect, but hopefully the US is doing the same thing.

- Dr. Baker clarified that the working group has no data suggesting that the 11-year old immunization will last through age 18. While they believe it will last that long and hope to have the data in the future, for this particular vaccine, there has not been enough uptake in adolescents to talk about herd. There is certainly no herd information for this vaccine in particular.

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Use of Vaccines during Pregnancy & Breastfeeding

Update on the Activities of the ACIP Working Group On Vaccination during Pregnancy and Breastfeeding

Carol J. Baker, MD
Advisory Committee on Immunization Practices

Dr. Baker reported that beginning in January 2007, the ACIP Working Group on Vaccination during Pregnancy and Breastfeeding reviewed the current ACIP recommendations on the use of vaccines during pregnancy and breastfeeding. The working group's charge was to establish "guiding principles" for developing recommendations in future statements, to facilitate consistency in recommendations issued by ACIP, and to promote harmonization across professional organizations. While the recommendations tend to be similar most of the time, the language is very different, which leaves them open to interpretation.

With respect to existing recommendations, the working group reviewed all of the existing ACIP recommendations and discussed them in March 2007, reviewed FDA vaccination indications and vaccine labeling language and discussed them in April 2007, and reviewed the recommendations of key professional organizations (e.g., AAP, ACOG, and AAFP) and discussed them in May 2007. The working group presented their findings during the June 2007 ACIP meeting regarding the wide variation within ACIP statements in language, format, rationale, and process. There were many differences between ACIP and FDA in terms of labeling concerning pregnancy and breastfeeding versus ACIP statements. There were a few examples of lack of harmonization with AAP or ACOG, such as the adolescent Tdap recommendation from AAP. The working group's central conclusion was that there is not enough evidence to make general recommendations for vaccination during pregnancy or breastfeeding for all vaccines and for specific subclasses of vaccines. Thus, each product will require a vaccine-specific statement. It is clear that lack of evidence is a fundamental dilemma.

Pertaining to their second charge (e.g., to develop guiding principles for future recommendations), the working group determined that the target audience for these guiding principles would be the ACIP working groups and CDC, given that together they would be drafting ACIP statements on vaccine for use in adolescent or adult women. The product would be an internal document for ACIP working groups and perhaps something posted on the website that would be relatively short and user-friendly. The status is that a draft of the guiding principles has been circulated to the working group, Dale Morse, Larry Pickering, Jean Smith, and Beth Bell who have sent back very helpful revisions. A revised version will be circulated to full ACIP for comment directly after the February meeting. The document includes guidance on structure and language of pregnancy and breastfeeding components of ACIP vaccine-specific statements; guidance on the process for formulating recommendations, with the key challenge being lack of evidence; and an appendix, which will include a review of key issues regarding vaccination during pregnancy and breastfeeding.

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Draft Guiding Principles for Standardization of ACIP Recommendations Regarding Vaccination during Pregnancy and Breastfeeding

Stephanie Schrag, PhD
(CDC / NCIRD / DBD)

Given that the draft guiding principles document would be circulated to the full ACIP panel, Dr. Schrag offered an overview of what they could expect to find therein. Pertaining to guidance on structure, it is suggested in the principles that all statements concerning a vaccine that could go into adolescent or adult women should have a background subsection on pregnancy and breastfeeding. The topics which should be addressed in this subsection are outlined and include disease burden for pregnant women, fetus, newborns, and young infants; vaccination during pregnancy, including the objective and rationale, immunogenicity and efficacy, and safety and timing; vaccination during breastfeeding including the objective and rationale, immunogenicity and efficacy, and safety and timing; cost-effectiveness (if pregnancy / breastfeeding issues are unique); alternatives or adjuncts to vaccination; logistics; and areas for future research. The idea is to narrow this subsection and keep the focus on pregnancy- and breastfeeding-specific issues. While these may look like a lot of topics to cover, unfortunately because of the lack of evidence, it is anticipated that these subsections will be fairly short. However, by having a common design, it will be easier to follow the rationale behind recommendations.

The guidance on language primarily focuses on the recommendations section of ACIP statements. The workgroup decided to provide standard language templates from which authors of statements could choose, such as Contraindication (e.g., MMR, varicella for pregnant women), Precaution (the vast majority fall here for pregnancy), Neither (e.g., Td), Pregnancy is an indication for vaccination (e.g., Inactivated influenza), and several timing templates. For pregnancy the timing templates refer to trimester of pregnancy, while for breastfeeding they refer to when within the post-partum period. Language templates were developed for pregnancy, and for breastfeeding. They were based on the working group's review of the existing ACIP statements, which made them confident that recommendations would fall into one of the provided categories.

Dr. Schrag shared sample language templates to familiarize the ACIP and working groups with the templates and to request that they be persistent in using these to avoid wide variation in their statements. For a sample vaccination recommendation, she chose the precaution template, which might read, "Pregnancy is a precaution and under normal circumstances vaccination should be deferred; vaccine should only be given when benefits outweigh risks." This is standard language borrowed from the ACIP official definition of "precaution" with "pregnancy" plugged in where it belonged. A sample timing template might read, "Vaccine may be administered at any time

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postpartum for all women, whether or not they intend to breastfeed." Currently, this is where most vaccines will fall.

Guidance is also provided on process. This was somewhat more controversial within the working group. In some ways, this already is the process which some working groups are following. However, with pregnancy and breastfeeding decisions, because there is so little evidence, they thought it was important to give working groups whatever help they could in terms of guidance. Suggestions are offered about data to review; issues to consider, such as whether there will be more data in the near-term; safety monitoring and whether adverse events could be detected if they occurred; and reviewing decisions of other respected organizations because sometimes their thought process will be helpful in the decision making. From their review of ACIP statements, the working group was able to outline several ACIP "precedents" that workgroups may wish to consider. For example, a precedent is that live vaccines are generally described in statements as posing most theoretical concern. Dr. Schrag emphasized that this is a theoretical concern, but all concerns around pregnancy primarily fall in that realm. Another example is that with breastfeeding, vaccination of breastfeeding women is generally viewed as safe by ACIP. Smallpox is the only contraindicated vaccine for breastfeeding women.

They also tried to help working groups make the most of their opportunity to use expert opinions, given that many of these decisions will require this due to the lack of data. A list is provided of suggested areas of expertise to include in deliberations, as are suggested strategies for obtaining unbiased input, and suggestions about what to do when expert opinion does not reach consensus within a working group.

In terms of next steps for these guiding principles, as Dr. Baker mentioned, the plan was to circulate the document to the full ACIP with a comment period during the first three weeks of March. They will then revise, finalize, and clear the document. The document will be posted on the ACIP website and circulated to working group chairs, it is hoped by April. There are also discussions in progress about developing an *MMWR* Notice to Readers. This seems to have been successful for the Economic Working Group. There may also be some internal CDC steps to take once the guiding principles are in public use. One idea is to review upcoming ACIP statements to assess whether they implement the guiding principles. Another option may be to identify, within CDC, a few subject matter experts who have thought about the issue of maternal immunization or immunization during breastfeeding so that they could be available for technical consultation as working groups attempt to grapple with these issues.

The third charge to facilitate consistency in ACIP recommendations was discussed at the October ACIP administrative meeting, where they received a very clear message from ACIP that the vaccine-specific working groups must resolve inconsistencies. The Pregnancy and Breastfeeding Working Group is not charged with making vaccine-specific recommendations. Also agreed was that the guiding principles document that has been developed is sufficient for facilitating the working group tasks in terms of the inconsistencies. CDC ACIP staff will ensure that the guidance is followed.

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Inconsistencies in existing statements will be addressed as they come due for routine updates, which will be more frequent than in the past. Certainly, all new statements coming out should follow the guiding principles from this point forward.

In terms of the charge to promote harmonization across professional organizations, it was very clear to this working group and also to ACIP that this was more of a wish than an actual charge. It was also the opinion of this working group, after reviewing the issues, that where data are lacking differences in expert opinion may continue to lead to lack of harmonization.

Many working group members shared in the concern that there really are no "teeth" in terms of whether these guiding principles will be used. Another concern pertained to the narrow scope of this working group. While this has allowed them to make a contribution, there has been a general sense that ACIP should be more revolutionary on the issue of pregnancy and breastfeeding, which has been somewhat neglected. Another concern pertained to vaccine-specific working group load and whether they will truly have the time to do justice to complicated issues like pregnancy or breastfeeding. Currently, the burden will fall to them. There was also disappointment that there is no way to prevent lack of harmonization across organizations (e.g., Tdap). In fact, it was an issue of discord that led to the formation of the Pregnancy and Breastfeeding Working Group.

Discussion

- Dr. Baker congratulated Dr. Schrag and her staff for doing an incredible amount of work, and acknowledged Dr. Neuzil's efforts on this prior to becoming chair of the Influenza Working Group.

- Jon Abramson (Wake Forest University Health Sciences) suggested that where there is lack of agreement between professional organizations, the reasons should be clearly outlined.

- Dr. Grogg expressed his hope that the statement would include an endorsement of studies in pregnant women where there is no a priori idea of risk. That kind of strong statement would be beneficial to investigators and organizations that may seek to conduct studies in pregnant women. This has relevance to vaccination of pregnant women for the sake of their newborns, which is a current idea.

- Dr. Baker responded that there was a great deal of enthusiasm for that concept and for outlining specific types of future research studies. The common theme will be addressed in the document. The group did not go into great detail, given that this was not one of their charges.

Human Papillomavirus (HPV Vaccines)

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Overview of Session and Working Group Update

Janet Englund, MD
Chair, ACIP HPV Vaccine Workgroup

Dr. Englund briefly described how recent developments over the previous couple of months impacted the direction of the HPV Vaccine Working Group. The HPV Vaccine Working Group had been preparing for a vote on the bivalent HPV vaccine and had discussed this in the October 2007 meeting. However, in December 2007 the FDA requested more data on the bivalent HPV vaccine and the licensure has not been granted to date. In addition, more information has been published and it is possible that there may be an FDA priority review of the quadrivalent HPV vaccine in females >26 years. Because of these developments, the discussion of recommendations for bivalent HPV vaccine and issues related to having two HPV vaccines have been postponed. However, the working group is moving forward into presentation of vaccine trial data and discussion of HPV vaccine recommendations for the group known as "older women" (26–45 year old women).

The working group is attempting to project dates for ACIP votes, given that the working group's discussions and workload depend upon the vaccines available for licensure and to be given to women. No vote was planned for the February 2008 meeting. There may be a vote in June or October 2008 on quadrivalent vaccine for females ages 27-45. There may be a vote in October 2008 or February 2009 on bivalent vaccines for females, although the age range is yet to be determined. There is also the potential for a vote in 2009 on quadrivalent vaccine in males.

With respect to the HPV Vaccine Working Group's activities, an incredible amount of new data appear weekly in various journals, publications, and meetings. The working group has spent a great deal of time reviewing and discussing these data and potential recommendations for women >26 years of age through bimonthly conference calls. Multiple conference calls have been convened with many experts who have provided the working group with a great deal of data, including the following: Dr. Haupt of Merck provided data on quadrivalent HPV vaccine efficacy and epidemiology in adult women; Dr. Winer of the University of Washington described the epidemiology of HPV in older women; Dr. Leichliter of CDC discussed sexual behavior in the US; Dr. Goldie of Harvard discussed cost-effectiveness; and Drs. Schiffman and Rodriguez, NCI investigators, provided data on the natural history of HPV. Following each of these conference calls, the working group has engaged in discussions of recommendation options.

Dr. Englund indicated that during this session, some of the most important and interesting information would be summarized, including: A bivalent vaccine update; quadrivalent vaccine end-of-study results in adult women; epidemiology of HPV as it

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relates to older women; an overview of cost-effectiveness analyses; and considerations for ACIP.

Update on Bivalent HPV Vaccine

Gary Dubin, MD
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Clinical Development and Medical Affairs
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GlaxoSmithKline

Dr. Dubin reported on the Cervarix®: GlaxoSmithKline (GSK) Cervical Cancer Candidate Vaccine Clinical Development Program in Women Over 25 Years. GSK's core efficacy studies have evaluated the vaccine in women between the ages of 15-25. A separate development program has been evaluating the vaccine in women over the age of 25. With regard to the rationale for vaccination of women over 25 years of age, it is fairly clear that even though HPV infections tend to occur at relative early ages and peak incidence rates occur between the ages of 15-25 for many oncogenic infections, the majority of women over 25 years of age have not been previously infected with HPV-16 and / or HPV-18. There is also a limited body of literature that indicates that new HPV infections can occur in sexually active women of all ages. In a prospective cohort study of women aged 15-45+ in Columbia conducted by Munoz, women were negative for HPV at entry and had normal pap smears. Over a follow-up period of five years, cumulative incidence rates of newly detected HPV infections were evaluated. In each of the age strata evaluated in this study, new were infections detected over time. The highest rates were seen in the youngest women and there was an age effect in terms of incidence rate, but even in the oldest age strata appreciable rates of new infections were detected. The overall cumulative five year rate in this study in women over 45 years of age was approximately 12%.

One of the questions that has been posed in considering the issue of vaccination of women over 25 years of age is whether women who have been previously infected with HPV-16 or 18 but who have clearer their infections (seropositive / DNA negative) are at risk of subsequent re-infection. It is known that many of these infections are transient and ultimately clear, but a sub-set of women will develop persistent infections. Those are the women who are at risk of progressing to clinical lesions, cervical pre-cancers, and cancer. To address the issue of whether women who have successfully cleared infections are protected against re-infection with the same type or remain at risk, data have been reviewed from the GSK Phase 3 efficacy study HPV-008, which was published in 2006 in the *Lancet.* This evaluation was performed using prospective incidence rate data in 15-25 year old women in the control arm only for a number of endpoints (e.g., incident infection, 6 month persistent infections, 12 month persistent infection, any grade CIN), stratified by initial serostatus. Women who were DNA positive were eliminated at study entry for the type that ultimately was found in a cervical sample or a lesion. Observed in this analysis was that the seropositive subset women remained at risk for all endpoints evaluations. The incidence rates in initially

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seropositive women were quite similar to those in women who were initially seronegative. Some of these events had relatively low frequency rates and there are fairly wide 95% confidence intervals. On a cautionary note, this did not necessarily mean that being seropositive / DNA negative does not provide any level of protection because these women were not randomized to their initial serostatus. There may be differences in risk behaviors between the serostratified subsets. However, what it does indicate is that women who are seropositive / DNA negative do have a risk of developing not only incident infection, but also infection that can persist and eventually lead to lesions. Overall, these incident rates appear to be quite similar to what is observed in a cohort of women who were seronegative.

The GSK Clinical Development Program in Women Over 25 Years has two studies that have either been completed or are ongoing which have evaluated the vaccine in this age range. One of the studies, HPV-015, is an efficacy study conducted in women over 25 years that has enrolled 5751 women and is ongoing. It is a double blind, randomized controlled multi-national study designed to evaluate efficacy against virological / cervical intraepithelial neoplasia (CIN) endpoints. An interim safety analysis was conducted in 2006, which has provided a very useful safety dataset in women over 25 years of age. Additionally in this study, baseline serologic data were assessed for HPV-16 or 18 to try to determine whether there were age-related differences in seropositivity rates for the two vaccine types. As a reference, data from the HPV-008 study were used, which evaluated women 15-25 years of age. There are some age-related differences in seropositivity rates, with the highest incidence of being double seronegative observed in the youngest age cohort, while a higher percentage of older women were found to be seropositive. However, a substantial percentage of women over 25 years of age remain seronegative for both types and some women remain seronegative for at least one of the two types. In total, approximately 86% of women over 25 years of age in this evaluation remained seronegative for at least one of the two vaccine types and, therefore, should be fully susceptible to infection with those respective types.

With regard to clinical development strategies, core development has been done evaluating efficacy in women 15-25 years of age in three studies: HPV001, HPV007, and HPV008 (which enrolled almost 19,000 women). These studies have shown efficacy against HPV-16 and 18 in persistent infections and CIN endpoints up to 5.5 years, as well as efficacy against HPV-45 and 31 persistent infection in each of the studies. The strategy used to extend efficacy to younger and older women has relied primarily on immunobridging. An immunobridging study has been conducted in girls 10-14 years of age, data from which were presented previously to the ACIP. All of the pre-specified non-inferiority criteria were met showing that the vaccine was highly immunogenic in this age range. The two studies in women 26-55 years are: HPV-014 and HPV-015. HPV-015 is considered to be a confirmatory efficacy study because the conclusions to date based on vaccination in this age range have been based on data generated in the HPV-14 immunobridging study.

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The HPV-014 immunogenicity and safety study is an open, age-stratified study conducted in Germany and Poland (N = 666). The study was designed to compare antibody seroconversion rates and antibody titers in women 26-55 years with those in women 15-25 years, the reference group in which efficacy has been directly demonstrated. Observed in this study was that at peak responses (one month after the third dose), all women in all age groups became seropositive for HPV-16 and 18 and high antibody titers were developed for each of the two types. In fact, 100% seropositivity was observed in all age strata after the second dose of vaccine. There was an age-related decline in peak immune responses, which were expected based on experience with other vaccines, but the antibody titers remained substantially higher than titers associated with naturally acquired HPV-16 or 18 infection. While these titers provide a useful benchmark, it does not necessarily mean that antibody titers above the natural infection threshold are protective because women who have antibody titers in this range are still at risk for acquiring infections. Therefore, GSK has tried to use a more biologically relevant benchmark for antibody titers that have been observed in its long-term efficacy study HPV-007. During this study antibody titers reached a plateau level during which protection against HPV-16/18 endpoints was sustained up to 5.5 (longest observation period reported in this trial to date). While the plateau level does not necessarily represent a protective threshold, it is known that antibody titers above that level should correspond with protection.

In the HPV-014 study, over time, a kinetic profile can be discerned in women 15-55 years of age. Looking at antibody titers through 18 months for HPV-16 following administration of the first dose, even though there is the expected kinetic decline in antibody titers, at the 18 month time point the titers are still in the same range as those observed in the efficacy study, meaning that these titers are expected to correlate with protection. Essentially the same is observed with respect to HPV-18: the same peak that is above the plateau level observed in HPV-007 and then a kinetic decline, but still within a range expected to correlate with protection.

One of the questions that might be raised in considering vaccination of women over 25 years of age regards whether with maturation or aging of the genital tract there may be differences in the ability of antibodies elicited in the serum to transudate into cervico-vaginal secretions. It has been shown in previous studies that antibodies elicited by virus-like particles (VLP) based vaccines can be detected in cervico-vaginal secretions and it is thought that this is a process that occurs by transudation. As part of the HPV-014, cervico-vaginal secretions were collected in a subset of the women to examine the correlation between serum and cervico-vaginal antibody levels. This was done in an age stratified manner. Excellent correlation, with very high correlation coefficients, was observed between serum and cervico-vaginal antibody levels in women ages 15 to 55 years. There is essentially a linear correlation for both HPV-16 and 18, showing that the higher the serum titer that is induced, the higher cervico-vaginal antibody titer that is induced. Importantly, no differences were observed in this correlation across the different age strata.

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Vaccine safety is a very important part of assessment with respect to whether vaccination should be considered in women over 25 years. As noted, an interim safety analysis was conducted in the HPV-015 study, which included about 2000 women. The safety profile observed in this study is quite similar to that observed and published in women 15-25 years of age. Higher rates of local injection site symptoms (e.g., pain, redness, swelling) are observed in women over 25 years than in the control group. However, most adverse events are of low grade intensity and are transient. No difference has been observed between the HPV vaccine group and the control group in compliance with completion of the 3-dose series, nor have any differences been observed in the two groups in rates of important safety outcomes, such as unsolicited adverse events; new onset of chronic diseases (including autoimmune diseases); medically significant events defined as events prompting physician or emergency room visits; or serious adverse events.

Dr. Dubin concluded that GSK believes that vaccination of adult women represents an unmet medical need. Most women have not previously infected with both vaccine types and, therefore, would potentially benefit from protection. An important consideration is the observation that previous infection does not appear to provide a significant level of protection against re-infection with the same type. The GSK HPV candidate vaccine is well tolerated and highly immunogenic in this age range. It is expected to protect women over 25 years of age based on the observation of 100% seroconversion to both HPV-16/18 in all women, and the observation that antibody solicited in all of the women for HPV-16 and 18 GMTs were elicited in a range that correlates with protection in the HPV-001/007 efficacy studies. Confirmatory efficacy data from the efficacy phase of the HPV-015 study are expected to be available in the near future.

Quadrivalent HPV Vaccine: End of Study Results in Adult Women

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Clinical Research
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Merck Research Laboratories

Dr. Haupt reviewed the End of Study data from Merck's clinical program in 16-26 year-old women. The group that defines the prophylactic efficacy of the vaccine is the group of women who are naïve to the relevant vaccine type at baseline, by both HPV DNA presence and serology. This constitutes the prophylactic efficacy group. Women in the trials were enrolled, randomized, and vaccinated regardless of their baseline vaccine type HPV status. Thus, there are three different groups of women who were already exposed to HPV at the time of vaccination. In addition, Dr. Haupt presented the results of the analysis of the impact of GARDASIL® on these populations. His discussion focused primarily on data from Merck's adult women clinical program, an overview of the study and baseline demographics, and a presentation of efficacy and safety results from women 24-45 years of age. In addition, he provided epidemiologic data from Merck's trial to help inform the committee as they deliberated on the possible implementation of GARDASIL® in 24-45 year-old women.

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With regard to the End of Study results for the 16-26 year-old population, Dr. Haupt discussed the prophylactic efficacy of GARDASIL® on CIN and AIS and prophylactic efficacy of GARDASIL® on external genital lesions. This study combines one smaller Phase IIB study of P007 and the two Phase III studies P013 and P015. Per-protocol efficacy population analysis, these women were naïve by HPV DNA and serology to the relevant vaccine HPV type at baseline, remained negative through the completion of the vaccine series (3 doses), and completed all 3 doses within a year. There were no protocol violators. Case counting began one month after the 3rd dose. The mean follow-up is approximately 44 months. These studies were originally planned to be 48 months, but were ended early on the advice of Merck's DSMB when the data were unblinded in the fall of 2005 and showed strong enough in support of efficacy and safety to offer vaccine to placebo recipients. Hence, there is a mean follow-up of 44 months because some women completed the 48 month follow-up and some did not reach that point. With regard to the composite endpoint (e.g., HPV 6/11/16/18-related CIN or AIS), there were 9 cases in the GARDASIL® group at the end of study and 225 cases in the placebo group, with an efficacy of 95%. Regardless of how the data are examined, stratified by type or disease severity, the efficacy estimates are very high with tight confidence intervals. The confidence intervals became narrower as these endpoints were followed over time. At the end of study confidence intervals for the combined 6,11,16,18 CIN or AIS endpoint was 92-98%. With respect to external genital lesion endpoints (e.g., genital warts, and vulvar and vaginal dysplastic lesions of any grade) once again, the efficacy estimates were very high against disease states or by type at 99-100% across all disease endpoints, with very tight confidence intervals.

With respect to efficacy against HPV 6,11,16,18-related disease by baseline serostatus and PCR Status, Merck investigators analyzed the efficacy in the 4 different groups of women based on their baseline DNA and serologic status, and included the 3 subsets that were previously exposed to vaccine HPV types at baseline. At baseline, all women were tested for HPV DNA and serology for the 4 vaccine types. Without knowledge of these results, women were randomized to receive GARDASIL® or placebo. At the time of data unblinding for analysis, women could fall into one of four groups based on her baseline vaccine HPV status. 1) naïve by both PCR and serology to their relevant type – this population defined our prophylactic efficacy population.; 2) positive by both PCR and serology to the relevant vaccine HPV type – this population represents women infected by that respective vaccine HPV type for at least several months.; 3) previously exposed women who were PCR positive but seronegative at baseline – this is a mixed population of recently and chronically infected women; and 4) previously exposed women who were PCR negative and seropositive - this group developed immunological responses that "cleared" their infection to produce undetectable vaccine type HPV DNA at baseline.

The analysis for women in these previously exposed subgroups was performed using an MITT-2 approach as opposed to a PPE approach as shown earlier for the prophylactic efficacy results (MITT-2 is defined as being vaccine HPV type naïve at baseline, with case counting starting 30 days after dose 1). What was observed in the

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women in the fourth group (PCR -,SERO+) was a fairly substantial reduction in the event rates for that population in the placebo group, which was the lowest event rate in the placebo group of any of the four groups. Therefore, it appears that at least as measured by Merck's assay, women who have mounted a serological response do, in fact, have lower event rates compared to other populations of women who were previously exposed. However, the protection afforded from natural immunity is not perfect, given that women still develop HPV but at a lower rate. We have previously demonstrated that the vaccine boosts women who are seropositive at baseline. In fact, in the GARDASIL® recipients, there was 100% efficacy against disease in that group. The group which was PCR positive and seropositive at baseline consisted of women who had been infected for at least several months because it takes at least 6 months or more for most women to mount a serological response. In these women who are relatively chronically infected for several months, there appears to be no efficacy observed—either positive or negative. There has been some concern about whether the vaccine could have a negative impact on women who are chronically infected; however, no negative impact was observed at all.

Dr. Haupt concluded that prophylactic efficacy of GARDASIL® in 16- to 26-year-old women is high through year 4. Point estimates for efficacy against disease endpoints were close to 100%. Efficacy was also seen in the subset of 16-26 year-old women who were PCR negative and seropositive at baseline, while no efficacy (positive or negative) was seen in the subset of women PCR positive and seropositive at baseline.

The remainder of Dr. Haput's presentation focused on data and issues relative to the 24-45 year-old population of adult women. With regard to extending the efficacy in young adult women to adult women, it has already been demonstrated that administration of GARDASIL® is highly effective in preventing HPV 6/11/16/18-related cervical, vulvar, and vaginal disease in 16-26 year old females who have not yet been infected and who are vaccinated. Merck believes that immunogenicity alone is not an appropriate metric for evaluating efficacy in adult women, given that an immune correlate of efficacy has not been defined. In fact, very high efficacy thus far has precluded the determination of such a correlate of protection. Also known is that immunological response to vaccination declines with age in both women and men. Differently than conducting an immunobridging study in a 9-15 year old population who are not being exposed to HPV, 24-45 year old women are sexually active and can be exposed. Therefore, efficacy studies in adult women are feasible. An efficacy demonstration provides the requisite rigor to extend findings from young adult women to adult women. Efficacy against persistent infection and disease is sufficient.

With that in mind, Dr. Haupt shared results from a composite endpoint efficacy trial, P019, which extends the efficacy from what has already been demonstrated in young adult females to the adult woman population. This was a multi-center, international study in which 3819 24-45 year old women were enrolled from the US / EU (27%), Latin American (42%), an Asia (31%). Women were randomized 1:1 to a GARDASIL® vaccine or placebo group. They were also randomized in a 1:1 stratification in the two ten-year age groups (24-34 year olds and 35-45 year olds). The exclusion criteria were

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designed to exclude women with recent evolving disease. Different from Merck's younger women's trials, there was no exclusion based on the number of lifetime sex partners. This was designed and planned as a 48 month study with visits every 6 months. The current analysis was planned when a pre-specified number of case counts were reached, so this analysis represents a mean of 2.2 years since enrollment.

The study included two co-primary endpoints, which were: 1) combined incidence of persistent infection, CIN, or external genital lesions (EGLs) caused by HPV 6, 11, 16, or 18; and 2) combined incidence of persistent infection, CIN or EGLs caused by HPV 16 or 18. The secondary endpoint was combined incidence of persistent infection, CIN, or EGLs caused by HPV 6 or 11. There was also a tertiary endpoint of combined incidence of HPV 16/18-related abnormal pap test results (ASC-US HR+, LSIL, HSIL, AGC, cancer), which shows the potential benefit to the healthcare reduction that could be afforded in this population through vaccination.

With regard to baseline characteristics for sexual activity in the study population, the mean number of reported lifetime sex partners was 3.7. There were 3 women total who were not sexually active at enrollment, but with 1 in one group and 2 in the other, Dr. Haupt rounded it out to 100%. The reality is that in 0-2 there are 3 women. The vast majority of women were sexually active. Although an exclusion criterion was not stipulated with respect to lifetime sex partners, the majority of the study population reported 1-2 lifetime sex partners at enrollment, with about 23% of them reporting more than 4 lifetime sex partners. The range was quite extraordinary, with some woman who enrolled in the trial reporting well over 100 lifetime sex partners. In terms of baseline vaccine type HPV status at enrollment based on serology and PCR, 2/3 of all the women were naïve by HPV DNA and serology to all 4 vaccine types. To put that into perspective, approximately 3/4 of the 16-26 years olds were naïve by HPV DNA and serology to all 4 vaccine types. Certainly, more women were getting exposed to the vaccine types, but the vast majority of the women were naïve to all 4 types. Much like what was observed in the 16-26 year old women, the majority of those who were infected were infected to only one type, which leaves a lot of opportunity to prevent other vaccine types from being acquired. Of the 24-45 year olds who were positive, most were positive to only one type (about 25%). Importantly, less than 2% of all women were positive to types 16 and 18, which are the women who would derive no benefit from the cancer prevention offered by GARDASIL®. Thus, 98% of women would derive some benefit from protection against at least 16 or 18.

Turning to the vaccine efficacy results in adult women 24-45 years old, Dr. Haupt reiterated that the endpoints were composite endpoints of persistent infection and disease. This was a per-protocol population analysis as discussed earlier (e.g., efficacy after 3 doses in women naïve to the relevant type at baseline), with a mean follow-up at 2.2 years in a planned 48 month study period. Efficacy was found to be 91% for 6/11/16/18-related infection / disease, which was statistically significant. This was also stratified by the two age strata and the efficacy was not different in those two strata, although the event rates in the older ten-year stratum were somewhat lower. Efficacy was observed to be 83% for 16/18-related infection / disease, which was statistically

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significant, and there was no difference in efficacy by the two age strata. Efficacy was found to be 100% against 6/11-related endpoints, with no difference across the two age groups.

This study is powered to evaluate composite endpoints of persistent infection and disease. It is not powered to look specifically at disease, but at the request of the HPV Working Group Dr. Haupt stratified the data by just the disease endpoints. Therefore, although at this point in the study time period, there are more persistent infection endpoints than disease endpoints, at the end of the 4-year study there are likely to be many more disease endpoints to evaluate. Nevertheless, even early on, substantial efficacy was observed by looking only at disease endpoints, with 92% efficacy against 6/11- 16/18-related CIN or EGL. Regarding the tertiary endpoint (e.g., the efficacy of GARDASIL® at reducing HPV 16/18-related pap abnormalities in women who were negative to 16 or 18 at baseline), the efficacy was very high. This offers a sense of the potential healthcare reduction that is likely to be observed as the result of vaccination in 24-45 year olds, which has already been demonstrated in the 16-26 year old population.

Concerning the safety analysis in the 24-45 year old population, there were very few serious adverse events leading to a physician visit or hospitalization, and none were attributed by the study investigators to be vaccine related. Nor did the serious adverse events differ between the GARDASIL® and placebo group. What is observed in the GARDASIL® in this population is exactly what was observed in the 16-26 year old population, which is that the vaccine hurts at the injection site, so a higher percentage of women experience pain, swelling, and redness at the injection site. Local injection site reactions rarely led to study discontinuation.

While a population benefit analysis is planned in the 24-45 year old age group at the end of study, epidemiologic factors and subject characteristics from the P019 clinical trial, as well as the published literature, can be used now to help define which women may benefit from vaccination. Dr. Haupt suggested that the population benefit for vaccinating 24-45 year olds is a balance between susceptibility to vaccine HPV types and the likelihood of acquiring new infections / disease from those same vaccine HPV types. With this concept in mind, he discussed data that helps to define the susceptibility of the 24-45 year-old population (defined by HPV DNA PCR testing and HPV seropositivity at baseline); provided data on the rate of acquisition of new infections from the placebo arm of P019 that helps to define the likelihood of becoming infected with vaccine HPV types; and showed the association of different subject characteristics to the rates of prevalent and incident infection.

Regarding HPV DNA prevalence to help define susceptibility, the published literature on DNA prevalence has typically looked at high- and low-risk groups and has not stratified by different types. There are limited data on vaccine type specific DNA prevalence in this age group, especially in the US general population. Where vaccine type DNA prevalence exists, it is primarily available for types 16 and 18. Based on a summary of the literature, roughly stratified by the two10-year age strata and largely from several European countries and Costa Rica, the prevalence rates for types 16 and 18 are

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higher in the younger ten-year age group (24-34 years), but low overall. Prevalence rates from P019 are similar compared to the published literature. P019 found that 6.1% of the 24-34 year old women and 2.8% of the 35-45 year old women were positive to type16, while 2.5% of the 24-34 year-olds and 1.6% of the 35-45 year olds were positive to type 18 at baseline across the entire population at enrollment. While data are limited, the bottom line is that the numbers are fairly low for point prevalence and they are higher in the younger age strata than the older age strata.

Susceptibility as defined by seroprevalence may be a more accurate measure of susceptibility because it is a closer approximation to cumulative HPV exposure. However, it may still be an underestimate of cumulative exposure because not all infected women mount a measurable serological response. There is more data in the literature in this age group using seroprevalence studies. As with the DNA prevalence, I have summarized the range of vaccine type specific seroprevalence data from the published literature by the 10-year age strata. The published data reflect quite a range of seroprevalence from 8-19%. A US National Health and Nutrition Examination Survey (NHANES) study published in 2002 showed a 17.8% seroprevalence for type 16 in 30-39 year-old women and a 23.9 % seroprevalence in 40-49 year-old women. In the literature review, the lower rates typically came from studies in Asia, which skewed the low range of a lot of the seroprevalence data. Also, the seroprevalence rates at baseline from P019 are in the mid-range of the published literature for both age groups. The seroprevalence rates are similar for both 10-year age groups. Based on the data from the Adult Women trial, we can conclude that even with correction for women who do not develop a serological response, the majority of women (e.g., approximately 75%) 24-45 years of age remain susceptible to vaccine HPV types.

Merck also looked at the association between different subject characteristics and the baseline prevalence of vaccine HPV types in an attempt to define populations that would have higher odds ratios of being infected with one or more vaccine HPV types. This analysis found that an increased number of lifetime sex partners was associated with higher HPV prevalence; an increased number of new sexual partners in the last 6 months was associated with higher HPV prevalence; and partner status other than first marriage was also associated with higher HPV prevalence.

In addition to susceptibility, the likelihood of acquiring new genital HPV infections contributes to defining which populations would derive value from vaccination. The incident and persistent infection rates in the placebo arm from the adult women study, stratified by the two 10-year age strata, was evaluated and compared to the placebo arm of young adult females from a sub-study of 16-26 year-olds that looked at infection rates (Protocol 012). The data demonstrate that the rates of new incident and persistent infections decline with increasing age. This likely represents the changes in sexual behavior over time. A MITT-2 population analysis of time to events of HPV 6/11/16/18-related persistent infection, CIN, and EGL by age group (after 1 dose) also showed that women 24-34 years of age have higher event rates for persistent infection and disease compared to the 35-45 year age group, representing the difference in rates of new

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infections / disease seen with age, perhaps due to changes in sexual behavior. The dramatic impact of GARDASIL® is demonstrated as well in the time-to-event graphs.

Similar to the earlier analysis of subject characteristics and baseline prevalence of HPV, Merck performed an analysis looking at the impact of the same baseline characteristics as predictors for new incident infections in the placebo arm. This analysis found that an increased number of lifetime sexual partners was associated with incident infections. In addition, an increased number of new sexual partners in last 6 months was more strongly associated with incident infections, as was partner status other than first marriage.

Thus, with respect to susceptibility and acquisition of infection, the majority of 24-45 year old women remain susceptible to vaccine HPV types. In addition, these women continue to acquire infections to vaccine HPV types. The incidence for vaccine type infections is inversely related to age. Very importantly, the subject characteristics that predict baseline HPV prevalence are the same subject characteristics that predict the likelihood of acquiring new infections. Thus, these characteristics cannot be used to define which population should or should not receive the vaccine because the ones who are eliminated based on prevalence are the same ones for whom there would be value in receiving the vaccine based on new infections.

In conclusion, Merck's studies have shown that prophylactic efficacy of GARDASIL® in 16-26 year old women is high through Year 4. Efficacy of GARDASIL® was also seen in the subset of 16-26 year-old women who were PCR negative and seropositive to vaccine HPV types at baseline. High prophylactic efficacy is also seen in 24-45 year old adult women. GARDASIL® is generally well-tolerated in adult women. Merck also presented epidemiologic data from the Adult Women clinical trial that provides key information which should help to inform the ACIP to arrive at the best population recommendation for the vaccine.

Epidemiology of HPV Infection in Older Women

Eileen Dunne, MD, MPH
Division of STD Prevention, CDC

Dr. Dunne presented information on the epidemiology of HPV infection with a focus on women older than 25. As a reminder of the natural history of HPV infection and development of cervical cancer, she first explained that most HPV infections are acquired soon after sexual initiation. Over 90% of these infections clear within 2 years, with most clearing in the first 6 months. Persistent infection with oncogenic HPV can lead to development of cervical cancer precursor lesions, or CIN 2/3. Persistent infection over decades can lead to cervical cancer. The US is fortunate to have a cervical cancer screening program through the use of pap tests and in some cases HPV testing to detect cervical lesions before they develop into cancer. These cervical cancer cases are due to a very small proportion of the total HPV infections that a woman may acquire over her lifetime. Concerning the cumulative incidence of any HPV infection

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among young college aged women by months after sexual initiation, Winer and colleagues showed that by 4 years, over 50% of these young women had acquired infection with any HPV type. A small proportion of HPV infections acquired will persist. Cumulative incidence of any HPV infection is greater than 80% by 50 years, and lower for HPV 6, 11, 16, 18. Most of these infections are acquired at younger ages. Persistent infection with oncogenic HPV types is the most important predictor of cervical pre-cancers, and cancers.

Prior to sharing data on prevalence and incidence of HPV infection with a focus on older women, Dr. Dunne outlined some of the challenges in describing the epidemiology of HPV infection. The dynamics of HPV acquisition, clearance, and persistence are complex. Prevalent infection reflects acquisition and duration of infection. Although prevalence is often high in young women, likely representing high acquisition, most infections clear and do not lead to disease. Prevalence of HPV decreases with age, reflecting for the most part, decreased acquisition. When prevalent infection is detected in older women, infection is likely to indicate persistent infection rather than newly acquired infections. As a reminder, many of these persistent infections detected at older ages have been acquired years earlier. Infection with multiple types commonly occurs, so a woman may acquire one or more types at one time, clear infections, and acquire others later.

While there are evaluations of incident infection among young women who are newly sexually active, there are few evaluations of incident infections in older women. Evaluations of incident infection are less feasible because they require intensive study of longitudinal cohorts of women, none of which are available for older women in the US. In the available cohort studies of older women outside the US, when “incident” infection is detected it is difficult to ascertain what is re-infection, new (first time) infection, or reactivation of previously acquired infection. Teasing apart the relative contribution of these to incident infection could inform questions concerning the prevention of these infections. to delineate which of these are occurring, an ideal study would follow women since first sexual activity, with data on exposure and HPV infection; however, these studies are unavailable. It is likely that incident infection in older women is a mixture of acquisition and re-activation and this may vary in different populations.

With regard to the prevalence and incidence of HPV infection, focusing on women older that 25 in the US, HPV prevalence peaks in the 20s and tends to decline with age. Smaller secondary peaks in prevalence among older women have been observed for unclear reasons in some geographic regions. A variety of sexual behaviors are risk factors for prevalent and incident HPV infection, including lifetime sex partners and recent sexual partners. In terms of prevalence of any HPV by age in females, NHANES data from 2003-2004 demonstrated that HPV infection peaks in the early 20s and declines with age. Reflected in these data were that the prevalence of any HPV was 45% in the 20-24 year old age group and a lower proportion of infections were due to HPV 6, 11, 16 or 18. Regarding the prevalence of high-risk or oncogenic HPV types and low-risk or non-oncogenic HPV types by age group, 2003-2004 NHANES data demonstrated that the highest prevalence of both types occurs in the 20-24 year olds

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and that low risk types did not decrease as much as high risk types with age. In a study of the prevalence of HPV-16 by age in Guanacaste, Costa Rica, Castle et al. demonstrated that there is a decrease in HPV prevalence after the early 20s. However, unlike NHANES there was a slight increase in prevalence in women over 45 years old in the Guanacaste Cohort. The investigators of the Guanacaste study explored reasons for this slight increase in prevalence in older women, demonstrating that this was due primarily to previously acquired infections that were persistent rather than new acquisition.

HPV antibodies are a better measure of previous exposure to HPV then DNA prevalence, but antibodies do not develop in all women who have been exposed to HPV. Referring to a graph of seropositivity to HPV 16 and HPV 11 from NHANES with an under-representation of the % of women with previous infection to these types, Dr. Dunne pointed out the dramatic increase in HPV 16 seroprevalence among young women due to acquisition of infection. The seroprevalence to HPV 16 is as high as 25%, and seroprevalence to HPV 11 is as high as 8%. The decline in HPV 16 seroprevalence among women in their 50s could be due to waning antibody or a cohort effect.

Some of the best data on incident infection in older women are data from the clinical trials and cohorts outside the US. Data on incidence from the quadrivalent vaccine clinical trials in older women (presented to the ACIP earlier by Dr. Haupt of Merck) provide information on acquisition of vaccine-type infection during the trial. These data demonstrate that with increasing age, the incidence of infection with HPV 6, 11, 16 or 18 decreased from 7.4 infections per 100 person years in 24-29 year olds to 1.9 per 100 person years in the 40-45 year olds. A study by Munoz and colleagues of a longitudinal cohort of women attending cervical cancer screening centers in Bogotá, Colombia similarly demonstrates decreased incidence with age of infection with HPV 16, 18, 6 or 11. In the Bogotá study, the highest rate of infections occurred among the women in their late teens and early 20s and decreased with age. There is some evidence that a proportion of these infections are due to acquisition. Epidemiologic data from longitudinal cohorts suggest that new sex partners and marital status are associated with newly detected infections. In addition, sexual behavior data from the US can provide data on women who may be at greater risk of acquiring infection due to new sex partners [Munoz et al., *JID* 2004, Herrero, JID 2005; Sellors CMAJ 2002].

Referring to data on sexual behavior from the 2002 National Survey of Family Growth (NSFG) for women 25-45 years of age, Dr. Dunne reiterated that a proportion of women have sex behaviors, such as number of new sex partners, which may lead to acquisition of HPV. In this study, the mean number of lifetime sex partners for women 25-45 years of in the US was 3.8. Most women ages 25-44 years had 1 partner in the past 12 months, but 7-10% of women had more than one partner. Divorced or separated women had a higher percentage of sex partners in the last 12 months. A 2006 National Center for Health Statistics Report (NCHS) by Mosher and colleagues examined sex partners in the past 12 months by age, demonstrating that most women had one partner. A much smaller percentage of women had more than 1 partner (between

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7-15 %). This proportion decreased with age. According to an NSFG data analyses by Leichliter from 2008 (unpublished), almost a quarter of women who are divorced or separated (21%) have had more than one sex partner in the past 12 months compared to 1.4% of married women and 13.8% of never married women.

In summary, HPV incidence declines with age. Although in the studies of incident infection in older women it is unclear whether infections detected are re-infections, reactivation of previous infections, or new infections, it is likely a mix of all of these. The natural history of incident infection in older women versus younger women is also unclear and questions remain regarding whether these incident infections significantly contribute to disease outcomes in older women.

Focusing on incident disease outcomes, such as CIN 2/3 and genital warts among women to frame the discussion around immunization of older women, Dr. Dunne stressed that it was important to remember that HPV infection precedes these disease outcomes by months for genital warts and usually by years for CIN 2/3. Based on an evaluation of Medstat health claims data from 2000 of genital wart diagnoses by age group [Insigna R, CID 2003], the peak in these diagnoses is in the early 20s. Studies have demonstrated that the average time between infection and wart diagnosis is about 3 months. Incident CIN 2/3 per 1000 enrolled women in a 1998 Kaiser Northwest study show a peak in these diagnoses is in the late 20s [Insigna RP, Am J Ob Gyn 2004]. The time between infection and CIN 2/3 is longer than for warts and is often years later.

In summary, among women in their mid 20s, with increasing age HPV prevalence decreases, HPV incidence decreases, and the likelihood of having already acquired HPV or HPV vaccine-type infection increases. Seroprevalence to HPV 16 is as high as ~25% for women in their mid 20s, although this underestimates the true exposure, or cumulative infection, to these HPV types because not all persons with infection develop antibodies. Disease outcomes, such as CIN 2/3 and genital warts, peak in women in their mid to late 20s. These diseases are preceded in months or years by HPV infection. There are questions that remain with respect to the natural history of incident infections in older women; it is not completely clear how these infections contribute to disease outcomes.

Cost-Effectiveness Studies

Harrell Chesson, PhD
NCHHSTP, CDC

Dr. Chesson reported on the cost-effectiveness of HPV vaccination in the US, with a focus on catch-up vaccination. There have been several published and on-going modeling efforts examining HPV vaccine cost-effectiveness. Previous cost-effectiveness presentations were made to the ACIP in February 2006 and June 2006 before the vote on the HPV quadrivalant vaccine. Since that time, additional studies have been conducted and there are now new cost-effectiveness estimates available that include age at vaccination and other vaccine benefits: cross-protection against

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other high-risk HPV types, prevention of cancers other than cervical, and prevention of recurrent respiratory papillomatosis (RRP). Dr. Chesson summarized cost effectiveness estimates, focusing on routine vaccination of 12-year-old girls as well as vaccination of older females (defined as everyone over 12 years old).

Health outcomes included in cost-effectiveness estimates in this review focused on CIN 1-3, cervical cancer, and genital warts (quadrivalent vaccine only). All modeling efforts in this review examine the cost-effectiveness of adding HPV vaccination of females to an existing cervical cancer screening program; that is, the studies estimate the number of cases of these outcomes averted, combine them into a common measure, and then estimate how much it costs to gain quality adjusted life years (QALYs). All of the modeling in this review focused on female vaccination and examined the cost-effectiveness of adding female vaccination to an existing cervical cancer screening program. Except where otherwise noted, the vaccine benefits excluded were prevention of cancers other than cervical (e.g., anal, vaginal, vulvar, oropharyngeal, et cetera); prevention of RRP; and cross-protection (e.g., protection against high-risk HPV types other than 16,18).

With regard to routine vaccination of 12 year old girls, referring to a summary of published US studies looking at the cost-effectiveness of vaccination in the context of current cervical cancer screening, Dr. Chesson explained that for each study, the cost of the vaccine assumed in the study was shown followed by one or more cost-effectiveness estimates. The cost-effectiveness estimates were grouped depending upon whether the vaccine was assumed to protect against HPV 16/18 or whether it was assumed to protect against the four vaccine types 6/11/16/18. The estimates could also be grouped by whether indirect effects (herd immunity) were included in the estimates. Those studies that included indirect effects were: Taira et al., 2004 for HPV 16/18; Elbasha et al., 2007 for HPV 16/18 and 6/11/16/18; and Chesson et al., 2008 for HPV 16/18 and 6/11/16/18. When indirect effects were not included for HPV 16/18, the cost-effectiveness ranged from $14,700 to $24,300. When indirect effects were included, the costs per QALY estimates ranged from $10,200 to $14,600. Looking at the quadrivalant vaccine, when excluding indirect effects, the cost-effectiveness was estimated at $10,300. When including indirect effects, the estimates ranged from $3,000 to $5,300 per QALY gained. Thus, vaccination for 12 year old girls appears to be cost-effective by most usual standards, ranging from $3,000 to $24,000 per QALY gained. All things being equal, the vaccine appeared to be more cost-effective when including protection against HPV 6/11 and indirect effects (e.g., herd immunity). Also important to note is that there was general consistency in the results across the range of different models used.

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Pertaining to vaccination of older females, the only published study known for the US beyond the age 15 years is by Elbasha and colleagues of Merck. They estimated that vaccinating females 12-24 years old would cost $4,700 per QALY gained compared to vaccinating 12-year-old girls only for a quadrivalent vaccine with lifetime duration of protection, including indirect effects. Although the published information is limited, there are several on-going studies that are examining the cost-effectiveness of vaccination in different age groups. The Merck model is an extension of the Elbasha et al., 2007 study. There is also a spreadsheet model that is an adaptation of the Chesson et al., 2008 published model, which is relatively simple compared to the other two models. There is also a model by Goldie and Kim of Harvard and colleagues, which is funded in part by CDC. Goldie and Kim used this model to examine vaccination in other countries and are now applying it to the US. While other efforts are in progress, there are preliminary estimates for these three studies.

The Merck model is a dynamic transmission model that assumes a $360 cost per vaccine series with lifelong protection. Vaccine efficacy with 3 doses was assumed to be 90% against infection with HPV 6/11/16/18, 95.2% against CIN, and 98.9% against genital warts. The penetration rate is defined as the annual rate of vaccination among those not previously vaccinated. The annual penetration rates with 3 doses of vaccine accounting for compliance by age are: 12 years: 39% (which increases linearly to 39% over the first five years of vaccination); 12-19 years: 20%; 20-29 years: 11%; and 30-44 years: 3%. With regard to compliance, the investigators assumed that 75% of those receiving the first dose received the second dose and that 75% of those receiving the second dose received a third dose. Health outcomes included CIN, cervical cancer, and genital warts, including the prevention of genital warts in males as a result of female vaccination. The cost per QALY of each given strategy is the incremental cost-effectiveness ratio of the given strategy when compared to the preceding strategy. All strategies include cervical cancer screening. Under these assumptions, the cost per QALY gained for 12-23 year olds was $8,600; for 12-29 year olds $46,400; for 12-34 year olds $103,600; for 12-39 year olds $156,400; and for 12-44 year olds $225,300. Thus, as the cutoff age of vaccination increased, the incremental cost per QALY increased as well.

The spreadsheet model is an incidence-based cohort model, which estimates the potential benefit of HPV vaccination based on the current burden of HPV-related disease in the US. This model also assumed a $360 per vaccine series with lifelong duration of vaccine protection and 100% vaccine efficacy. It was assumed that there would be no type-specific benefit to persons exposed to a given HPV vaccine type prior to vaccination. Indirect effects (e.g., herd immunity) were excluded; therefore, assumptions about coverage are not particularly important. Health outcomes included CIN, cervical cancer, and genital warts. This model suggested that the cost per QALY gained of vaccinating 12 year olds compared to no vaccination would be $8,600. Including a catch-up vaccination up to age 18 would cost $10,900 per QALY gained. As the cutoff age of vaccination was increased to 34 years old, the cost per QALY increased as well to $226,100. Not only does the cost per QALY increase as age at vaccination increases, but also it seems to increase at an increasing rate.

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The Goldie / Kim model is a dynamic HPV transmission model combined with an individual-based model of the natural history of HPV. They assumed a vaccine cost of $500 per series based on $360 for 3 doses plus office visit, administration, and patient time. Duration of vaccine protection was assumed to be lifelong and vaccine efficacy was assumed to be 100% among those without prior history of type-specific infection in the base case analysis. With regard to coverage, routine vaccination in pre-adolescents was assumed to be 25% in Year 1 and 75% by Year 5. Coverage in older ages (catch up) was assumed to be 25% per year. The cervical cancer screening rates based on conventional and liquid-based cytology were assumed to be: 53% annual, 17% biennial, 11% triennial, 15% five-year, and 5% never screened. Health outcomes included CIN and cervical cancer and in some analyses, genital warts and juvenile-onset RRP. When they focused on CIN and cervical cancer only, they estimated that vaccination of 11-12 year olds compared to no vaccination would cost less than $50,000 per QALY; in 11-18 year olds < $100,000; in 11-21 year olds > $110,000; and in 11-26 year olds > $150,000. These results are preliminary, so these are shown in terms of ranges of estimates. As the other models found, as the cutoff age of vaccination was increased, the cost per QALY gained increased as well. When they included warts and RRP, as would be expected, the inclusion of additional benefits made the cost per QALY gained estimates more attractive: 11-12 year olds < $40,000 per QALY; 11-18 year olds < $90,000; 11-21 year olds > $100,000; and 11-26 year olds > $125,000.

To summarize, Dr. Chesson showed a summary table of these three studies reflecting the incremental cost per QALY gained by vaccinating older age groups (quadrivalent vaccine). The cost-effectiveness ratio for expanding vaccination to a given cutoff age shows the incremental cost per QALY gained compared to the nearest cutoff age above for which a cost-effectiveness ratio is provided. For example, the incremental cost-effectiveness ratio associated with increasing the cutoff age of vaccination from 24 to 29 is $46,400 in the Merck model. If $100,000 was used as an example of a threshold for cost-effectiveness, the Merck model suggests that this threshold would be reached at a cutoff age of vaccination of about 34 years; whereas, the spreadsheet model suggested this would occur somewhere around ages 26-29 and the Goldie / Kim model suggested that it would occur somewhere around age 21. These results are really quite different, although there are some reasons which account for this difference. For example, the Merck model includes prevention of genital warts in males as a result of vaccination of females and the other two models do not. The Goldie / Kim model assume $500 per vaccine series, while the other two models assume $360 per vaccine series.

In conclusion, it is known that routine HPV vaccination of 12-year-old girls is cost-effective by usual standards and these results were generally consistent across a range of models. The models also suggest that vaccination becomes less cost-effective as age at vaccination increases. The age at which vaccine is no longer “cost-effective” is ambiguous owing to the wide range of results across the different models. The reasons these models are so different is unclear at this time; however, the Merck team and Goldie / Kim team are collaborating to determine what accounts for these differences. It

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is also thought that some disparity in the model results would be expected, given the uncertainty of the natural history of HPV, as well as the different modeling assumptions and methods used to address this uncertainty.

Regarding next steps, the modeling of cost-effectiveness of vaccination by age will continue. Investigators hope to understand the differences in models and the results, and to determine the most plausible ranges for cost-effectiveness estimates by age. Modelers will also continue to examine the impact of including other vaccine benefits on vaccine cost-effectiveness, including cross protection, RRP, and other cancers. Although these were not addressed during this presentation, perhaps they can be addressed during a future ACIP meeting.

Consideration for Vaccine Recommendations among Women >26 Years of Age

Lauri Markowitz, MD
NCHHSTP/CDC

Dr. Markowitz reviewed the projected dates for a vote as outlined by Dr. Englund at the beginning of this session, following which she recapped the conclusions of the HPV presentations. With regard to the quadrivalent HPV vaccine in women 27-45 years of age, they heard that there is high efficacy for prevention of HPV 6,11,16,18 and related CIN or external genital lesions among those naïve to the respective HPV vaccine type. Moreover, the vaccine is generally well-tolerated. Key points demonstrated by the epidemiology and cost-effective analyses presented were that HPV acquisition occurs soon after sexual debut, and that HPV prevalence is highest in the US in 20-24 year olds. While infections occur in females >26 years of age, incidence decreases with increasing age. A variety of questions remain about some aspects of HPV natural history, particularly in older women. HPV vaccine is prophylactic and will have the greatest impact and will be most cost-effective when administered before exposure to HPV. Models show that cost-effectiveness of vaccination decreases with increasing age, although the age at which vaccine is not ”cost-effective” differs by model.

The current quadrivalent HPV vaccine recommendations in the US are routine vaccination of females 11-12 years olds, with catch-up vaccination for females 13-26 years of age. After reviewing a variety of data over the last couple of months, the working group has begun discussions on what should be recommended for women 27-45 years of age. The four possible recommendations that the working group has considered include: 1) Not recommended; 2) Permissive recommendation; 3) Targeted catch-up recommendation that would be behavior risk-based; and 4) Extend the catch-up recommendation to all or part of this age group.

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With respect to the first option not to recommend the quadrivalent HPV vaccine in women 27-45 years of age, some of the rationale is that there is a higher likelihood of prior infection and lower incidence in this age group. In addition, it is less cost-effective and there is secondary prevention for cervical cancer in this country that is recommended for this age group. There were a variety of concerns, which are outlined in subsequent options.

The rationale for a permissive recommendation of quadrivalent HPV vaccine for women 27-45 years of age is that some individuals could benefit from vaccination. However, there are concerns regarding whether insurance will cover the vaccine in this age group if there were a permissive recommendation, in which case, some women who could benefit would not be vaccinated. There also may be a lot of enthusiasm for the vaccine, which could result in its use in persons for whom there is little / no benefit.

There was some discussion of a risk-based targeted catch-up recommendation of quadrivalent HPV vaccine for women 27-45 years of age. but this recommendation was not pursued any further. The rationale for considering this option was that some individuals could benefit from vaccination. However, concerns were raised that the risk factors for prevalent infection and past exposure are similar to those associated with incident infection so it would be difficult to develop risk based recommendations for targeting persons who could benefit. In addition, it is very difficult to use sexual behavior criteria for a vaccination program. Furthermore, there are currently no clinically available tests to identify who has been infected or is immune to a specific HPV type.

The rationale behind the consideration to extend the catch-up recommendation in all or part of this age group is that some women could benefit from vaccine; however, it is difficult to target vaccination to specific risk groups. Also, a recommendation such as this could allow easier access to vaccine than a permissive recommendation. Concerns again regarded the likelihood of higher prior infection and lower incidence in this age group, as well as vaccine use in persons for whom there is little / no benefit. Additionally, such a recommendation could discourage pap testing and the cost per QALY may be very high in all or part of this age group.

The working group is still very early in their deliberations of recommendation considerations for quadrivalent HPV vaccine in 27-45 year old women. Some people thought that the group should wait for further data and for trials to be completed. The recommendation options still being considered by the working group include: Not recommended, permissive recommendation, and extension of the catch-up recommendation in all or part of this age group.

The HPV Vaccine Working Group's plans are to continue to develop recommendation options for women 27-45 years in preparation for a possible vote in June or October 2008. At the same time, the working group will continue to prepare for recommendations for the bivalent vaccine and will prepare for consideration of vaccine recommendations for males in 2009.

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Discussion

- Referring to Dr. Chesson's presentation of the three cost-effectiveness models, Dr. Lieu said that while the models and assumptions may be very high quality, she was troubled that the results were not presented in a way that would be most useful to the ACIP as the policy making body. For example, when the ACIP considers new policy recommendations, they want to see the cost-effectiveness analysis done incrementally. There is already a recommendation for vaccination of the 12-26 year old age group. Under consideration by the ACIP is vaccination of the 27-45 year olds. With that in mind, Dr. Lieu requested that the working group insist that the modelers of the on-going models provide information on the incremental cost-effectiveness of vaccination of the 27-45 year olds, given that that is the recommendation the ACIP will consider in either June or October 2008. She thought that by the way the tables presented were structured, it appeared that each time the older age groups were considered, the younger age groups were combined with them thereby giving an average cost per QALY. That is not the incremental approach needed.

- Dr. Chesson responded that the tables to which Dr. Lieu was referring did give the incremental costs per QALY. For example, the $46,400 estimate on the table titled "Cost-effectiveness of vaccination by age groups: Merck model results" pertains to vaccinating 12 to 29 year olds as compared to vaccinating 12-24 year olds only. Thus, it looks at the incremental cost effectiveness of adding 25, 26, 27, 28, and 29 year olds to the 12 – 24 year age group.

- Dr. Lieu thought the tables were unclear and that it would be helpful for ACIP to have the particular age range of 27-45 years.

- Dr. Chesson replied that his understanding was that the Merck model is fairly complicated and has to be grouped by age groups. It just happens that the 26 year olds fall in between their model's age groups. This is the closest approximation that they could offer looking at the incremental cost-effectiveness of the new recommendations.

- Dr. Cieslak noted that on one of the later slides, Dr. Chesson did show an age, cost, QALY curve that was continuous and ended up at $300,000.

- Dr. Chesson responded that that was from the simplified spreadsheet model in which it was very easy to look at as fine an age group as desired, even one year at a time.

- Dr. Judson raised the issue of safety of the vaccines compared to the placebos, given that he remained unclear regarding what Merck and GSK used as their placebos in terms of whether they were the adjuvants or everything that is in the vaccine minus the L1s. Adjuvants are often intended to be highly biologically active.

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- Dr. Haupt responded that the placebo Merck used in adult women is everything except the L1-VLPs, so it does include amorphous alumhydroxy (alum) sulfate. During the October 2007 ACIP meeting, Merck reported that they had done a saline comparison in one of their adolescent trials, in which approximately 50% of the local reactions were due to having a needle and solution inserted into the muscle, 25% are probably related to the aluminum, and 10% may be related to VLP.

- Dr. Dubin replied that in GSK's efficacy study conducted in 15-25 year olds, a licensed hepatitis A vaccine was used as a control, which they felt was an acceptable safety benchmark that also provided benefit to subjects. In the on-going study in women over 25 years of age, alum was used as a control which is the same dose of alum contained in the vaccine and in hepatitis B.

- Dr. Judson pointed out that when they were studying the hepatitis B vaccines and the earlier HIV vaccines, there was no question that the placebos were highly reactogenic. The only way they could say the vaccine was safe or not reactogenic was to compare it to reactogenic placebo. Related to the critical issue of what the endpoint is when doing cost-benefit, it was unclear whether CIN 1 should even be included because far more important is CIN 2/3. In the GSK data, the incidence of 16 and 18 are lumped together; however, beyond 26 or 27 years of age they are really not the same. It is known that the 16 accounts for 75% of the cervical cancer prevented, so if most of those infections in later ages tend to be 18 without a compensatory increase, there would be a much smaller fraction of preventable disease in those age groups.

- Dr. Dubin responded that the immunogenicity data he showed was stratified by age. In the efficacy study, the analyses will be done as a composite 16 and / or 18 endpoint and also for the individual types. GSK believes that the composite endpoint does give the best representation of the overall effect of the vaccine. It includes the 16 and the 18 endpoints, but of course, the individual stratified data must be examined as well.

- Dr. Pickering pointed out that one of the recommendations for the economic analysis presentation was for standardization to assist in the ACIP's understanding. Referring to Dr. Chesson's slide titled, "Summary: Incremental cost per QALY gained by vaccinating older age groups (quadrivalent vaccine)" includes all three models (e.g., Merck, Spreadsheet, Goldie / Kim). To follow up on Dr. Lieu's comments, the cutoff age for vaccination is given, but the initial age for beginning vaccination is not clear. Also stated is that the Merck model includes prevention of genital warts in males as a result of vaccination of females, but the table does not state whether this is true for the other two models. In addition, <$90,000 can be $10,000 or it can be $50,000 so it is also not clear what that means. With that in mind, Dr. Pickering suggested that it would be helpful if the tables were stand alone, ACIP members could interpret what they meant, and there was some clarification when trying to compare these studies.

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- Dr. Markowitz said the working group agreed and had struggled a lot with how to present the cost-effectiveness data and the models. They wanted to give the ACIP a sense of what the modeling data was currently showing in case there was going to be a vote in June 2008. The working group did not have access to the exact numbers for the Goldie / Kim model, given that these investigators were not comfortable with the working group presenting those. Hence, that is why the Goldie / Kim data are presented as they are. She stressed that the working group did not have control over the way the models are run and what goes into them, so they cannot actually standardize them. The best approach was to point out what the difference are between them.

- Given concerns expressed by some regarding use of the word "older" to describe those beyond the age of 12 in some cases, Dr. Schmader pointed out that the word "older" is used extensively in the scientific literature to describe people above the age of 60-65. to avoid confusion, it is perhaps preferable to use the phrase "women aged 27-45" and to eliminate the word "older."

Vaccine Safety Updates

Introduction

John Iskander, MD, MPH
CDC / OD / ISO / OCSO

Dr. Iskander reminded everyone that the FDA licensed combined measles, mumps, rubella, and varicella virus vaccine (MMRV), ProQuad®, in 2005 for use in children 12 months to 12 years of age. ACIP recommended use of MMRV in 2006 for the first and second dose for measles, mumps, rubella, and varicella vaccination. Pre-licensure studies on MMRV compared its safety with the safety of MMR and varicella vaccines administered separately at the same visit (referred to subsequently as MMR+V). Among children age 12–23 months, two systemic vaccine-related adverse events occurred at a significantly higher rate among MMRV recipients 5-12 days following vaccination: Fever (≥102F): 21.5% vs. 14.9%; and Measles-like rash: 3.0% vs. 2.1%. Fever and rash usually occurred within 5-12 days after vaccination, were of short duration, and resolved without complication (Shinefield et al PIDJ 2005).

There are also pre-existing post-licensure safety data on both MMR and varicella vaccine. It is known that MMR vaccine is associated with febrile seizures 8-14 days post-vaccination with an attributable risk of approximately 1 additional febrile seizure for every 3,000 to 4,000 doses administered (Barlow et al NEJM 2001). Varicella vaccine is not associated independently with an increased risk for febrile seizures, after adjusting for the concomitant administration of MMR (Black et al PIDJ 1999).

Dr. Iskander also expressed his gratitude to Drs. Klein and Marin for the use of some of their materials as part of the background.

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Overview of VSD Rapid Cycle Analysis (RCA)

Tracy Lieu, MD, MPH
ACIP Harvard Pilgrim Healthcare
For the CDC Vaccine Safety Datalink Investigators

Dr. Lieu presented an overview of the VSD Rapid Cycle Analysis (RCA) method, explaining that this is an approach which has been used over the past five years to enable early detection of vaccine adverse events. Early detection systems are needed for vaccine safety, given that rare adverse events may be impossible to detect in pre-licensure studies. Subsequent to licensure, reports to passive surveillance systems (e.g., the Vaccine Adverse Event Reporting System) often need rapid follow-up; however, follow-up studies can take months to years using traditional approaches.

The Vaccine Safety Datalink (VSD) Project provides the opportunity for early detection. The VSD is the nation's active surveillance system for vaccine safety, which consists of eight health plans that contribute data on more than 5.5 million persons annually. This represents about 1.9% of the United States (US) population. At the end of 2005, the population included 2.3 million children and 3.2 million adults, while the size of the annual birth cohort was 94,000. The eight VSD sites are geographically diverse and include: Group Health Cooperative, Northwest Kaiser Permanente, Northern California Kaiser Permanente, Southern California Kaiser Permanente, Kaiser Permanente Colorado, Health Partners, Marshfield Clinic, and Harvard Pilgrim.

The VSD data are derived from the computerized data available at these eight sites. The data include vaccination records; information on the dates and diagnoses of health outcomes that occur in the hospital, emergency department, and outpatient settings; and selected patient characteristics. These data are linked using a study ID that is unique to each individual and are kept at each of the VSD sites. While the data are accessible to CDC, they are not stored at CDC.

Rapid Cycle Analysis (RCA) is a relatively new approach to surveillance that takes advantage of VSD's strengths. The VSD now updates data on all vaccines and all outcomes every week. Rapid Cycle Analysis takes advantage of this, conducting updated analyses every week. There is on-going surveillance via Rapid Cycle Analysis of VSD Data for most of the new vaccines introduced in the past few years. Menactra® is monitored for Guillain-Barre syndrome; Rotateq® is monitored for intussusception, gastrointestinal bleeding, and other outcomes; MMRV and Tdap are monitored for seizures and other outcomes; and monitoring is in the process of being implemented for HPV and influenza. This work is the effort of many collaborators (e.g., investigators, epidemiologist, biostatisticians, and analysts) at CDC and throughout the eight VSD sites. The Coordinating Center includes CDC, Harvard, and Northern California Kaiser. Dr. Lieu extended special credit to James Baggs and Eric Weintraub of CDC for this system. Several years ago, they imagined the data structures that make rapid cycle

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analysis possible and they pushed the sites to implement these data structures. The result is the current ability to update and analyze the data on a weekly basis.

The basics of RCA are that for each vaccine, specific outcomes are chosen to be monitored. Thus, RCA is hypothesis testing, not data mining. Each week, the number of outcomes that have occurred in vaccinated persons are evaluated and this is compared to the expected number of outcomes based on a comparison group. Sequential analysis methods are utilized, meaning that each week, the analysis includes data from all previous weeks. However, this leads to a problem in that repeated testing of the same data increases the chance of false-positive results, which must be adjusted for statistically. The statistical solution to this is maximized sequential probability ratio testing (maxSPRT). This was a technique developed by the Harvard-based biostatistician, Martin Kulldorff, about four years ago. maxSPRT is a refinement of a classical statistical method first described by Wald in 1945. In maxSPRT, the null hypothesis is that there is no excess risk. The alternative hypothesis is that there is an increase in risk. The test statistic is the log likelihood ratio, which depends upon the observed versus the expected number of events.

To illustrate how maxSPRT works, Dr. Lieu shared an example of an analysis using data on Rotashield® vaccine and intussusception. Historical data were used from VSD sites. Rotashield® vaccine was licensed in August 1998. By July 1999, there had been 15 reports of intussusception to the Vaccine Adverse Event Reporting System (VAERS), the nation's passive surveillance system. The vaccine was suspended soon after this and was withdrawn a few months later. Referring to a graphic illustration [slide 13], Dr. Lieu explained that the Y axis showed the log likelihood ratio, which is the test statistic, and that the critical value of 3.3 meant that if the log likelihood ratio surpassed that value, this represented a signal—a statistically significant increase in risk. Hence, if this vaccine had been monitored using maxSPRT, the analysis would have signaled in May 1999, two months before the increase in risk was actually recognized in VAERS.

Setting up a rapid cycle analysis is straightforward at one level. First the outcomes to monitor for each vaccine are chosen. Subsequently, a comparison method is chosen (e.g., historical, concurrent, or both). The upper limit is then set for when to stop surveillance. Bearing in mind that RCA is hypothesis testing not data mining, only a few outcomes are selected based upon pre-licensure data, known biologic properties of the vaccine, and any early analyses available from VAERS. Additional criteria are then applied to narrow down which outcomes to monitor and those selected need to be clearly defined. For example, using "Guillain-Barre syndrome," a distinct clinical entity that receives a distinct code, is much more appropriate than using a broad, vague category such as "neurologic problems." In addition, the outcomes suitable for monitoring need to be acute-onset, biologically plausible, and relatively uncommon. The reason for choosing relatively uncommon adverse events is that the common adverse events usually will have already been identified in pre-licensure trials. Extensive preliminary testing is also done of the sets of ICD-9 codes that are used to select the codes that best match the actual clinical outcomes being evaluated.

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Two different comparison methods have been used for RCA: historical and concurrent. The historical comparison method uses incidence rates from historical data. The advantage of this method is that knowing the historical rate of rare events allows earlier recognition that a small number of cases may be unusual. For example, if 4 cases of Guillain-Barre syndrome occur very early in vaccinees, while 0 were expected, this can be identified as a signal very early. A limitation of the historical comparison method is that background rates may vary over time, so this method can be prone to bias from secular trends in coding. The concurrent comparison method uses matched controls (e.g., patients making preventive visits who are not receiving the vaccine of interest). The advantage of this method is that it avoids false signaling or missed signals due to secular trends. The limitations of the concurrent comparison method are that it is often not simple to define an appropriate control group and vaccines may be adopted rapidly, leaving few controls available for the comparison group. In the VSD's current RCA, the controls for Menactra® are teens making preventive visits; the controls for Rotateq® are infants who received any other vaccine other than Rotateq®; for MMRV the controls are toddlers who received MMR or MMR+V; the controls for Tdap are teens who received Td; and for HPV the controls will be female teens and 18-26 year old females with preventive visits.

RCA methods detect signals, which are values above the specified statistical thresholds, meaning that they are above chance events. Because this is a surveillance method, it is important to remember that not all signals represent a true increase in risk. When a signal occurs, a series of evaluations are conducted using traditional epidemiologic methods. First, data quality is checked because sometimes there is an issue with data quality which, when adjusted causes the signal to vanish. Also checked is whether the comparison groups are defined appropriately. If comparison groups are not truly comparable to the vaccinated group, this could create bias and a false signal, and another comparison group must be found. If the signal remains present after these checks, the analysis is conducted using a different control group. For example, if the signal first appeared and an historical control was used, an analysis is conducted using a concurrent control group as a cross-check. An analysis can also be done using a different vaccine. If a different vaccine results in the same signal, this tends to point to some type of bias as the explanation for the initial signal. A temporal scan analysis is then conducted to determine whether the potential adverse outcome clusters during a post-vaccination time window following vaccination. If the outcome clusters, this tends to be evidence that there may be some biological mechanism at work. Finally, a definitive study is conducted using logistic regression analysis. In the definitive study in general, charts are reviewed to confirm or exclude cases as true cases of the outcome of interest.

To illustrate how careful evaluations of signals are, Dr. Lieu shared an example of a signal that turned out to be false. Rotateq® was being monitored for gastrointestinal (GI) bleeding. The primary analysis used the historical-comparison method. In November 2006, 6 GI bleeding diagnoses had occurred among 3,400 vaccine recipients as compared with 1.3 that would have been expected from the historical incidence rate. This had a relative risk of 4.7 and the log likelihood ratio was 4.6, which was a

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statistically significant signal. Upon careful examination, it was discovered that the historical incidence rate had not been adjusted for age and secular trend. Once the historical incidence rate was adjusted in the appropriate manner, the signal disappeared. By February 2007, 36 GI bleeding diagnoses had occurred among 27,000 vaccine recipients as compared with 18 that would have been expected from the historical incidence rate. The relative risk was 2.0 and the log likelihood ratio was 6.7, which again resulted in a signal. To evaluate this signal, a maxSPRT analysis was run comparing GI bleeding in recipients of other vaccines who had not received Rotateq® with the historical incidence rates. The signal remained, which led investigators to believe that the problem was not the Rotateq® vaccine, but was instead the historical incidence rates. Subsequently, a maxSPRT analysis was run comparing Rotateq® recipients with a concurrent comparison group of children who had received other vaccines and there was no signal. This was further reassurance that Rotateq® did not result in increased risk. Finally, a definitive analysis was done, which was a logistic regression comparing Rotateq® recipients with the concurrent comparison group. Again, there was no signal. Age, seasonality, and VSD site were associated with the likelihood of a GI bleeding code, but Rotateq® exposure was not. The conclusion of this signal evaluation was that there was no true increase in risk of GI bleeding after Rotateq®.

The context of this story is that the evidence is very carefully examined when signals are found as the result of RCA. This method has been validated, but it is relatively new. The outcomes to be studied need to be chosen thoughtfully to ensure hypothesis testing and not data mining. As noted, signals do not always represent true increases in risk. When a signal occurs, traditional epidemiologic studies must be used to provide more definitive answers. With respect to next steps, VSD plans to implement surveillance using RCA whenever a new vaccine is introduced. The statistical methods have been described in recent publications, and a protocol is in place for evaluating signals. Moreover, findings will be communicated to ACIP and other key groups on a routine basis.

RCA Results for Measles Mumps Rubella Varicella Vaccine (ProQuad)

Nicola Klein, MD, PhD
Northern California Kaiser Permanente for the
CDC VSD Investigators and MMRV RCA Team

Dr. Klein presented preliminary findings from the VSD project, which is evaluating risk for seizures after MMRV vaccine. As mentioned earlier, the combination MMRV was licensed by the FDA in 2005 for use in children 12 months to 12 years of age, and ACIP recommended its use in 2006. Febrile seizures and measles-containing vaccines have been previously associated with febrile seizures 8-14 days post-vaccination. MMR has been associated with 1 additional febrile seizure for every 3,000 to 4,000 doses administered. Pre-licensure studies found higher rates of fever and measles-like rash 5–12 days after MMRV vaccination compared with separate, same-day administered MMR and varicella vaccination in children aged 12–23 months (Shinefield, *PIDJ* 2005).

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The MMRV RCA study includes children aged 12-23 months and monitors for six outcomes (e.g., allergic reactions, arthritis, ataxia, meningitis and encephalitis, seizures, and thrombocytopenia). The post-vaccination observation window is 42 days, which was chosen to enable monitoring for all six of the stated outcomes. Expected rates of seizures, ataxia, and allergic reactions were calculated based on historical rates among MMR recipients in the VSD who either did or did not receive concomitant varicella vaccine. Participating VSD sites include: Group Health Cooperative, Kaiser Colorado, Kaiser Northwest, Harvard Pilgrim Health Care, Health Partners, Northern California Kaiser and Marshfield Clinic. Specifically in regard to the MMRV RCA seizure outcome, "seizure" was defined as "the first instance coded by ICD-9 codes for epilepsy or convulsion in the emergency department or in the inpatient setting within a 42-day period." MMRV usage began in the VSD in January 2006. Data analysis began in late June 2007. As of January 2008, more than 60,000 doses have been administered.

The MMRV RCA study generated a seizure signal for the 42 days post-MMRV vaccine, which means that the number of observed seizures in the 42 day post-vaccination time window first exceeded the number expected, based on historical MMR recipients, by enough to justify a signal in the week of 2/11/07. Cumulative doses at that time were 25,779. Specifically, 50 seizures were observed post-MMRV. Based on historical rates the expected number of seizures was 38, which generated a relative risk of 1.57 and a log likelihood ratio of 5.17, which exceeded the pre-specified critical value of 4.12.

At this point, the investigators moved into the investigation and analytic phase by doing temporal scans and traditional regression analyses. Furthermore, they recognized that MMR recipients were probably not the most appropriate comparison group, so they chose to evaluate the comparison group of children receiving MMR and varicella vaccine at the same visit. Examining the temporal distribution of seizures following MMRV vaccination, between days 7 and 10 a sharp peak was observed in seizures following vaccination, which peaked at about 21 seizures. By comparison, looking at the temporal distribution of seizures after MMR vaccination and simultaneous varicella vaccination, a sharp peak was observed again between 7 to 10 days, which peaked at 15 seizures. A secondary peak was observed between days 19 and 26 that was identified on the secondary scan. With regard to the temporal distribution of seizures after MMR vaccination without varicella vaccination, a peak was observed between days 6 to 10, peaking at 3 seizures. In the temporal distribution of seizures after varicella vaccination without MMR, no peak was observed at 7 to 10 days, although there is some clustering between days 21 to 24. When the statistics were done on each of these graphs to determine what the most likely clusters were, in the temporal scan results on seizures in the 42 days after vaccination, both MMRV and MMR and separate same day varicella vaccine had highly significant clusters from days 7 to 10. MMR without varicella had significant clusters from days 6 to 10; whereas, for varicella this was seen at about day 21.

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With this information in hand, the subsequent analyses were focused on the 7 to 10 day post-vaccination window. Putting this all together from the temporal scan statistics and looking at the 7 to 10 day window, the unadjusted rates for seizures of any etiology were 9.6/10,000 for MMRV; 4.9/10,000 for MMR + V; 3.5/10,000 for MMR alone; and 1.5/10,000 for varicella alone. There are approximately twice as many seizures following MMRV as compared to MMR plus separate same day varicella vaccine, which is slightly more than is seen for MMR without varicella. Subsequently, a traditional logistic regression analysis was done to further evaluate the risk of seizure in the 7 to 10 days after MMRV compared to MMR plus separate varicella vaccine. The odds ratio was 2.0, with significant confidence intervals of 1.4-2.8. This analysis was adjusted for age and influenza season. Also found was that the association between MMRV and seizures was not influenced by sex, VSD site, concomitant vaccines, and / or seizure temporal trends.

Given the historical knowledge of the association between MMR and febrile seizures and the increase in fever following MMRV in this 5 to 12 day window, the question arose regarding whether these were febrile seizures. There was good reason to believe that they were febrile seizures when the investigators examined outpatient visits for fever by day after vaccine at Northern California Kaiser Permanente between 1995-2008. For MMRV vaccine, within days 7-11 a sharp peak was observed in outpatient clinic visits for febrile illness. A peak was also observed following MMR and separate same day varicella and following MMR alone, although these peaks were not as prominent. When the charts were examined for the cases that occurred between 7-10 days post-vaccination, the vast majority were febrile seizures (95% following MMRV and 94% following MMR + V). A logistic regression analysis was then conducted using chart-confirmed cases of febrile seizures in the 7-10 days post-vaccination period (comparison groups were children receiving MMRV vaccine vs. children receiving MMR and varicella vaccines at the same visit). This resulted in an odds ratio of 2.3, with significant confidence intervals of 1.6-3.2. Again, this is adjusted for age and influenza season.

To put this into a clinical context, consideration was given to what this actually meant for the risk difference in practice. Therefore, an attributable risk of 5.2/10,000 (95% CI 2.2, 8.1) was calculated for the 7-10 day post-vaccination window for MMRV compared to MMR and varicella vaccines. This means that for every 10,000 children who receive MMRV instead of separate MMR + varicella vaccines, there will be approximately 5 additional seizures 7-10 days after vaccination. Another way to think about this is to take the inverse of the above risk difference for MMRV compared to MMR + varicella vaccines in the 7-10 day window: 1,939 (95% CI 1,234, 4,516). What that means is that there will be approximately 1 additional seizure 7-10 days post-vaccination for every 2,000 children vaccinated with MMRV instead of MMR + varicella vaccine.

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Also of concern are the outcomes for children who have febrile seizures. Some of the chart review findings observed were that there was no difference between hospitalization for the febrile seizure event between children who receive MMRV and MMR + V. There were also no deaths within this window within either group, there was no difference in first seizure event between the two groups, and both had a low rate of positive family history of having seizures. However, data are missing for about 40% of the cases for both groups.

With regard to the risk for seizure of any etiology during the entire 42-day window following MMRV vaccine compared to separate same day varicella vaccine, a logistic regression analysis was conducted using the automated data and comparable comparison groups as shown in the earlier logistic regression. This analysis was also adjusted for age and influenza season. An attenuation of the odds ratio is seen, as would be expected given the increase in size of the vaccine window. The odds ratio was 1.32 and the confidence intervals were 1.05-1.64. The attributable risk for MMRV compared to MMR + varicella vaccines was 5.1/10,000 (95% CI 0.5, 9.7), which is very similar to what was observed in the 7-10 day window. Based on this analysis, it is not clear to what extent there are additional seizures occurring outside that window. However, finding from this analysis were more preliminary than the 7-10 findings and there are on-going investigations for the 42-day window.

As noted earlier, the MMRV RCA study is also monitoring for encephalitis and meningitis. As of January 2008, 2 cases of ICD-9 coded encephalitis had been reported in >60,000 MMRV doses administered. Both of these cases were among those being investigated for seizures and both occurred 7-10 days after MMRV in late 2006. With respect to the preliminary findings, the charts were reviewed for both cases and no etiology was identified for encephalitis for either case. Per their charts, both were diagnosed by a neurologist as having encephalitis. Case 1 was a febrile seizure case that occurred in December 2006. The clinical workup was negative (CSF: 1 WBC, 0 RBC, glucose 103, protein 135, neg for bacteria, viruses, and HSV PCR). Regarding the outcome as of February 2007, according to the neurologist, the child is largely back to baseline, was on some anti-seizure medications, and had possible mild developmental delay. However, the charts are limited for this child so it is not clear whether there was a pre-existing mild developmental delay. No further information was available. Case 2 was an afebrile seizure case that occurred in November 2006. An extensive clinical workup was negative, including laboratory investigation by the state. (CSF: 1 RBC, 1 WBC, glucose 53, protein 26, cultures neg). The child's outcome as of late 2007 was residual sequelae, including a seizure disorder and language delays. Dr. Klein emphasized that this is only two cases, and that monitoring for encephalitis and meningitis will continue via RCA.

The question has been raised concerning potential adverse events in older children who receive a second dose of MMRV. While the MMRV RCA study is monitoring children aged 12-23 months, post-vaccination seizures were examined among 4-6 year olds at the Northern California Kaiser Permanente VSD site. Within both the 42-day (9/35,185 MMRV; 19/68,915 MMR) and the 7-10 day (2/35,185 MMRV; 3/68,915 MMR) post-

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vaccination windows, there are no differences observed between MMRV and MMR group. However, there are very few cases in the 7-10 days post-vaccination for either group. Thus, there is very limited power to make conclusions from this information.

In summary, RCA surveillance detected a seizure signal following MMRV, clustering 7-10 days after vaccination in children aged 12-23 months. Chart review data confirmed that greater than 90% of seizures were febrile. The adjusted odds ratio is 2.3 for having a confirmed febrile seizure 7-10 days post-MMRV compared with separate same day MMR + varicella vaccine. Increased risk with MMRV cannot be explained by concomitant vaccines, temporal trends in seizure, VSD site, age, or influenza season. There was no difference in hospitalizations post-vaccination, or personal or family history of seizures between MMRV and MMR + varicella vaccine recipients. Attributable risk for seizures on days 7-10 after MMRV is 1 per 2000 doses when compared to separate MMR + varicella vaccines. RCA will continue to monitor for encephalitis. The VSD has limited power to assess risk of seizures after MMRV among older children receiving a second dose of MMRV vaccine.

Discussion

- Dr. Duchin (NACCHO) commented that it was good to see this type of scrutiny regarding the adverse event data. Noting that the critical cutoff for the log likelihood ratio seemed like a very important value, he requested further clarification and inquired as to whether this was objectively set.

- Dr. Klein responded that the critical cutoff is objectively set and is based on what would be expected and the observed value; that is, based on who the controls are determined to be and based on historical controls.

- Dr. Neuzil pointed out that this was a lot of information to digest, especially when seeing the data for the first time. For example, in the temporal scan results, the denominators and other information are not given. It would be beneficial to see incidence data and denominator data. In addition, she wondered whether there was a hypothesis considering whether there would be any difference in the children who receive MMRV as one vaccine or separately, given that this seemed to be the critical question. With that in mind, she also inquired as to whether anything was known about what vaccine options were available at each site: What did the HMO pay for? Were parents given an option? Is there anything that may have influenced the decision to give one child two different vaccines and one child a combination?

- Dr. Klein clarified that the temporal scan statistics were really comparing each graph within itself to determine what the most likely cluster is within each graph. The denominators for the temporal scan statistics as shown are also the denominators on the corresponding graph for that vaccine [slides 7-11]. That is, it is essentially looking at what the most likely cluster seems to be occurring not by chance alone within that graph compared to the other 42 days. With regard to the vaccine options available at each VSD site, certainly there are practice variations amongst the sites.

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Certainly, MMRV is used much more readily at some sites than others. However, the investigators are not able to determine whether individual level practice variations influenced the decision to give one child two different vaccines and one child a combination.

- Dr. Iskander added that not included in this analysis was the site of the Phase IV licensure safety study, some of the results from which would also be presented during this session. Usage of MMRV has specifically been monitored across all of the VSD sites; however, given the shortage situation, MMRV usage is relatively low at this time. His sense from having examined the data was that it was more a function of stock on hand, size of the patient population, etc.

- Dr. Lett requested further interpretation of the similar excess number of seizures observed in the groups when followed out to 42 days, and why fever after varicella vaccine alone was observed at approximately 21 days.

- Dr. Klein responded that one way to interpret the attributable risk in the 42-day window was that if the excess cases within the window were all due to the narrow time window of 7-10 days, one would not expect there to be an increase in attributable risk over and above what would be seen for the 7-10 window. On a cautionary note, she reiterated that the 42-day window was still being examined. With regard to varicella alone clustering at approximately 21 days, her understanding was that replication occurs closer to the two to three week range rather than the earlier timeframe. Thus, there is rationale for thinking that there may be associated fever at that time.

- Dr. Seward added that fever after varicella vaccine alone observed at approximately 21 days could be a chance finding. It is observed in the fever curves that the fever for varicella is low and falls within the time period that would be expected.

- Dr. Stinchfield expressed gratitude to the VSD team, pointing out how reassuring it was to be able to let parents know that vaccine delivery is being very closely monitored. She also noted the importance of keeping the incidence of febrile seizures in measles disease and in varicella disease in the clinical context.

- Dr. Iskander replied that while he did not have exact date on incidence of febrile seizures in measles or varicella disease, 14-18 months is the peak incidence for febrile seizures. Consistent with the data Dr. Klein presented, by age 4-6 the incidence is much lower.

- Dr. Morse noted that in examining concomitant vaccine, it appeared that consideration was given to whether children who received the combined vaccine may have received other vaccines simultaneously.

- Dr. Klein responded that they closely scrutinized the data pertaining to concomitant vaccinations. This was definitely of concern, especially with the change in

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recommendation between the use of MMR and varicella to MMRV and other vaccines such as hepatitis A, for which there were also changes in the recommendations at that time.

Phase IV Results for MMRV Vaccine

Patricia Saddier, MD PhD
Epidemiology Department
Merck Research Laboratories

Dr. Saddier reported interim results on febrile seizures from the ProQuad® (MMRV) post-licensure observational safety study. The MMRV vaccine is the combination of two vaccines: the MMR vaccine and the varicella vaccine. Merck developed this combination vaccine to simplify the immunization schedule. The rationale for the MMRV combination vaccines was that it would decrease the number of injections, increase vaccine compliance, and increase vaccine coverage rates. MMRV was identified by ACIP as a key component to successful implementation of the recommendation for a second dose of varicella vaccine. ProQuad®, Merck's MMRV vaccine, was introduced in the US in Fall 2005. ProQuad® supplies have been limited since June 2007 due to manufacturing issues unrelated to vaccine safety or efficacy.

As mentioned in earlier presentations, MMR is known to be associated with fever and febrile seizure. Referring to data from the M-M-R™ II trial conducted in 2001-2002 over a 42-day period, which included 1266 subjects vaccinated with a first dose of MMR in their second year of life, Dr. Saddier pointed out that fever occurred throughout the entire 42-day period due to the replication of the vaccine viruses and to other febrile illnesses that may have occurred during the duration of the trial. Fever was more common in the 5-12 days following vaccination.

Clinical trials of ProQuad® (MMRV) conducted in 12-23 month olds receiving their first dose have shown that fever and measles-like rash are the only systemic adverse events more frequent with MMRV than MMR+ V given at the same time. In the ProQuad® group, 45% of the fevers occurred in the 5-12 days post-vaccination. In the clinical trial, the number of febrile seizures observed was small, with 8/ 5,731 cases in days 5-12 and 13/ 5,731 cases in the overall 0-42 day time period. In the clinical trials, febrile seizures were lower in the ProQuad® group than in the MMR + V comparison group (5/1,997 cases in days 5-12 and 8/1,997 in the overall 0-42 day time period). Lower fever rates were observed after the second dose than after first dose. To complement the clinical trial data on febrile seizure as well as the general safety of ProQuad® in routine practice, a large-scale post-licensure observational study was designed with FDA input.

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Febrile illnesses are common in young children, and febrile seizures are the most common neurological event occurring in young children. Febrile seizures are observed during infectious diseases (e.g., roseola, otitis, pneumonia, measles, varicella) and following vaccines resulting in fever (e.g., DTaP, pneumo conjugate, MMR). Febrile seizures are typically of short duration generally lasting less than 15 minutes and resolve without sequelae. With respect to incidence, febrile seizures are primarily observed before 5 years of age with a peak incidence at approximately 18 months of age. By 5 years of age, 2-4% of children have had at least one febrile seizure. The background incidence of febrile seizures in the second year of life when ProQuad® is given is 1-2 /1000 children. The incidence of seizures is 0.6-0.7% in children with measles.

With regard to the pre-specified study objectives, the primary objective was febrile seizures occurring 5-12 days after first dose of ProQuad® in children 12-60 months of age. Other protocol time windows were pre-specified in the protocol and included 0-4 and 0-30 days. Febrile seizure in the 0-4 day time window was pre-specified in the protocol with the understanding that febrile seizures occurring in this time window were unlikely to be associated with MMR, MMRV, or varicella. Also anticipated was that concomitant vaccines known to be associated with febrile seizure in this time window may differ between the ProQuad® and the MMR + V comparison groups due to varying recommendations and varying availability of vaccines over time. A good example of that is the availability of Prevnar® over the last few years. The secondary objective of the study was a general safety evaluation of all children vaccinated between the ages of 12 months-12 years of age receiving ProQuad® as either the first or second dose of MMR and / or varicella and observed over a 30-day time period. In terms of the general safety evaluation, there was no suggestion of a safety signal in the interim analysis.

The post-licensure observational cohort study is conducted at Kaiser Permanente Southern California (KPSC). The original objective was to include over 25,000 children vaccinated with ProQuad® as a first dose between 12-60 months of age. To ensure that only MMR and varicella disease / vaccination negative children would be included, only children having a continuous membership between the age of 6 months and until 90-days post-vaccination are included in the main analysis. All study results were reviewed and interpreted by an external, independent Safety Review Committee (SRC) composed of a vaccine specialist, a pediatric neurologist, and a pharmacoepidemiologist.

To put rates of events observed in the ProQuad® group into perspective, several comparison groups were used. The primary comparison group consists of historical controls vaccinated concomitantly with MMR+V prior to the availability of ProQuad® on the market. These control children are individually matched on age, gender, date of vaccination, and dose sequence. Two other comparison groups are primarily for the general safety evaluation. These are the self-comparison periods classically used in vaccine safety studies in which children are used as their own controls. There is a post-vaccination self-comparison 60-90 days after MMRV and a pre-vaccination self-comparison period 30-60 days before MMRV.

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For the febrile seizure objective, febrile seizure cases were identified following a two-step procedure. First, all potential cases were identified from the automated medical record database. This included all children with a health care contact in outpatient, emergency room, or hospital setting within 30 days of vaccination, including at least one of the following ICD-9 diagnosis codes: 345.X (epilepsy); 780.3 (convulsion), 780.31 (febrile convulsion), 780.39 (other convulsion); 779.0 (neonatal seizures); and 333.2 (myoclonus). A wide net was cast to maximize the detection of potential cases. These potential cases are referred to as "unconfirmed seizures." The second step was to confirm the diagnosis of febrile seizure. A group of seizure experts designed an abstraction form to extract the relevant information from the medical record. They also established an operational definition for febrile seizure modeled after the Brighton Collaboration's definition. The medical records of all potential cases were reviewed and abstracted. This information was provided to an Adjudication Committee that is distinct from the study's external Safety Review Committee. The Adjudication Committee is composed of three Kaiser Permanente physicians unrelated to the rest of the study. They reviewed the information provided to them to confirm or not the diagnosis of febrile seizure based on a pre-specified procedure and having no knowledge of the vaccination status of the cases being reviewed. The adjudication process identified "confirmed febrile seizures."

Dr. Saddier reiterated that the main time periods of interest included: 1) 0-4 days post-vaccination, during which febrile seizures were likely unrelated to MMR, V, or MMRV, but possibly were related to concomitant vaccines; 2) 5-12 days, the main period of increased fever with MMRV and the primary period of interest for febrile seizures; and 3) 5-30 / 0-30, the period of viral replication for all four components (measles, mumps, rubella, varicella).

Regarding study progress, the study began in February 2006 when ProQuad® first became available at KPSC. Study accrual was completed June 30, 2007. There is a time lag of approximately 9 months between when a child is vaccinated and when all of the data are available in the database. This includes a 3-month follow-up period for the study and the need to wait for approximately 6 months to ensure that all of the health care received by a child during the study period is coded in the database, including care received outside the Kaiser system. An interim report was submitted to the FDA in December 2007, which included all children vaccinated with ProQuad® through the end of September 2006. For the final study report, consistent with the 9-month time lag, the database cutoff for final analysis will be March 31, 2008. Merck is on track for submission of the report to the FDA by December 2008.

In terms of the results of the study, the interim analysis on febrile seizures included 14,263 children vaccinate in 2006 with a first dose of ProQuad®. Of those, 99% were vaccinated in the second year of life. These children were of diverse ethnic backgrounds, and 51% were males. There were also 14,263 children in the comparison group who were vaccinated in 2005 with a first dose of MMR + V given at the same

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time. These children were individually matched to ProQuad® vacinees on age, gender, and date of vaccination.

With respect to review and adjudication of unconfirmed seizure cases, between the two groups 91 unconfirmed seizures were identified in the medical record database. Of those, 77 medical records were reviewed / adjudicated. Medical records were unavailable for 14 of these, given that they were in cases seen outside the Kaiser Permanente system for which parental authorization to retrieve the medical record could not be obtained. Of the 77 cases adjudicated, 33 were confirmed febrile seizures that occurred within 30 days of vaccination. This represents 43% of the 77 medical records available. In terms of how the cases were distributed between the two groups, in the 0-4 day period, there were more cases of unconfirmed seizures in the ProQuad® group (n=16) than in the comparison group (n=13). After adjudication, the numbers were the same in both groups with more cases of confirmed seizures in the ProQuad® group (n=4) than in the comparison group (n=5). It is important to note that all cases of confirmed febrile seizures also received a concomitant vaccine, including Prevnar® and / or DTaP. In the 5-12 day time period, there were more cases of unconfirmed (n=17) and confirmed (n=7) cases in the ProQuad® compared to the MMR+V group (unconfirmed n=11; confirmed n=3). For the longer term period of 0-30 or 5-30 days, there were fewer cases of confirmed febrile seizures in the ProQuad® group (0-30 n=14; 5-30 n=10) compared to the MMR+V group (0-30 n=19; 5-30 n=14).

Although no formal comparison was pre-specified in the protocol, the relative risk and attributable risk were included to facilitate the understanding of the results. In the 5-12 day time window, the 7 cases observed following ProQuad® compared to the 3 cases following MMR+V group translates into a relative risk of 2.3 with a wide confidence interval that is not statistically significant. The attributable risk, or risk difference, is 0.3/1000, which is not statistically significant. In the 0-30 or 5-30 day time period, the relative risk (0-30 0.7; 5-30 0.7) did not increase and the attributable risk is negative, meaning that there are no additional cases of febrile seizure in the ProQuad® group compared to the MMR+V group. Over the 30-day time window, more confirmed febrile seizures occur in the 5-12 day time period. Beyond day 12, there are actually more febrile seizures in the comparison group than in the ProQuad® group [Graph: Confirmed Febrile Seizures by Day of Onset].

A strength of the interim analysis is that MMR+V controls are closely matched to MMRV recipients. In addition, cases were adjudicated by an independent Adjudication Committee that utilized a medically accepted definition of “febrile seizure.” As a result, 43% (33/77) of potential cases with available medical records met the case definition for febrile seizures. This rigorous record review also showed that many outpatient codes actually represent past medical history of seizures or epilepsy rather than new seizure events. A limitation of the interim analysis is that the small numbers of cases precludes any firm conclusions. In addition, no adjustment was made for other factors, such as annual variability due to background febrile infectious diseases, or the use of concomitant vaccines. Also a limitation is that medical records were available for only 85% of the cases and the missing records were not completely balanced between the

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two groups, which may be important when dealing with small numbers (e.g., MMRV missing 6; MMR+V missing 8).

Dr. Saddier shared additional data received in the last couple of weeks from the investigator. Although these preliminary data on the entire study population are unvalidated and unadjudicated at this point, validated and adjudicated results are expected to be available by July-August 2008. The unvalidated, unadjudicated data show that in the 5-12 day time period, there are more cases of unconfirmed febrile seizures in the ProQuad® group (n=47) than in the MMR+V group (n=28). In the longer 5-30 day time period, there are also slightly more cases in the ProQuad® group (n=86) than in the MMR+V group (n=73). These numbers are preliminary and the unconfirmed numbers can still change until the end of March at which time the database will be locked for the main analysis. Moreover, these numbers are expected to change substantially after the adjudication process.

In summary, febrile seizures are included in the labels for ProQuad®, M-M-R™II, and VARIVAX®. The ProQuad® label has been updated to include interim study results on both the 5-12 and 0-30 day time periods. Interim validated results are available on ~14,000 of ~30,000 children vaccinated with a first dose of ProQuad® and followed for 30 days. These interim results showed that the number of adjudicated confirmed cases of febrile seizures is low; that there is an apparent increase in 5-12 day period with an attributable risk or risk difference of 0.3/1000 [95%CI: -0.2, 0.8]; and that there is no difference in the overall follow-up time period (e.g., 5-30 day period attributable risk: -0.3/1000 [95%CI: -1.0, 0.4]; 0-30 day period attributable risk: -0.4/1000 [95%CI: -1.2, 0.5]). That is, in both the 5-30 and 0-30 day time periods, the attributable risk is negative, meaning that there are no additional cases of febrile seizures in the ProQuad® group compared to the MMR+V group. The final febrile seizure analysis is expected to be available in July-August 2008, or earlier if possible. Approximately 30,000 MMRV recipients and approximately 30,000 MMR+V recipients will be included in the final analysis. The final analysis will provided validated and adjudicated results, which will be shared with FDA, CDC, and ACIP in a timely fashion. The final report, including the general safety component of the analysis, will be completed by the end of the year as per Merck's commitment to CBER. Merck will continue to collaborate with regulatory and public health authorities, and with medical and scientific experts on the interpretation of the febrile seizure data.

Discussion

- Dr. Morse requested further information regarding the amount of vaccine currently in circulation, as well as the ability to potentially examine other cohorts of children to acquire additional information.

- Barbara Kuter (Merck) responded that with regard to the availability of vaccine, the best estimate is that in the private sector in the month of January 2008, about 4% of doses of varicella containing vaccine were ProQuad®. The number of available doses is small and are expected to dwindle substantially over time.

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- With regard to the potential for examining other cohorts of children, Dr. Iskander replied that the target age group of 12-23 months in the VSD RCA represented about 50% overall of all of doses of ProQuad® used within 7 of the VSD sites. From January 2005 to January 2008 that totaled about 130,000 doses. The remaining 50% of ProQuad® is divided amongst all ages above 2 years old. Above age 7, there is very limited use. There will be extremely limited power in other age groups, as shown by Dr. Klein in the older age group.

- Dr. Lieu expressed appreciation to Merck for sharing these data with the ACIP. She thought those who had seen the data previously were struck by the fact that the relative risk observed in this study by Merck was 2.3, which was quite similar to the odds ratio observed in the VSD study. The VSD study had 43,000 doses of MMRV and over 300,000 doses of MMR+V. The Merck study is reporting on 14,000 doses of MMRV at this point. With that in mind, Dr. Lieu inquired as to how much power the analysis has to find that relative risk is statistically significant, and at the end of the study if there are 30,000 doses, how much power would be attained to find that relative risk, if it remains the same, is statistically significant.

- Dr. Saddier responded that the power on the interim analysis is low. The interim analysis was conducted per a regulatory commitment to provide interim data before the final report. There was an understanding that it would not be powered at that time. She did not have a computation of what the power would be once all 31,000 children are included.

- Regarding the rapid cycle analysis, Dr. Martin Myers (National Network for Immunization Information) inquired as to how the investigators managed the lag time in the data being available.

- Dr. Lieu replied that there is some lag in terms of the completeness of data in the HMOs that participate in the VSD. They do allow a lag period to ensure that the data are complete. In addition, all of the data that were available at the time of the logistic regression were included.

Summary and Vote

Mona Marin, MD
Division of Viral Diseases, NCIRD, CDC

Dr. Marin provided a brief update on MMRV vaccine supply and safety. MMRV has not been widely distributed in the US since June 2007 and is not expected to be available again until 2009. However, some providers might have some supplies in stock. As part of post-licensure safety monitoring, in October 2007 following FDA review of adverse event reports submitted to VAERS and Merck's worldwide adverse experience system, the MMRV vaccine label was updated to include "convulsion" and "febrile seizure" among adverse reactions post-vaccination. The label was updated again recently to

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include some interim results. In February 2008, preliminary vaccine safety study results on MMRV vaccine and febrile seizures were presented to the ACIP by both VSD and Merck investigators.

The current ACIP recommendations for prevention of varicella and measles, mumps, and rubella are harmonized with a schedule that includes two vaccine doses with the first dose recommended at 12-15 months; the second dose recommended at 4-6 years; and catch-up vaccination recommended for older children, adolescents, and adults. Vaccination options include 1) simultaneous administration of varicella vaccine and MMR vaccine at separate sites and with separate syringes; 2) non-simultaneous administration of varicella vaccine and MMR vaccine (the two vaccines should be administered at least 4 weeks apart); and 3) use of combination MMRV vaccine (for persons aged 12 months-12 years).

Regarding the use of combination vaccines, the ACIP general recommendations on immunization state that:

> Use of combination vaccines can reduce the number of injections required at an office visit. Licensed combination vaccines can be used whenever any components of the combination are indicated and its other components are not contraindicated and if licensed by the Food and Drug Administration (FDA) for that dose in the series. Use of licensed combination vaccines is preferred to separate injection of their equivalent component vaccines to reduce the number of injections and missed opportunities to protect through vaccination.

Similar language was included in the 2007 ACIP varicella statement referring to combination MMRV vaccine. The current ACIP recommendation is as follows:

> 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. Whenever any components of the combination vaccine are indicated and the other components are not contraindicated, use of licensed combination vaccines, such as MMRV vaccine, is preferred over separate injection of equivalent component vaccines.

Given the recent findings from post-licensure safety surveillance, CDC proposed that the ACIP consider changes to the ACIP recommendations for MMRV vaccine use to replace the preference for use of MMRV vaccine over simultaneous administration of MMR vaccine and varicella vaccine with no preference in the varicella ACIP statement. If the ACIP agrees with this change, the proposed language is as follows:

> 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 combination MMRV vaccine over separate administration of MMR and varicella vaccines. After weighing risks and benefits, providers can

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choose whether to administer combination MMRV vaccine or MMR and varicella vaccines separately, for prevention of measles, mumps, rubella, and varicella diseases among their patient population.

Next steps would consist of communication materials on the CDC website, including: 1) health-care provider fact sheets to inform providers of preliminary findings and changes approved; 2) Vaccine Information Statement (VIS) for MMR and varicella vaccines, updated with "seizures caused by a fever have been reported after MMRV vaccine;" and 3) Q&A's. An *MMWR* Notice-to-Readers would present preliminary findings and inform readers of the change to "no preference" for use of combination MMRV vaccine. An ACIP working group would be established to continue to evaluate MMRV vaccine safety findings and vaccination policy options.

Discussion

- Dr. Iskander reaffirmed that the ISO supports this proposed policy change and has had input into it.

- Dr. Seward pointed out that this would also apply to the MMR vaccine policy, with no preference stated for MMRV over MMR vaccine and varicella vaccine. MMRV was not licensed when the last ACIP MMR vaccine policy was published in 1998, so there is no preference for a combination MMRV over MMR vaccine and varicella vaccine for prevention of measles, mumps, rubella and varicella. It will be made very clear in a Notice to Readers, if the committee votes, that this applies to vaccine policy for the four diseases.

- Dr. Stinchfield added that the Combination Vaccine Working Group was aware of this as well, and as the chair of this working group, she also supported the proposed change in language. Given the safety, shortage, delivery, and other issues, there are a number of reasons why it would be better not to state a strong preference.

- Dr. Plotkin expressed concern that this vote would be premature based on data which have not yet been thoroughly analyzed. Considering the absence of a large amount of vaccine in the system, it seems to be a rush to judgment that is not required by any emergency. In addition, the estimated excess incidence of febrile seizures is between 1000 to 2000 or 3000 doses by both studies. If this logic applies, then they might get into the Wakefield logic that they should also separate MMR. Publishing the recommendation as suggested certainly would give license to physicians to do that.

- With respect to timeliness and transparency, Dr. Schuchat commented that it was very helpful to have Dr. Lieu's presentation about how the RCA works, how signals are detected, and the steps that are taken to evaluate those signals. She also thought it had been quite some time since the original signal was detected and an extremely thorough presentation was given. Unfortunately, there has not been a longstanding working group that could process the information as they have been

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able to do with some other complex information. The concept of the consistent findings that do not disappear with the larger numbers and have apparently become clearer instead of less clear, as opposed to the GI bleeding information for another product, left some people feeling uncomfortable for a clear preference for the MMRV over the MMR vaccine and varicella vaccine since that clear preference was stated before there was any question of increased risk. She thought that was one reason the ACIP was being asked to consider a recommendation at this point.

- Speaking as a clinician, Dr. Baker said she thought febrile seizures concern parents deeply. While it would be beneficial to have the final analysis and more data prior to making a decision, the signal has been sustained. This seemed to be an issue in which being safe was the prudent course.

- Dr. Lieu acknowledged that as an ACIP member, it was difficult to see new data at a meeting and then suddenly be asked to make a decision about it. This signal was observed before the October 2007 ACIP meeting, and the investigators have been scrutinizing the chart reviews and data in an effort to determine whether this finding represented a true increase in risk. Having lived with these data intimately for over six months, she said she was quite comfortable with the language as proposed in which the ACIP would not state a preference. A preference is currently stated for MMRV vaccine, and knowing the data as she does, she would be quite uncomfortable leaving that preference on the table for another four months. She also thought that an ACIP working group should be formed to help advise those who worked with the data on what more would be useful to ACIP in this situation.

- Dr. Cieslak agreed that the suggested change seemed sensible, given the data.

- Dr. Neuzil also agreed that the proposed change was a compromise and a middle ground. She emphasized the significance of the working group process, pointing out that it would have been beneficial to have reviewed any data available prior to the October 2007 meeting. It sounded as thought the Combination Working Group was aware of these data, but she wondered whether that group had the opportunity to deliberate the issue of changing recommendations from the usual position of combination vaccines and potentially changing back, or any mixed messages that might send.

- Dr. Stinchfield responded that this was a recent conversation in preparation for this meeting. Thus, she had not seen all of the data. The conversation was more conceptual in terms of the existing language versus the proposed language.

- Dr. Iskander thought that the concept of forming a working group pertained to forming a joint ISO, NCIRD, ACIP working group, recognizing that the Combination Working Group already has a fairly heavy workload. He thought forming such a working group was a concept that ISO would endorse. Clearly, additional investigations need to be conducted.

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- Angela Calugar commented that the 2006 general recommendation statement refers readers to the 1999 combination vaccine preference statement. The ACIP Combination Working Group is in charge of reviewing that statement from 1999. The MMR vaccine was recommended before that combination vaccine preference was strongly recommended. The current situation is different, so the Combination Working Group is reviewing the statement itself. The working group decided to review all preventable diseases in combination vaccines and discuss each one with the subject matter experts and epidemiologists when preference is strongly recommended, no preference is stated, or a preference is stated for a single antigen vaccine, for example in an outbreak situation. This group is engaging in a comprehensive analysis of all of these situations. They learned about the MMRV situation just last week, so the Combination Working Group had not had an opportunity to discuss the circumstances or consider the data. Nevertheless, she thought the change was timely and supported the proposed language.

- Alan Hinman understood the utility of clarifying that there are apparently some increased risks of febrile seizures associated with the use of the quadrivalent vaccine as opposed to the MMR+V; however, the wording of the proposed statement seemed subject to too much interpretation. He strongly urged the ACIP to reconsider the wording and table the vote until the next day after having an opportunity to think about it further. He thought the ACIP still had a strong preference to MMR vaccine compared to separate antigen measles, mumps, and rubella vaccines. It was not clear to him that this was apparent in the proposed language.

- Dr. Judson agreed. Based on the data, there appeared to be a slight trade off between convenience and the potential for increased seizures, but at a low rate. It seemed that they were “passing the buck” back to the provider by making a very nuanced change, which most people who were not privy to these deliberations would not read or understand. His preference was to make no changes until the analyses are complete.

- Speaking from the provider perspective, Dr. Iskander thought the current standard of practice for the vast majority of practitioners was use of separate MMR+V because it is what they have. The existing ACIP recommendation basically says to providers that they are not doing what is recommended. Therefore, he believed the proposed change would make more real world sense to providers. He also stressed that in the case of the RCA data, *preliminary* did not mean that the relative risk would become non-significant.

- Given the data presented, Dr. Bocchini (AAP) thought the proposed language change was a reasonable compromise.

- With respect to parents, Dr. Temte (AAFP) agreed that their child experiencing a febrile seizure is a significant, life-changing event that will affect the care of that child for years. Given the data, proceeding with the proposed recommendation would

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reaffirm the internal controls for which the ACIP says they advocate, that they do take safety seriously, and they do that in a very transparent manner.

- As a pediatrician and as a parent of a child who had a febrile convulsion, Dr. George Peter (Brookline, Massachusetts) said he basically supported the concept of the change, but wondered whether the reason would be given regarding why the ACIP has taken this action.

- Dr. Marin responded that in anticipation of a change, provider materials have been developed to inform practitioners about the preliminary findings and the policy change, if there is one. The Vaccine Information Statement has been updated for the varicella vaccine and MMR vaccine to mention that febrile seizures have been observed in MMRV vaccine, which is consistent with the package insert. Both of these documents can be posted on the CDC website following this meeting. A Notice to Readers is also planned for the *MMWR* to disseminate the results. An ACIP Working Group would also be useful to continue evaluating the results, with the understanding that there may be no more data in the absence of MMRV on the market.

- To address some of the concerns raised by the committee, Dr. Tan (AMA) suggested removing the second sentence reading, “After weighing risks and benefits, providers can choose whether to administer combination MMRV vaccine or MMR and varicella vaccines separately, for prevention of measles, mumps, rubella, and varicella diseases among their patient population.”

- Dr. Englund agreed that that sentence would lead to more confusion and concern. Leaving out the last sentence still makes the “no preference” statement without leaving it open to interpretation.

- Dr. McKinney pointed out that for the VIS statement, the language reading “seizures caused by fever have been reported after MMRV vaccine” would be more accurate if it read “after the first dose of MMRV vaccine” and would still give physicians the option.

- Looking at the statement, Dr. Neuzil did not believe it sounds as though the ACIP was as confident in the data for 4-6 years.

- Dr. Iskander responded that febrile seizures are a much less common event over all at ages 4-6, the VSD study was not designed to study that age group and is not powered to do so. He did not believe that they were likely to have additional data on the 4-6 year old age group. Certainly, they will be consistent with the FDA labeling.

- As evidenced by the discussions, Dr. Neuzil pointed out that everyone was interpreting the proposed language differently. It seemed that they could improve the language and help the provider by being more clear in how the statement is written.

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- Dr. Marin responded that the Notice to Readers will explain the results were for children aged 12-23 months.

- Dr. Neuzil maintained that the language should be included in the recommendation, given that they were making a specific vote based on specific data.

- Dr. Lieu said she would be content if they removed the preference, however that was done. The choices were to motion for the first sentence, which seemed simple and did not express preference, and to delete the second sentence directed toward providers. Or, a group could be assigned to further refine the language.

- Dr. Englund supported the suggestion to move ahead with only the first sentence, particularly given that pediatricians already bear a heavy burden. She did not believe they needed to expound a great deal and more information could always be added later.

Motion

Dr. Englund made a motion to accept the proposed change to the ACIP recommendations for MMRV use which states, "ACIP does not express a preference for use of combination MMRV vaccine over separate administration of MMR and varicella vaccines," and to eliminate the second sentence proposed which states, "After weighing risks and benefits, providers can choose whether to administer combination MMRV vaccine or MMR and varicella vaccines separately, for prevention of measles, mumps, rubella, and varicella diseases among their patient population." Dr. Baker seconded the motion. The motion carried with 10 affirmative votes and 2 members voting no.

Public Comment

- Mary Beth Leeber traveled from New York with her 9-year old daughter, Lauren, a meningococcal survivor, to urge the ACIP to support public education of meningococcal disease and the availability of the vaccine that may help prevent this down to the age of 2. She knew nothing of meningococcal disease until she sat helplessly watching Lauren, when she was 5-years old, fight this disease. In the fall of 2003, Lauren began feeling sick and had flu-like symptoms. The pediatrician diagnosed her with a virus and sent her home, where her fever rose above 104 and could not be broken with TYLENOL® or MOTRIN®. Lauren then broke out in red spots, at which time she was taken to the hospital and they learned that she had meningococcal disease. As a result, doctors had to amputate Lauren's right hand, the tips of her fingers on her left hand, and both of her legs below her knees. Lauren also experienced kidney failure and had to endure dialysis twice a week for about three months until Mary Beth was found to be a match and Lauren was able to receive her mother's kidney. As a result of this, Lauren must take

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immunosuppressants for the rest of her life. While Lauren was fortunate, not all families affected by meningococcal disease are as fortunate. Lauren will have to live with the long-lasting effects of this disease for the rest of her life. The meningococcal conjugate vaccine was not FDA approved for children down to age 2 when Lauren was infected with the disease. Now that it is, Mary Beth Leeber, along with the parents affiliated with the National Meningitis Association believe that it is important for health care providers to educate parents about its availability so that they can make an informed decision about whether to vaccinate their child. She wished that Lauren's pediatrician had educated her about meningococcal disease, its symptoms, and the importance of vaccination. No parent should have to witness their child go through what Lauren did, especially when it can be prevented. She urged the ACIP to think of Lauren and the other children aged 2-10 years affected by meningococcal disease, and to encourage health care providers about this disease and the vaccine to help prevent it. Lauren Leeber added that if she had known about the vaccine, she would have gotten it. She said she would not want her worst enemy to get meningococcal disease. In conclusion, she wished the committee a good day and thanked them for listening to her story.

- To follow up on Mary Beth and Lauren Leeber's request, Dr. Pickering stressed that CDC will continue its educational activities for this vaccine and hope that other professional organizations will follow NFID in ramping up their own educational activities about prevention of this disease.

- Dr. Morse thanked Mary Beth and Lauren Leeber for bringing the human touch to this discussion, stressing the importance of public comment to this organization. It reminded him of a quote by Julius Richmond that he thought ACIP should always remember when they look at numbers and statistics, "Statistics are people with their tears wiped dry."

- Dr. Alan Hinman (Voices for Vaccination) reported that Voices for Vaccination is a newly organized group, which hopes to represent the millions of Americans who support vaccinations in this country. Voices for Vaccination plans to provide science-based, credible, independent evidence as a basis for their statements. To demonstrate their independence, Voices for Vaccination will accept funding neither from the government nor from vaccine manufacturers or distributors. Voices for Vaccination has a steering committee in place, which includes representatives from the Academy of Pediatrics, Academy of Family Physicians, the American Medical Associations, and a variety of groups including Meningitis Angels and Families Fighting Flu.

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- Dr. Tan (AMA) reported that the AMA was delighted to coordinate a release of "Roadmap for Clinical Practice: Improving Adolescent Immunization" to coincide with the Call to Action that was released by NFID on Adolescent Immunization. He referred those present to the information table in the back of the room for the complete monograph and a small portable version with a CD included.

- Dr. Lewis (AHIP) delivered a request from AHIP's local physicians regarding the current recommendation in the vaccine schedule for varicella vaccine for ages 4-6 kindergarten. This seemed to be from a time when there were not regular 18-month and 2-year visits for vaccinations. With the new hepatitis A second dose, there are now standard visits. The rationale for waiting until 4-6 years to get children fully covered for MMR and varicella was not apparent. With that in mind, Dr. Lewis requested that this be reviewed by the ACIP vaccine schedule working group.

- Dr. Pickering responded that this would be referred to the Childhood and Adolescent Immunization Schedule Working Group for review and consideration.

Closing Remarks

Dr. Pickering indicated that all communications pieces being prepared would be disseminated to ACIP members, and that a working group would be formed to further examine the extensive materials that would need to be presented at the next ACIP meeting.

Dr. Morse indicated that due to the late hour, the Vaccine Supply session would be moved to the next morning. With no further business posed, he officially adjourned the first day of the February 2008 ACIP meeting.

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Thursday, February 28

Vaccine Supply

Gregory S. Wallace, MD, MS, MPH
Chief, Vaccine Supply and Assurance Branch
Immunization Services Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Wallace presented updates on influenza vaccine production and distribution, varicella zoster-based bulk vaccine supply, HepA vaccine supply, and Hib vaccine supply.

The influenza vaccine supply available in the US for the 2007-2008 season includes: Fluzone®, Inactivated TIV (sanofi pasteur); Fluvirin™, Inactivated TIV (Novartis Vaccine); FluMist™, LAIV (MedImmune Vaccines); Afluria®, Inactivated TIV (CSL Biotherapies); Fluarix®, Inactivated TIV (GlaxoSmithKline Biologicals); and FluLaval™, Inactivated TIV (ID Biomedical Corporation) [Slide 4: Table includes formulations and age indications]. There has been an increase in the number of doses and producers.

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

Projecting demand in a changing world is difficult, given that the doses produced can be increased, but the demand does not necessarily follow. Between 2003-2004, production dropped down to predict more accurately the demand and distribution; however, that was followed with the shortage year between 2004-2005. Between 2006-2007, both production and distribution ramped up tremendously, but where the true demand ultimately will be is difficult to predict. It is likely to be affected by the expanded ACIP recommendation made on the previous day. In the decade between 1999-2007, production grew to 140.6 million doses, with distribution having grown to 112.8 million

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doses. While there was record production in 2007, record numbers also were not distributed. Thus, while influenza has presented challenges in the past several years, increased production and distribution capacity has alleviated some of these challenges. Nevertheless, administration capacity remains unknown and is of concern. It is also unclear where demand and the market will go from here.

Regarding varicella-based vaccine supply, varicella zoster virus (VZV) bulk is used to manufacture varicella vaccine, MMRV vaccine, and zoster vaccine. CDC received reports last year that the VZV bulk process had resulted in lower than expected yields, that the manufacturer was going to temporarily suspend production, but that there was adequate bulk to produce varicella vaccine and zoster vaccine. At that time, no changes were made in the current vaccine policy recommendations to protect against these diseases. An *MMWR* Notice to Readers was published February 23, 2007 stating that the manufacturer would be prioritizing production of varicella vaccine and zoster vaccine and that the MMRV, ProQuad®, vaccine was expected to be depleted by the end of 2007. As soon as that statement was made, there was a run on vaccine and the ProQuad® depleted faster than expected due to increased demand.

The current status of the MMRV Supply is that ProQuad® orders were suspended in June with the exception of a small amount of doses in the late lot release that was targeted primarily to Kaiser facilities. The remediation process is in progress at the manufacturer, and as noted, the current VZV bulk is adequate to produce varicella and zoster vaccine and meet the current recommendations from ACIP. Earlier Varivax® shipping delays have been resolved. There has been no change in the recommendation for vaccination to protect against varicella disease or zoster, and varicella vaccine (Varivax®) and zoster vaccine supplies are adequate to meet needs. Although the remediation process for resuming MMRV production is in progress, ProQuad® is not expected to be available this calendar year.

Pertaining to Hepatitis A vaccine, in July 2007, CDC was informed of vaccine supply issues by Merck, one of the two manufacturers that there were backorders accumulating of pediatric and adult VAQTA®. At that point, the Merck supply beyond September was not known. However, GlaxoSmithKline reported that an adequate supply is available and was also ramping up to prepare supply for the stockpile. Therefore, they were able to fill the gap at that time. The Stakeholder Supply Group members examined these issues and no changes in the ACIP recommendation were advised at that time. Merck VAQTA® orders remain suspended for the adult and pediatric vial formulation, but are estimated to return to the market in the late third to fourth quarter of 2008 depending upon the adult or pediatric formulation. The supply available from the alternate manufacturer, GlaxoSmithKline, remains adequate.

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Turning to the Hib vaccine supply, CDC was informed in November PedVaxHib® was currently unavailable for shipment. CDC activated the Vaccine Supply Stakeholder Working Group to consider the issues. At that time, stockpile doses were released to meet the November demand in the public and private sector. The alternate manufacturer, sanofi pasteur, was contacted regarding their ability to meet projected increased need for their product. CDC also worked with the Indian Health Service (IHS) to collaborate on the specific needs for the American Indian / Alaskan Native (AI / AN) population, given their increased risks and the need to have a vaccine that gives them earlier immunity. CDC evaluated public and private sector demand, projected supply, stockpile availability, and the potential for alternative sources through investigational new drugs (INDs) or other vaccines in the pipeline. In December, there was a voluntary recall of certain lots of PedVaxHib® and Comvax®. This prompted an urgent regrouping of the Vaccine Supply Stakeholder Working Group, and within six days they were able to communicate interim recommendations to deal with the supply issues through an *MMWR Dispatch*. Allocations and stockpile releases were adjusted due to the recall and updated supply. The interim Hib recommendations included the following: 1) Defer the routine Hib vaccine booster dose administered that occurs at ages 12-15 months, except for specific high-risk groups; 2) High-risk groups should continue to receive the 12-15 month booster dose (e.g., asplenia, sickle cell disease, HIV infection, immunodeficiency syndromes, malignancies); and 3) Providers who use PRP-OMP® Hib (PedVaxHib® & Comvax®) to serve AI / AN children in AI / AN communities should continue to use PRP-OMP, including administration of the 12-15 month booster dose. The remaining Merck PedVaxHib® / Comvax® in the stockpile is reserved for AI / AN communities. CDC is working with sanofi pasteur, the alternative manufacturer, to ensure availability of ActHib® to meet the interim recommendations. Merck currently estimates returning to the market at the end of 2008.

When CDC met with the stakeholder groups and manufacturers, the interm recommendations were based on the projected supply from the manufacturers as well as historical use. Good data were available on what the private sector and public sector grantees have purchased over the last couple of years. The problem is that there is no inventory to alleviate any short-term problems, nor is there any extra vaccine to fill any inventory. This is a tightrope and the pipeline is an issue. At this point, the Stakeholder Working Group is not considering reducing the recommendation even further. Decreasing demand another 30% would risk vaccine not being used and children not being protected adequately. This has been observed in the past, for example, during the Manactra® shortage, vaccine was not used and was ultimately thrown away. It is imperative to recognize how difficult such a situation is, and the importance of not making a bad problem worse.

Discussion

- Dr. Baker inquired as to whether data were available that would allow for a determination of whether there is any VFC private provider mismatch at this time.

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- Dr. Wallace responded that CDC has been working closely with the alternate manufacturer and is getting a fair share of what is available. While the pipeline issues persist, the supply is being distributed equitably not only between VFC and the private sector, but also between grantees.

- Speaking as someone who oversees a vaccine distribution program, Dr. Duchin expressed his gratitude for CDC's efforts when problematic situations arise. He requested that Dr. Wallace give further details about the overall strategy to avoid and / or mitigate challenging situations such as those described.

- Dr. Wallace replied that the supply issue was a longstanding one not only for ACIP and CDC, but also for the National Vaccine Advisory Committee (NVAC) and the Department of Health and Human Services (HHS). There are stockpile programs and offering more incentives to manufacturers has been discussed throughout the years. Offering incentives met with some success in the influenza arena. CDC is also retooling the stockpile to have better inclusion / exclusion criteria. Over the last 10 years, with the changes in market share and in recommendations, there has really been no steady state to enable CDC to cover all of the bases they would prefer to cover.

- Phil Hosbach (sanofi pasteur) reported that sanofi pasteur is attempting to balance the demand for their product, which is a global product. It is anticipated that through June 2008, sanofi pasteur can meet the current revised recommendation (e.g., 3 doses in the primary series) with about 1 million doses a month. Approximately 60% of that goes to CDC, which is the typical market share for the public versus the private sector. The second half of the year is less visible, given that there are a number of variables that could impact supply. They anticipate that they will have Pentacel® licensed before the next ACIP meeting, which would provide substantially more doses to the market in the second half of the year. sanofi pasteur has a limited number of filling lines throughout the world for the products that they fill. ActHib® requires a diluent and that diluent filling line is shared with a number of other products that cannot be sacrificed to fill more diluent. However, there are other diluents for ActHib® and the DTap IPV liquid, known as Quadracel® in Canada, is actually the diluent for Pentacel®. That would free up more diluent and make more Hib vaccine available for the second half of the year.

- Dr. Pickering inquired as to whether, upon licensure of Pentacel®, there would be a concomitant decrease in single antigen Hib.

- Phil Hosbach (sanofi pasteur) replied that he did not believe so, although he indicated that he would check and report back to the ACIP. They anticipate that they could add as many as a million doses per month to what they have for ActHib®.

- Michael Decker (sanofi pasteur) stressed that as always as a manufacture, they do not know when a product will be licensed. However, they do know that they have an FDA Prescription Drug User Fee Act (PDUFA) action date that falls before the next

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ACIP meeting, so there is every reason to hope that there will be action before the next ACIP meeting. If the action does not occur until the action date, product availability would be "on the street" about six weeks following the next ACIP meeting.

- Dr. Stinchfield inquired as to whether the interim recommendation for deferral of the 15-month Hib dose remained in place, potentially until the end of the year.

- Dr. Wallace replied that CDC has received reports that some providers have not gotten that message. Therefore, while some providers are scrambling to keep up and do not have doses exactly when needed, other providers had larger supplies and continue to give the 15-month booster dose. CDC is working to clarify that the interim recommendations remain in place, and also continues to work with the Stakeholder Working Group to monitor the supply. The recommendations can be changed quickly if necessary.

- Phil Hosbach (sanofi pasteur) pointed out that based on communications coming out of the public and private sectors, there is reason to believe that a substantial number of providers are still using four doses.

- Dr. Stinchfield requested further information about the work CDC has in progress to alleviate distribution gaps.

- Dr. Lance Rodewald, Immunization Services Division, responded that CDC is aware that there are a number of challenges with respect to vaccine distribution. Some of the issues became apparent during the influenza season during which there was concern that there would be a backlog in ordering of such a tightly timed vaccine. This resulted in the implementation of several changes to help assuage the backlog. One of the lessons learned is that CDC needs to modify the contract to make it more outcomes-based so that rather than having orders set up to ship on Monday, Tuesday, and Wednesday, it will be set up so that once an order is placed it will be in the provider office in X days (probably 5 days). The other challenge has been information technology. CDC is in a very vulnerable situation currently, given that CDC's primary ordering system was designed to handle hundreds of orders for bulk vaccine from states. This system had to be retooled to handle tens of thousands of orders for individual providers. Hence, CDC's system is stressed to capacity and as a result sometimes drops orders. While CDC is designing and implementing a longer term solution, it will not be ready for a year and a half. The new ordering system will allow providers themselves to order their VFC vaccine. CDC is working on reporting structures to help track orders throughout the system as well (e.g., provider orders, manufacturing shipments, et cetera). The main measure of success in the distribution process is the ability to have an order placed and received by the provider in a timely manner. A more comprehensive overview could be added to a future ACIP agenda to further describe the efforts underway.

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- Dr. Stinchfield requested that the comprehensive overview suggested by Dr. Rodewald be added to the next ACIP meeting agenda.

Measles Outbreak: San Diego, California

Jane Seward, MBBS, MPH
Division Viral Diseases, NCIRD, CDC

Dr. Seward updated the ACIP on the measles outbreak in San Diego, California. She first reminded everyone that measles caused a considerable disease burden in the United States (US) prior to licensure of a measles vaccine in 1963. Before the vaccine was licensed, 3-4 million measles cases per year occurred that resulted in severe complications, such as 4,000 cases of encephalitis and 150,000 respiratory complications (pneumonia). In addition, there were 48,000 hospitalizations and about 450 deaths per year. About 500,000 cases were reported each year. The US began vaccinating with measles vaccine in 1963. Within about five years, reported measles cases dropped dramatically to about 20,000 cases per year. With better implementation and catch-up vaccination due to implementation of school requirements, reported measles cases declined to about 2,000 cases per year by the mid 1980s. This was followed by an increase in measles with outbreaks in highly vaccinated populations and then a measles resurgence affecting primarily unvaccinated children < 5 years from 1989-1991 at which time there were 55,000 measles cases reported and 123 deaths.

With full implementation of a 2-dose vaccine policy and better implementation of school laws, measles declined to extremely low levels following the measles resurgence. Measles elimination, defined as “interruption of endemic disease transmission,” was declared in 2000. The US has maintained less than 1 case per million in the US since 1997. Thus, measles in the US in 2008 is no longer an endemic disease. There are about 50 cases reported each year, all of which are related to imported cases. Imported cases occur from developing countries, as well as developed countries such as Europe and Japan. The US epidemiology in the last few years is characterized by outbreaks predominantly in unprotected populations. In 2005, there was an outbreak of 34 cases in Indiana in an unvaccinated religious community. This was the result of an imported case from Rumania. In 2006, there was an outbreak of 18 cases in young adults in Boston, primarily among one-dose vaccinees and foreign born adults with unknown vaccination histories. In 2008, there is a current outbreak with 12 cases in unvaccinated children in San Diego.

The outbreak in San Diego began with an unvaccinated child whose onset of rash was January 25th upon return from Switzerland where there has been a measles outbreak on-going for over a year. Over two generations, there have been 11 additional cases in San Diego. More specifically, the index case was a 7-year old child with rash onset 12 days after returning from Switzerland. The additional 11 cases have occurred in children ranging in age from 10 months to 9 years. All of the children are unvaccinated, 8 due to personal belief exemptions, 3 because they were less than 12 months old, and 1 due to timing of her routine vaccination that occurred 6 days after an unrecognized

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exposure. She was two years old, so this was a delayed vaccination. Of the children infected, four were infected in a pediatrician's office when the index case presented there on January 25th. One of those children, an infant, was hospitalized for two days for dehydration. One of the infants traveled by plane to Hawaii while infectious necessitating quite a response in Hawaii. While a measles genotype is pending, CDC is betting on D5, which is the genotype circulating in Switzerland.

The public health response has been extreme, with a great deal of work done at the local and state health department levels, with some assistance from CDC. There has been enhanced surveillance for measles with identification of cases and identification of all people exposed, or the contacts. Vaccination, immune globulin, and / or voluntary quarantine have been required for persons without evidence of immunity. At the time the *MMWR* report was written, 70 children were quarantined. There have been numerous public health communications through Health Alerts and an *MMWR* aimed at increasing awareness for measles in travelers and their contacts, the importance of infection control, and the message that vaccination protects against measles. This *MMWR* was published on February 22nd as an early release article and will to be included in the regular *MMWR* the week of February 25th.

Dr. Seward concluded that measles importations continue to occur in the U.S and may result in outbreaks. Measles is highly infectious and the disease can be severe. Susceptible populations remain at risk for measles. Vaccine exemptors have a greatly increased risk of measles compared to vaccinated persons, and they pose a risk to their communities. Incidence of measles in a community is associated with the frequency of vaccine exemptors. Health care providers are no longer familiar with measles in the US because it is relatively rare, so they need to be reminded that it can still occur. There were lapses in infection control in the San Diego outbreak as also occurred in Arizona with another importation of measles from Switzerland. The good news was that the US "wall of immunity" held fast, with no cases occurring in exposed vaccinated children. There would have been a much larger outbreak if the US did not maintain such a high one- and two-dose coverage in the population. The public health response was swift and effective, which also limited the outbreak size by vaccinating, giving immune globulin, and quarantining children without evidence of immunity. Thus, the high population immunity in the US does protect those who cannot be vaccinated. Moreover, child care and school requirements are an effective strategy for achieving high population immunity. Nevertheless, the on-going challenge is to sustain high vaccine coverage to maintain measles elimination.

Discussion

- Dr. Baker inquired as to whether Dr. Seward had any perception of whether the media messages pertained to the importance of vaccinating children.

- Dr. Seward replied that she thought that was a very clearly communicated message. In San Diego, the K-8th grade school the child attended had 350 children, of whom 10% had a personal belief exemption. Some of the parents claiming personal belief

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had their children vaccinated, although the majority did not so their children were placed on quarantine and were out of school for 21 days. So, there was a considerable cost to the local and state health departments and the community for this outbreak. There has been a lot in the local press and the *San Diego Tribune* about this outbreak and about the fact that some of those unvaccinated children were infected in the pediatrician's office.

- Dr. Neuzil pointed out that there is a lot of travel to Western Europe where people do not go to travel clinics because they do not consider it a risk. With that in mind, she requested further information about why Switzerland and Western Europe were of such high risk and whether that was an educational message that needed to be disseminated.

- Dr. Seward responded that the message does need to be disseminated. It was included in the *MMWR.* The message is strongly conveyed on the CDC travel website that the best way to protect US travelers is to follow existing vaccine policy for routine vaccination, including vaccination of children 6-11 months with one dose if they travel overseas. Measles has been on-going in Switzerland for over a year. New York City is dealing with two cases, probably resulting from an importation from Israel. Israel and Germany are experiencing small outbreaks currently related to Switzerland. There is on-going endemic transmission in a number of European countries.

- Dr. Schaffner inquired as to why these countries had not eliminated measles when they certainly could.

- Dr. Seward replied that there is considerable ongoing effort to achieve measles elimination in the European Region, in the Western Pacific Region, and in other regions of the world. There was a EuroSurveillance Weekly article recently, which was devoted to this issue, highlighting the on-going outbreak in Switzerland. Importations from Switzerland to the US, Germany, and other countries were mentioned in the article. The message was in the *MMWR Dispatch* about that. Switzerland has 1-dose coverage of 86% and 2-dose coverage of 70%. It does not take a lot of drop in measles vaccine coverage to get on-going measles transmission.

- Dr. Katz (IDSA) pointed out that a number of the resource-poor nations, such as Vietnam, have a much higher measles vaccine coverage than many of the Western European countries. That is likely because of the morbidity and mortality that resource-poor nations have experienced in the past in contrast to what has been seen in the so-called "wealthy nations." The young healthcare workers who are not familiar with measles, and the four individuals who became infected in the pediatrician's office, highlight the importance of information dissemination. People tend to think of direct aerosol transmission. However, it was shown years ago that there is droplet persistence, and that two hours after a patient left a doctor's office

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there would still be communicability because virus was still present in the environment.

- Dr. Campos-Outcalt (AAFP) commented that when infections are transmitted in a healthcare facility, it reflects a general lack of awareness regarding infection control practices. With that in mind, he stressed that professional organizations must continue to emphasize the need for infection control policies for common and uncommon infectious diseases, as well as for preparedness. In addition, he inquired as to when the immune globulin option would be preferable to vaccine.

- Dr. Seward replied that this option would be used for those who cannot be vaccinated, such as children under the age of 6 months and people who are immune compromised who cannot receive a live viral vaccine. In San Diego, it was primarily given to very young infants who were exposed. A vaccine could be given at six months, but not before that.

- Dr. Nobuhiko (National Institute of Infectious Diseases, Japan) indicated that last year they had an outbreak in Tokyo with peak age group affected being young adults. Two years ago, they introduced a 2-dose policy of vaccinating with MMR at one year old and before school entry. In December 2007, the Minister of Health and Welfare announced their target of measles elimination. They have recently organized a National Immunization Committee, which held a meeting two weeks ago in which they recommended supplementary immunizations for children ages 13 and 17 years old.

Agency Updates

CDC / CCID / NCIRD

With regard to adult immunization, Dr. Schuchat indicated that CDC released information in January 2008 from the 2007 Adult National Immunization Survey about the status of coverage for adult vaccines. There was quite a bit of press uptake of that. At the time, zoster coverage in people 60 and over was 2%; Tdap coverage in 18-64 year olds was 2%; and HPV coverage in 18-26 year old women was about 10%. CDC considers this a baseline from which to move forward. Dr. Schuchat also announced that the next National Immunization Conference will be March 17-20, 2008 in Atlanta. Extensive information about the conference can be found on the CDC website. In addition, she called attention to two *MMWR*s than have recently been published. The February 15th *MMWR* included an article updating the progress in reducing pneumococcal disease since the conjugate vaccine was introduced, which focuses on children under 5 years of age. There is a complementary article in the February issue of *Pediatrics* discussing the effects of pneumococcal conjugate vaccine on otitis media. One of the compelling results reported was an approximately $400 million a year savings in otitis-related visits and antibiotic use. The second article in the February 15th issue of the *MMWR* was the flipside of the Hib story. While they had just heard the challenges being experienced with the Hib vaccine supply in the US, on a global basis,

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there has been tremendous progress in accelerated decision making and adoption of Hib vaccine for routine use in resource-poor countries. The Global Alliance for Vaccines and Immunizations (GAVI)-designated countries have greatly increased use of Hib vaccine. From 2004-2007, the number of countries using Hib vaccine has increased from 13 to 47 of the GAVI-eligible countries that are either using the vaccine or have adopted it and received GAVI approval. That represents an increase from 18% to 65% of the eligible countries. Dr. Schuchat assured everyone that this did not affect US supply, given that the formulation used in the GAVI countries differs from the US formulation. The GAVI formulation is generally a combination with whole-cell pertussis. This is exciting news on the global immunization front.

Center for Medicare and Medicaid Services (CMS)

Ms. Linda Murphy reported that she had had the opportunity to discuss the issue of revising the regional maximum administration fees for VFC with her leadership. CMS continues to believe that determining local reimbursement rates is a function best performed at the state level, given that local market factors and budgetary constraints must all be factored in the rates setting process. While some states have reached the maximum rates, many others have not. CMS continues to encourage providers and states to work together to determine appropriate fees. CMS does not believe that this is the best time to make any changes to the *Federal Register* notice of October 3, 1994.

Department of Defense (DoD)

Dr. Ted Cieslak acknowledged that there is clearly a lot of activity within the DoD with respect to vaccines. Given that extensive presentations were on the agenda later in the day regarding anthrax vaccine and Japanese encephalitis vaccine, he deferred further discussion during this update. With respect to smallpox vaccine, he reminded everyone that he had presented the safety data informally at the June 2007 ACIP meeting. They continue to observe approximately 1 significant reaction to vaccinia per month. With regard to influenza vaccine, Dr. Wayne Hachey noted that with mandatory immunization for all uniformed personnel, the DoD's vaccination rates range from mid 80% to low 90% depending upon the services. This season, the DoD influenza policy reinforced universal immunization for the entire DoD population with a number of initiatives targeting the DoD's beneficiary population and trying to reduce some of the barriers to immunization for military dependents. For recruits, vaccine effectiveness was about 85% with confidence intervals of 77-90%, 92% for H3N2, and 54% for the current strain of H1N1. Fortunately, they observed H1N1 early in the season so they were not severely impacted in terms of reduced vaccine effectiveness. In that population, similar breakthrough rates were observed for both live and attenuated vaccine. Hence, the two appear to be comparable for that age group.

Veteran's Affairs (VA)

No update.

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Food and Drug Administration (FDA)

Dr. Florence Houn reported that following the ACIP discussion on febrile seizures following combination measles-mumps-rubella-varicella vaccine (ProQuad®), the FDA worked with the manufacturer to include information on some of the observational data. That information now appears in labeling.

Heath Resources and Services Administration (HRSA)

Dr. Geoffrey Evans commented that 2007 was a busy year for HRSA. With regard to the monthly statistics that HRSA disseminates, in total the program has received over 12,000 claims. Of those, claims for 4,200 vaccines given prior to 1988 have all been adjudicated with a final payout of $902 million dollars. Of the vaccines given post 1988, 5,200 are autism claims and 2,800 are non-autism claims. Of the 2,800 non-autism claims, 2,100 have been adjudicated, leaving 770 non-autism claims undergoing adjudications. Those are predominantly HepB claims that were filed in a rush in 1999 to meet a deadline for claims. It took quite some time for the courts to institute a process for adjudication of those claims, but they are now being adjudicated rather briskly. Flu vaccine was added to the program in 2005 following the change in the flu recommendation, so 184 of the 770 non-autism claims were the result of the two-year deadline ending in July 2007. While that was more than would typically have been expected for any one type of vaccine, they anticipated that it might be as many as 500-1000 given that they received 400 claims at the time of the HepB filing deadline. Fortunately, it turned out to be a fairly small number relatively speaking. Those are also being adjudicated. The 184 claims were primarily adults for mylenating conditions of one type or another.

Awards for the post-88 program are up to $856 million, so in total, the program had awarded $1.7 billion in compensation for pre- and post-88 claims. None of the compensation for post-88 has been for autism claims, with the exception of one claim that has been conceded by the government for compensation. This claim was part of the omnibus proceeding. The trust fund currently stands at $2.7 billion and is growing at a rate of about $300 million per year. $100 million of that is interest alone. Adding flu to the program significantly increased the amount of funds going into the trust fund, given that there is a 75 cent excise tax on each dose of flu vaccine. The autism process began in 2002. Following 5 years of discovery, the court began to develop a process so that instead of three special masters hearing these cases, three theories will be adjudicated. Each of the three theories will include three test cases. The first theory was the combined theory of MMR vaccine and mercury in vaccines. In June 2007, the court heard the general aspects of that theory and one test case. Two other test cases followed in October and November. Post hearing briefs are being submitted. HRSA had hoped that the court would decide the general theory plus the three test cases by spring 2008 because the second theory of Thimerosal® only is scheduled for May 2008, which will include all three test cases over a three-week period. It will be difficult for the court to issue a decision on the first theory that was adjudicated in the midst of gearing up for the second theory. It is likely that the court will not release a decision until June

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2008. The third theory is MMR alone, for which the court has said they would like to hold that hearing and hear its three test cases by the end of September 2008.

National Institutes for Health

Dr. George Curlin assured everyone that the NIH research enterprise continues despite level funding for the past several years. Research funding remains level for vaccines as well.

Indian Health Services (IHS)

No update.

National Vaccine Program Office (NVPO)

Dr. Bruce Gellin reported that NVPO has a new Deputy Assistant Secretary for Health, Don Wright. When he came to the department in November, among other things he faced early on was the Hib. Dr. Wright is the former Director of Occupation Medicine at the Occupational Safety and Health Administration (OSHA), and he has a substantial interest in healthcare worker influenza immunization. Dr. Gelling explained that NVAC was not represented during this meeting, given that Gary Freed is rotating off and Gus Birkhead will be the new chair. With respect to activities, the 1994 National Vaccine Plan is in the process of being updated. The Institute of Medicine (IOM) will assist in this process. Dr. Gellin indicated that the updating process was due to begin with a meeting on March 10, 2008 and that effort was expected to take a year. Dr. Claire Broome chairs this committee. Following the NVAC meeting, there was a session on immunization information sessions that was co-hosted but the National Coordinator for Health Information Technology. Recommendations are expected to come forward from this meeting pertaining to increasing participation, as well as vaccine financing. Vaccine financing is a major part of NVAC. A stakeholders meeting regarding financing is scheduled for late April 2008, about which Dr. Gellin indicated he would provide further information for those interested. NVAC has expanded the Vaccine Safety Working Group to include a number of experts similar to the lineup on the IOM's vaccine safety committee. There is a public meeting on April 11, 2008 during which CDC's Immunization Safety Office's research agenda will be reviewed, in addition to discussion of future activities. The Adolescent Working Group has developed a paper that will be disseminated for public comment on adolescent vaccinations, which includes discussion regarding venues, communications, financing, consent, surveillance, and school mandates.

Discussion

- With regard to the CMS statement, Dr. Duchin (NACCHO) reminded everyone that inadequate reimbursement for administration of pediatric vaccine remains a major obstacle at the local level. The result is that numerous health care providers have given up administering vaccines, which many others are considering doing as well.

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It is inequitable that pediatricians and family practice physicians who administer vaccines to children are discriminated against in the context of those who administer vaccines to adults with respect to reimbursement. This will provide a significant obstacle to reach the objective of expanding the recommendations for influenza vaccine to all children through 18 years of age. Thus, he encouraged the federal government to take a leadership position to ensure fair and equitable reimbursement for those who provide child vaccinations.

- Dr. Murphy replied that the update she presented to the ACIP from CMS was not a message she had looked forward to delivering.

- Dr. Temte (AAFP) concurred with Dr. Duchin. As a family physician, Dr. Temte practices in a university clinic with a very high under-served population. While he has the benefit of being in the university setting, they lose money. The State of Wisconsin gives them $3.28 per administration. With the new recommendations for influenza and all of the other vaccines, those who provide care for poor people are enduring the brunt of the effect of poor pass-through. He implored Dr. Murphy to take that message back to Washington, DC.

- Dr. Katz (Infectious Disease Society of America) inquired of the DoD what had occurred with respect to adenovirus vaccine.

- Dr. Hachey responded that the DoD remains hopeful. The new vaccine is still in development, but should be ready in one to two years. At that time, it will be given to new accessions. This continues to be a problem for DoD. The outbreak described at the last meeting has decreased, but continues to simmer, potentially with adenovirus 14.

Rotavirus Vaccines

Rotavirus Vaccines Working Group Update

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

Dr. Cortese presented the Rotavirus Vaccines Working Group update, given that Dr. Chilton was unable to attend. She reported that Rotarix®, the attenuated monovalent human rotavirus vaccine produced by GlaxoSmithKline, is currently under review at the Food and Drug Administration (FDA). The Biologics License Applications (BLA) was submitted to the FDA on June 1, 2007. It has been studied as a two-dose series at ages 2 and 4 months. The currently available pentavalent human-bovine reassortant rotavirus vaccine, RotaTeq®, produced by Merck, was licensed in February 2006. The ACIP made recommendations in February 2006 for routine infant vaccination at ages 2, 4, and 6 months. During the October 2007 ACIP meeting, Rotarix® safety and efficacy

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data were reported by Leonard Friedland of GlaxoSmithKline and safety, coverage, and age-adherence estimates were provided on the RotaTeq® vaccine.

The Rotavirus Vaccines Working Group's timeline was to prepare draft proposed recommendations for the ACIP by the February 2008 meeting, and to propose possible ACIP recommendations for a vote during the June 2008 ACIP meeting if Rotarix® is licensed by that time. If so, a new ACIP statement would be written to cover both rotavirus vaccines. Thus far, the Rotavirus Vaccines Working Group has reviewed data on Rotarix®. The proposed recommendations, to be presented during this meeting, were drafted to include Rotarix® and to address issues that arise related to having two products to prevent the same disease. The working group has continued to review post-marketing data available on RotaTeq®, along with the Immunization Safety Office (ISO) and the FDA.

In drafting the proposed recommendations and attempting to address issues with two products, the working group members used the available data and spent a considerable amount of time discussing expectations and a timeline for additional data. They used the opinions of working group members with expertise in various areas, and considered programmatic issues. The additional topics which the working group plans to address by the next ACIP meeting include the development of proposed recommendations for Rotarix® and an update for RotaTeq® as indicated, which addresses special populations, special circumstances, contraindications, and precautions. In addition, the working group will review any additional information on safety and efficacy and cost-effectiveness data for Rotarix®.

Working Group Considerations & Draft of Proposed Recommendations

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

Dr. Cortese reiterated that safety monitoring of the currently available vaccine, RotaTeq®, by the ISO has continued. The assessment at this time was the same as that which was presented at the October 2007 ACIP meeting. The currently available data from the Vaccine Safety Datalink (VSD) and Vaccine Adverse Event Reporting System (VAERS) do not indicate that the vaccine is associated with intussusception, and monitoring will continue. A manuscript by Penina Haber, Manish Patel, and others presenting these data through September 2007 has been accepted for publication in *Pediatrics*.

With regard to the live attenuated human rotavirus vaccine, Rotarix®, Dr. Cortese reminded everyone that it is a monovalent vaccine, a G1P8 strain.. It was studied as an oral 2-dose vaccine series.. As noted, the BLA was submitted to the FDA June 1, 2007. This vaccine is already in use in national vaccine programs of some countries, including Mexico and Brazil.

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Rotavirus strains are commonly designated using a dual classification system similar to that used for influenza. The rotaviruses are classified by two neutralizeable outer capsid proteins and in this way are designated G and P types. John Gentsch and his staff at CDC genotyped a convenience sample of several hundred rotavirus samples collected from patients each year. These isolates come from about 12 laboratories throughout the United States (US). Examining the proportion of isolates by strain type over the past 11 rotavirus seasons (1996-2007) from these 12 laboratories, it is observed that the distribution varies by year and by each site. In all of those years, G1P8 strains predominated on average making up about 75% of the isolates typed, ranging from 51% to 91%. On average each year, the remaining types each contributed 10% or less to the total (G2P4, G3P8, G4P8, G9P8, G9P6, other). G2P4 made up approximately 20% of the isolates in three different seasons (1998-99, 1999-00,2005-06). G9P8 reached 21% in the 2002-03 season.

To set the stage for presentation of the working groups proposed recommendations thus far, Dr. Cortese briefly reviewed data from the major clinical trials of Rotarix®, which as noted, were presented in detail at the October 2007 ACIP meeting by Leonard Friedland of GlaxoSmithKline. Two major clinical trials were conducted with Rotarix®, one in Latin America (Rotarix 023) and one in Europe (Rotarix 036). The Latin American study was the major safety trial, which particularly evaluated intussusception. About 63,225 infants were monitored for intussusception in the Latin American trial. Efficacy was measured in both studies, and two doses were given in both trails. The age range for the first dose was slightly different in each trial. In the Rotarix 023 trial in Latin America, the first dose was administered at 6 –13 weeks 6 days. In the Rotarix 036 trial in Europe, the first dose was administered at age 6–14 weeks 6 days. The second dose was given 1 to 2 months after the first dose in each trial.

According to the FDA analysis of the safety data from the Latin American trial, the data did not indicate an increased risk of intussusception among infants studied who received vaccine compared to the infants who received placebo. During the first 30 days, 7 cases of intussusception were detected in infants who received vaccine, and there were 7 cases in the placebo group as well. Efficacy results are available for both studies. The primary endpoint for efficacy assessment in the Latin America trial was severe rotavirus disease, which was defined clinically as diarrhea that required overnight hospitalization or oral or IV re-hydration at a healthcare center. A commonly used clinical scale, the Vesikari Scale, was used in the European trial and was also reported for some of the endpoints in the Latin American trial. On this scale, a value of 11 or higher is classified as severe disease. The point estimate for each efficacy endpoint was 85% or higher in the Latin American study, and the estimates were generally higher in the European trial (95% severe, 100% hospitalization, 87% any). The type-specific point estimates were 88% or higher in both studies for G1P8, G3P8, and G9P8, and G4P8 efficacy was calculated only in the European trial. For all of these, the 95% confidence intervals did not include zero. For G2P4, the vaccine efficacy point estimates were positive, but the 95% confidence intervals included zero. For the analyses that went through the second season, the vaccine efficacy estimate

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was not statistically significant from the Latin American trial, but was in the European trial.

Working under the premise that the Rotarix® vaccine may be licensed by the June 2008 ACIP meeting, and that the new statement will include both vaccines if this occurs, the Rotavirus Working Group's proposed general recommendations thus far included the following:

> ACIP recommends routine vaccination of US infants with rotavirus vaccine . . . Two different rotavirus vaccines, Rotarix (GSK) and RotaTeq (Merck), are licensed for use in infants in the US.
>
> ACIP considers Rotarix and RotaTeq series equally safe and efficacious. Efficacy studies demonstrated approximately 85-98% protection against severe rotavirus disease, and 72-87% protection against any rotavirus disease.
>
> ACIP recommends vaccination of infants with 2 doses of Rotarix administered orally at ages 2 and 4 months.
>
> ACIP recommends vaccination of infants with 3 doses of RotaTeq administered orally at age ages 2, 4, and 6 months [currently stated in the ACIP recommendation].

Referring to a summary table of the recommended ages and doses for both Rotarix® and RotaTeq®, Dr. Cortese pointed out that ACIP proposes to harmonize the maximum ages for doses between both vaccines, with one of the considerations being that the working group thought that harmonization, when reasonable, would be an advantage for the program overall. The maximum age recommendations differ somewhat from the maximum ages in the trial protocols.

For the interval between doses, the working group proposed to state, "Doses of rotavirus vaccine should be separated by an interval of 4 weeks or more." The recommended ages for doses would then define the usual interval between doses as 2 months. Here, they would be stating the minimum interval between doses and not an upper limit. Four weeks is the minimum interval between doses for most infant vaccines in the current schedule. For RotaTeq®, there would be no change from way the current ACIP recommendation is likely interpreted, "Subsequent doses should be administered at 4-10 week intervals…" This would be a slight wording change for that vaccine, but it would not be a change in the way the recommendation is likely interpreted in that the recommendation does not explicitly state that doses should not be given if 10 weeks have passed since the previous dose. There are data on a limited number of infants in the RotaTeq® trial who received vaccine doses more than 10 weeks apart. Generally, the data were similar to those from the study overall, but again the numbers were small. This recommendation would be harmonized between the two vaccines, and the working group felt that harmonization of the recommendations whenever reasonable is programmatically advantageous.

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For the maximum age for the first dose, the working group proposed to state that, "The first dose of rotavirus vaccine should be administered between ages 6 and 13 weeks. The maximum age for Dose 1 is 13 weeks 6 days. Vaccination should not be initiated for infants aged 14 weeks or older . . ." For this wording, the working group operated under the premise that if Rotarix® is licensed, the FDA labeling may indicate that the maximum age for Dose 1 of Rotarix® is 13 weeks, that being the limit used in the Latin American trial. If the vaccine is licensed and labeled with a different maximum age for dose one for Rotarix®, the working group proposed that that label's maximum age be the one recommended for both vaccines. For RotaTeq®, that could represent an expansion of 1 to 2 weeks from that used in the trial. The current ACIP recommendation states that the maximum age is 12 weeks. The working group thought that this was an appropriate recommendation, given that the available data from the trial and from two years of US post-marketing do not indicate that RotaTeq® is associated with intussusception in the age groups recommended for vaccination.

For maximum age for the last dose, the working group proposed to state that, "All doses of rotavirus vaccine should be administered by age 32 weeks. The maximum age for last dose is 32 weeks 6 days." For RotaTeq®, this would be an expansion for the maximum age for the last dose by 6 days from that used in trial. This would not be a change from the way the current ACIP RotaTeq® recommendation is likely interpreted, which states, "All doses should be administered by age 32 weeks…" For Rotarix®, this would be an expansion of the maximum age for the last dose by 8 weeks from that used in the large safety trial. The working group's reasoning for this proposal was that data from the trial do not suggest that Rotarix® is associated with intussusception in the age groups studied. Further, the background rates of intussusception are similar at ages 24−32 weeks. And, if mixed (or potentially mixed) series are allowed and 3 doses are recommended, the 32 week age limit is practical.

Regarding interchangeability of products in vaccine series, the working group recognized that there will be some infants who change providers after receiving one dose and before finishing the series by age 32 weeks. The second provider may not have the same product as the first provider, or know which product was used. The working group considered all of the possible options, from not allowing any mixing at all to trying to start the series over if a new product was used, and reached a consensus on the following proposal:

> It is recommended that the vaccine series be completed with the same brand of rotavirus vaccine whenever possible. However, if the product used to start the series is unknown or not available, the provider should complete the series with the product available.
>
> If any dose in the series was or may have been RotaTeq®, a total of three doses of rotavirus vaccine should be given. The interval between rotavirus vaccine doses should be 4 weeks or more, and all doses should be given by age 32 weeks (maximum age for last dose is 32 weeks 6 days)."

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With respect to "mixing" in a series, the working group considered that currently there are no data and that data are not expected to become available. The working group's opinion was that mixed series would not pose additional risk and a series would be effective against rotavirus disease. Programmatically, it would be a practical requirement to address this issue. In terms of giving 3 doses of rotavirus vaccine if any dose in series was or may have been RotaTeq®, no data are available or expected on such a mixed series. However, this follows the general concept of ACIP Hib vaccine recommendations for mixed series, where one product (Hib-OMP) had a 2-dose primary series and the other products had 3-dose primary series, and three were doses to be given in a "mixed" infant primary series. There are differences of course between these types of vaccines, and some data were available on mixed series of Hib vaccines.

In conclusion, Dr. Cortese reminded everyone of the additional tasks to be addressed by the working group, including the development of proposed recommendations for Rotarix® and an update for RotaTeq® as indicated, for special populations, special circumstances, and contraindications and precautions; review of any additional information on safety and efficacy; and review cost-effectiveness data for Rotarix®.

Discussion

- Dr. Paul Offit (GSK), a co-inventor of RotaTeq®, acknowledged that the interchangeability issue is difficult given that there are no data upon which to base the recommendation. He clarified that if giving one dose of Rotarix® and then two doses of RotaTeq®, that would mean children would be receiving 3 doses of G1-containing virus, which would give them protection against G1. They would also get 3 doses of P serotype 8, or P genotype 1A-containing viruses, which would give them protection against G1, G3, G4, and the G9 viruses that are also P genotype 1A. However, this would be dropping down to two doses of G2 from what was 3 doses of a G2-containing vaccine. There was some evidence in the smaller European trial of heterotypic immunity. However, there was no evidence of heterotypic immunity in the larger Latin American trial. It is very possible that there may not be a G2 indication for Rotarix®. Dropping from a 3-dose to a 2-dose G2-containing schedule, the presumption is that about 10-15% of what would have been G2 protection would be lost. That, in combination with the fact that most circulating strains are G1 strains, the G2 account for anywhere from 5-15%, suggests that there will be somewhat less G2 protection. He also applauded the working group's attempts to try to harmonize the two schedules as much as possible, particularly with regard to making it easier for the clinician. He reminded everyone that the reason the first dose recommendation of 6-12 weeks and then a maximum third dose recommendation of 32 weeks was that as compared to what had been done for Rotashield® (2, 4, and 6 months) was due to the concern it would extend beyond the way the 70,000 person trial had been conducted. At the time of that recommendation, they were coming off of a vaccine which was known to cause intussusception. Also known was that natural intussusception occurs in the 5-9 month age range. Thus, they were attempting to adhere as closely to the large trial

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protocol and the FDA licensure as possible. At approximately 12 million doses of RotaTeq® vaccinations, there is no evidence that it causes intussusception, and the first dose recommendation is somewhat confusing for physicians and physicians are rewarded for not knowing what the recommendation was (that is, the recommendations now state that if an infant inadvertently receives dose 1 at age 13 weeks or greater, the series can be continued). Hopefully they will reach a point that enough vaccine has been administered to enable them to remove the restrictions that are difficult for physicians to understand.

- Dr. Neuzil noted that there are some data now on less than 3-dose efficacy. She wondered if the working group had considered any modeling, or whether anyone was working on any modeling that might give them an idea of what could be expected, taking into account the issue of strains and also less than full dose efficacy.

- Dr. Baker requested clarification regarding the recommendation if it was not known what the first dose was.

- Dr. Cortese replied that if the manufacturer of the first dose is unknown, the recommendation would be that a total of 3 doses be given, so the child would receive two more doses.

- Dr. Judson requested a rough estimate of the cost per dose for RotaTeq® and Rotarix® per series.

- Leonard Friedland (GSK) responded that the price of Rotarix® has not been set yet in the US, given that the vaccine is not yet licensed. With respect to G2 protection, GSK strongly believes that Rotarix® protects against G2P4 type. In the European trial (Rotarix 036), there was statistically significant efficacy against G2P4. The reason that G2P4 was not statistically efficacious in the Latin American study (Rotarix 023) or in the first year of the European (Rotarix 036) trial was that the number of cases was small. The point estimates were always positive in all of the studies, including meta-analyses of pooled studies from Phase II and Phase III. Only 5% of the placebo subjects in the European and Latin American trials had G2P4, so they just happened to run the trials when circulating types of G2P4 were low. In the RotaTeq® data, there were also small numbers of cases of G3 and G4 that occurred in the studies, and statistically significant efficacy was not reached for the primary endpoints. So, Rotarix® does protect against G2P4 and it has been shown when larger numbers of cases occur, including those of pooled studies.

- With Rotarix® licensed in over 100 countries, Dr. Gellin (NVPO) inquired as to whether Dr. Friedland could give a range of prices in countries with economies comparable to the US.

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- Leonard Friedland (GSK) responded that there is tiered pricing, but that he did not readily know the private marking prices. He agreed to check pricing information and provide feedback to the ACIP prior to the end of the meeting.

- In response to Dr. Neuzil's comment about efficacy in less than a full dosing regimen, Michele Goveia (Merck) pointed out that most of the data presented about RotaTeq® were breakthrough cases of rotavirus disease only until the next dose was given, so short-term efficacy follow-up. In response to the cost inquiry, she indicated that the retail price for RotaTeq® is approximately $68 per dose, while VFC pricing is approximately $55 per dose.

Adoption of Rotavirus Vaccine

Shannon Stokley, MPH
National Center for Immunization and Respiratory Diseases

Ms. Stokley reported the results of the "Physicians' Attitudes Regarding a New Rotavirus Vaccine: A National Survey." This work was done through a collaboration between CDC and researchers from the University of Colorado. Approximately one year after the introduction of the new rotavirus vaccine in February 2006, a survey of pediatricians and family medicine physicians was conducted. The study objectives were to determine, through this national survey of pediatricians and family medicine physicians: 1) Rates of adoption of new rotavirus vaccine; 2) knowledge of and compliance with ACIP recommendations for its use; 3) Perceived barriers to adoption; and 4) Understanding of FDA / CDC post-marketing surveillance reports that were published in March 2007. The study was conducted in a sentinel physician network, which was developed as part of the Vaccine Policy Collaborative Initiative. Physicians included in this network have agreed to complete approximately 3 to 4 surveys per year related to immunization issues. This mechanism has been found to be very useful for receiving information in a timely manner and to help inform immunization policy decisions.

The network recruited physicians from a random sample of 2500 American Academy of Pediatrics (AAP) and 3500 American Academy of Family Physicians (AAFP) members. The study was designed to be representative of AAP and AAFP with respect to region of the country (NE, S, MW, W), location (urban, suburban, rural), and setting (private, managed care, community / hospital-based)–AAP only. Respondents spending less than 50% of their time practicing primary care were excluded. The survey was pilot-tested in a community advisory panel, which included a group of 6 pediatricians and 6 family medicine physicians from throughout the US. The survey was administered by mail or email, depending upon the physician preference stated at the time of enrollment, during August – October 2007. During that time, the survey was sent to 429 pediatricians and 419 family medicine physicians. Response rates were 84% for pediatricians and 79% of family medicine physicians returned the completed survey. Of the family medicine physicians, 68 were excluded who reported that they do not treat infants less than 6 months of age. Ultimately, 359 pediatricians and 264 family

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medicine physicians responded. Respondents did not differ from non-respondents with respect to sociodemographic factors, region of the country, practice setting, or location. Of note, more family medicine physicians (33%) were practicing in the Midwest and in rural areas compared to pediatricians (21%).

Physicians were asked about their current practices for administering rotavirus vaccine to their patients. Significant differences were observed between the two groups. The majority of pediatricians (85% compared to 45% of family medicine physicians) are routinely administering the vaccine to their patients. However, there were significantly more family medicine physicians who do not offer the vaccine (42% compared to 11% of pediatricians). Physicians were also asked about their current practices for recommending the vaccine. Significantly more pediatricians (70%) strongly recommend the vaccine compared to family medicine physicians (22%). Of the pediatricians, 17% said that rotavirus vaccine was not necessary for their patients compared to 44% of the family medicine physicians. Of the pediatricians, 88% said that rotavirus vaccine should be routinely recommended for all eligible infants compared to 64% of the family medicine physicians. Because the vaccine has strict scheduling requirements, the physicians' knowledge was assessed about the timing of the vaccine. Physicians were asked when the latest time was that the first dose could be administered. Pediatricians (69%) were more likely than family medicine physicians (30%) to answer correctly. They were also asked by which age all 3 doses should be given. Again, pediatricians (62%) were more likely to answer this question correctly compared to family medicine physicians (32%). Overall, few physicians reported administering the first and third doses of the vaccine outside of the recommended ages. Notably, 40% of physicians in both groups reported that the recommendations were too complicated.

Perceived barriers to giving rotavirus vaccine included failure of some insurance companies to cover the vaccination; the "up-front" costs to purchase the vaccine; lack of adequate reimbursement; respondent's concern about the safety of rotavirus vaccine; and the addition of another vaccine to the schedule. These issues are frequently mentioned whenever we survey physicians about implementation of a new vaccine. Differences were observed between the two groups of physicians. Pediatricians cited failure of some insurance companies to cover the vaccination; the "up-front" costs to purchase the vaccine; and lack of adequate reimbursement as their greatest barriers. Family medicine practitioners cited these limitations as well; however, they were significantly more concerned about the safety of the rotavirus vaccine and the addition of another vaccine to the schedule.

The FDA / CDC post-marketing surveillance report on intussusception in the *MMWR* on March 16, 2008 concluded that the post-marketing surveillance data did not suggest an association with the Rotateq® vaccination and intussusception, and reaffirmed the vaccine policy recommendation to routinely administer the rotavirus vaccine to US infants. Of the 407 physicians who reported that they either heard about or read the FDA/CDC reports, the majority of pediatricians (91% compared to 62% of family medicine physicians) responded that the number of cases of intussusception reported did not exceed the number expected. More family physicians (25%) than pediatricians

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(8%) were uncertain about whether the number of cases reported exceeded the number expected by chance. Overall, the post-marketing reports did not cause the physicians to alter their practices regarding the vaccine. However, 3% of pediatricians and 11% of family medicine physicians reported that they stopped giving the vaccine because of the reports. With regard to the physicians' attitude toward the reports, in general, the majority of physicians somewhat or strongly agreed that the messages were communicated clearly (pediatricians 79%; family medicine practitioners 63%) and that they were helpful (pediatricians 60%; family medicine practitioners 67%). Only a third of the physicians agreed that the reports should not have been publicized because they raised concern unnecessarily. However, compared to pediatricians (35%), a greater proportion of family physicians agreed (58%) that the reports increased physician's concern about rotavirus vaccine's safety, increased parents' concern about the vaccine, and decreased parental acceptance of the vaccine.

In summation, Ms. Stokley pointed out the study had two important limitations. The physicians in this study are part of a network and they have agreed to complete surveys throughout the year. Thus, there is a potential for bias in those who respond to surveys. In addition, all data rely on self-reported vaccination practices rather than measured practice. With regard to the results, 85% of pediatricians, but only 45% of family medicine physicians reported currently routinely offering the new rotavirus vaccine to all eligible infants. The attitudes of pediatricians and family medicine physicians about the vaccine differed, with family medicine physicians more often reporting that rotavirus vaccine is not a necessary vaccine and that rotavirus vaccine should not be routinely recommended. Knowledge regarding timing of doses of rotavirus vaccine was twice as high among pediatricians than among family medicine physicians. As with other new vaccines, concerns regarding reimbursement, up-front costs, and inadequate reimbursement were perceived as the major barriers to implementation in both groups. Family medicine physicians also had substantial concerns regarding vaccine safety in general, about rotavirus vaccine specifically, and about overloading an already crowded immunization schedule. In general, the FDA / CDC post-marketing surveillance reports were understood by the physicians and were thought to be reported clearly. Compared to pediatricians, more family medicine physicians reported increased vaccine safety concerns due to the reports. What the survey really highlights is that there are clearly differences between pediatricians and family medicine physicians with regard to adopting a new vaccine. With that in mind, efforts should be increased to address the gaps in knowledge and other concerns about new vaccines and vaccines in general.

Discussion

- Dr. Sumaya wondered whether the investigators could stratify the percentage of the family medicine physicians' clientele that are children, particularly very young children, to determine whether there are any differences in the groups who see 25%, 50%, et cetera and those who see more young children to determine whether they are aligned better with the pediatrician group.

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- Ms. Stokley responded that she was not sure whether they had the percentages of the family medicine physicians' clientele that are children, but they do have other characteristics regarding the percent of their patients who are on Medicaid or the children's health insurance program. They may be able to run the analysis stratified by those characteristics.

- Dr. Duchin (NACCHO) asked whether there was a way to determine whether the immunization coverage rates varied among the different groups. For example, was it possible that these children are vaccinated somewhere else rather than their family practitioner.

- Dr. Stokley replied that this survey was not designed to measure coverage. If they had asked about coverage it would have been self-reported, so reliability may have been an issue. It is possible that there are data from NIS that indicates where children are receiving their vaccines, but from this survey they are not able to determine whether the patients of practitioners who were not recommending the vaccine went elsewhere to be vaccinated.

- Dr. Temte commended the survey group because he thought the results reflected exactly what family medicine practitioners are doing. There has been a long tradition of skepticism within the family medicine specialty in terms of general recommendations. Sometimes this has served them well, for example with Rotashield®, they were correct in their skepticism. However, they may not be with Rotateq®. Within the scope of practice, treating infants is a part of what family medicine practitioners do, but they also have to attend to the latest recommendation for use of statins in people over 85. Family medicine practitioners have such a broad range of responsibilities, they are going to be slow to acquire new recommendations and make them part of their practices. Although over time the number of family medicine practitioners recommending RotaTeq® will increase over time, adoption will likely be slow. That was the case with varicella vaccine in the first two years, during which family medicine practitioners were in the 30-40% range. There is also vaccine fatigue due to the rapid increase over the last four years in new vaccines and new recommendations, at least among AAFP's membership, which is why it is important for ACIP to address implementation issues.
- Dr. Baker noted that there is a difference in the AAFP memberships' perception of the words "recommended" versus "strongly recommended." Rotateq® is "recommended."

- Dr. Campos-Outcalt responded that in terms of AAFP's internal recommendations, there is a tendency to adopt and use the US Preventive Service Task Force (USPSTF) recommendation scheme, which has two levels of recommendations: "strongly recommend" and "recommend." Generally, the evidence is somewhat stronger for the "strongly recommended" recommendations. Their members tend to pay attention to that and adopt less aggressively the "recommended" versus "strongly recommended" recommendations. There are also issues of reimbursement that are affecting AAFP members in that they lose money on each

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vaccine, yet they are being asked to make up for it with volume. That reaches the point of diminishing return for a lot of their members. Not only do reimbursement issues need to be addressed, but also educational efforts need to be enhanced. Another issue is that family physicians as a whole have been moving toward an evidence-based methodology for recommendations, given that they are bombarded with recommendations from numerous groups who want their recommendations adopted. Therefore, AAFP has adopted a system of evaluating and ranking recommendations based on their evidence base. Just as ACOG has done, AAFP is moving toward encouraging some evidence-based rating for immunization recommendations for their membership. AAFP has always been supportive of the harmonization of schedules, and the implementation recommendations have the highest rates of implementation of any recommendations. However, there will likely be increasing questioning regarding the evidence level behind recommendations, so this must be addressed as well.

- Dr. Curlin (NIH) said that the landmark IOM study about vaccine priorities in the early to mid 1980s did not include rotavirus.

- Dr. Iskander pointed out that there is evidence from recent survey research pertaining to flu vaccine in which a similar proportion of practitioners perceived that the flu vaccine causes the flu and state that they learned this from CDC. That suggests that perhaps that not only is knowledge an issue, but perhaps memory is an issue as well. There are some upcoming educational opportunities, such as the publication of the data in a peer-reviewed journal and Merck's educational campaign that is focused on the safety of their product to a large extent.

- Stan Plotkin was startled to see that 24% of pediatricians and 58% of family practitioners had increased concern about rotavirus vaccine safety after a negative message. This would suggest that the messages are being misinterpreted, which may also mean that perhaps the messages are not clear. With that in mind, he suggested that CDC and those who write safety messages to physicians and the public take this survey very seriously. Perhaps at the end of any statement, there should be a message in bold that clearly states the conclusions.

- In response to the earlier question about the cost of vaccines, Jane Quinn (GSK) reported that Rotarix® is licensed in approximately 100 countries with about 20 million doses distributed thus far. Most of those have been in large government tenders, such as Mexico and Brazil. Those countries do not reveal the results of their pricing contracts and tender awards. While she could not provide a specific range of prices across those many countries, generally the cost per regimen or immunization series has been similar between Rotarix® and Rotateq®.

Implementation of Approach to Economic Analysis

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Tracy Lieu, MD, MPH, Member
ACIP Ad Hoc Working Group on Economic Analysis
Mark Messonnier, PhD and Martin Meltzer, PhD

Dr. Lieu discussed the guidance for presentation of economic studies to ACIP. ACIP's charter specifies that committee deliberations should include consideration of population-based studies, such as efficacy, cost-benefit, and risk-benefit analyses. Hence, it is part of ACIP's job to consider cost-effectiveness. There is interesting language in the VFC legislation indicating that ACIP decisions should be based on health and economic value rather than on budget impacts. Thus, ACIP is not meant to worry about the exact budget impact of its recommendations, but rather on their economic appropriateness. Having said that, ACIP has spent a fair amount of society's money is recent years. In 1985, the cost of the vaccine doses needed to fully immunize a child from birth to age 17 at federal contract prices was $45. By 1995, that cost was $155. In the last five years, ACIP has caused that cost to rise to $900 for males and $1,200 for females because they receive HPV vaccine. Almost all of the cost increase has been due to new vaccine programs that ACIP has recommended primarily in the past four years. With almost every vote, the ACIP hears economic presentations and is asked to digest an immense amount of economic information, which is sometimes not very easy to digest.

Thus, the context of developing an implementation approach to economic analyses was that the ACIP and the working group wanted guidelines so that the presentations made during ACIP meetings could be clearer and most beneficial to the ACIP's deliberations. They also wanted a quality assurance process so that the economic analyses can be reviewed for standardization of methods and for reasonableness of assumptions because as someone who does these analyses, Dr. Lieu stressed that they were very easy to bias depending upon how they are set up and they can be extremely difficult to understand when presented in a 10-minute PowerPoint presentation. Over the past three years, ACIP and its *Ad Hoc* Working Group on Economic Analysis have been developing guidance, which has been published as a Notice to Readers in the *MMWR.* In summary, the guidance is that those who conduct economic analyses should follow a prescribed set of methodologic guidances and should also submit a written report of methods and results, along with slides and other presentation materials 8 weeks in advance of the ACIP working group meeting regarding the intent to present or 8 weeks in advance of the ACIP meeting if the presentation is also being made there. Reviewers will return comments, which is the responsibility of NCID and Drs. Messonnier and Meltzer to manage. The reviewers will return comments so that the presenters or authors can revise as needed. This guidance will be effective for the June 2008 ACIP meeting and for future meetings. Further information about the guidance can be acquired at: http://www.cdc.gov/vaccines/recs/acip/economic-studies.htm. Dr. Lieu extended special gratitude to Drs. Jean Smith and Larry Pickering for shepherding this process, stressing that it would improve the quality of the work that ACIP reviews.

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Discussion

- As the chair of the HPV Vaccines Working Group where things are changing weekly and monthly, Dr. Englund expressed concerned about the 8-week time limit, especially as new vaccines are licensed and / or vaccine issues arise. While she agreed that the 8-week idea was good, there should be some type of emergency provision for altering that timeframe should issues arise that do not allow for adherence to that stipulation.

- Dr. Messonnier responded that there are provisions for true emergencies or true urgent need for shortening that timeline. However, poor planning does not constitute an emergency. An effort will be made to accommodate late breaking information, and there is a specific provision in the guidance for how that will be done. He also noted that the term "should" appears in the language, but instead it is "must." That is, these guidelines must be followed for economic studies that are to be presented.

Rabies Vaccines and Biologicals

Charles E. Rupprecht VMD, MS, PhD
Chief, Rabies Program
PRB / DVRD / NCZVED / CCID / CDC

Dr. Rupprecht presented information regarding concerns regarding the availability of biologicals for the prevention of human rabies, as well as strategies to mitigate those concerns. In addition, he solicited input from the ACIP with regard to mitigation plans. Rabies is receiving increasing global concern as evidenced by the World Health Organization (WHO) inclusion of rabies in vaccines of special concern, and the emergence of new lyssaviruses that are not covered by current licensed rabies biologicals. Unfortunately, there is misinformation that rabies is rare in the United States (US), unless one has the benefit of living in Hawaii. Rabies is an acute, progressive, viral encephalomyelitis due to an animal bite. The case to fatality rate is the highest of any infectious disease. Agents reside in the genus *Lyssavirus* and the disease remains a leading viral zoonosis as regards global public health significance, primarily related to infected dogs in developing countries, and mammalian wildlife hosts in the developed world. With respect to the US, while human rabies is uncommon (1-8 cases per year), the risk of exposure is not, with approximately 20,000 – 40,000 human exposures per year. Approximately 7,000 – 10,000 animal rabies cases are diagnosed per year. Wildlife reservoirs include raccoons, skunks, foxes, mongoose, and bats. Rabies is distributed in every state except Hawaii.

Human rabies prevention is accomplished by avoiding exposure, and through pre-exposure vaccination and post-exposure prophylaxis (PEP). Rabies biologicals include rabies vaccines for pre-exposure and PEP, and rabies immune globulin, which is used only in PEP. Vaccines and immune globulins are included in discussions about relative supply. It is difficult to manage epidemiological considerations of pre- or PEP for those who may be at risk for exposure, as opposed to those who have laboratory-confirmed

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exposure. Pre-exposure vaccination is provided to subjects at risk before occupational or vocational exposure to rabies. Subjects include diagnosticians, laboratory and vaccine workers, veterinarians, cavers, travelers, et cetera. This simplifies PEP management. In contrast, PEP is provided to subjects after rabies exposure and consists of wound care, rabies immune globulin infiltration, and vaccine intramuscularly. If prompt and proper, survival is virtually assured after viral exposure. Thus, PEP is more easily controlled because one can discuss with providers and public health departments the utility of need and utilization based upon existing ACIP recommendations, as opposed to pre-exposure vaccination, which may or may not be used appropriately for those groups at true risk.

The only two available licensed human rabies vaccines in the US are the human diploid cell vaccine, Imovax® (HDCV), and the purified chick embryo cell RabAvert® (PCEC). The RVA product and intradermal application of vaccine are no longer available in the US. The two human rabies immune globulins (HRIG) available in the US are HyperRabTM® S/D and Imogam® Rabies-HT. Both are supplied in vials at ~ 150 IU/ml. Effects upon vaccine and RIG are interdependent, in the sense that when there is an effect on one, meaning vaccine supply, obviously it will have a consequent effect, but with a lag time, upon RIG. Pre-exposure vaccination is given intramuscularly on days 0, 7, and 21 or 28. Serology occurs every 6 months to 2 years (if remaining at risk), rather than through routine boosters. If antibody titer is not adequate, a single booster dose is administered. If ever exposed, a vaccine dose is given intramuscularly on days 0 and 3, regardless of rabies virus neutralizing antibody titer. Post-exposure prophylaxis is three-pronged in approach, including: wound care, which involves washing of the lesions very well with soap and water (and a tetanus booster ad hoc); infiltration in and around the wound (not gluteus) with RIG (20 IU/kg); and administration of vaccine on days 0,3,7,14, and 28. Pre-exposure vaccination is simpler and obviates the need for human RIG in a previously vaccinated person.

The issues affecting the relative supply of rabies biologicals are complex and the absolute need is unpredictable. Primary need is based on zoonosis burden, episodic incidents involving multiple human exposures, routine regulatory oversight, planned commercial production changes, shifting market dynamics, and untoward scenarios. These issues will impact human RIG and pre- and PEP utilization. Currently, strategies to minimize shortages are multi-faceted, with more long-term operations involving research and development for future biologicals, or imminent products that are in the current pipeline for licensure, as well as more short-term solutions, such as recommendations for utilization of biologicals that are in potentially short supply. Potential solutions to shortage forecasts include routine multi-disciplinary prevention and control efforts, changes in regulatory review of rabies biologicals, considerations of requests for alternative products and manufacturers, creation of managed strategic stockpiles, improved incentives for applied research and development of novel biologicals, and implementation of contingency recommendations to maximize proper use of critical supply to patients most at risk.

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Immediate solutions will focus upon recommendations of a working group for contingencies, when supply forecasts are shifting from 'less than adequate' to a projected shortage, and range the gamut from new health communications to providers and constituents in the state health departments, potential changes in exposure criteria / triage of patients, pre-exposure vaccination alterations, and PEP management modifications. The 2008 ACIP recommendations that are in press, at the proof stage, recognize the urgency of prophylaxis as opposed to the emergency of utilization. In addition, currently, there is differential utilization of currently licensed vaccines, to the extent that at least one manufacturer's product is being utilized only via the interactions of public health consultants for PEP use. Also important for mitigation is engagement of other basic legal parameters, unrelated to vaccination of humans (e.g., national / state dog and cat vaccinations, greater rapidity of diagnostic testing, enhanced observations of biting animals, non-importation of animals from canine-enzootic countries, improved stray animal control in the local area, et cetera). For the re-assessment of exposures in terms of potential mitigation, if shortages were to come to bear, the focus should be on bite exposures, as opposed to non-bite scenarios, and upon re-emphasizing the fact that indirect non-bite exposures have never resulted in human rabies cases (e.g., contacts with blood, urine, feces, et cetera are not considered exposures). Many scenarios, such as merely seeing a rabid animal, being in the same room, petting, et cetera, are not considered grounds for prophylaxis (e.g., a de-emphasis on the "bat in the bedroom"). Improved health communications that focus upon what true rabies exposure is, and what it is not, will become increasingly important as inadequate supply issues manifest.

Similarly, in regard to pre-exposure vaccine supply issues, it should be recognized that one cannot divert all vaccine supplies to exposed individuals only, because there are individuals who work with rabies virus directly, or who are at potentially high risk of exposure to such rabid animals, for example. Also important to remember is that a certain amount of the vaccine doses must be utilized for human RIG campaigns. Currently, forecast of human RIG supplies for 2008, and possibly into 2009, should be reasonably robust. However, the concerns about vaccine availability will impact that situation beyond 2009. Besides the issues of better defining exposure, and potential utilization differences in the pre- vs. PEP realms, such as potential intradermal applications, there are similar issues with regard to PEP supply with respect to the application of vaccine doses or in alternative schedules, in an effort to conserve supplies. Both considerations have already been suggested, implemented, and recommended by the WHO. If regulatory issues concerning currently licensed vaccines are resolved in a timely and satisfactory manner, there should not be any major supply shortages to be anticipated in 2008 and 2009. However, if this cautious optimism is not realized, at some time during the expected high season of exposures in the summer of 2008, the burden rates for PEP will be expected to affect vaccine supply, and will severely limit the opportunity to maintain adequate coverage in all exposed individuals by the end of 2008, prompting necessity of alternative actions in current ACIP recommendations.

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In summary, supplies of human rabies biologicals for pre- or PEP in the US are manageable at present, but are expected to be less than ideal over the next several years. The CDC, FDA, HHS, industry, and local and state public health authorities continue to work together towards productive solutions to this problem. Formation of a national multi-disciplinary rabies working group will assist in the formation of new ad hoc recommendations related to "contingency plans", beyond the current ACIP recommendations, in the event that projected true shortages are forecast in the future.

Discussion

- Dr. Pickering reminded everyone that when there have been vaccine supply problems, ACIP has handled them in a couple of ways. Most of the vaccine supply issues have involved vaccines in the recommended childhood/adolescent or adult immunization schedules and have been handled by a CDC stakeholder group that meets regularly when supply issues arise. Similar groups are formed when supply issues arise for travel medicine vaccine as was done for the salmonella vaccine shortage and is currently being done for the yellow fever vaccine shortage. The ACIP work groups that are formed generally deal with vaccines and recommendations for vaccines that are long-term and the ACIP will vote on any changes that are recommended by CDC or ACIP work groups that deal with shortages.

- Similar to what Dr. Rupperecht described, Dr. Schuchat thought that most likely a group made up of public health experts, veterinary community experts, CDC and other subject matter experts would be convened to contemplate the issues and potential contingencies that need to be planned for. A lot of the planning would not actually be around vaccine or immune globulin. Instead, it would be around messaging and narrowing down the scenarios. Perhaps ACIP could provide a liaison to that group to ensure that there is clear communication and understanding. However, such a group would be convened as done in other vaccine shortages—separate from an ACIP standing working group.

- Dr. Turner (ACHA) was interested to see de-emphasis on the "bat in the bedroom." In his world, that is an extremely common scenario. Their students live in old apartment buildings and old fraternity houses that do not have screens on the windows. On numerous occasions the health department has directed them to give students post-exposure prophylaxis merely because they saw a bat—not because the have been bitten. That accounts for approximately three fourths of the post-exposure prophylaxis that they administer. He asked for clarification regarding whether Dr. Rupprecht was stating that this is the current recommendation.

- Dr. Rupprecht replied that it is often easier to write a script than to spend a lot of time on the phone or in consultation either with a clinician or a concerned member of the public. Oftentimes, ACIP recommendations are misconstrued and taken out of context. Current CDC / ACIP recommendations do not recommend prophylaxis for a "bat in the bedroom." The recommendations address risk assessments and

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reasonable assessments toward the degree of exposure. Thus, they are re-emphasizing interactions with state health departments and those who provide such public health information, so that merely seeing a bat or being in the same room with a bat does not mean prophylaxis is needed. This is an emerging area, because many of those who are not at risk are being over-vaccinated.

- Dr. Judson indicated that he was the director of a local health department for 20 years, and that is a common scenario. There are contacts at the state level upon whom the local state departments can rely for firm support that no prophylaxis is required due to merely seeing a bat, the assurance of which is particularly important with respect to a disease that is 100% fatal.

- Dr. Rupprecht responded that this is the reason that CDC has had increased outreach through several constituent groups throughout 2007 (e.g., CSTE, NASPHV, members of the Rabies Compendium Committee) who would also be included as liaisons in membership on the proposed ad hoc working group and the establishment of potential communication schemes to provide various resources in the advent of a shortage.

- Dr. Cieslak said that when last he reviewed the ACIP rabies vaccine recommendation, it read “should consider.” Almost all of the state health departments in the Pacific Northwest read “should consider” as it better be given.

- Dr. Rupprecht indicated that there were some who believe the recommendation should read “should” and others who thought it should read “must,” which was probably due to a misunderstanding about the relative risks. The recommendations coming out in 2008 should be interpreted that “when there is a reasonable probability of exposure, prophylaxis occurs.” How that point is phrased and actually interpreted at the local level will be a key. He also noted that the proposed ad hoc working group would include not only multi-disciplinary representation, but also a diverse geographic representation, because the epidemiology of rabies varies geographically.

- With respect to how the supply is being managed, Dr. Gellin (NVPO) inquired as to whether there had been any consideration of stockpiles, should there be supply issues.

- Dr. Rupprecht replied that over the last few years, there have been numerous discussions about the potential needs for stockpiling rabies biologicals to ensure that supply issues are addressed, and CDC hopes that these discussions will continue.

- Rajiv De Silva (Novartis) emphasized Novartis’s on-going commitment to being a long-term partner with public health in the area of rabies vaccination and to ensure the highest standards of safety and reliability in the supply. There is currently a limited supply of RabAvert®, the Novartis vaccine, on the US market. This limited supply is currently being distributed for post-exposure prophylaxis only. Based on

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current consumption, there is sufficient supply for four to six months. Novartis endorses the concept Dr. Rupprecht proposed for the formation of an ad hoc working group to consider contingency plans during this period. They would also appreciate any specific guidance the ACIP could provide in terms of any criteria that Novartis should consider in distributing its limited supply. With regard to the factors affecting its supply, Novartis received a warning letter from the US FDA related to deviations from common good manufacturing practices at their Marburg, Germany facility where the Novartis rabies vaccine is manufactured. Novartis takes this matter very seriously and is working closely with the FDA, and has already provided a response to the warning letter and is awaiting FDA commentary. Until this commentary is received and Novartis understands the FDA feedback for remediation plans, there is no certainty with respect to the timing of re-supplying the US with RabAvert®. In a separate but related matter, upon the acquisition of Chiron Corporation by Novartis going back to April 2006, Novartis undertook a thorough review of all manufacturing practices. Based on that review, in February 2007 Novartis voluntarily suspended the manufacture of RabAvert® to make some upgrades to their manufacturing process. Those upgrades have been completed and Novartis filed a supplemental license application to the FDA for those upgrades in December 2007. They are currently in the review period for that license as well. Novartis remains committed to resolving these matters and ensure a longer-term supply of RabAvert® to the market. Since becoming aware of the limited supply, Novartis has been in close communication with NVPO / CDC.

- Phil Hosbach (sanofi pasteur) indicated that sanofi pasteur is the other rabies manufacturer and that they were aware of this potential issue in the summer of 2007. They quickly alerted NVPO that they were observing more activity in demand for their vaccine. From the fourth quarter 2007, sanofi pasteur was essentially supplying most if not all of the marketplace with vaccine, both pre- and post-exposure. sanofi pasteur has limited capacity in manufacturing. They can potentially supply half of the marketplace over the next couple of years. Unfortunately, given that they have to supply more of the vaccine during this difficult time, that will also affect what is available later in 2008 and even into 2009. sanofi pasteur is committed to working closely with NVPO / CDC to ensure that they are appropriately distributing their vaccine supplies. sanofi pasteur is currently limiting supplies and carefully monitoring, but they do not know the ordering patterns of the other half of the marketplace as they supply 50% typically. Although many customers are new to them, they are diligently attempting to work with customers to ensure that no one is over ordering in any way.

- Dr. Morse indicated that CDC would proceed with forming an ad hoc working group to address shortage issues.

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Update: General Recommendations

Ciro Sumaya, MD, MPH, Chair
ACIP General Recommendations Working Group
Andrew Kroger, MD, MPH
CDC / EIPB

Dr. Sumaya mentioned that he was not present during the first day of the meeting, given that he was participating in a Congressional briefing on a crisis—the public health workforce—which he thought was very relevant to the work of the ACIP, the CDC, and all of the organizations represented.

He then reported that the General Recommendations Working Group provides a general type of reference on vaccines and immunizations. This working group publishes its recommendations in an *MMWR* at approximately 3-5 year intervals. There was a publication in 2002, 2006, and one is projected for 2009. The General Recommendations Working Group addresses immunization issues relevant to all vaccines, and addresses topics ad hoc that cannot be attributed to a single vaccine. This task is shared with other working groups (e.g., combination vaccines). The proposed contents for the 2009 publication include the following sections: Introduction (which will include a greater emphasis on risks and benefits); Timing and Spacing of Immunobiologics; Contraindications and Precautions; Preventing Adverse Reactions; Managing Adverse Reactions; Reporting Adverse Events after Vaccination; The National Vaccine Injury Compensation Program; Vaccine Administration; Storage and Handling of Immunobiologics; Altered Immunocompetence; Special Situations; Vaccination Records; Vaccination Programs; and Vaccine Information Sources. Many of the sections have been included previously and are being updated, while a number of sections dealing with prior stand-alone reports are being incorporated as well (adult and adolescent information, for example). There will be some reformatting as well to combine some sections and subsections. Other additions that will be proposed include information about the Women Infants and Children's Program (WIC) and vaccination administration, and the military's approach to recordkeeping for immunizations.

The general recommendations on immunization are directed primarily to providers who are administering many different vaccines every day to many age groups and in multiple settings. Providers come from various backgrounds (e.g., physicians, nurse-practitioners, nurses, pharmacists, medical assistants). The general recommendations report provides general information about immunobiologicals, providing practical guidelines on vaccine administration and technique. The goal is to make the publication user-friendly. The text will be accompanied by tables for quick reference.

Dr. Kroger shared the General Recommendations Working Group's methods, as well as some content information. As noted, the goal for the next iteration of the publication is 2009. This is the low end of the 3-5 year range for the interval between documents. The reason the working group is attempting to publish another version so quickly is because the content is continually changing. From day one following the publication of

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the 2006 document, there were clarifications, revisions, errata, new items that came to the fore. There were new vaccine recommendations made (e.g., adult Tdap and HPV), new recommendations for old vaccines made (e.g., HepB and varicella), et cetera. There is also a movement to retire stand-alone ACIP statements that deal with general issues. The working group's approach is to update the content and references, add new information as it becomes available, harmonize with the American Academy of Pediatrics (AAP) Red Book, and incorporate retired or soon-to-be retired ACIP statements. The ACIP statements to be incorporated include: Adolescent immunization (1996); Adult immunization (1991); Assessment and feedback—two pages that directs public health agencies to assess the provider vaccination rates (1996); Immunocompromised—has already been retired and all of the important content was brought into the last iteration (1993); Vaccination and WIC—requests public health agencies and WIC providers to collaborate to assess immunization rates (1996); Vaccine side effects, adverse reactions, contraindications and precautions—much of this content has been brought forward and will require minor changes (1996); and Combination vaccines—these are general principles as they relate to combination vaccines, and the extent to which these will be brought into the general recommendations or published as stand-alone documents has to do with the timeline of publication and production of these recommendations (1999).

With respect to the General Recommendations Working Group's methods, the group has met since June of 2007 to determine important content changes. Discussions among working group members have consisted of monthly teleconferences and an ad hoc face-to-face gathering during the last ACIP meeting. The working group has begun to make content revisions, writing revisions of the separate sections within the working group. Similar to what was done with the last iteration, the working group plans to provide updates to the ACIP during the next two meetings. By the June 2008 ACIP meeting, the working group will have a draft of the revised content with potential language changes. Additional conference calls will be scheduled to focus specifically on various areas. The working group plans to present the final document to the ACIP by February 2009. The draft will be disseminated to ACIP members prior to the meeting. With clearance and publication, the hope is to have a publication date of December 2009 to meet the goal of a 2009 publication.

With regard to content changes, as noted stand-alone ACIP *MMWR*s dealing with general recommendations will be incorporated into the 2009 iteration. Clarification on prevention of adverse reactions has come to the attention of the working group in the last few months. This section of the document will address injury from syncope. There are now VAERS data that show a high proportion of syncopal events with new vaccines being used, so the language does need to be changed slightly. Updates also need to be made to appropriate sections.

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Some of the information in the stand-alone documents is carried forward into the schedule that is published every year. For adolescents that includes the vaccine-specific recommendations. The 2009 general recommendations will highlight these adolescent vaccine-specific recommendations, specifically the 11-12 year old immunization visit, a holdover from the 1996 document. Also included will be information about reconstructing the unknown vaccination record, and clarification of the concept of "catch-up" vaccination. "Catch-up" means to catch-up an entire cohort with a new vaccine and it also means to catch-up a child who is behind in his or her vaccination series. Some changes need to be made to the language to clarify this. For adult vaccination, vaccine-specific recommendations will be highlighted and there will be discussion of the unknown vaccination record (for example, whether military status can be used as a proxy to a record). Another important content change in preventing adverse reactions will be to highlight prevention of injury following syncope, with an effort to harmonize with the AAP language, and a pending *MMWR* that maintains CDC's encouragement for a 15-minute observation period. Section updates include timing and spacing, which is the first section in the document. Table 1 lists all of the minimum recommended ages and intervals for every dose of a vaccine. Some changes need to be made with LAIV, as well as Menactra®. Some minor changes need to be made to contraindications / precautions as well.

In conclusion, Dr. Kroger reiterated the offer to present incremental sections to ACIP during the next two meetings, and potential to have a vote on the interim sections to obtain ACIP's approval on the various sections. Given the pace of the working group, it seems that adolescent- and adult- specific principles will be ready by the June 2008 meeting. A similar process would be done in October, with the final draft presented at the February 2009 meeting.

Discussion

- Dr. Neal Halsey (Johns Hopkins University) said that having participated in a couple of earlier revisions of this document, it always seemed to take a couple of years to complete and within a year after completion, the guidelines are out of date. He thought the time had come to make this an electronic document that is updated every year just like the immunization schedule. Recommendations could be linked to all other recommendations and notes could be inserted mid-year as necessary.

Dr. Gerberding

Dr. Julie Gerberding, Director
Centers for Disease Control and Prevention

During the second day of the February 2008 ACIP meeting, Dr. Gerberding stopped by to address the committee. She said she had never been aware of any committee that had more important work to do than the ACIP, or of any voluntary committee that had ever asked more of its members than CDC did of the ACIP. She extended her personal

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respect and appreciation to the people who work so diligently to get the science right, carefully study the issues, and take on many of the controversies, difficulties, ambiguities, and uncertainties to bring it all together in a way that has resulted in a history and tradition of guidance around immunization practices about which they could all be proud. Prior to working at CDC, Dr. Gerberding had the opportunity to serve on a few CDC advisory committees; thus, she had a sense of what was involved and what the members were giving up to engage in this work. She requested that the CDC staff applaud and appreciate the ACIP members for their time and expertise.

She also expressed gratitude and appreciation to the ACIP for their work in the development of the influenza guidance. The previous day was a landmark day in influenza history in her opinion, and as evidenced by the media interest. Getting the science to come together to build these recommendations was a giant step. Another giant step will be executing on the guidance, which will take a network of the health system, an informed public, an informed provider community, and an informed payer community that is willing to be creative and help them find ways to deliver. This was relatively easy to do in terms of vaccines for very young children, but there are many more challenges with respect to routine vaccines for adolescents and adults. Dr. Gerberding recognized that it was not the responsibility of the ACIP to figure out how to execute on the guidelines, but it was the collective responsibility of many of them in the room. Together they must be willing to find broader and more creative ways to support the effective universal use of the recommendations that are made to achieve maximum benefit.

Dr. Gerberding entered the room when Dr. Rupprecht was reporting on the rabies shortage. Traveling throughout the world, she said she had a good sense of how important rabies is globally. She thought she would be remiss if she did not use this opportunity at the podium to thank the rabies team at CDC for their incredible success in eliminating canine rabies in this hemisphere. She was in India when they launched the rabies vaccine and was with the manufacturer the day they put it on the market. The entire sector there was only reflecting back to Dr. Rupprecht and his team at CDC, and their fine science that led to the rabies vaccine that is saving lives in some of the most difficult to reach parts of the world. She expressed her gratitude to Dr. Rupprecht and his team, and to everyone else present who was making a successful contribution to the world's health.

Dr. Morse expressed appreciation to Dr. Gerberding for taking the time to stop by, which meant a great deal to the committee. He also extended gratitude for the time she spends on a daily basis in terms of communication, and for mobilizing the remarkable team from CDC that puts in tremendous hours in this work and in support of the committee. The ACIP could not function as well without the CDC's support of the committee and its partners.

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Japanese Encephalitis Vaccines

Update from the Japanese Encephalitis (JE) Vaccine Working Group

Dr. Patsy Stinchfield
Chair, ACIP JE vaccine working group

Dr. Stinchfield updated the ACIP on the activities of the Japanese Encephalitis (JE) Vaccine Working Group. The first issue with which this working group has been dealing is that the only JE vaccine licensed for use in the US is no longer being produced. sanofi pasteur estimates that available supplies of the vaccine may be exhausted as early as mid-2008. With respect to this issue, the working group tasks have been to monitor the availability of JE vaccine for US travelers, and to work to mitigate any possible supply issues. The second issue is that a new vaccine has been developed, which is still in the pipeline. Intercell filed a Biologics License Applications (BLA) in December 2007 for this new JE vaccine. The new vaccine will be licensed for use in adult travelers. The working group tasks related to this issue are to draft ACIP recommendations for use of new JE vaccine in adult travelers, and to address future availability of JE vaccine for US children.

To deal with these issues, the Interagency Working Group formed in March 2006 has been officially made an ACIP Working Group formed in October 2006. Three meetings and regular conference calls have been held. The working group has received regular updates from manufacturers regarding currently licensed and two new vaccines. The working group is collaborating with Department of Health and Human Services (HHS), Department of Defense (DoD), and sanofi pasteur to offset potential supply issues. Dr. Stinchfield especially thanked DoD for a potential creative solution to this possible problem.

Japanese Encephalitis (JE) Vaccine for U.S. Travelers

Marc Fischer, MD, MPH
Arboviral Diseases Branch
DVBID, NCZVED, CDC

Dr. Fischer explained that Japanese encephalitis is a mosquito-borne flavivirus that is closely related to West Nile virus and St. Louis encephalitis virus. JE virus infection is the most common cause of encephalitis in Asia. Between 30,000 and 50,000 cases of JE are reported to the World Health Organization (WHO) each year. JE is a devastating illness with a case-fatality ratio of approximately 20 to 30%, resulting in an estimated 10,000 to 15,000 deaths annually. In addition, 30 to 50% of survivors have significant neurologic sequelae. This is likely to be an underestimate of the true burden due to inadequate surveillance and lack of diagnostics in the areas where the disease occurs.

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JE virus is transmitted in an enzootic cycle between mosquitoes and vertebrate animals. The mosquito becomes infected after biting a viremic animal. The infected mosquito then transmits the virus to another animal where the virus can amplify further. Although many animals can become infected with JE virus, pigs and wading birds are the most important reservoirs. If an infected mosquito bites a human, the person may become infected. However, JE infected humans are a dead end host in the JE virus transmission cycle because they develop only brief and low levels of viremia. Unlike dengue virus, humans do not amplify JE virus, and JE virus is not transmitted from person to mosquito or directly from person to person. That is, humans play no role in the maintenance or amplification of JE virus, and the virus is not transmitted directly from person-to-person. Therefore, even in endemic areas where human cases do not occur due to high vaccine coverage or natural immunity, JE virus may still circulate in an enzootic cycle, and non-immune visitors to that area may be at risk for disease. *Culex* mosquitoes are the principal vectors for both zoonotic and human transmission of JE virus throughout Asia. The primary JE vectors bite most often in the outdoors during the night.

There is no specific antiviral therapy currently available for JE. The only treatment is supportive therapy for the symptoms and complications. JE is primarily a disease of childhood. In endemic areas, almost all cases occur in children younger than 15 years old. There are two general transmission patterns of JE in Asia: 1) Seasonal epidemics, and 2) Endemic or sporadic disease. In temperate areas of Asia, such as China, Japan, Korea, Nepal, and northern parts of Vietnam, Thailand, and India, seasonal transmission occurs with summer epidemics that usually peak between June and September. In tropical areas of Southeast Asia and southern India, seasonal transmission varies with local patterns in bird migration, monsoon rains, and irrigation practices, and disease may be transmitted year round without clear evidence of a summer peak. These cases tend to be less recognized because there is not a normal seasonal peak. Human JE infections occur primarily in rural areas where large numbers of mosquitoes breed in flooded rice fields that are in close proximity to pigs and other livestock. However, these same conditions also exist within or at the edges of many Asian cities.

Estimating the risk to travelers is quite difficult. Extrapolating risk from resident populations who are exposed during a transmission season, estimates have been as high as 10 to 200 cases per 1 million persons per week. In studies of Western military personnel in Korea and Vietnam in the 1950s through the 1970s, this is consistent with immunized personnel's risk and rates of disease, with several hundred cases reported among military personnel during those military campaigns. Crude estimates based on published cases report that 39 travel-related JE cases were reported from 1973-2007. All had prolonged travel (>30 days) or visited rural areas. Of the 39 cases, 12 were US citizens (6 military, 6 civilians). Approximately 5 million US citizen entries were made into Asian countries in 2004. Based on this information, there appears to have been less that 1 case per 1 million US travelers per year. The conclusion is that the overall risk of JE for travelers is very low, but varies based on season, destination, duration, and activities. Prolonged travel in rural areas with active JE virus transmission likely

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carries similar risk as for the susceptible resident population. Shorter trips may confer increased risk if there is extensive outdoor or nighttime exposure in rural areas. The primary mosquitoes that transmit this virus tend to bite almost exclusively outdoors at nighttime, particularly at dusk and after midnight. That is really the exposure that puts people at risk for the virus. Short-term travel restricted to major urban areas confers very minimal risk for JE.

Inactivated mouse brain-derived JE vaccine has been licensed in the US since 1992 for adults and children (≥1 year). It has been used to effectively control JE disease in several Asian countries since the 1960s. The vaccine is manufactured by Biken of Japan and is distributed by sanofi pasteur. The vaccine showed 91% efficacy at 2 years after two doses in randomized controlled trials performed in 65,000 children in Thailand. Currently, the vaccine is used in a three-dose regimen in the US and most non-endemic countries and it is administered on days 0, 7, and 30. The third dose was added after additional immunogenicity studies were conducted in non-endemic personnel that showed that because they are not routinely exposed to the virus, they need an extra dose of the vaccine (mouse brain-derived JE vaccine production and components include Nakayama JEV strain cultured on mouse brains, concentrated / purified via ultra-filtration and ultracentrifugation, formalin inactivated, gelatin stabilizer, Thimerosal® preservative, and ≤2 ng/mL myelin basic protein—threshold of detection).

A significant issue regarding this vaccine is that some adverse events associated with the vaccine have been reported, particularly at the time that the recommendations were being written in the 1990s and continuing to the present. Local and mild systemic adverse events are similar to many other vaccines and are not particularly remarkable. However, there are also reported hypersensitivity or allergic reactions such as urticaria and angioedema of the extremities, face, and oropharynx reported among travelers. Some recipients have bronchospasm, respiratory distress, or hypotension. Most of these patients have been treated as outpatients with antihistamines and sometimes steroids, but at least in one report, up to 10% of patients have been hospitalized. Several deaths were temporally associated with vaccination, but none had evidence of urticaria or angioedema. Neurologic adverse events have been rarely reported among travelers (e.g., encephalitis, seizures).

A unique feature of allergic hypersensitivity reactions is that they may be delayed after vaccination, especially if they occur after the second or third dose of vaccine. With the first dose, most reactions occur within 48 hours. With the second dose, the median occurrence of reactions is three days, with a range up to 14 days after vaccination. This had led to the current recommendations that a traveler complete the 3-dose vaccination series at least 10 days prior to their expected travel to allow for medical monitoring should they develop a reaction. A few studies have suggested that these allergic reactions may be associated with a gelatin stabilizer that is used in the production of the vaccine. As noted several deaths were temporally associated with vaccination, but none had evidence of the allergic signs of urticaria or angioedema. In addition, because this is a travel vaccine being administered primarily to adults, most of these individuals with many of the reactions and the fatalities had received other vaccine products. One

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individual who died, who was in the military, was also on pseudoephedrine at the time making the cause of death unclear. With respect to the rates at which these hypersensitivity reactions occur, there is a wide range based on a number of studies. There are approximately 10 to 600 cases per 100,000 vaccinees; however, the estimates vary by study method, country, year, and vaccine lot.

The second type of severe reactions that have occurred are neurologic adverse events following mouse brain-derived JE vaccine, which have been rarely reported among travelers (e.g., encephalitis, seizures, headache, changes in mental status, gait disturbances that mimic Parkinsonism, Guillain-Barre Syndrome, acute disseminated encephalomyelitis). These adverse events have been reported primarily in travelers, with the exception of the acute disseminated encephalomyelitis, for which there have been case reports of children in Japan and Korea receiving the vaccine. These are all temporal associations with receiving the vaccine. Causality has not been established. The rate of reported neurologic adverse events is somewhat more consistent, although there are fewer studies. In general the rates have tended to range from 0.1 to 0.2 cases per 100,000 vaccinees in the largest surveillance activities that have been conducted in Japan and the US. One outlier study generated a lot of attention in which the rate was 2.6 per 100,000. That study included 10 cases that were not severe encephalitis or encephalomyelitis. They had minor but concerning neurologic adverse events temporally after receiving the vaccine. In 2005, Japan suspended routine immunization with mouse brain-derived JE vaccine.

Decisions regarding the use of JE vaccine for travelers must balance the low risk of disease and the low probability of serious adverse events following immunization. JE is a severe disease with a high case-fatality rate and substantial sequelae. There is no specific treatment, and an effective vaccine is available. Conversely, the risk of JE disease itself among travelers is low, although it is difficult to quantify. The risk varies based on season, duration, location, activities. There is a low risk of severe adverse events following mouse brain-derived JE vaccine.

Given these considerations, ACIP currently recommended JE vaccine for travelers over 1 year of age who plan to spend more than 30 days in Asia or a significant time in rural endemic areas (CDC 1993). They recommended that evaluation of an individual traveler's risk should take into account itinerary and activities, and best-available information on the current level of JE activity in the travel area. The vaccine should be considered for travelers planning extensive outdoor activity in rural areas, while short-term travelers whose visits are restricted to major urban areas generally should not be advised to receive the vaccine because the risk of adverse events may be higher than the risk of disease in that group.

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A recent issue regarding the availability of the currently licensed vaccine is that the only JE vaccine licensed for use in the US is no longer being produced. In 2005, Biken discontinued production of JE-VAX®. The DoD uses 70-80% of the JE vaccine in the US and has stockpiled enough vaccine to meet their needs for the next 3-5 years. However, in the fall of 2007, sanofi pasteur sent a letter to practitioners estimating that remaining supplies of JE vaccine for civilian travelers may be exhausted by mid-2008. HHS and DoD are working with sanofi pasteur to offset potential supply issues.

Although there are several candidate JE vaccines, only two new JE vaccines have been evaluated in clinical trials in the US. The first is IC51, which is an inactivated cell culture-derived vaccine developed by Intercell (Vienna, Austria). The second is a live attenuated chimeric vaccine (Chimerixax-JE®) developed by Acambis (Cambridge, Massachusetts). In December 2007, Intercell (Vienna, Austria) filed a BLA with the FDA for the use of a new inactivated Vero cell culture-derived JE vaccine (IC51) in adults (Tauber 2007). Because there are several effective vaccines in Asia, it would be impractical and probably unethical to conduct a controlled efficacy trial at this point for new vaccines. Thus, new vaccines in the US will likely be licensed based on an immunologic correlate of protection. The correlate of protection that has been favored by most experts is using neutralizing antibody titers of ≥1:10 as a reasonable immunologic surrogate for protection against JE. With regard to the approach to evaluating new JE vaccines, the plaque reduction neutralization test (PRNT) used should be standardized and validated. Neutralizing antibody titers should be correlated with protection in a suitable animal model. “Non-inferiority” should be established in a comparative immunogenicity trial with the currently licensed and new vaccine. Safety of the new vaccine should be evaluated in ~5,000 subjects.

Currently, licensed JE vaccine may no longer be available for U.S. travelers after mid-2008. The new JE vaccine, IXIARO® manufactured by Intercell, will not be available for US adults until the end of 2008. Hence, the new vaccine will not available for the Beijing Olympics in August 2008. In addition the vaccine will not be licensed for children under the age of 18 until at least 2010. Without further action, the working group concluded that there will be a gap in the availability of JE vaccine for US travelers in 2008 or early 2009 and the lack of availability for children may persist for several years.

In terms of mitigating future JE vaccine supply issues, availability of JE vaccine for US travelers is continuing to be monitored by CDC and the ACIP working group. Work with HHS, DoD, and sanofi pasteur will continue with respect to potentially moving some JE vaccine from the DoD stockpile back into the civilian market to bridge the gap prior to the new vaccine’s licensure and availability. An *MMWR* Notice to Readers is planned to educate travelers and practitioners regarding the current ACIP recommendations for use of JE vaccine. Information will also be included about the risk to travelers of JE, and recommendations and availability of JE vaccine for US participants and visitors to the Beijing Olympics will be discussed. ACIP will begin to draft recommendations for use of the new JE vaccine, which will likely be presented in April or October 2008, depending on the current progress of the new vaccine. At some point, the future

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availability of JE vaccine for US children must be addressed as well. This may be somewhat addressed by the same process of shifting some JE vaccine from the DoD stockpile back into the private sector.

Japanese Encephalitis Vaccine Availability in the US

Mr. Phil Hosbach
sanofi pasteur

Mr. Hosbach reported that in September 2003, BIKEN notified sanofi pasteur that it would no longer produce JE-VAX®, Japanese Encephalitis Vaccine. In October 2003, sanofi pasteur notified the military and CDC. Subsequent discussions resulted in the formation of a stockpile for the military and for the private market, based on historical demand. Product was manufactured in 2005 prior to the BIKEN plant closure and has an expiry of Q1 2010. The historic annual demand has been approximately 100,000 – 115,000 doses per year, with the private and public sector receiving approximately 30,000 doses / year and the military sector receiving approximately 75,000 doses per year. The US Military Stockpile includes 410,000 doses (135k doses supplied in January 2006 and 275k doses supplied in January 2007). Historic sales of JE-VAX® have been fairly steady from 2000-2006 with a range of 86,742 doses to 203,127 doses. The spike to 203,127 doses occurred in 2006 due to shipment for the military stockpile. There have also been some spikes in the civilian market possibly due to increased business travel to Asia. Miscalculation of need also occurred because in 2004, sanofi pasteur anticipated that another manufacturer would be licensed by early 2008, given that the two other manufacturers were in Phase III studies.

In 2007, sanofi pasteur distributed 314,070 doses of JE-VAX®, of which 39,030 were delivered to the civilian market and 275,040 delivered to the military market. In 2005, the Military received 28,128 doses and in 2006, the Military received 142,140 doses. As noted, the 2006 and 2007 doses were distributed as part of the military purchase toward their stockpile. Doses available for civilian use as of January 2008 included 23,031 doses as of January 1st; 1,980 doses sold as of January 21st; 21,051 doses in available inventory; 2,298 doses reserved for future pediatric use (Rationale: To support 1 year of pediatric market demand in anticipation of next generation product achieving initial license status of $\geq$18 years of age); and 18,753 doses remain available for sale.

Significant supply restrictions have been instituted allowing only 9 doses to be ordered every 30 days. These restrictions are anticipated to be in place until JE-VAX® completely stocks out. Exceptions will be granted on a case-by-case basis, for example exceptions may be granted to travel clinics which need to vaccinate those who are traveling to the Olympics or Olympians who need to receive the vaccine. JE-VAX® is a non-returnable product to ensure that it will be used once in physicians' offices. Again, based on 2007 sales and current inventory, sanofi pasteur is expected to stock out of JE-VAX® in June 2008.

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Unique and probably unprecedented is that discussions are in place for sanofi pasteur potentially to buy back a total of 45,000-50,000 doses from the US Military for private sale. It is hope that this will be resolved within a few weeks. The proposed plan is a tiered approach with the initial purchase of 20,000-25,000 doses. The tiered approach provides risk sharing based on licensure of a next generation product. While 45,000 - 50,000 doses would provide an additional 8-12 months of supply based on historical demand and would help with anticipated increased demand for the 2008 Olympics, 20,000-25,000 doses could support the transition until the next generation product is available for sale in the US.

New Inactivated Cell Culture-Derived JE Vaccine for Adult Travelers

Erich Tauber, MD, Vice President
Clinical Development & Medical Officer
Intercell

Dr. Tauber first described Intercell's new inactivated cell culture-derived JE vaccine for adult travelers, IXIARO®. The vaccine is produced with Vero cells. The virus strain used for production is the attenuated strain SA14-14-2, which has been used in China in over 200 million doses as a live vaccine. IXIARO® includes aluminum hydroxide as an adjuvant and there are no stabilizers or preservatives in the final formulation. The final formulation is a liquid and the anticipated label dosage will be 2 doses given 4 weeks apart on Days 0 and 28 (6 mcg/0.5mL). The JE-VAX® virus strain is wild type Nakayama, with virus growth in mouse brains. JE-VAX® contains no adjuvant, and contains porcine gelatin as a stabilizer and Thimerosal® as a preservative. This is a lyophilized formulation with a 3-dose regimen given at Days 0, 7, and 28 (1.0 mL).

As noted, efficacy trials of any new JE vaccine are not feasible due to ethical issues. FDA licensure of IXIARO® will be based on immunogenicity criteria (non-inferiority versus licensed vaccine), with the indicator of efficacy being PRNT50 ≥ 1:10 (e.g., serum dilution giving a 50% reduction in a plaque reduction neutralization test). The WHO Expert Panel accepts PRNT50 ≥ 1:10 as protective (Hombach et al, 2005). Phase III clinical trials with IXIARO®, which have been submitted as part of Intercell's biologics license application, included 3,558 subjects who were exposed to IXIARO®. Approximately 3,500 subjects were exposed to 2 doses. In total, over 7,150 doses of IXIARO® have been administered. Intercell's license application in the US consists of 4 different clinical trials conducted in the US: 1) IC51-301: Pivotal Immunogenicity vs. JE-VAX®; 2) IC51-302 Pivotal Safety vs. Placebol; 3) IC51-303 Long-term Safety and Immunogenicity Follow-Up; and 4) IC51-308 Concomitant Vaccination with HAVRIX®.

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The Pivotal Immunogenicity vs. JE-VAX® study (IC51-301) included 867 randomized healthy adults ≥ 18 years of age from 11 sites in North America and Europe (primarily the US, with a smaller proportion in Germany and Austria). The treatment groups received IXIARO® in 2 doses injected four weeks apart (given on days 0 and 28, with a placebo administered on day 7) and compared it with JE-VAX® in the licensed 3-dose regimen (Injection on days 0, 7, 28). The primary endpoint for this study was seroconversion and geometric mean titers set four weeks after the last immunization. Other endpoints included safety and tolerability.

With respect to adverse events following immunization, one serious adverse event (0.2%) was observed in the IXIARO® group. This subject suffered a myocardial infarction three weeks following the last immunization, which was judged as unlikely to be related to the vaccine. There were no serious adverse events observed in the JE-VAX® group. Overall for possibly or probably related or early withdrawal, there was similar distribution between the two vaccines, with 159 (37.1%) possible or probable severe adverse events observed in the IXIARO® group and 149 (34.3%) observed in the JE-VAX® group. In the IXIARO® group, 7 (1.6%) subjects terminated early due to adverse events, as did 8 (1.8%) in the JE-VAX® group. There were no deaths in either group. The overall safety picture is fairly identical for the IXIARO® and JE-VAX® groups. There is a slightly different picture between the two groups with respect to local tolerability assed via subject diaries. For IXIARO® (N=421), there were 227 (54%) local tolerability symptoms as compared to 295 (69.1%) in the JE-VAX® group (N=427). This difference was found to be statistically significant. There were 9 (2.1%) reports of severe local tolerability symptoms in the IXIARO® group as compared to 59 (13.8%) in the JE-VAX® group. This difference was also found to be statistically significant.

Pertaining to the first primary endpoint, agreement was made with the FDA that immunogenicity would be demonstrated if the 95% confidence interval for the seroconversion rate difference did not fall below 10%. Of the IXIARO® group (N=365), 95.5% seroconverted as compared to 95.3% in the JE-VAX® group (N=370). Immunogenicty results were virtually identical in the two groups, and IXIARO® met the non-inferiority margin. The second primary endpoint was geometric mean titers, with the non-inferiority margin demonstrated if the 95% confidence interval for geometric mean titer ratio did not fall below 1/1.5 (0.67). In the IXIARO® group (N=365), the geometric mean titers were 243.6 compared to 102.0 in the JE-VAX® group (N=370). Again, the IXIARO® group met the non-inferiority margin. In terms of the distribution of $PRNT_{50}$ of IXIARO® compared to JE-VAX®, most of the vaccinees in both groups reached protective antibodies and most had titers in the range of 100 or higher. Long-term immunogenicty data are available for 12 months post-vaccination for IXIARO® (N=181) subjects and 6 months post-vaccination for the JE-VAX® (N=82) subjects. The IXIARO® cohort's geometric mean titers began at 310.8 at 2 months post-vaccination and, as would be expected for an inactivated vaccine, these titers declined to 83.5 at 6 months and 41.2 at 12 months post-vaccination as compared to 99.5 at 2 months and 34.1 at 6 months in the JE-VAX® cohort. That is, the geometric means titers stayed well within the protective margins of 1:10. Regarding seroprotection rates, JE-VAX®

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vaccinees began with 98.9% at 2 months, 95% at 6 months, and 83.4% at 12 months as compared to JE-VAX® vacinees who had 97.6% at 2 months, 72.7% at 6 months.

The pivotal safety study, IC51-302, was a double-blind placebo controlled study with approximately 2,675 randomized healthy adult subjects ≥ 18 years of age. Subjects were from 39 sites in 8 countries (e.g., US, AT, DE, IR, RO, UK, AU, NZ). In this study, IXIARO® (2 injections Days 0/28, IM) was compared to a placebo (2 injections Days 0/28, IM). The placebo was more or less a diluent of vaccine (phosphate-buffered saline solution with 0.1% Al(OH)3). The IXIARO® group included 2012 subjects, while the placebo group included 663 subjects.

Regarding adverse events following immunization in the IXIARO® group (N=1,993),10 (0.5%) serious adverse events were reported, 774 (38.8%) possibly or probably related serious adverse events were reported and 254 (12.7%) medically attended adverse events were reported. In the placebo group (N=657) 6 (0.9%) serious adverse events were reported, 254 (38.7%) possible or probably serious adverse events were reported, and 80 (12.2%) medically attended serious adverse events were reported. Of the IXIARO® vaccinees, 12 (0.6%) terminated participation early due to an adverse event as compared to 5 (0.8%) placebo vaccinees. There were no deaths in either group. Reports of any tolerability symptoms were 1095 (54.9%) in the IXIARO® vaccinees and 365 (55.6) in the placebo vaccinees. Reports of any systemic tolerability symptoms were 768 (38.5%) in the IXIARO® vaccinees as compared to 260 (39.6%) in the placebo vaccinees. None of these reached statistical significance or clinical relevance. Adverse events of special interest (such as pyrexia, rash, rash maculo-papular, rash pruritic, injection site rash, urticaria, et cetera) were overall quite rare in both IXIARO® and placebo vaccinees. No cases have been observed of encephalitis, meningitis, anaphylaxis, or convulsions in this study.

Safety data have been pooled for a 6-month safety analysis from all 7 studies which have been conducted thus far. Subjects in follow-up studies were matched with preceding studies and only counted once. All subjects who received a dose of IXIARO® were analyzed in the IXIARO® group. The pooled 6 months safety analysis included 4,715 subjects, of whom 3,558 subjects were exposed to IXIARO®. Of the 3,558 exposed subjects, 3,310 subjects completed 6 months of safety follow-up. This summary of adverse events showed that in the IXIARO® group (N=3,558), 38 (1.1%) of subjects reported at least one serious adverse event compared to 3 (0.7%) in the JE-VAX® group (N=435) and 13 (2.0%) in the placebo group (N=657). In the IXIARO® group, 27 (0.8%) subjects reported at least one serious adverse event leading to withdrawal, compared to 8 (1.8%) in the JE-VAX® group and 5 (0.8%) in the placebo group. There was one death in the IXIARO® group from metastatic lung adenocarinoma, which was judged as unrelated. The numbers were quite comparable for all three groups in terms of adverse events of special interest, and no cases were observed of encephalitis, meningitis, or anaphylaxis in any of the groups. None of the differences reached statistical significance.

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In summary, non-inferiority of IXIARO® against the licensed vaccine, JE-VAX®, was demonstrated for seroconversion rates as well as for geometric mean titers. Seroconversion rates, defined as proportion of subjects achieving a titer of PRNT50 ≥ 1:10, were over 95% for the first 6 months and over 83% after one year. Systemic tolerability and adverse events were similar between IXIARO®, placebo, and JE-VAX®. IXIARO® appeared to have a more favorable local tolerability profile than JE-VAX®.

With respect to regulatory status and supply of IXIARO®, as noted the BLA was submitted in December 2007. Proposed indications as per the draft label from BLA include the following language, "Indicated for active immunization against JE disease for persons 18 years of age and older who are at risk of exposure to JE virus. Vaccine should be used in persons who plan to reside in or travel to areas where JE is endemic or epidemic, especially if travel will occur during the transmission season." Intercell will be the manufacturer and holder of the BLA and will distribute IXIARO® to the US Military. Novartis will distribute the vaccine to the US civilian markets. Intercell will provide sufficient capacities to supply the US and EU travelers' markets and the military.

In terms of pediatric investigational plans for IXIARO®, safety and immunogenicity will be established in children and adolescents between 1 and 17 years of age. Studies are ongoing and planned, including: A Phase II dose confirmation study ongoing in India; A Phase III immunogenicity and safety trials in endemic countries in Southeast Asia, to be initiated after adult licensure; and a supportive immunogenicity study is to be conducted in the US. A pediatric label is currently projected for the 2010 / 2011 timeframe.

Intercell's IXIARO® development program has successfully reached the point of license application submission. Phase 3 studies have demonstrated an appealing safety and immunogenicity profile. Current product development results support the adult target population. Intercell and Novartis are committed to make IXIARO® available to the target population and to develop the product further. Sufficient supply capacities and commercialization capabilities are intended to be provided. Studies to support pediatric use have been initiated and further studies are planned. Technical product life cycle activities will be commenced post licensure.

Discussion

- Dr. Baker pointed out that age was stated only as ≥ 18. She wondered if Dr. Tauber could provide a range, a median, and information on adverse events or immunogenicty by age.

- Dr. Tauber responded that Intercell has analyzed subjects from ages 18 to 84 years of age in these studies. In the immunogenicity study, the oldest subject was 80 years of age. No marked differences were observed in immunogenicity between the age populations.

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- Dr. Neuzil pointed out that the average business traveler and average Olympic traveler likely would not spend a month in Asia or travel to rural areas. With that in mind, she inquired as to whether Dr. Fischer had any idea from surveys of clinics or travelers how appropriate the current use of vaccine was.

- Dr. Fischer replied that while CDC has been trying to obtain such information, this is difficult to do, given that the vaccine is administered in very small amounts through a very wide number of clinics. This is not like yellow fever, for which there are registered clinics. An attempt was made to contact specific clinics and to work through certain HMOs and the VSD; however, no data were obtained. A survey was completed of travelers departing three airports in the US last summer (e.g., East, Midwest, and West Regions) that have direct flights to Asia. That data is currently being analyzed. Based on early analyses of these data, it appears that the vaccine is under-used according to the current recommendations. Among travelers with itineraries for which JE vaccination should have been considered according to ACIP guidelines, a small proportion (10-15%) reported having received JE vaccine.

- Dr. Baker indicated that she runs a children and adult travel clinic, in which they find that US born individuals are likely to seek out immunizations if they plan to visit for a long time or to immigrate to at risk countries. However, a number of first generation immigrants return to live in rural areas with their families for a month or two and take their young children, but do not immunize. Hence, she would submit that this vaccine is under-used.

- Stephen Foster (APHA) added that as a consultant for a travel medicine clinic, he agreed that this vaccine is under-used.

- From the DoD perspective, Dr. Hachey pointed out that the military is faced with an occupational hazard from being in outdoor, nighttime, and rather austere rural settings. With that in mind, in the negotiations with HHS and sanofi pasteur, consideration was given to the status of the military stockpile. Their numbers reflect a supply of about 270,000 doses that should last closer to 2.5 to 3 years based on current use. Use over the past couple of years has been approximately 90,000 doses, with a typical range of approximately 70,000 to about 110,000. A major unknown is what the military's presence will be in at-risk areas as world events change over time, which is not predictable. Thus, the DoD is greatly interested in what occurs with the new proposed vaccine and when that will be FDA-approved as a potential replacement. With that replacement, the military's ability to augment the civilian supply, particularly for pediatric use, would become a more viable option.

- Dr. Morse inquired as to whether there is a need for a booster with the current or new vaccine.

- Dr. Fischer replied that for the current vaccine there are some immunogenicity studies that show waning immunity. The recommendation is to consider a booster at 2-3 years after completing the primary series.

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- Dr. Tauber added that with respect to the new vaccine, based on the current immunogenicty data 83% seroprotection has been observed through 12 months. Intercell is currently evaluating the 2-year follow up period and will know more in a few months.

Anthrax Vaccine

Anthrax Working Group Update

Dale Morse, MD, MS
Advisory Committee on Immunization Practices

Dr. Morse indicated that the Anthrax Vaccine Working Group was formed during the fall of 2007, and that they were presenting material to the ACIP during this meeting as part of their work toward combining the 2000 anthrax statement and 2002 supplement into one document. The terms of reference for the working group include a review of new data on Anthrax Vaccine Adsorbed (AVA) including: a) Safety and immunogenicity data from an interim analysis of CDC's dose reduction and route change study in anticipation of FDA evaluation of Emergent Biosolutions' BLA; b) recently published safety studies; c) publications detailing the 2001 anthrax attacks; d) post-exposure prophylaxis with vaccine and antibiotics; and e) pre-exposure vaccination. The goal is to revise the existing statement and supplement into a single document.

The 2000 ACIP recommendations for pre-exposure prophylaxis indicated routine vaccination for groups at high risk of exposure to *B. anthracis*, with 6 doses administered subcutaneously, followed by annual boosters. The post-exposure prophylaxis recommendation following aerosol exposure to *B. anthracis* spores indicated the administration of 3 doses of AVA plus 60 days of antimicrobials. The 2002 supplement pertained to the use of anthrax vaccine in response to terrorism, with a recommendation that groups at repeated risk for exposure (e.g., LRN personnel in certain situations, remediation workers) be given priority for pre-exposure vaccination. Also endorsed was the use of a 3-dose vaccine regimen plus antimicrobials under an IND for post-exposure use in civilians.

Since its inception in October 2007, the Anthrax Working Group has reviewed clinical trial data in support of a pending licensure change request, recent publications of DoD safety data, DoD programmatic experience, concerns surrounding vaccine, and 2000 / 2002 recommendations regarding first responders. The working group is in the process of developing an updated statement.

With regard to the objectives of this anthrax session, because the working group anticipates presenting the new statement to ACIP in June 2008, and it has been several years since anthrax was presented to the ACIP, they were presented with background information on Anthrax Vaccine Adsorbed, the only licensed vaccine available in the US

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for pre-exposure use and manufactured by Emergent Biosolutions. Also presented were an overview of several recent publications focusing on safety data, and available data from an ongoing clinical trial evaluating a change in schedule and route of administration. The clinical trial data were presented during this ACIP meeting, given that the FDA was in the process of considering these data and was scheduled to rule on a BLA by March 5, 2008.

Future activities of the working group are to review additional data including reproductive health studies, AVA efficacy data, antimicrobial post-exposure prophylaxis, and groups at elevated risk of inhalation anthrax. Subsequently, a draft of the revised statement will be written and will be presented to the ACIP during the June 2008 meeting for a vote.

Background Information on Anthrax Vaccine

Jennifer G. Wright, DVM, MPH
National Center for Immunization and Respiratory Diseases
Anthrax Vaccine Research Program

Dr. Wright explained that anthrax disease is caused by the gram positive, spore forming bacterium Bacillus anthracis when spores enter the body through the skin, the GI tract, or the respiratory route. Anthrax has been recognized as an illness for centuries, but there has been a dramatic reduction in US cases since the early 1900s, in part due to vaccination of livestock and import regulations placed on animal hides. The primary current concern is the use of anthrax as an agent of biowarfare and, in fact, this recently occurred during the fall of 2001 in the US.

It is known that anthrax spores are the most likely bioweapon. In 1979, a release of anthrax spores from a laboratory in Sverdlosk resulted in the deaths of at least 60 persons in the community. The 2001 US mail incident resulted in the deaths of 5 persons. Anthrax spores are relatively easy to produce, can be stored for a long time, and can be dispersed in the air through a variety of mechanisms. They are odorless, colorless, tasteless, and difficult to detect. In addition, inhalation anthrax is highly lethal. The spores may survive for greater than 40 years, causing widespread illness and death among unprotected persons. When an anthrax spore enters the body and germinates, three proteins are produced: Edema Factor, Protective Antigen (or PA), and Lethal Factor. Protective Antigen combines with each factor to produce a toxin. The Anthrax Vaccine Adsorbed (AVA), produces antibodies against PA; thereby, blocking the production of edema and lethal toxins.

AVA primes the immune system to recognize and block PA, which is common to all anthrax strains. Efficacy for this vaccine has been demonstrated against numerous anthrax strains in many animal studies. There is currently no other product approved by the FDA to prevent anthrax pre-exposure. This vaccine is quite old, with a long history. In the 1950s there was the “Ft. Detrick” formulation, often mistakenly referred to as the “Merck” formulation. “Ft. Detrick” was made from a cell culture filtrate and precipitated

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with alum. This is also the formulation which was studied extensively by Dr. Brachman. In the 1960s, the manufacturing process was improved, resulting in increased PA concentration and increased purity and potency. This new formulation was referred to as the "Lansing" formulation. In the 1970s, it was the "Lansing" formulation which was licensed using data from the Brachman studies. The vaccine was recommended for those at high risk of exposure to anthrax. Today, the vaccine is known as Anthrax Vaccine Adsorbed and is manufactured by Emergent Biosolutions. It is an aluminum hydroxide precipitate and is a sterile, cell free filtrate made from an avirulent strain of *B. anthracis*. The final product contains 1.2 mg/ml of aluminum and contains as preservatives benzethonium chloride and formaldehyde. The vaccine schedule is somewhat onerous, consisting of 6 injections administered over 18 months, plus annual boosters. The vaccine is only licensed for subcutaneous administration. The immunization schedule is based upon animal immunization studies conducted in the mid-20th century and carried over into Brachman's trial.

Dr. Brachman's studies of the "Ft. Detrick" formulation demonstrated vaccine efficacy in humans and provided data later used for licensure. The study was conducted between 1955 and 1959 among mill workers who worked with raw, imported goat hair. It was a randomized, placebo controlled trial with 2 study groups. Dr. Wright pointed out that a copy of the 1962 *American Journal of Public Health* (*AJPH*) publication was placed on the information table outside the meeting for those who were interested in the details. Dr. Brachman primarily observed mild local reactions, with no work interruption noted. Systemic events were noted in fewer than 0.2% of recipients. For this study, the efficacy of the vaccine was noted to be 92.5% jointly against cutaneous and inhalation anthrax. There were 5 cases of inhalation anthrax which occurred among unvaccinated persons and no cases among vaccinated persons.

Vaccine efficacy has also been demonstrated in several non-human primate studies. In these studies, 65 monkeys were vaccinated and challenged at time points ranging from 6-100 weeks later. 62 monkeys survived, for a vaccine protective efficacy of 95%. It is important to note that correlates of immunity to infer from animals to humans have not been fully developed and that this work is part of the CDC Congressional mandate.

There have been numerous independent scientific reviews of the Anthrax Vaccine conducted since 1985, including the following:

- FDA Advisory Panel on Bacterial Vaccines and Toxoids
  - *Federal Register*, 1985
- Defense Health Board (DHB)
  - advisory group to DoD, 1994-present
- Cochrane Collaboration, Oxford
  - *Vaccine*, 1998, 2004
- Working Group on Civilian Biodefense
  - *JAMA*, 1999, 2002
- CDC's Advisory Committee on Immunization Practices
  - *MMWR*, 2000

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- Anthrax Vaccine Expert Committee (AVEC)
  - *Pharmacoepidemiology and Drug Safety* , 2002, 2004
- National Academy of Sciences (IOM), 2002
- FDA Review of VAERS reports
  - supports FDA's Final Rule and Final Order, 2005

Perhaps the most important one is the National Academy of Sciences (IOM) report, which was published in 2002 prior to the completion and publication of a majority of the studies presented during this ACIP meeting. The IOM report concluded that AVA is a reasonably safe and effective vaccine for adults. The committee found no evidence that people are at increased risk of experiencing adverse events following receipt of AVA when compared to the general population, nor did they find any convincing evidence that people faced elevated risks of development of adverse events over the long-term, although data are limited in this regard, as is true for all vaccines.

Anthrax Vaccine Adsorbed: Overview of Safety Studies

Ted Cieslak COL MC USA
DoD Liaison Officer

COL Cieslak reviewed some of the recent anthrax safety data. He acknowledged that this vaccine has had a colorful and controversial history throughout its recent use in the military. Much of the criticism of this vaccine falls into one of three broad categories: Safety, Efficacy, or Programmatic. Programmatically, this is a very onerous vaccine with a 6-does series, which engenders significant recordkeeping problems, particularly in a military population that is very mobile. There have been stops and starts in the manufacturing process, court injunctions and resulting confidence problems in this vaccine. While the efficacy data looks very good, it is scant. The safety data is increasing dramatically in its cumulative weight. There are now dozens of safety studies that are convincing with respect to the safety of this vaccine.

There are some significant problems in evaluating safety data with respect to this vaccine. There are two preparations of this vaccine referred to as the "Detrick" and "Lansing" preparations. Dr. Brachman's original study conducted in New Hampshire in the late 1950s employed the "Detrick" preparation, but after his study was completed, minor changes were made to the formulation that resulted in what is now known as the "Lansing" formulation. COL Cieslak stressed that it is the "Lansing" preparation that was licensed by the FDA. Hence, some criticisms of the vaccine have been leveled at the fact that the licensed vaccine is actually not the exact vaccine that was studied. Attempts to conduct meta-analyses on many of these studies are hampered by the fact that some of the studies employed passive surveillance while others employed active surveillance. Moreover, there is a lack of standard definitions in some of these studies, so for examples, many of the studies will define a moderate reaction as a reaction up to 10cm in diameter while other studies will use 5 inches, which is closer to 13cm. Many of these studies are very small. Virtually every one of them can be criticized as being either small, of short duration, unable to detect rare side effects, aimed at very specific

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endpoints, et cetera. Nevertheless, the cumulative weight of all of these studies is now becoming overwhelming. Also problematic is that many of these studies examine only a specific problem, for example, one study looked only at optic neuritis as an endpoint. Efficacy studies are hampered by the fact that there is a very low incidence of inhalational disease, and that terrorist-induced disease may be different in many respects (including dose) from naturally occurring inhalational anthrax. There is some controversy over which should be the appropriate animal model. In addition, there have been confidence problems in this vaccine engendered by a number of manufacturing difficulties.

With that said, the military has garnered an incredible amount of experience with this vaccine. Since beginning mandatory anthrax immunization for Soldiers, Sailors, Airmen, and Marines, over the last decade the military has administered more than 7.2 million doses of anthrax vaccine to about 1.9 million services members. There have now been over 20 studies that have resulted in over 35 safety publications and 7 reviews by independent panels of civilian physicians. The first started in 1978, with a civilian panel advising the FDA. The findings from this study were published in the *Federal Register* in 1985. Much of the publication at that time predates the military's widespread use of this vaccine and it is based on both the Brachman data and then a lot of CDC data that continued to follow Brachman's patients as well as other patients who obtained this vaccine on an IND status who were occupationally at risk. The Armed Forces Epidemiologic Board is a board of civilian experts that advise DoD on epidemiologic matters. Over a decade, this board re-reviewed the anthrax data every couple of years. The Cochrane Collaboration found this vaccine to be safe and effective. D.A. Henderson at Johns Hopkins assembled a group of civilian experts, Working Group on Civilian Biodefense, which found this vaccine to be safe and effective. The ACIP examined this in 2000, as did the Anthrax Vaccine Expert Committee in 2002, and the IOM's report was published in 2002. The most recent of these reviews was the comprehensive, peer-reviewed report of the National Academy of Sciences and its IOM, which concluded that anthrax vaccine works and is as safe as other vaccines. The amount of safety data since 2002 has increased 10-fold; therefore, it behooves them to re-examine this vaccine. COL Cieslak referred those interested in reviewing all of the studies to the "Detailed Safety Review of Anthrax Vaccine Adsorbed, 27 November 2007," MILVAX Agency, accessible at www.vaccines.mil.

COL Cieslak divided the safety studies upon which he reported into seven broad categories, acknowledging that the categories were somewhat artificial and that some overlapped categories and had multiple foci and purposes: Historical, Hyperimmunization Studies, Short-Term Health Effects, Long-Term Health Effects, VAERS-Based Assessments, Reproductive Health Studies, and Dosing Change Studies.

Historical studies included the Brachman Study and the CDC Observational Study. The Brachman Study involved 379 subjects. Clearly, that is not enough patients to detect very rare but perhaps important safety problems. The CDC Observational Study continue to follow Brachman's patients as well as other patients occupationally at risk,

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most of whom received the vaccine prior to licensure in 1970 under an IND and some who were added after the vaccine became licensed (N=6,986). The Brachman Study was the pivotal clinical trial that led to licensure, which involved safety and efficacy data. Brachman's study included 1249 total patients (379 vaccine recipients, 414 placebo recipients, 340 persons in an observational group). Brachman randomized his patients either to vaccine or placebo-controlled, but he also included in the efficacy analysis those patients who opted not to participate in the study and did not receive either vaccine or placebo (e.g., the observational group). Brachman's subjects (N=495) received 2688 doses of vaccine. The number of subjects differs because only 379 received the full series. However, for safety data purposes the 495 patients, not all of whom received the full series of vaccines, were included. There was a 30% incidence of mild reactions; 4% moderate reactions; <1% severe; and 0.2% systemic as compared to the CDC study of 6986 subjects who received 16500 doses and in which there was a 3-20% incidence rate of mild reactions;1-3% moderate, <1% severe; and <1% systemic. The Fort Bragg study (486 subjects; 486 doses) is the one outlier that shows a very high rate of systemic reactions (14% mild, 5% moderate, <1% severe, 23% systemic), which may have been because it involved Special Forces Operation Soldiers who were in very vigorous training and the study included myalgia as one of the systemic reactions. Naturally, a lot of these solider reported that they had sore muscles. The RIDD study included 1583 subjects who received a total of 10722 doses. Other vaccines have higher systemic incidence reports, such as DPT (40%) and HepB (15%).

The hyperimmunization category included the Ft Detrick Multivax Study (N=99) and Ft. Detrick Long-Term Study (N=142). The Ft Detrick Multivax Study was a multi-dose, multi-vaccine safety study at Ft Detrick in 97 USAMRIID scientists who were followed from 1944-1971. They received 52-134 ml of vaccine (mean 97 ml) and 6-93 skin tests (mean 55). While this is a small study from which it would be difficult to draw any conclusions, no unusual diseases or symptoms were observed. These scientists also received a host of other licensed and investigational vaccines for their work in the BSL-3 laboratories at Ft. Detrick.

Categorized as short-term health effects were the Ft Detrick SIP Experience (N=1,583); TAMC-601 Survey (N=601); US Forces Korea Study (N=2,824); ROTC Cadet Study (N=73); DMSS Hospitalization Cohort (757,540 person-years); NHRC Hospitalization Cohort (N=170,723); Optic Neuritis Study; Canadian Forces Study (N=403). COL Cieslak pointed out that the number of studies that could be categorized as short-term health effects was very different from eight years ago when the ACIP first examined this vaccine. He said he thought that the USAMRIID SIP study (1973-1999) was important because it bridged the period between FDA licensure and the kick-off of the military's Anthrax Vaccine Immunization Program (AVIP) begun in 1998. Most of the recipients were USAMRIID scientists and technicians. This study is hampered by the fact that it was passive surveillance. To detect reactions, it basically relied on these scientists and technicians reporting to the Special Immunizations Clinic at Ft. Detrick, which is their version of an occupational health clinic. This clinic was in the same building down the hall from where these subjects worked, so that should not have been too much of an onerous burden, but probably did result in the underreporting of very mild side effects.

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In this study, 1,583 scientists and technicians received a total of 10,722 doses. Given the yearly boosters required following the initial 6-dose regimen, some of these scientists and technicians scientists received incredible numbers of anthrax vaccine (273 received >10 doses; 46 received >20 doses). There were 101 systemic reactions reported in the 10,722 (1%); 1 case of acute demyelinating disorder; and 383 local reactions (3.6%). COL Cieslak stressed that this was fairly impressive safety data in a very large number of subjects.

One of the first studies conduced after the institution of the ACAP was the USFK records study, conducted by the Preventive Medicine Department at the 121st General Hospital in Seoul, Korea studying US Forces in Korea. One of the drawbacks of the study is that the soldiers who returned for a subsequent dose of anthrax vaccine were asked to complete a questionnaire. It did rely on soldier recall of what had happened to them two weeks previously upon receiving the previous dose. Nevertheless, the questionnaire was reasonably well designed to address all of the precautions in the package insert, asking the soldiers whether they had experienced any of the stated problems with their previous dose of vaccine. Among the 2,824 vaccine recipients, local reactions were reported as mild (<5 cm) 6-14%; moderate (5-12 cm) 4-13%; and large 0.4-4%. Systemic reactions reported included itching in 6-37%, 1.9% limited duty, 0.3% lost duty days, and 1 hospitalization for an allergic reaction. These findings suggest that anthrax is a pretty safe vaccine.

The Naval Health Study is a larger and more recent study published a couple of years ago. This study examined 170,723 Navy anthrax vaccine recipients ages 17-45 years of age (148,502 males / 22,221 females). This was a retrospective cohort study conducted from 1 Jan 1998- 31 Dec 2001, which examined hospitalizations using 14 broad ICD-9 code categories. No increase was observed in hospitalizations for any cause during that timeframe in vaccinated sailors versus unvaccinated sailors. Other nations have had similar experiences of very low incidence of serious reactions and a relatively small, but palpable incidence of local reactions. The Canadian Forces Safety Survey examined 576 vaccine recipients (SW Asia Veterans). Of the local reactions reported, 10.1% were mild (<5 cm); 0.5% moderate (5-12 cm); and none large. Systemic reactions (1.5%) included 5 fever, 2 indigestion, and 1 multiple nodules. All resolved in 2-5 days. Armed with much of that data, in 2002, the IOM chose to include a table in their report reviewing the incidence of local and systemic reactions of the anthrax vaccine and comparing it to a lot of conventional vaccines. Anthrax compares reasonably favorably to most conventional vaccines.

Acknowledging that the distinction between short-term safety and long-term safety was somewhat artificial, COL Cieslak indicated that included in the category of long-term health effects were: USAF ACC Study (N=4,045); Millenium Cohort Study (N=15,041); Army Disability Discharge (N=154,456); and Army Aircrew Study (N=6,820). Highlighting the Army Disability Discharge Study, he indicated that this study examined the entire Army population of 716,833 soldiers, of whom 154,456 were vaccinated. Over a 4.25 year study, the disability discharge processing was monitored to determine who applied for a disability discharge, what it was for, and whether it was temporary or

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permanent. Based on this study, soldiers who received the anthrax vaccine compared to those who did not were no more likely to have a disability or to be processed or discharged for a disability regardless of how the data were hashed out.

The fifth category of safety studies COL Cieslak highlighted pertained to VAERS-based assessments. Through November of 2007, the military had given 6,988,723 doses of anthrax vaccine to 1,836,772 million service members. In 2002, the refusal rate was 0.076%. The military used to track the refusal rate, but no longer does so. Through February 2008, 5918 VAERS forms were filed. Of those, 5618 were deemed non-duplicate, unique VAERS filings and 4329 were from military sources (61.9 reports / 100,000 doses). Of the 5618 non-duplicate filings, 5063 were "non serious," 555 were "serious," and there were 25 deaths, 127 life-threatening complications, 261 hospitalizations, and 139 permanent disabilities. With respect to the frequency of adverse effects on the VAERS forms, the top 10 reported included: 925 (16%) arthralgia; 897 (16.0%) headache; 839 (14.9%) pruritis; 767 (13.7%) pain; 655 (11.7%) injection site erythema; 608 (10.8%) pyrexia; 562 (10.0%) injection site edema; 562 (10.0%) injection site pain; 551 (9.8%) rash; and 532 (9.5%) erythema. Numerous other temporally associated conditions were reported on VAERS forms in association with anthrax vaccine as well.

In the interest of full disclosure, COL Cieslak shared the reasons stated for cause of death on the VAERS form for the 25 subjects who died, pointing out that it seemed unlikely that many of these were causally related. Those who died were a heterogeneous group, with multiple diseases, receiving various numbers of doses, receiving various vaccine combinations, and some had underlying (pre-existing) medical conditions (e.g., 3 individuals with ALS). The causes of death included: Polyarteritis nodosa; aplastic anemia, invasive aspergillosis; 2 myocardial infarctions; cardiorespiratory arrest; rapid-onset ALS; rapid-onset ALS vs. multifocal motor neuropathy; suicide (gunshot to head); multiple sclerosis; biliary neoplasm; chronic fatigue, suicide (overdose); cardiac arrhytmia, myocardial fibrosis; and systemic lupus erythematosus; drug overdose; DVT, multiple pulmonary embolisms; coronary artery occlusion; heat-related death; suicide (hanging); death from grand mal seizure; cardiac sarcoma; cardiac arrest after physical training; multiorgan failure; unintentional burn; nephrosclerosis, multiorgan system failure, unspecified autoimmune disorder; heart failure, seizures, depression, suicide; and ALS.

The sixth group of published safety studies included two published reproductive health studies. The first was a Female Reproductive Study (N=4,092) that examined female military service members who received an anthrax vaccine and then later became pregnant, studying the women's ability to conceive and the outcome of the pregnancy. No difference was found between immunized and un-immunized female service members. The second study was a very small Male Fertility Study (N=254), which showed no influence on fertility. COL Cieslak noted that CDC has considerably more data on the issue of reproductive health that is still being analyzed, and that this is an issue the Anthrax Vaccine Working Group is currently considering in more detail.

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The seventh category pertained to dosing change studies, of which there were three: Ft Bragg Booster Study (N=495); Dose Reduction / Route Change Study (N=173); and NIDBR Study (N=363). More specifically with regard to the Reduced-Dose / Route-Change Study, Phil Pittman and his colleagues at USAMRIID conducted a pilot study which they published several years ago examining the conventional first three doses of the 6-dose primary series (e.g., 0-2-4 week subcutaneous) and compared those to 2 doses (0-4 week subcutaneous) versus a 2-dose intramuscular series. This study included 173 vaccine recipients randomized to one of those three groups. Basically, the rate of local reactions from the vaccine given subcutaneous was significant at 5-32% in males and 39-69% in females, and was significantly greater in females that in males. When the vaccine was given intramuscularly, the rate of local reactions decreased dramatically (0-7% in both genders). That pilot study paved the way for a much larger study being conducted by investigators at CDC.

In conclusion, over the last decade the military has administered approximately 7.2 million doses of AVA to nearly 2 million soldiers. While in the beginning decisions were being based on some relatively limited safety data, the situation has changed dramatically over the last decade. There are now more than 35 publications of human safety data in the peer-reviewed literature that document the cumulative safety of this vaccine, and there have been 7 reviews by independent panels. All of these reaffirm the safety and effectiveness of AVA.

Presentation of Data on Anthrax Vaccine from the Anthrax Vaccine Research Programs' Ongoing Clinical Trial

Jennifer Gordon Wright, DVM, MPH, Dipl. ACVPM
Conrad P. Quinn, PhD
Centers for Disease Control and Prevention
Anthrax Vaccine Research Program

Drs. Wright and Quinn presented data from an ongoing clinical trial assessing how to optimize the use of AVA, assessing an altered route of administration, evaluating surrogate markers of protection, and evaluating immunologic memory. This is a randomized, double blind, placebo controlled Phase IV clinical trial with a Data Safety and Monitoring Board chaired by Dr. Stanley Plotkin. Investigators enrolled 1564 healthy, civilian adults who were aged 18-61 years at time of enrollment. Exclusionary criteria included specific allergies, immunosuppression, and pregnancy. Participant obligation consisted of 25 office visits over 43 months, with 8 injections, 17 blood draws, 22 in-clinic exams, and 8 patient diaries.

Because this is a long study, having begun enrollment in May of 2002, an interim analysis of all enrollee data through the fourth dose was planned, but because enrollment occurred over 2 years, the plan was revised to include only the first 1005 participants enrolled. The interim analysis was completed and submitted to FDA in February 2005, and 2 response letters from the FDA were generated, one in September 2005 and one in April 2006. Issues for clarification raised in the April 2006 letter

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required the entry of additional data, along with an analysis of this data, which resulted in the response to this letter not being submitted to FDA until August 2007. A ruling from the FDA is expected at any time. Looking ahead to the future, CDC will be conducting a final analysis in late 2008 / early 2009, with a final report submitted to the FDA in mid 2009.

Dr. Wright presented reactogenicity (or safety) data before turning the podium over to Dr. Quinn to present the serologic data. She pointed out that it was important to note that for reactogenicity, they would be looking at solicited adverse events. While the investigators collected and analyzed the data in 2 manners (e.g., according to protocol and intent to treat), in the interest of time they reported only the intent to treat data during this meeting. She did note that for reactogenicity, the ATP and ITT findings were similar.

Referring to the schedule of injections, Dr. Wright stressed that this is a very complex study with 6 treatment groups. The group receiving the licensed regimen receives 6 subcutaneous vaccine injections administered at 0, 2 and 4 weeks, 6, 12 and 18 months, followed by 2 annual boosters. The direct comparison group for route change receives vaccine intramuscularly at the same points as the first group. Groups 7IM, 5IM and 4IM are allowing the investigators to assess reduced dose regimens. For these participants, some of their AVA doses are replaced by saline doses. In addition, there is a saline placebo group, with half receiving their injections intramuscularly and half receiving them subcutaneously. Since at the time of the interim analysis persons in 7IM, 5IM, and 4IM had received the 3 IM doses at the same points in time, these 3 groups were combined for this analysis. However, they will be kept separate in the final analysis. With regard to the study groups and participants, each of the 6 study groups were similar in size, with the number of participants per group ranging from 165-170 persons; further, there was a similar percentage of males and females in this analysis. The mean age of participants was 38.4 years and 76% of participants were white and 95% were non-Hispanic.

Focusing on reactogenicity data, Dr. Wright pointed out that she would only be presenting data collected from the in-clinic exams during this meeting, but that it was important to note that the investigators did collect, analyze, and present to FDA adverse event summary data, which is a compilation of in-clinic exam data, phone follow-ups, progress reports, and patient diaries. Statistical comparisons between in-clinic and adverse event summary data produced similar results; however, the proportion of people experiencing each event was higher with adverse event summary data. During this meeting, Dr. Wright reviewed one solicited adverse event from each of 2 categories: injection site and systemic. She reviewed a “per dose” analysis as well as a “repeated measures model” analysis, explaining that repeated measures analyses are used when there are multiple, repeated measurements or evaluations over time for each person as in this trial.

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Referring to an example of a local adverse event, warmth, Dr. Wright called attention to the difference between the TRT-4SQ group and the TRT-4IM group, with the TRT-4IM group being less reactogenic than TRT-4SQ for all doses analyzed. When saline replaced AVA at dose 2 in the TRT-COM group, as expected, the proportion reporting this adverse event dropped to levels compatible with the saline control group. Dr. Wright showed a slide with a summary of local endpoints assessed, but did not cover each endpoint shown. She stated that it is important to note that "generalized pain", as demonstrated on the summary slide, is not the same as pain at the moment of injection. While there was no difference between groups with respect to "generalized pain," there was a significant reduction in pain immediately upon injection for those receiving an intramuscular injection. Bruising was better captured through adverse event summary data and was observed less frequently with intramuscular administration.

Referring to the local adverse reaction of warmth based on data from a repeated measures model, Dr. Wright pointed out that in this model overall reporting of the adverse event still decreased with a change to intramuscular administration, but that the most important "take home message" was that the absolute gender difference was significantly decreased with intramuscular administration. There is also still a statistical difference with respect to reporting of the adverse events between women and men. Another summary slide was shown which demonstrated that for every endpoint (e.g., warmth, tenderness, itching, generalized pain, arm motion limitation, erythema, induration, edema, nodule, bruise) with the exception of arm motion limitation, more women than men reported the adverse event. The summary data demonstrate that changing from subcutaneous to intramuscular administration reduces the frequency of most injection site adverse events in women and men and results in substantially diminished absolute differences in adverse events between women and men.

An analysis of the systemic adverse event, fatigue, in a per dose manner showed that there was no difference between TRT-4IM and TRT-4SQ with respect to reporting this adverse event. Interesting to note is the rates of reporting for this adverse event among the control groups. While slightly more AVA recipients than controls reported this event, generally speaking there are similar proportions across all groups. Based on the solicited systemic adverse events that were analyzed during the interim analysis (e.g., fatigue, muscle ache, headache, fever, one or more systemic, total systemic) there was no difference in reporting of systemic adverse events between TRT-4IM and TRT-4SQ groups.

Data from the repeated measures model allowed for the comparison of gender groups with respect to the presented solicited adverse event, fatigue. Again, there was no difference between subcutaneous and intramuscular administration with reporting of the adverse events. However, it is important to note that once again there was a significant difference between genders for reporting of this adverse event, and this held true even amongst the control groups. The fact that there were no interactions present in the model indicates the gender difference was somewhat consistent across the treatment groups. In general, the gender effect was statistically constant across the treatment groups for all solicited systemic events and route of administration was not significant.

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Serious adverse events are reported to the FDA for all clinical trials, and blinded assessments are made by an independent medical monitor. At the time of the interim analysis, there were 51 serious adverse events occurring among 47 participants and none were assessed as being causally related to the study agent. As of February 20, 2008, there were 229 reports of serious adverse events in 186 persons, with 9 of those events in 7 persons assessed as "possibly" related to the investigational agent. Possibly related serious adverse events included: tear of shoulder supraspinatus tendon; generalized reaction night of 6th vaccine; bilateral pseudo tumor cerebri with bilateral disc edema; new onset of generalized seizures, hydrocephalus consistent with aqueductal stenosis; new onset bilateral arthralgia; 2 events of bilateral invasive breast cancer. This is a blinded assessment, and the true study group of these participants will not be known until early 2009, at which time an unblinded analysis may be performed. It is important to note that a November 2006 review of VAERs and DoD data found no obvious trend for AVRP "possibly" related SAEs among persons receiving AVA.

Four reports of shoulder pain in clinical trial participants resulted in the DSMB requesting that the investigators track and monitor any additional participants developing shoulder pain which met the case definition of new onset or exacerbation of existing pain lasting > 7 days beyond the first 2 weeks following injection and with no alternative explanation. A 2003 masked review conducted by the DSMB showed no association with a particular treatment group. However, CDC did request that the sites lower the site of injections to at least 3 fingerwidths below the acromion to avoid potentially injecting into the bursa. All reports are assessed for potential relatedness to the study agent by a blinded, independent medical monitor. To date, there have been 36 cases, with 5 assessed as "probably" related to the study agent.

In summary, the TRT-4IM group experienced local adverse events at lower frequencies and also lower severity and for shorter durations than did the 4SQ group. Route of administration did not significantly influence the occurrence or duration of systemic adverse events. Women reported significantly more adverse events than men for both local and systemic adverse events. With respect to systemic adverse events these differences were statistically similar across treatment groups, even among the control groups. To date, there have been 9 serious adverse events assessed as "possibly" related to the investigational agent and 5 instances of shoulder pain assessed as "probably" related to the study agent. These are still blinded assessments.

Dr. Quinn then reported on the immunogenicity analyses, explaining that the serological data in the analyses are a non-inferiority of the anti-protective antigen IgG (anti-PA) antibody responses at week 8 and month 7. Month 7 is the critical time point for the evaluation because in this study, this reflects completion of the minimal primary vaccination schedule of 0, 4, and 26 weeks and then moving to a booster at 42 weeks. The primary endpoints are anti-PA IgG geometric mean concentration (GMC); anti-PA IgG geometric mean titer (GMT); and proportion of responders with a 4-fold rise in concentration. The non-inferiority criteria, based on the primary endpoints, were that the upper bound of the 95% confidence intervals for the ratio of the 4-SQ group to the

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test groups' GMC and GMT were less than 1.5, and that the analogous upper bounds for the differences in proportions of four-fold response was less than 0.10. Dr. Quinn reviewed the schedule of injections and the study groups.

The primary endpoints are based on an enzyme linked immuno-absorbent assay (ELISA) that quantities antibody responses to the PA antigen in the vaccine. This assay is specific, sensitive, precise, and accurate. It is based on interpolation of serum responses between the test serum curve and a human reference standard that is made at CDC. The important points about this assay are that it has a minimum detectable concentration (MDC)of 0.06µg/ml; reliable detection limits (RDL) of 0.09µg/ml, an empirical lower limit of quantification (LLOQ) of 3.7µg/ml anti-PA IgG in the test serum sample; high intra-assay precision (%CV) of 3.1% – 10.0%; high inter-assay precision of 4.2% – 11.0%; a good dynamic range of 0.07-2.19µg/ml anti-PA IgG; high accuracy reflected by the low standard of percent error of 6.3%; and it has good dilutional linearity. Most importantly, the diagnostic sensitivity (95.1%) and specificity (98.5%) are high, as are the negative predictive values (98.6%) and the positive predictive values (95.0%). The assay was redesigned and re-built specifically for this study, it has been validated, and the master file is at FDA.

With regard to the frequency of non-responders, at 7 months (the critical time point for this study) both the 4SQ (0/139) and 4IM (0/145) groups had no non-responders in the entire cohort, and there only 0.5% non-responders in the 3IM group. In the placebo group, there was one false positive, which reflects the specificity and sensitivity of the assay. Looking earlier in the schedule (8 weeks), there again are very low frequencies of non-responders in all groups and a very high frequency of non-responders, as one would expect, in the placebo group: 4-SQ: 2/153 (1.3%); 4-IM: 3/154 (1.9%); 3-IM: 21/446 (4.7%); and PLAC: 157/158 (99.4%).

Two of the primary endpoints are based on IgG concentration and dilutional titers. Anti-PA titer and IgG concentration are very highly positively correlated. For the purpose of this presentation, Dr. Quinn noted that he would speak about geometric mean concentrations and antibody concentrations exclusively.

With regard to immunogenicity results, at month 7 all groups were non-inferior to the licensed regimen for all endpoints. At week 8, the 4-IM group was non-inferior to the 4-SQ regimen for all three primary endpoints and the 3-IM group was non-inferior for the proportion of participants with a 4-fold rise in titer. Looking at the serological curves, at the 7 month time point (e.g., the end of the priming series of the study regimen) the antibody levels are very high, they are non-inferior, and they are reaching in excess of 200 µg/ml geometric mean concentrations. This is the important time point because it reflects perhaps an antigenic challenge, the immune priming for which is established by the preceding injections at weeks 0, 2, 4 in the 4IM and 4SQ groups and weeks 0 and 4 in the 3IM group. At week 8, the antibody responses are significant although magnitudes are different. These high levels of seroconversion are also reflected in the frequency of 4-fold responders, approaching 100% seroconversion at 7 months, with 98.2% in the 3IM group. Working backwards through the schedule, there is also a very

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high frequency of responders at week 8; between 95% and 99%. This high frequency of responders is also reflected in the reverse cumulative distribution (RCD) curves. Over 95% of all three groups reached 50µg/ml anti-PA IgG in serum, which is a significant and high level of antibody. Looking at the early priming responses to 2 or 3 injections, 60-80% of participants reach the 50µg/ml level.

One of the important components in the study design is not just the magnitude of the antibody response, but its ability to elicit a functional response to anthrax toxin and to neutralize that toxin. The neutralization data were not included in the interim analysis, but there is a very high positive correlation between the magnitude of the anti-PA IgG response and the ability of vaccinee serum to neutralize anthrax lethal toxin.

Another important component of this study was the relationship between human responses to vaccination and protection. Anthrax is not a disease for which an efficacy study can be readily conducted, so correlate of protection models are being built using studies in Rhesus Macaques. In parallel to the AVA human clinical trial, a dose ranging and immunogenicity study is being conducted in Rhesus Macaques. These animals receive dose ranges of the human vaccine dose from 1/5 down to 1/40 dilutions, so their immune response is being modulated by giving them different antigen loads. For both the human and the Rhesus Macaques cohorts, the investigators will build complex humoral and cellular immune profiles. Virulent *Bacillus anthracis* aerosol challenge has been completed in these Rhesus Macaques and investigators are working on mathematical models to developed immunocompetence models. From these immunocompetence models, non-human primate immune correlates of protection will be identified. We will link the cellular and immunological profiles from the human study to hopefully identify human surrogate markers of protection and thus put in place the last piece of the puzzle for relating vaccine elicited immunological responses to protection in humans. .

Thus, Dr. Quinn reiterated that the AVRP interim analysis serologic conclusions were that for the Month 7 (primary decision point) geometric mean concentrations, there were high levels of anti-PA IgG in all groups; there were less than 0.5% non-responders; the anti-PA IgG geometric mean concentrations exceeded 200 µg/ml in all groups; and there are greater than 98% 4-fold responders, with greater than 95% achieving at least 50 µg/ml of anti-PA IgG. Working back through the schedule, at week 8 there were also high levels of anti-PA IgG in all groups, a maximum of 5% non-responders, geometric mean concentrations greater than 50 µg/ml and up to 100 µg/ml; and greater than or equal to 95% 4-fold responders, with greater than 60-82% of responders reaching the 50 µg/ml of anti-PA IgG. Additional data generated at the Week 8 time point are that the antibody responses were significantly higher in females in the 4-IM and 3-IM groups, but not in the 4-SQ group (p=0.12). There was also a general decrease in antibody response with increase in age. However, none of these differences were evident at Month 7.

Reactogenicity conclusions were that intramuscular administration was associated with significantly fewer and less severe injection site adverse events. No serious adverse

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events that were reported during the first 7 months were assessed as causally related to AVA.

Dr. Wright pointed out that these data are being provided to the ACIP because they are important immunogencity and safety data which will be included in the revised statement. In addition, the FDA is reviewing a Biologics License Change Application submitted by Emergent BioSolutions using the data generated from the interim analysis. In this BLA, Emergent BioSolutions has asked to add an indication to drop the 2 week dose, to add an indication for IM administration, and to add language regarding missed doses. CDC hoped to be able to further discuss the FDA decision, anticipated the first week of March, during the June 2008 ACIP meeting. In addition, Dr. Wright recapped the Anthrax Vaccine Working Group planned activities.

Discussion

- In relation to safety, Stanley Plotkin (sanofi pasteur) thought this was a very carefully conducted study with numerous observations. Referring specifically to the chronic shoulder pain issue, it struck him that this kind of observation is not generally done in safety studies—not with this intensity. It is not known yet whether there will be an association between any vaccine group and the control. The point in terms of civilian use and vaccines in general is that alum-containing vaccines should be carefully given; that is, not into the shoulder joint. There is a question of proximity to the shoulder and this might be something to consider for the general vaccination recommendations. The high risk group was exposed to enormous quantities of spores in the air in the original Bachman study, so it was very impressive that none of the vaccinated subjects developed inhalation anthrax. Thus, the vaccine seems to be highly efficacious. In a mass exposure, 5% failure to respond is not an insignificant number. At 6 weeks, antibiotic treatment would be stopped, so the titer at that time is going to be important. With regard to the serologic data and a recommendation for post-exposure use in the event of a terrorist attack, he asked whether Dr. Quinn regarded the 3-dose immunogenicity results as sufficient in that situation.

- Dr. Quinn responded that there were two very important components to the way those groups responded to the 2 and 3 injections at 0, 2, 4 or 0 and 4 weeks. First, if the 26-week injection was considered a surrogate for exposure and how well subjects were prepared by the previous injections (whether there were 2 or 3), everybody was very well prepared immunologically for this “challenge”. Second, even the 3IM group had very significant responses to the vaccine, with 95% 4-fold responders and high proportions got to at least 50 ug/ml levels of antibody. Those are significant levels. If they were willing to extrapolate from animal models, such as rabbits and Rhesus Macaques, certainly it is known that for the rabbits that 50 ug/ml of anti-PA IgG, whether elicited by vaccination or passively by transfer is a very high level of protection. To address the question specifically, the two dose regimen does perhaps give sufficient protection, although the antibody levels might not reach the levels of the 3-dose regimen post-exposure.

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- Dr. Pickering wondered, since this is an alum-containing vaccine and generally all alum-containing vaccines are given intramuscularly, why this was initially given subcutaneously. He also inquired as to why the 2-week dose was being dropped although the 4-dose intramuscular studies show very good levels.

- Dr. Wright responded that it was her understanding that originally most vaccines were administered subcutaneously and that because this is an older vaccine, it is administered subcutaneously because that was routine when it was developed and licensed. No one has ever looked to change the route of administration until now. At this time, all that has been assessed are the first four doses (out of a 6 dose priming series). The 6-dose series is cumbersome and it would be nice to remove additional doses if they aren't truly needed. If the FDA were to rule that the 2-week dose could be dropped, it would then be a 5-dose primary series. The investigators are considering possibly dropping additional doses in the future.

- Tom Zink (Health & Longevity) congratulated the working group on being so swift, thorough, and responsible in the way they proceeded to look at this. He was especially grateful on behalf of those he was representing, the Emergency Responders of the United States, many of whom have put together a consensus statement wishing to receive this vaccine so that their protection can equal that of the Weapons of Mass Destruction Civil Support Teams, and also on behalf of those who would like to receive this vaccine soon, perhaps through the National Stockpile (NSP) that is going to go to waste in the next two years as has been documented in public testimony by the General Accounting Office (GAO). He also indicated that he put together three pieces, which could be found on the back table for those interested, that represented his opinions and those of the Institute for Biosecurity at St. Louis University.

Public Comment

- Karen Beauvais (Generation Rescue) indicated that she is the mother of an autistic son who has recovered with IV chelation. Through thorough biological testing, she learned that her son sustained mercury damage of over 277 times the Environmental Protection Agency (EPA) allowable amount of mercury in his vaccines. She had her other three children tested as well. Her 13-year daughter suffered from learning disabilities, scoring consistently lower than her grade level on her Iowa Standard Tests year after year. Following a year of IV chelation, her daughter began to score two to three years ahead of her grade level. Ms. Beauvais said that she took her children with full confidence to her pediatrician thinking that they would be vaccinated with vaccines that were rigorously tested and regulated by the US government. She said that as she read the news the previous day, she learned that the ACIP voted to advise flu shots, which still contain 25 micrograms of mercury, to adolescents and small children. This means that eventually this vaccine will be included in the school vaccine schedule. She noted that in one of the test

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cases recently reviewed and ruled upon, the VICP concluded that a test case child had underlying conditions that were exacerbated by vaccines. Ms. Beauvais said that she came to the ACIP as a mother who fully bought into vaccination to request that the ACIP consider stating a preference for mercury-free vaccines, and that they consider the Material Data Safety Sheet from Eli Lilly, the first statement of which reads, "This product contains Thymerosal®, a chemical known by the State of California to cause birth defects and other reproductive harm."

- Sarah Beauvais, the 13-year old daughter of Karen Beauvais, read the following definition of "mercury" from the dictionary, "Mercury, a poisonous, silvery liquid metal. Mercury is used in thermometers and barometers." Sarah said that by putting mercury in vaccines, they might as well put the mercury from a thermometer in children's blood. She also shared a story of her younger brother exhibiting strange behavior (e.g., tearing off his diaper, smearing feces on the wall, running down the street, and sometimes disappearing) upon returning home from receiving his vaccines, and how he was soon diagnosed with autism. She requested that the ACIP consider their sons, daughters, nieces, and nephews in making their decisions about what to give children.

Motion

Dr. Baker made a motion to adjourn, which Dr. Chilton seconded. With no further business posed, Dr. Morse officially adjourned the February 2008 ACIP meeting.

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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National Vaccine Advisory Committee (NVAC)

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Deputy Commissioner Office of Public Health
New York State Department of Health
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Pharmaceutical Research and Manufacturers of America (PhRMA)

BRAGA, Damian A.
President, Sanofi Pasteur
Swiftwater, Pennsylvania

PARADISO, Peter, Ph.D.
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Wyeth Vaccines
Collegeville, Pennsylvania

Society for Adolescent Medicine (SAM)

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ACIP
February 27-28, 2008
US Visitors List

Temte	Jonathan	United States	AAFP
Ray	Jill	United States	American Academy of Pediatrics: Georgia Chapter
SIEVERT	ALAN	United States	American Academy of Pediatrics: Georgia Chapter
Saari	Thomas	United States	American Academy of Pediatrics: Immunization Task Force
Bowser	Andrew	United States	ABCB Consulting and Media, Inc.
Wells	Katelyn	United States	AIM
Wood	Laurel	United States	Alaska Immunization Program
Peter	Georges	United States	Alpert Medical School of Brown University
Campos-Outcalt	Doug	United States	American Academy of Family Physicians
Bocchini, Jr.	Joseph	United States	American Academy of Pediatrics
Kimberlin	David	United States	American Academy of Pediatrics
Leger	Marie-Michele	United States	American Academy of Physician Assistants
Saslow	Debbie	United States	American Cancer Society
Turner	James	United States	American College Health Association
Schmader	Kenneth	United States	American Geriatrics Society
Grogg	Stanley	United States	American Osteopathic Association
Jeoffroy	Jean-Robert	United States	Arizona Department of Health Services
Yamauchi	Terry	United States	Arkansas Children's Hospital
Prilutskiy	Yuriy	United States	Bank of America
Baker	Carol J.	United States	Baylor College of Medicine
Middleman	Amy	United States	Baylor College of Medicine
Goldenthal	Karen	United States	Bethesda Biologics Consulting
Dreier	Thomas	United States	Biomedical Advanced Research and Development Authority (BARDA)
Colwell	Chris	United States	Biotechnology Industry Organization
Backer	Howard	United States	California Department of Public Health
Hammer	Sandra Jo	United States	California Department of Public Health
Angbazo	Janet	United States	Capital Primary Care
Aydlotte	Susan	United States	Centers for Disease Control and Prevention
Bresee	Joseph	United States	Centers for Disease Control and Prevention
Miller	Elaine	United States	Centers for Disease Control and Prevention
Vinluan	Michael	United States	Centers for Disease Control and Prevention
Cieslak	Ted	United States	Centers for Disease Control and Prevention
Gershman	Mark	United States	Centers for Disease Control and Prevention
AHMED	FARUQUE	United States	Centers for Disease Control and Prevention
Kossover	Rachel	United States	Centers for Disease Control and Prevention
Kroger	Andrew	United States	Centers for Disease Control and Prevention
Murphy	Trudy	United States	Centers for Disease Control and Prevention
Doss	Jillian	United States	Centers for Disease Control and Prevention
Rue Cover	Alison	United States	Centers for Disease Control and Prevention Logistics Health Incorporated: Contract Employee
Murphy	Linda	United States	Centers For Medicare & Medicaid Services
Morita	Julie	United States	Chicago Department of Public Health
Offit	Paul	United States	Children's Hospital of Philadelphia
Englund	Janet	United States	Children's Hospital, University of Washington
Willeke	Karen	United States	Colorado Department of Public Health and Environment

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Huffman	Margaret	United States	Colorado Department of Public Health and Environment
Reynolds	Joni	United States	Colorado Immunization Program
Cooney	Lenore	United States	Cooney/Waters Group
Vigliarolo	Peter	United States	Cooney/Waters Group
Wang	Edward C	United States	CSL Behring
Mazur	Marie G.	United States	CSL Biotherapies
Dalrymple	Donald "Dack"	United States	Dalrymple & Associates, LLC
Hachey	Wayne	United States	Department of Defense
Lieu	Tracy	United States	Department of Ambulatory Care and Prevention Harvard Pilgrim Health Care and Harvard Medical School
Rowe-West	Beth	United States	Division of Public Health / Immunization Branch
Johann-Liang	Rosemary	United States	Division of Vaccine Injury Compensation / Health Resources and Services Administration
Katz	Samuel	United States	Duke University Medical Center
Hackman	Jeffrey	United States	Emergent BioSolutions, Inc.
Hecht	herbert	United States	Emergent BioSolutions, Inc.
Hopkins	Robert	United States	Emergent BioSolutions, Inc.
Schmitt	Tracey	United States	Emergent BioSolutions, Inc.
Shofe	Allen	United States	Emergent BioSolutions, Inc.
Smith	Jeffrey	United States	Emergent BioSolutions, Inc.
Waytes	Tom	United States	Emergent BioSolutions, Inc.
Jackson	Washington	United States	Emergent BioSolutions, Inc.
Kim	Hye Mi	United States	Emory University
Oresntein	Walter	United States	Emory University
Pazol	Karen	United States	Emory University
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Lastinger	Jennifer	United States	Families Fighting Flu
Moise	Julie	United States	Families Fighting Flu
Scott	Laura	United States	Families Fighting Flu
Stein	Gary	United States	Families Fighting Flu
Yaksich	JoAnna	United States	Families Fighting Flu
Lake	Thomas	United States	FastVax
halstrom	erik	United States	FFF Enterprises
Noll	Luke	United States	FFF Enterprises
Treharne	Vivienne	United States	Florida Department of Health
Hassan	Joseph	United States	Fleishman-Hillard
Humphrey Franklin	Donelle	United States	Georgia Division of Public Health
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ursino	gregory	United States	GlaxoSmithKline Pharmaceuticals
Derkacz	Michael	United States	GlaxoSmithKline Pharmaceuticals
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Friedland	Leonard	United States	GlaxoSmithKline Pharmaceuticals
Keenan	Rich	United States	GlaxoSmithKline Pharmaceuticals
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McLaughlin	Jeffrey	United States	GlaxoSmithKline Pharmaceuticals
Obara	Timothy	United States	GlaxoSmithKline Pharmaceuticals
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Rennels	Margaret	United States	GlaxoSmithKline Pharmaceuticals
Wighton	Timothy	United States	GlaxoSmithKline Pharmaceuticals
Sammons	David	United States	GlaxoSmithKline State Government Affairs
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Dubin	Gary	United States	GlaxoSmithKline Pharmaceuticals
Penrod	Deborah	United States	GlaxoSmithKline Pharmaceuticals
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Weed	Leslie	United States	Healing Every Autistic Life
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Malinoski	Frank	United States	MedImmune, Inc.
Rousculp	Matthew	United States	MedImmune, Inc.
MacDonald	Peter	United States	MedImmune, Inc.
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Haupt	Kim	United States	Merck & Company, Incorporated
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Cohen	Hillel	United States	Novartis Vaccines
Guzman	Jose	United States	Novartis Vaccines
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Jorgensen	Daniel	United States	Pfizer, Inc.
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Decker	Michael	United States	sanofi pasteur
Filipski	Brian	United States	sanofi pasteur
Gurunathan	Sanjay	United States	sanofi pasteur
Hosbach	Philip	United States	sanofi pasteur
Johnson	David	United States	sanofi pasteur
Kearney	Stacy	United States	sanofi pasteur
Plotkin	Stanley	United States	sanofi pasteur
Shannon	Ellen	United States	sanofi pasteur
Smith	Stephen	United States	sanofi pasteur
Williams	Scott	United States	sanofi pasteur
Jankelevich	Shirley	United States	South Carolina Department of Health
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Moore	Kelly	United States	Tennessee Department of Health
Gall	Stanley A	United States	The American College of Obstetricians & Gynecologists
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Keyserling	Harry	United States	The Society for Healthcare Epidemiology of America
Ward	Joel	United States	UCLA Center for Vaccine Research

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Clover	Richard	United States	University of Louisville
Chilton	Lance	United States	University of New Mexico
Zimmerman	Richard	United States	University of Pittsburgh
Bennett	Nancy	United States	University of Rochester
Foster	Stephan	United States	University of Tennessee
Schaffner	William	United States	Vanderbilt University School of Medicine
Nichol	Kristin	United States	Veterans Affairs
Abramson	Jon	United States	Wake Forest University Health Sciences
Gabor	Gerald	United States	Wisconsin Immunization Program
Garrett	W. Matthew	United States	Wyeth Pharmaceuticals
Paradiso	Peter	United States	Wyeth Pharmaceuticals
Abraham	Brian	United States	Wyeth Pharmaceuticals
Lichtner	Jenny	United States	Wyeth Pharmaceuticals
O''Neill	Kevin	United States	Wyeth Pharmaceuticals
Kulp	Lynda	United States	Wyeth Pharmaceuticals
Mason	Dean	United States	Wyeth Pharmaceuticals

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ACIP
February 27-28, 2008
International Visitors List

Tan	Litjen (L.J)	Singapore	American Medical Association
Langley	Joanne	Canada	Dalhousie University/IWK Health Centre
Thanapaisal	Thippayawan	Thailand	Emory University Rollins School of Public Health
Miyazaki	Chiaki	Japan	Fukuoka West Rehabilitation Center for Children Japan Pediatric Society
Schuind	Anne	Belgium	GlaxoSmithKline
Rollet	Pierrick	France	GlaxoSmithKline Biologicals S.A.
Dosanjh	Jag	United Kingdom	GlaxoSmithKline Pharmaceuticals
Odio	Carla Maria	Costa Rica	Hospital nacional de Ninos in San Jose, Costarica
Asante-Abedi	Susan	Ghana	IMS Health
Tauber	Erich	Austria	Intercell AG
Kelly	Kevin	Canada	Merck & Co., Inc.
Kerba	Johanne	Canada	Merck Frosst
Major	Maria	Canada	Merck Frosst Canada Ltd.
Saddier	Patricia	France	Merck Research Laboratories
Tran	Trung	Vietnam	Merck Research Laboratories
JUMA	MOHAMED	Tanzania	Ministry of Health Zanzibar
Nobuhiko	Okabe	Japan	National Institute of Infectious Diseases, Japan
Gowler	Jeremy	Canada	Novartis Vaccines and Diagnostics, Inc.
Nogard	Claude	France	Novartis Vaccines and Diagnostics, Inc.
Dawson	Tracey	United Kingdom	Novartis Vaccines and Diagnostics, Inc.
Hills	Susan	Australia	PATH
Virani	Shainoor	Canada	Public Health Agency of Canada
Virani	Shainoor	Canada	Public Health Agency of Canada
Virani	Shainoor	Canada	Public Health Agency of Canada
Virani	Shainoor	Canada	Public Health Agency of Canada
Werker	Denise	Canada	Public Health Agency of Canada
Mascarenas	Cesar	Mexico	sanofi pasteur, Inc.
Tornieporth	Nadia	Germany	sanofi pasteur, Inc.
Shindman	Judith	Canada	sanofi pasteur Limited
ALLAVOINE	THIERRY	France	sanofi pasteur MSD
Kitchin	Nicholas	United Kingdom	sanofi pasteur MSD
ndonga	linus	Kenya	Strategic Poverty Alleviation Systems (SPAS)
Otoo	Andrew	Ghana	Wyeth Pharmaceuticals
York	Laura	Canada	Wyeth Pharmaceuticals

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