

**CENTERS FOR DISEASE CONTROL AND PREVENTION**  
**NATIONAL IMMUNIZATION PROGRAM**  
**RECORD OF THE MEETING OF THE**  
**ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES**  
**October 15-16, 2003**

**DRAFT**

Meeting Held at the  
Atlanta Marriott Century Center Hotel  
Atlanta, Georgia

## Table of Contents

<b>MINUTES OF THE MEETING</b> .....	2
<b>OPENING COMMENTS</b> .....	2
<b>INFLUENZA SESSION</b> .....	3
<b>VOTE ON INFLUENZA RECOMMENDATION</b> .....	28
<b>IOM VACCINE FINANCING REPORT</b> .....	29
<b>SMALLPOX SESSION</b> .....	32
<b>INVASIVE PNEUMOCOCCAL DISEASE SESSION</b> .....	41
<b>FEBRUARY ADVISORY STAKEHOLDER ENGAGEMENT SURVEY</b> .....	50
<b>RECOMMENDED ROUTINE AND CATCH-UP SCHEDULE FOR 2004</b> .....	52
<b>MENINGOCOCCAL WORKGROUP UPDATE</b> .....	53
<b>HEPATITIS SESSION</b> .....	54
<b>VOTE: VFC RESOLUTION</b> .....	56
<b>YELLOW FEVER VACCINE SAFETY WORKGROUP REPORT</b> .....	57
<b>AGENCY UPDATES</b> .....	58
<b>ATTACHMENTS</b> .....	63
<b>AGENDA</b> .....	64
<b>ATTENDANCE</b> .....	66

**CENTERS FOR DISEASE CONTROL AND PREVENTION  
NATIONAL IMMUNIZATION PROGRAM  
ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES  
MINUTES OF THE MEETING  
October 15-16, 2003**

**OCTOBER 15, 2003**

A meeting of the Advisory Committee on Immunization Practices (ACIP) was convened by the Centers for Disease Control and Prevention's (CDC) National Immunization Program (NIP) at the Atlanta Marriott Century Center Hotel in Atlanta, Georgia, on October 15-16, 2003. The meeting agenda was posted on CDC's Website (<http://www.cdc.gov/nip/>) and is attached. The meeting was convened by ACIP Chairman Dr. Myron Levin at 8:30 a.m.

Those present are listed on the attached sheets.

**OPENING COMMENTS**

Dr. Melinda Wharton greeted the attendees for ACIP Acting Executive Secretary Dr. John Livengood.

Drs. Modlin, Brooks and Tompkins had rotated off the committee. New members expected to be seated by the February 2004 meeting, and their terms are: Dr. Jon Abramson (1 year), Dr. Ed Marcuse (2 years), and Drs. Ban Ishu Allos, John Treanor, and Robin Jones Womeodu (4 years). Dr. Levin will be ACIP Chair for his remaining one year on the ACIP.

New representatives to the ACIP include: Dr. Stephen Phillips (DOD *ex-officio*), Dr. Margaret Rennels (AAP liaison) and Dr. Anthony Braga (Pharmaceutical Research and Manufacturers of America liaison). Staff appointments announced were: Ms. Demetria Gardner, Committee Management Specialist to support the ACIP; and Dr. Louisa Chapman, Assistant to the Director for Immunization Policy.

Workgroup meetings scheduled during the ACIP meeting were: Influenza, Rotavirus vaccine, Evidence-based Recommendations and Meningococcal.

The ACIP home page is [www.CDC.gov/nip/acip](http://www.CDC.gov/nip/acip); the email address is [acip@cdc.gov](mailto:acip@cdc.gov). The 2004 meeting dates will be on 2/24-25, 6/23-24, and 10/27-28/04. Public comment periods are scheduled during each meeting.

The members were asked to be conscious of maintaining a quorum so the committee can conduct its business. The ACIP charter provides that *ex-officio* members be asked to vote in the absence of a quorum, and requires the members to state any conflicts of interest. Upon statements of such conflicts, the member would forego participation related to certain vaccine activities. However, since such work also enhances the members' activity as a consultant to CDC while serving on the ACIP (e.g., serving on vaccine trial Data Safety Monitoring Boards (DSMB), CDC on occasion issues limited conflict-of-interest waivers. With those, the member can participate in all discussions, but cannot vote on issues related to those vaccines. The following members stated such work conflicts: Dr. Levin (clinical trials for Merck and GlaxoSmithKline); and Dr. Poland (research grant from Merck). Of the liaisons, potential conflicts were stated by Dr. Rennels (Wyeth, Merck and GSK multi-center vaccine trials).

**AGENDA**

## INFLUENZA SESSION

*Background.* Dr. Zimmerman introduced the topic with a summary of the four-year examination of the substantial burden of influenza disease among children. In response, ACIP in 2001 “encouraged” immunization in those aged 6 to 23 months. This was the first step in a one-to-three year transition from the present recommendation only for those at high risk to a universal recommendation. The issues that have been tracked to ensure successful implementation of the latter include financing in place to support such a recommendation, adequate vaccine supply, relevant education under way, and data in hand from feasibility studies for issuing a season-based as well as an age-based recommendation. A formal vote was anticipated on this day (or a “straw vote” until the February 2004 meeting) on whether to issue a universal recommendation for influenza vaccination. The AAP and AAFP have been so advised to ensure that the influenza recommendations remain harmonized.

### Overview

Presenter: Dr. Keiji Fukuda, NCID

The ACIP influenza vaccination policy was set in February 2003. This day’s focus was on how a newly licensed live attenuated influenza vaccine (LAIV) may fit into that policy. FDA approved the licensure of MedImmune’s LAIV, FluMist™ the first activated vaccine approved in the U.S. Dr. Fukuda summarized the history of ACIP recommendations on the use of influenza vaccine.

### Mortality/Morbidity Impact of Influenza on Young Children

Presenter: Dr. Tim Uyeki, NCID

*Morbidity:* Studies of attack rates of laboratory-confirmed clinical illness during epidemics show them to be consistently highest among young children. In Houston in 1976, influenza A (H3N2) estimated attack rates as follows: For children aged <1 year the rate was 36%, 35% for those 1-4 years, 21% for those aged 5-19 years, and 13% for those 20 and older (Glezen WP. Rev ID 1980;2(3):408-420). The 1986-87 25-year retrospective study by Neuzil *et al.* examined data for four seasons and found the attack rate to range from 13.5% to 27% during 1986-87 A (H1N1), 1992-93 B, 1993-94 A (H3N2), and 1995-96 A (H1N1, H3N2). Glezen *et al.* estimated Houston’s resulting peak school absenteeism in the 1975-76 Houston epidemic at 12% and at 40% in 1976-77.

Studies of outpatient and emergency room presentations of children for lab-confirmed illness show febrile upper- and lower respiratory illness, as well as gastrointestinal involvement. Common complications include otitis media and exacerbation of chronic illness such as asthma. Less common complications include myositis and febrile seizures.

Hospitalized conditions for lab-confirmed illness include exacerbation of chronic illness, complications in the immunocompromised, respiratory disease (e.g., pneumonia, bronchitis, croup, bronchiolitis), sepsis-like syndrome (fever without a source), dehydration, and gastrointestinal illness. Uncommon but reported complications include myocarditis, invasive bacterial infection and neurological complications. Data of a retrospective study (1999-2002) at Montreal Children’s Hospital parallel the U.S. presentations. Of 182 children identified, 70% were aged <2 years and 70% were previously healthy; and 12% were admitted into pediatric intensive care for a mean duration of 5 days. Admitting diagnoses were suspected sepsis (30%), lower RTI or pneumonia (30%), asthma or bronchiolitis (13%), and febrile seizures (9%). A significant risk factor was age <1 year.

More attention is being paid to the neurological complications associated with influenza.

*Japanese data.* These include febrile seizures (sporadically reported in the U.S., Taiwan, Korea, Europe, and Canada, more often reported in Hong Kong) and encephalopathy or encephalitis. The latter has been reported in Japan since the 1990s and is primarily seen in young children. This is distinguishable from Reye Syndrome with no history of aspirin ingestion. The children had high fever that rapidly progressed to encephalopathy within 1-2 days. Outcomes were poor. Of 148 lab-confirmed cases reported for 1998-99 in Japan, 82% were aged < 5 years; 53% were female, 85% were previously healthy, and 80% had seizures. Almost a third (32%) died and 28% had neurologic sequelae. Unpublished Japanese data reported recently at an international influenza conference were of 300 lab-confirmed cases reported for 1999-2002. The 2001-02 mortality was 15% and 25% had neurologic sequelae.

U.S. data on influenza-associated encephalopathy come from sporadic reports. Passive surveillance of suspected cases in the last five years (data requested by CDC, probably underestimated, published in *MMWR*, journals and on ListSers) in children <18 years old indicated altered mental status or personality change within 24 hours, occurring <5 days from the onset of a febrile respiratory illness, and evidence of influenza virus infection. Preliminary data (1999-2003) indicate 23 cases reported from 15 states, including 16 from January to April, 2003. The median age was 5 years (range 6 months - 14 years). Only 10% were of Asian descent; 75% were white or Hispanic. The median time to encephalopathy was 2 days; there were two fatal cases (9%) and 26% had neurological sequelae. The cases were associated with both influenza A (65%) and B (26%) infection; A/B: (9%).

A CDC Epi-Aid to Michigan, investigated severe pediatric morbidity and mortality, (January-February 2003) in response to 14 cases of severe illness associated with influenza. There were four fatal influenza A cases (ages: 2, 5, 6, 14 years), all among previously well children who were not vaccinated against influenza. Another ten were serious non-respiratory cases, with a median age of 2.5 years (range 14 months - 9 years). Nine were influenza A (H1N1, H1N2, H3N2), and one was influenza B. The vaccination status of these children was unknown.

In an investigation of unexplained but influenza-associated deaths in non-hospitalized, previously healthy children, from January to March 2003, CDC tested available specimens. Preliminary data revealed nine influenza-associated deaths in 5 states, all cases who collapsed or were found unresponsive. The median time from fever onset to death was 2 days, the median age was 6 years (range 2 - 14 years); 56% were female and all were unvaccinated. Influenza A was identified in 44% cases and influenza B in 56%. No other common etiologies were identified. One of the 9 fatal cases' autopsy showed substantial brain edema, suggesting death from encephalopathy. There was some evidence of pneumonitis in four cases. Overall, the pathophysiology or exact cause of death was unclear, but influenza was consistently associated.

*Summary:* Children are heavily impacted by influenza during seasonal epidemics. Numerator data indicate that a small percentage die and a larger number are hospitalized, but most are seen as out-patients or in ERs, or not at all. Young children have the highest attack rates and frequency of hospitalizations. Neurological complications such as influenza-associated encephalopathy are a major problem in Japan. Preliminary data suggest that influenza has been associated with encephalopathy cases and sudden deaths in the U.S.

*Discussion* included Dr. Plotkin's comment that the neurological sequelae from flu are biologically plausible. It is easy to adapt flu virus to become neurotropic in mice. Injection into the brain produced severe cerebral edema without much cellular response.

### **Influenza-Associated Hospitalizations/Deaths in the U.S.**

Presenter: Dr. William Thompson, NIP

*Deaths:* Children aged <1 year have a <1 per 100,000 person-years risk of death from influenza. The risk of those aged 50-64 is 7.5, and that for those aged 65+ is 98.3.

*Hospitalizations:* The hospitalization risk per 100,000 person-years was 115 for those aged 0-4 years; 22 for those aged 5-49 years; 90 for those aged 50-64 years; and 472 for those aged 65 and over. A comparison of data on influenza-associated hospitalizations for children aged <5 years (per 1000 person years) was done between the National Hospital Discharge Survey (1.2) and three other studies: Barker, 1982: 1.2; Neuzil, 2000: 2.6; Izurieta, 2000: 0.9; and Neuzil, 2002: 1.4. Such hospitalizations for children aged <2 years were calculated by Neuzil (2000) at 4.8; Izurieta (2000) at 1.9; Neuzil (2002) at 3.5; and 2.4 by the NHDS.

The relative risk ratios, comparing hospitalizations rates to deaths, clearly reflected the highest risk of hospitalization as an influenza-associated outcome among young children, relative to dying. No other age group even came close.

Of the annual U.S. influenza-associated hospitalizations (230,000 respiratory and circulatory diagnoses), children aged <2 years account for 17,000. Of the 36,000 respiratory and circulatory illness deaths, children aged <5 years account for 92.

### **New Vaccine Surveillance Network (NVSN)**

Presenter: Dr. Marie R. Griffin, Vanderbilt University Medical Center

The CDC-supported NVSN conducts population-based surveillance for vaccine-preventable illness among children. It involves sites in Nashville, TN, Rochester, NY, and Cincinnati, OH. Dr. Griffin used data from those sites to measure influenza-related visits by children aged <5 years to hospitals, ERs, and outpatient venues.

The Rochester and Nashville sites have 46,977 and 37,813 children enrolled, respectively. With the recent addition of Cincinnati, they will cover close to 1% of U.S. children aged <5 years. Race and ethnicity is similar to the U.S. population, with some over-representation of blacks and under-representation of Hispanics.

Inpatient surveillance began in October 2000. The enrollment criteria were outlined. The study process included an interview with parents/guardians, chart review, and nasal/throat swabs for culture and PCR analysis. Specific methods for culture/PCR were described. Statistical analysis for incidence was weighted for the non-enrollment and non-sampling days, by age and site. Of 1677 hospitalizations for ARI or fever, 1037 (62%) occurred from November to April. Of those, 74 (7%) were related to influenza (~4% of ARI/fever for the whole year). About half (53%) of the children admitted were aged <6 months, 31% were aged 6-23 months, and 16% were 24-59 months. Asthma or other high-risk conditions were present among 16%; 22% were given oxygen but not placed in an ICU. The median period of symptoms prior to admission was 3 days (range 1-10) and median length of stay was 2 days (range 1-15). The results were remarkably similar to those presented by Dr. Thompson. For every 1000 admissions, 1.8 were influenza-related, but broken down by age it was 9.08 for those aged <6 months; 1.75 for those 6-23 months and 0.59 for those 24-59 months. High-risk children's rates were higher (2.95 versus 1.69 for no risk), but most of the children were healthy.

The distribution of the discharge data for total ARI and influenza among children <5 years showed influenza presenting similarly to other ARIs, but with a few differences to other viral respiratory illnesses. More children presented with fever (sepsis ruled out) and febrile seizures; only about 10% were diagnosed with pneumonia, and 20% or less with bronchiolitis, asthma or croup.

The characteristics of hospitalizations were charted by age group for rates per 1000. The rate for those <6 months was 9.1, declining to 1.8 for the 6-23 month-olds, and 0.6 for those aged 24-59 months. Only 5% of children at <6 months were identified with high-risk conditions, versus 26% and 33%, respectively, for those aged 6-23 and 24-59 months. Blood cultures were done on almost 80% of children to age 23 months and 50% of those aged 24-59 months. Urine cultures and spinal taps were particularly done for those <6 months to rule out sepsis. The older children (6-23 and 24-59 months) were more likely to have x-rays; 15%-30% of children received oxygen in the hospital.

Outpatient surveillance began in 2002-03, both fairly mild influenza years, during the four-month respiratory viral season. The enrollment criteria and study process were again outlined. To evaluate influenza visits of children aged <5 years, surveillance sites were set up in emergency rooms and outpatient practices. No cultures were done; only swabs for PCR were taken. In all, ~10-20% of all ER ARI visits during the season were reviewed, and 4%-8% of all outpatient ARI visits. Five percent of ER visits were for influenza, as were 9% of outpatient visits. More than half (53%) of children aged <6 months were inpatients, a ratio that reversed for the older children up to age 59 months.

Of the ER visits, 50% were for fever/sepsis; 5% were diagnosed as influenza and 8% of those were high-risk children. None were hospitalized. Similarly, 25-50% of all outpatient visits were due to ARI/fever, 9% were for influenza, and 9% of those were in high-risk children. Again, none were hospitalized.

Study limitations include mild influenza seasons during this surveillance, no serology done for the inpatients and PCR only done for the outpatients, who were assessed for only one year to date. The representativeness of the two sites relative to the rest of the U.S. remains at question.

*Summary:* For the 2000-2003 influenza seasons, hospitalization rates due to influenza were 1-2/1000 children aged <5 years, 1-3/1000 children aged 6-23 months and 7-12/1000 children aged <6 months. About 5% of all ARI/fever visits to ERs (2002-03) were due to influenza, as were ~9% during the same period for all ARI/fever outpatient visits.

The NVSN population-based surveillance data confirmed that the influenza burden is relatively high in very young children who are hospitalized and that influenza constitutes 5%-10% of ARI/fever outpatient visits during the respiratory viral season. The NVSN serves as a resource for policy makers and continued vaccine evaluation.

*Discussion included:*

- *Surprisingly few infections were due to influenza. Was that because the interval was fairly wide? If you isolated influenza at narrower intervals, would the proportions due to influenza be higher than 5%-10%?* Yes; the respiratory season reviewed was four months; the influenza season is normally only about 2 months. Analyzing a shorter period would raise rates.
- *Did you do a distribution of the rates by month for the children <6 months?* No, but that could be done.

### **Trivalent Influenza Vaccine Effectiveness/Safety in Young Children**

Presenter: Dr. Kathleen Neuzil, University of Washington

An ACIP Workgroup of Drs. Neuzil, Kathy Edwards and Eric France evaluated the available data on vaccine safety and efficacy/effectiveness. To answer the question of whether influenza vaccination will help young children, they conducted a Medline search for trivalent inactivated influenza vaccine (TIV) studies in children, as well as the Medline articles' referenced studies. They focused on studies of

children aged <3 years. They did not include foreign studies since the TIV abroad is not directly comparable to U.S. vaccines. Dr. Neuzil reviewed their results.

Vaccination of all high-risk individuals has been recommended since 1960. Before 1981, whole virus vaccines and vaccines with variable antigen content were used. Some safety/efficacy studies included young children. Split monovalent vaccines and trivalent vaccines showed no excess systemic reactions compared to earlier vaccines or placebos, and local reaction rates were in the 1-2% range.

Although not all directly comparable, current vaccine safety/efficacy studies fall into three main groups:

- a) Small safety/immunogenicity studies (no efficacy/effectiveness endpoints) by Piedra (1993) and Gonzales (2000) showed no or low (6-7%) local reactions and 16-18% with rhinitis, cough or fever in those aged 6-35 months. Weakness: no control group.
- b) Four randomized, controlled studies compared the current inactivated vaccine (split virus, 15  $\mu$  xxx of each antigen) to the earlier cold-adapted live attenuated vaccine as well as placebo. Three were part of the Baylor Family Studies (Gruber 1990, Clover 1991, Piedra 1991) randomizing the children, aged 3-5 years old, by family. The Edwards study (1994) looked at children aged 1-5 years
- c) Efficacy based on seroconversion:
  - a. Neuzil *et al.* (Infect Dis J 2001; 20: 733) showed efficacy rates from 44-48% for H1N1 and H3N2 for children aged 1-5 months. This was based on seroconversion, but when based on culture positivity, the efficacy rates were much higher (80-90%). The rates for those aged 6-10 months were higher (75-72%) for H1N1 and H3N2, respectively, as they for were those aged 11-15 months (80% and 70%). The Baylor studies reflected similarly higher rates for older children and underestimation when gauged by seroconversion.
  - b. Heikkinen *et al.* (AJDC 1991; 145:445) studied 187 Finnish children aged 1-3 years and in daycare, who were vaccinated twice with the U.S. TIV vaccine, and 187 unvaccinated children. No safety data were reported. Influenza was cultured from 5 vaccinees and from 29 controls (VE=83%). TIV also was associated with an 83% reduction in acute otitis media associated with influenza and a 36% reduction in overall acute otitis media morbidity.
  - c. Clements *et al.* (Arch Ped Adoles Med 1995) studied 186 day-care attendees aged 6-30 months, of whom 94 received TIV twice. The others received hepatitis B or no vaccine. No safety data were reported. All the children were examined with biweekly otoscopy by observers blinded to children's vaccine status. The influenza vaccine was protective against AOM during the influenza season.
  - d. Hurwitz *et al.* (J Inf Dis 2000;182:1218) studied 127 day-care attendees (24-60 months) randomized to two doses of TIV (60) or hepatitis A (67). Adverse reactions were assessed by parents and both vaccines were well tolerated. VE (determined by serology for prevention of infection) was 31% for H3N2, 45% for influenza B, and 45% (.05-.66) overall. The study found no significant differences in effectiveness measures. In the households vaccinated for influenza, contacts of influenza-vaccinated day care children had 42% fewer febrile respiratory episodes compared with unvaccinated household contacts of control children.
  - e. Hoberman *et al.* (JAMA 2003; 290: 1608-16) studied TIV effectiveness in preventing otitis media among 786 healthy children aged 6-24 months. Of those, 525 received two doses of TIV (half in the 6-12 month age group) and 261 received a placebo. No serious adverse events (SAE) were definitively related to vaccine/placebo, but there was no reduction seen in AOM, the primary effectiveness endpoint. However, the efficacy rates against influenza in children aged 6-12

months, 13-18 months and 19-24 months were 63%, 66% and 69%, respectively, in year 1. Of 66 children with immunogenicity data, 88.6% to 96.8% developed seroconversion against strains in the vaccine formulation. This study was the only one with analysis by age group (6-12, 13-18, 19-24 months). VE was fairly consistent in year one when attack rates were high (63-69%). And, 88.6% to 96.8% of the 66 children with immunogenicity data seroconverted against the vaccine strains.

A chart comparing the above studies showed the vaccine to be consistently well-tolerated. However, influenza vaccine efficacy will change yearly depending on attack rates. For example, the 66% VE of the mild 1999-2000 influenza season dropped to a negative 7% in 2000-2001 and the studies' VE ranged from 31% to 83%.

*High-Risk Populations* have been the subject of small studies of children with a variety of underlying conditions. Vaccine safety and immunogenicity results appear comparable to those seen in healthy children, but the studies are hard to compare due to their size and the wide range of the children's ages. Groothuis *et al.* (Pediatrics 1991; 87: 823) studied TIV among children with congenital heart disease and demonstrated local reaction safety down to 3-5 months of age.

Foreign studies are hard to compare, but have produced safety profiles and immunogenicity outcomes similar to those in the U.S.

These studies' limitations include variations in age groups, study design, safety assessment, results reporting, and small numbers of children enrolled.

*Summary, TIV Safety Studies Among Children:* About 1000 children aged 6-24 months received the current TIV vaccine in U.S. trials, most receiving multiple doses. The TIV was well-tolerated in all ages, but there was insufficient power to assess uncommon adverse events.

*Summary, TIV Efficacy Studies Among Children:* Efficacy varies by year and age group, but averages in the 50% range. TIV efficacy and effectiveness studies of children aged 6-24 months old reflected a 66% efficacy for culture-confirmed influenza and seroconversion in 88.6% to 96.8% of children aged 6-24 months (Hoberman), efficacy/effectiveness of 44% and 48% by seroconversion (Edwards), and 83% culture-confirmed efficacy (Heikkinen). However, no study has had sufficient numbers of children to address an endpoint of hospitalization.

*Discussion* included:

- *Was efficacy based on seroconversion and immunogenicity, or seroconversion as a diagnosis of influenza disease?* The latter. Children were coming in with clinical illness, but due to study methods, only a few children had cultures. But if they seroconverted post-vaccination to the end of the season and that was associated with a clinical illness, that was considered a lab-confirmed influenza episode.
- *Of previous data shown by Dr. Uyeki of Dr. Neuzil's 2000 and 2002 studies of burden of illness, one study paralleled the others presented, but another was a little higher. Both were done in Nashville, but the studies with the higher rates were done in a Medicaid program, with children presumably of a lower SES. The lower rates were seen in a vaccine clinic, which may have seen children of a higher SES. But the enrollment numbers in that study were also lower, so the confidence intervals were wider. That fact appears to make the two studies equivalent. Have results ever been delineated by SES?* No, not in the efficacy/effectiveness studies.

## **Evaluation of Inactivated Influenza Vaccine in Children Aged 6-24 Months**

Presenter: Dr. David P. Greenburg, Children's Hospital of Pittsburgh

The Heikkinen and Clements studies indicated a 32-36% reduction of incidence of acute otitis media (AOM) after TIV vaccination among children aged 6-36 months, and Belshe's study indicated a 30% reduction of febrile illness in their study of children aged 15-71 months. This study's primary objective was to determine the reduction in the proportion of children aged 6-24 months with AOM after vaccination with trivalent inactivated vaccine. The secondary objectives were to measure the safety and immunogenicity of influenza vaccine, efficacy of the vaccine against influenza, the average number of episodes of AOM, the proportion of days with middle ear effusion (MEE), and the vaccination's effect on direct and indirect medical costs. The study design involved healthy infants aged 6-24 months in primary care at Children's Hospital and pediatric offices in the community. It was a double-blind, block-randomized (2 vaccine:1 placebo), placebo-controlled study in which two doses of vaccine/placebo were given four weeks apart.

Surveillance of two separate cohorts was done biweekly from November to March in 2000 and 2001. In the first year, from April to October 2000, monthly visits were also done. Acute care visits were also done for fever and symptoms of a respiratory illness or AOM. AOM diagnosis was done primarily through pneumatic otoscopy, but also by tympanometry, acoustic reflectometry, and video-otoscope (computer capture of eardrum).

*Study Endpoints.* Influenza culture was taken from the throat cultures of children demonstrating any AOM or respiratory symptoms. Blood samples were taken from a subset before the first dose and four weeks after dose two, to gauge immunogenicity. Safety evaluation was done only of serious/unexpected adverse events, since the vaccine was already licensed for this age group. Healthcare utilization was evaluated at each visit to assess the cost associated with child's illness.

*Demographics.* About half the children were aged 6-12 months; about half were Caucasian and 42% were African American. Fifty-one percent had private insurance, and 48% had public insurance; 47% were CHIP clinic patients and 53% came from the community. About a third of the children lived in homes with exposure to cigarette smoke and two-thirds had other children in the household. About 20% had a history of recurrent AOM before the study and 27% were enrolled in day care. In year two, it was determined that about 70% of the vaccine and placebo groups had had Prevnar™ vaccine previously.

*Immunogenicity.* Vaccine response of the vaccine group in years one and two showed a  $\geq 90\%$  titer response to the three influenza vaccine strains, H1N1, H3N2, and B. In year one, culture-confirmed H1N1 and H3N2 influenza appeared in 30 cases; and in year two, H1N1 and B appeared in 13 cases. Efficacy was 66% in year one and -7% in year two. The placebo recipients' influenza rates were 15.95% in 2000 and 3.3% in 2001. Higher efficacy was seen with increasing age, but not at a statistically significant level: 63%, 66%, and 69% respectively for those 6-12 months, 13-18 months and 19-24 months.

The rates of febrile respiratory tract infections per person month in the two groups were about equal in 2000 (0.23 versus 0.25 episodes;  $p=0.71$ ) and only slightly higher in the vaccine group (0.23 versus 0.17 episodes;  $p=0.03$ ) in 2001. The proportion of children with at least one episode of AOM was charted, showing little difference between the groups in 2000's influenza or respiratory season and for the 1-year follow-up. In 2001, a slightly higher rate of AOM occurred in the vaccine group, but with no statistical significance. When broken out by age group, however, the 19-24 month-old age group demonstrated a 32-42% reduction of AOM compared to the placebo group, but this also was only statistically significant when the one-year follow-up was included. Additional analysis of vaccine effectiveness versus placebo against culture-proven influenza-associated AOM showed 62% efficacy, similar to that of the Heikkinen

study.

*Safety:* Data on hospitalizations (including the same-day surgical insertion of myringotomy tubes) were not different in terms of statistical significance. None of the SAEs were definitely related to either group, but three cases in the vaccine group were outlined as possibly related, all of whom recovered quickly.

Neurological SAEs in the vaccine group were also outlined. One 13-month-old had a staring episode on vaccination day; all the others occurred days to months later.

Unsolicited SAEs possibly or definitely related to vaccination were reported in both groups in parent self-reports, 8 in the vaccine group and 4 in the placebo group, for fever or fussiness/crying within 72 hours, lump at the injection site or sore leg/difficulty walking.

There were no differences between the two groups for physician or ER visits, use of antibiotics, illness or missed work among family members due to illness of a child. In 2001, there was a higher rate of hospitalizations in the vaccine group for insertion of myringotomy tube.

Conclusions for selected measures of safety and efficacy were that: 1) trivalent inactivated influenza vaccine was safe and immunogenic in infants aged 6-24 months; 2) efficacy against influenza was 66% in the first year of the study, but there were too few cases of influenza in the second year to accurately measure this; and 3) there was no reduction in the overall incidence of AOM, but effectiveness against influenza-associated AOM was 62% in the first year of the study.

The possible reasons that these results differ from previous studies could be: 1) the age of the subjects, 2) the predominance of other upper respiratory viral infections causing otitis that could not be distinguished from the influenza vaccine; 3) the diversity of the community-derived population in this randomized, double-blind, and placebo controlled study design; and 4) the study's use of standardized diagnosis of AOM and MEE, and the limited number of investigators seeing these children.

*Discussion* included:

- A suggestion to similarly evaluate the data for sepsis related diagnoses, as was done for AOM, will be followed and the ACIP will be advised.
- *Were any of the infants breast fed, and did the 27% of children in daycare include those in at-home daycare settings?* The study did not look at breast feeding as a confounder, and the 27% does seem low. All forms of daycare were included, defined as a minimum of two other unrelated children in the setting. Half the children enrolled at the hospital were of lower SES and were expected to more likely be in a home setting than in a formal daycare setting.
- *Did you ask about vaccination of household contacts?* That was not specifically asked, but the rate was probably very low, since an entry criterion was that no one in the household would have a condition of high risk from influenza. If such a person was in the household, the child should get vaccinated and not be randomized to control or placebo.
- *Was the response of the placebo group to disease circulating?* The serogroups did not seem to match what the study was isolating, but some cases may have been related to disease circulating in the community. It is more likely that children aged 6-12 months may have been showing maternal antibody.
- *Were children aged 6-12 months chosen because they are more prone to OM?* They were targeted to evaluate the population at very high risk of OM. The seroconversion rates were adequate. There was some trending for higher immunogenicity among the older age groups, but overall there was very little difference.
- *What would the effect of vaccine on overall OM be over the whole year?* The first year cohort was followed over the whole year, and while there was a greater proportion of children with

AOM overall, there was no significant difference between the two groups. The Clements study looked at AOM pre- and post-influenza season and also found no difference in rates. But viewed in terms of the entire year, the overall effect would likely be substantially less.

- Dr. Schwartz stated that Scandinavian studies indicate culture-proven virus in the middle ear of those with OM, showing RSV in about 15% of cases and influenza in about 5%. Based on those data and the time period that influenza might circulate as a proportion of the entire year, it could involve a 5% impact overall compared with the 6-7% seen with PCV. It is important to get those numbers right. When people hear 83% of influenza-associated otitis, or 31-36%, it has a different meaning than what this committee has heard about other vaccines in the past. Dr. Greenberg agreed. The Finnish Kaiser study examined respiratory illness culture-proven from a nasopharyngeal sample, but when an MEE sample was analyzed, the RSV rate was in the 70% range and 42% for influenza. The narrower the population evaluated and the more specific for viral respiratory pathogen, the more correlation will be seen. There is a parallel to PCV in the Finnish study, which showed 57% of AOM prevented, in terms of serotype specific to the vaccine, but the overall rate of AOM reduction was 6%. The broader the field examined, the less effect is seen. That is true of influenza vaccine as well. While he did not doubt that lower AOM rates due to influenza would be seen because the vaccine prevents influenza, a reduction over all the year would depend on how heavy the RSV and influenza season were, and the age group evaluated.

### **VAERS/VSD TIV Safety Data Update**

Presenter: Dr. John Iskander, NIP

Since 1990, CDC and the FDA have operated the Vaccine Adverse Events Reporting System (VAERS), a national spontaneous reporting system for vaccine safety. VAERS reports were examined that involved the vaccination of trivalent influenza vaccine (TIV) in 6-23-month-olds during the 2002-03 influenza season (07/01/2002-06/30/2003).

The baseline VAERS data for the previous three influenza seasons (1999-2002) averaged only 17 TIV reports per year among that age group, and the previous 12 seasons averaged nine reports. Only one Guillain-Barré Syndrome (GBS) report was lodged every other season for this age range .

*Descriptive epidemiology.* Sixty-eight total adverse events (AE) were reported, of which nine (13.2%) were serious by regulatory criteria (hospitalization, death, “life-threatening” illness or disability) . This represents 4% of all VAERS reports involving flu vaccine for the past season. Seventy percent of reports involved administration of at least one other vaccine. Infants aged 6-11 months were 33% of the reported cases, mostly (59%) males.

The VAERS form does not directly ask about the indication for vaccination, but it does ask about pre-existing or underlying illness. About a third reported none and the most of the others cited asthma, seizures or allergies to medication or food. The most common reports related to safety and, from most to least reported, were fever, rash, urticaria, agitation (crying), and vasodilation (flushing). These are similar to the safety profile of any typical childhood vaccine. An analysis of the most serious AE reports found two reports each of febrile and afebrile seizures and one report each of possible febrile seizure associated with OM/pharyngitis, CVA, meningococemia, intussusception, and vomiting/metabolic acidosis.

The febrile seizures were identified through that symptom code or, that for fever or convulsion. Five reports met these criteria, three among the nine “serious” reports due to associated hospitalizations; four of five reports involved at least one other vaccine (DTaP 3, IPV 3, PCV 1, Hep B 1, Hep B/Hib 1) and one patient had a pre-existing seizure disorder.

In 2002-03, there were no reports of death, Guillain-Barré Syndrome (GBS), or the Bells Palsy associated with adult influenza vaccine. Ten reports (14.5%) met the screening criteria for ocular/respiratory syndrome (ORS), which is clinically similar to allergic conjunctivitis but has an onset within 24 hours of vaccination. Of the ten reports, only one was associated with hospitalization, which will be explored further.

*Conclusions:* There has been a four-fold increase in age-specific reports between the 2001-2 and 2002-3 seasons, which may be due to increased vaccine uptake. The data were limited but reassuring. There were no unexplained signals suggesting the need for a controlled follow-up study. The febrile seizures detected would be expected in this age group and have not been associated with serious sequelae.

*Limitations.* The VAERS data limitations include VAERS' inability to determine the causality of reports, variable under-reporting, and the lack of a denominator. These in particular involve a small number of total reports, the lack of any age-specific denominator data or age-specific dose distribution, and the unknown extent of under-reporting for specific events of interest.

*Vaccine Safety Datalink.* Dr. Eric France *et al.* at Kaiser Permanente/Colorado screened a large cohort of children who received the TIV for evidence of medically attended events (MAE) following vaccination ("hypothesis generating") to judge the safety of TIV use among children aged 6-23 months. Given that an individual experienced an MAE, it explored the odds that the MAE occurred in the post-vaccination risk period compared to a control period during the 2002-03 influenza season.

The analysis used two control periods, 14 days before and 14 days after vaccination, but the pre-vaccination period was not used to avoid the "healthy vaccinee effect." This was a risk-interval analysis, in which an individual serves as his or her own control, and which is controlled for high- versus average risk and unknown confounders.

Outpatient records for this age group 1-14 days post-vaccination included 8476 shots. There was no signal of a serious medical outcome occurring more often in the two weeks following influenza vaccination, nor were any neurologic outcomes identified in that time. An impetigo signal was identified in nine cases within three days of vaccination, but showed no association to the vaccination site itself. Asthma, rhinitis, dyspnea, and pharyngitis were reported, but with no association to the risk period.

For the 2003-04 season, enhanced surveillance of 6-23-month-olds is planned. VAERS will do a detailed review of candidate ORS cases and will develop a specific denominator with the NIS. The surveillance will emphasize neurological outcomes. The VSD will conduct a Phase II pediatric safety study among ~35,000 6-23-month-olds, with up to six weeks of follow-up. A pilot at one VSD site will be done of a rapid cycle (i.e., real time) analysis of VSD information gathered from a large HMO, to work on a supplementary hypothesis-generating system to supplement VAERS.

*Discussion included:*

- *How many children were vaccinated of the 8400 doses? Also, the second control interval is also a risk interval for swine influenza vis-a-vis GBS, so the neurological AEs from TIV would only be definitively seen in the risk period of the first two weeks. Given that this study was not powered to look at GBS, were there any demyelinating conditions seen in the 10 weeks post-vaccination? Data from another, broader VSD analysis of six influenza seasons, with a 6-week risk window after vaccination, found only one incident GBS case with a one-day onset interval. Dr. Iskander did not know the denominator of children or doses for those six seasons, nor the breakdown of how many were first versus repeat doses.*
- *Regarding ORS, was another vaccine looked at for an association, and would the neurological*

*definition in the VSD study have detected that?* The primary vaccine for which ORS was studied has been the influenza vaccine. ORS has been identified as being likely present among adult cases reported to VAERS. This is expected to vary from season to season, but that analysis could be done as an internal comparison, using the same screening definition used for other vaccines in the same surveillance period. ORS has not yet been explored in the VSD. The same screening definition could not be used, but other clinical case definitions could be used. First, clarification is needed as to whether what was seen in VAERS represents a coherent case series.

## **IOM Report on Neurological Consequences of Influenza Vaccine**

Presenter: Dr. Kathleen Stratton, Institute of Medicine

The Institute of Medicine's Immunization Safety Review committee had released its seventh report on the previous Monday. At the request of CDC and NIH, it addressed the safety of the influenza vaccines, focusing on neurologic complications and, more specifically, demyelinating neurologic conditions.

The committee broke out the 1976 swine influenza year from all other years, as the IOM found a causal relationship to Guillain-Barré Syndrome (GBS) in only that case. All other years had a small signal, but the evidence was inadequate to accept or reject a causal relationship between influenza vaccine and the following disorders:

- Based on several well-conducted studies, neither MS relapse in adults, nor onset or incident MS in adults. However, since the latter's mechanism would be similar to that for relapse, where it was not seen, the link was thought to be unlikely.
- Other demyelinating conditions other than GBS or MS, based on lack of good controlled studies of these rare conditions. There was virtually no evidence bearing on a causal relationship between the vaccines and the demyelinating conditions in children 6 to 23 months of age specifically.
- ORS, not a neurologic condition, was not examined. Similarly, the Bells Palsy associated with the inactivated vaccine used in Germany was not reviewed, as the NVAC workgroup requested a focus on other conditions.

Only theoretical support was found for biological mechanisms of immune-mediated processes and direct neurotoxic effects. There is weak evidence (one animal study) to indicate molecular mimicry/bystander activation that could lead to demyelinating conditions in humans.

Modifications to current communications on influenza vaccines and neurological complications were recommended to encourage acceptance and utilization of the influenza vaccine, especially at-risk populations.

The Committee's recommendations:

1. Advised no policy review of licensure or any of those policies on the basis of concerns about neurologic complications.
2. Have enhanced surveillance in place before an ACIP recommendation is implemented for universal annual influenza vaccination of young children. With VAERS and the VSD rapid cycle previously described, this is already under way
3. Develop better methods for detecting these rare adverse events. Continue research on animal models of immune-mediated neurologic disease to better understand at least the biologic mechanisms and the genetic variability in terms of human responsiveness and potential genetic susceptibility. This has not been demonstrated yet in terms of vaccine-related adverse events, but it is a frequent concern in these reviews. Are there special predispositions to the adverse effects?

4. Conduct research to better understand the pathogenesis of influenza
5. Analyze the 1976 swine influenza vaccine (potentially in stock at Baylor University) for the presence of *C. jejuni* antigens, NS1 or NS2 proteins, or other possible contaminants.
6. Continue research using animal and *in vitro* models as well as humans for biological mechanisms to identify potential genetic susceptibility.
7. Conduct communications research to deepen/expand fundamental understanding of the knowledge and beliefs about influenza vaccine, in order to improve the communication strategy and facilitate a higher uptake of this vaccine.

The next meeting, and the final one of this IOM contract, will be held on February 9, 2004. The committee will review the new data on vaccines and autism to see if any update of its first two reports on this topic is needed.

### **Economic Valuation of Influenza Vaccine in Children**

Presenter: Lisa Prosser, MS, Harvard Program on the Economic Evaluation of Medical Technology

This study was funded by the VSD and the CDC/Harvard Project on Vaccine Economics. The goal was to evaluate the cost effectiveness of alternative strategies for reducing influenza-related morbidity in children. Since existing economic analyses for these interventions do not include public preferences for influenza-related morbidity, this study was conducted to 1) determine those preferences according to health states affected/prevented by influenza, 2) weight them, and 3) to develop an economic model to evaluate the cost effectiveness of each strategy.

This analysis is part of a larger study that evaluated inactivated vaccine, live attenuated influenza vaccine, and testing and treatment options with antiviral drugs for children age 6 months to 17 years. The results presented focused on inactivated influenza vaccine use among 6 to 23-month-old children.

Such decision analysis aids the understanding of tradeoffs in the face of some unknown data in the analysis. Key variables can be identified through sensitivity analysis, and threshold analyses can be done to identify for which parameters at certain levels an intervention might become cost effective (CE) or cost saving (CS). This provides the best possible information to decision-makers by quantifying the cost, the risks, and the benefits of all the available alternatives.

The probabilities of influenza-related events vary both by age and by risk status. A computer simulation was used to estimate cost and effects for influenza-related illness for three population subgroups: children aged 6-23 months, 2-4 years, and 5-17 years, as well as by high- or low risk for influenza-related complications. The analytic model tracked children according to four possible responses to getting influenza: no physician visit, physician visit, hospitalization, and death. Each of these involves cost and quality adjustments that were summed for the final analysis, as well as cost/quality of life reductions for vaccine adverse events. Inputs to the simulation model were provided in detail and were based on primary data, published literature, and expert opinion when little other data were available. For low-risk 6-23 month-olds, they calculated probabilities of illness (flu and its outcomes, vaccine effectiveness), costs with/without physician visit, hospitalization, total vaccination cost (vaccine, administration, parent time) at \$64.77, and the health preferences used to evaluate the Quality Adjust Life Years (QALY) lost (otitis media, GBS, pneumonia hospitalization).

The preliminary results of cost (and ranges) per event avoided by use of inactivated influenza vaccine (IIV) were:

*Low-risk groups.* The costs per influenza event avoided were outlined for 6-23-month-olds (\$330),

outpatient visit (\$650), hospitalization (\$15,000), and death (\$17 million). The fifth percentile was cost saving but at the 95th percentile the cost was \$2900/case avoided. Inactivated vaccine is probably not cost saving for this age and risk group, but investment is required to avoid illness.

Calculation of dollars per event avoided allows comparison to other such analyses, but not to interventions calculated with the dollars per quality-adjusted life year (\$/QALY) method. The study calculated those as well, without including their survey's preference rates. It was noted that CE ratios increase as age increases, corresponding with the decrease in the risk of influenza-related complications.

For low-risk groups, the \$/QALY CE results for those aged 6-23 months were a mean of \$8000 and a median of <\$1000. Overall, IIV was found to be cost saving about 12% of the time in this age group, and at ~80% would probably cost <\$25,000 per QALY. The median/mean CE for those 2-4 years were \$22,000/\$1000, and for those 5-17 years, they were \$93,000/\$11,000. For high-risk groups the \$/QALY were cost-saving for 6-23 month-olds at both the median and mean. For those aged 2-4 years, the cost was <\$1000 median and mean, and \$6000/\$1000, respectively, for those aged 5-17 years. In general, the CE results are more favorable for children at high risk for influenza complication due to this age group's higher risk for that. For all of these calculations, it was also noted that the CE estimates vary greatly according to the variability in the input parameters.

IIV CE was charted for:

- Influenza rate, showing a rapidly dropping \$/QALY, from about \$14,000 for the low-risk 2-4 year-olds and about \$9000 for those 6-23 months old, at a 2% to 4% influenza rate, and then a gradual decline from a 6% to 20% disease rate, at which rate the \$/QALY approached zero for both groups. The average illness rate was ~16% for these two age groups, but in years of lower influenza illness rates, the CE ratios increased substantially.
- Vaccine effectiveness (assuming a 69% VE) for the same groups showed a steady and gradual decline in the \$/QALY CE, ranging from ~\$1000 to \$2500 at a 40% VE, to ~\$100 to \$500 at a 90% VE.
- Total costs of vaccination by \$/QALY were charted in a straight-line progression from zero at \$30/vaccination, to about \$1700/QALY at \$120/vaccination.

The study's conclusions were that:

- IIV has C/E ratios comparable to other preventive interventions for high-risk children and low-risk children under 5 years of age. Some appropriate comparators are pneumococcal conjugate vaccine (CE ratio of ~\$4000/QALY) and inactivated vaccine for high-risk children (\$2,000/QALY).
- C/E results are sensitive to: 1) number of additional visits required, indicating the potential of alternative settings for delivering vaccination in children (i.e., lowered total vaccination cost produces more CE); and 2) illness rates and vaccine effectiveness.

*Discussion* included:

- Dr. Anders Nelson,<sup>1</sup> a pediatrician in private practice, expressed concern that the calculated \$64.77 total vaccination cost appears to involve a huge investment that could discourage practitioners from implementing it. His practice, which does thousands of vaccinations, pays \$7.50 for the two doses, ~\$1.50 to actually provide the vaccine, plus an additional 6%. They hold 30-minute vaccine clinics four days a week that require five minutes from entry to exit. Dr. Prosser complimented him on his efficiency and responded that the model uses AAP or VFC rates for administering the vaccine (\$7.50, which may be an underestimation), \$10 for one or \$20

---

<sup>1</sup> The trade association that Dr. Nelson represented at this meeting is supported by a grant from Aventis Pasteur

for two visits and cost of parents' time (~\$33, two hours time). The cost of parents taking time off from work to care for sick children was included in the health state evaluation by parents, of total time cost as well as time taken from other usual activities. The illness rates in the literature were also used. These are somewhat lower than attack rates, which can rise to ~30%

- *Was herd immunity factored in?* It was not included in the base case, but there was a scenario assuming a secondary attack rate of ~16% and two adults in the household. This reduced CE ratios by ~15% and presented a more CE outcome that was presented.

The lack of a clear threshold for vaccination makes it difficult to compare its CE to other interventions. Another confounder is that people are more willing to pay for some interventions than others. However, flu vaccine among high-risk children ranges from cost-saving to \$2,000 per quality-adjusted life year; pneumococcal conjugate vaccine is ~\$4000/QALY when preferences are included.

### **Economics of Routinely Vaccinating Healthy 6-23 Month-olds**

Presenter: Dr. Martin Meltzer, NCID Office of Surveillance

To calculate cost-benefit (CB), a Monte Carlo model was used. This has built-in variability for such diverse factors as differing attack rates and vaccine effectiveness from year to year. The analysis examined a high- and non-high-risk mixed cohort of 1000 persons from a societal perspective, and included all costs regardless of who pays or benefits.

The 2,228,653 person-years data set of the Neuzil study (N Engl J Med 2000 342: 225-31; J Pediatr 2000; 137: 856-64) was used. It included children aged <15 years from 1974-1993, who were enrolled in the Tennessee Medicaid program continuously from birth, or at least for one year.

The differences were charted between the two risk groups for hospitalizations, which vary year to year. Influenza-attributable outcomes per 1000 children in deaths, hospitalizations, and outpatient visits indicated that on average a median of 1.9/1000 of non-high-risk individuals will be hospitalized each year. Then hospitalizations, outpatient visits and deaths were deducted from the attack rates of clinical illness to calculate the number of those staying at home and not seeking care. Again variability was emphasized. For example, the median hospitalization rate of 2/1000 was multiplied in 1981-82, to 12/1000 children in the non-high risk group. This model allows for such rare occasions.

The median rates of influenza-attributable outcomes per 1,000 high-risk and non-high-risk children were charted for deaths (0.009/0.005), hospitalizations (7.9/1.9), outpatient visits (121.6/78.5), as was the distribution of risk of hospitalization due to influenza among 6-23-month-olds in this database (1.9/1000).

The costs of health outcomes (death, hospitalization, outpatient) were based on average foregone salaries and calculated at >\$1 million for death, \$4000 for hospitalization, \$348 for outpatient, and \$110 for those ill with no medical visit (Meltzer *et al.* Emerg Infect Dis, 1999;5:659-671). Of those, indirect costs were 100%, 13%, 62%, and 98%, respectively. The major portion of the calculation was for time off work.

Calculation of the cost per dose administered was affected by the setting and size of the administered dose. It factored in the costs of vaccine (mean and median VE of ~70%), labor and overhead, a half-hour of patient time, travel and side effects. The total for a walk-in corporate clinic was \$28.51 and \$61.41 for a solo scheduled visit to a small clinic.

The model assumed that only a third of the cohort would require two doses, a potential underestimate. Another potential underestimate was the VE, which was charted by mean (69%), median (70%), and mode (77%) and for the 10th (52%) and 90th (85%) percentiles. Little is known about the distribution of

vaccine effectiveness, however, and the VE was assumed to be equal for all health outcomes (hospitalization, home care, etc). The net returns to society for vaccinating children of different risk levels with attack rates of 20-30% was charted, with the cost per dose administered calculated at \$30 and \$60. It demonstrated a largely non-CE value, at either vaccination cost, to vaccinate all those not at high risk. A more CE value was charted in vaccinating 90% non-high risk and 10% high risk, the likely composition of a group at this age (but again, with great variability in population subsets). A very clear median net saving to society by vaccinating only high-risk children was charted, and at its 95th percentile, the great economic value of deaths averted raised the value to nearly \$560,000 saved per cohort vaccinated.

A higher attack rate of clinical illness was also calculated at 30-40% and showed very little difference.

Overall, these results demonstrated the great unlikelihood of a median net savings to society when non-high risk groups are vaccinated, unless the net dollars per dose administered are below \$30 per dose. The bottom line was that it cannot be stated that vaccinating 6-23 month-olds will guarantee a net savings to society. The true value of vaccinating these cohorts was in the averted rate of death. Although not thought of as the first reason to vaccinate, it was very influential in terms of economic savings to society.

The conclusions of the analysis were that:

- The variability of large CEs was due to rates of health outcomes that change from year to year.
- The most important inputs to the model were the death rate, rate of outpatient visits, and cost of vaccination.
- Vaccine effectiveness was calculated within a range of 0% to 83%.
- The distribution of effectiveness was uncertain, especially when applied to specific health outcomes such as death or hospitalization.
- After a point of down slope (e.g., from greater efficacy), the cost per dose administered rises, but these calculations remain estimates. While the economies of scale of widespread vaccination will decrease costs, the system will be overloaded at some point and costs will increase again.
- The question for the future will be how to better and more efficiently deliver vaccination, While ACIP does not make recommendations on how the vaccination is done (e.g., walk-in versus scheduled clinics), the liaison partners' communications with their constituencies can greatly contribute to this ongoing research discussion.
- The majority of savings are indirect, at 79% within a confidence interval of 61%-95%.
- Consistent cost savings are unlikely in non-high risk groups unless the cost per dose administered is <\$30. It is most efficient to vaccinate those at high risk, results that are consistent with Prosser *et al.*
- For vaccination of the non-high risk groups and 10% of the high-risk group, the threshold is about \$48 per dose administered. The 5th percentiles are still negative regardless of the cost, within \$30 to \$60 of the cost per dose administered.

*Discussion* included:

- *Why was herd immunity not included, given that there are published data on this?* The available data sets are small, and the variability of their mixing matrices (i.e., “who infects whom and where”) has not been well tested due to the great difficulty of doing so. The Hurwitz data include herd effect, but in terms of economics, they could not demonstrate actual net savings from either a societal or household level. More demonstration of the extent of herd immunity protection and its variability from year to year is needed. Studies to date address only a couple of years at most.

Another question enters, of why people vaccinate their children. In general, it is probably to protect the child, not to preventatively protect the adult. This is hoped to be included in the model in future.

- *How would you compare these data with those of the >65 year-old age and 5-64 year age group?* There has been no study of immunizing all those aged >65, but since they have a high percentage of persons at high risk, it could be suspected that the net return graph would be similar. Dr. Plotkin defined this as an important point. If society is ready to invest in vaccination of those who are older, it should be ready to do so for children.
- *Do both models presume that vaccination will eliminate all disease attributable to influenza?* Most respiratory disease is not associated with influenza. The data on rate of health outcomes attributed to influenza is based on Neuzil's large hospitalization database. But a prospective study is needed to determine the accuracy of that, tracking to see what is attributable to influenza and what is not. The model assumes that influenza vaccination could prevent 70% of hospitalizations and physician visits. But that is an assumption; such detailed data is not available.
- *Some of the distributions of hospitalization risk due to influenza were negative; why?* Dr. Neuzil explained that this 25-year retrospective Medicaid cohort study looked at differences in rates between seasons. Hospitalizations increased with the RSV and influenza seasons. The 25-year companion study done of a vaccine clinic (based on culture-positive data) showed similar out-patient visit rates and slightly lower hospitalization rates. The out-seasons could show a negative value, but over many years, she believed it to average out. She added that, while hospitalizations drive the way the vaccine's importance is generally gauged, deaths and outpatient visits emerged as more important in her study. Dr. Meltzer agreed that this occasionally occurs, but in his model, a negative hospitalization rate was valued at zero.
- *Please provide more comparison on other recommendations and costs, such as mammography, colorectal screenings, etc.* Dr. Meltzer commented that 10 economists will give 20 different answers. Society has accepted certain interventions with a wide range of QALYS and rejected others. The intervention, the disease and age group, all make a difference. The literature tries to set a threshold, but few economists believe that these are supported by empirical data.
- Dr. Prosser reported that screening and mammography are valued at \$10,000-20,000 and up; it is more CE for older women. The appropriateness of comparisons is important. Screening program risks can be quite different and can reduce adverse event risks from currently high levels. This relates to comparative thresholds and how cost benefit and cost effectiveness analyses differ according to the sensitivity of the inputs. For example, CB analyses are driven by the rate of hospitalization and are less sensitive regarding out-patient visits.
- *So pneumococcal vaccination is half as expensive in terms of QALYs. Are there similar vaccines, such as varicella?* All the vaccines recommended so far by the ACIP have been cost saving, looking at direct medical costs, until PCV. That is really the first comparable vaccine to IIV, at a median value of PCV of \$8000, .
- Dr. Nelson1 reiterated his concern about the projected costs. Since many vaccinations occur at well-child visits (or well children accompanying sick siblings), immunization costs are substantially lower. He agreed that the multiple modalities of vaccine administration need to be examined. Dr. Meltzer noted the estimate in the current issue of *Pediatrics* that about 75% of children would require at least one visit, because they do not all come during the September-November vaccination season. This puts pressure on some practices and increased waiting times except in well-run clinics. In the past, estimates focused on vaccine and labor costs; no one had done intensive research on realistic costs.

### **Shedding and Infectivity of Cold Adapted Influenza Vaccine (CAIV)**

Presenter: Dr. Katherine Coelingh, MedImmune

*Background:* Dr. Keiji Fukuda reported on CDC's recent notification that some hospital healthcare workers had received live attenuated influenza vaccine. Some of them are being told not to return for work for 21 days because the package insert states that children's shedding period ranges from 1-21 days. There are no shedding data for adults. Dr. Kathy Coelingh of MedImmune had been asked to do that analysis to clarify and provide further guidance to hospitals.

*MedImmune Presentation.* Dr. Coelingh reported that there were no data on FluMist™ itself, but there are data from about six NIH studies of the investigational vaccine which was made from the same master donor viruses in FluMist.™ They showed no evidence of transmission after vaccination. After challenge, percent shedding, mean peak titer, and mean duration of shedding are higher in young children than adults. Children shed for 5-19 days, but adults shed at least two logs lower and for a mean duration of only 0.6-1.9 days. While the human infectious dose (TCID-50) in young children ranges from 2.5-4.6 (TCID-50) logs, that in adults is 4.9-6.4 (TCID-50). All of these studies were done in either sero-negative naive children or in adults with extremely low HAI antibody titers. A chart from a review by Brian Murphy was also shared that presented these data graphically.

MedImmune plans in its post-marketing study to examine healthy adults' shedding of FluMist™ vaccine. The cohort will be enrolled from June to October 2004.

*Discussion* included:

- *Will you seek additional information on immunocompromised persons?* No, it will be among healthy adults. However, there was a related study by Jim King and colleagues at the University of Maryland. This involved 57 HIV-infected adult patients in the intervention arm (with relatively high CD-4 counts) and matching non-HIV positive, but influenza-immune, primed, healthy subjects in the placebo arm. Shedding was very minimal. Viral cultures taken post-vaccination at 3-5, 7-10, and 28-35 days showed no shedding in the 54 healthy subjects and in only one HIV-positive adult at day five for one day.
- *Was the mean up to 1.9 of viral shedding in adults the mean of a median or a range?* The individual shedding was in a range, but those data came from published studies. Data access to clarify that is uncertain.

### **Feasibility of Implementing Expanded Influenza Vaccination of Children Aged 6-23 Months**

Presenter: Dr. Marika Iwane, NIP

*Surveys.* Dr. Iwane reviewed several surveys conducted about the expansion of influenza vaccination among 6-23 month-olds.

- AAP survey in 2000 (before the ACIP's "encouragement" notice) of 600 AAP members. Of those, 20% favored expansion to vaccinate children aged >6 months, 43% did not, and 27% percent were unsure. They suggested AAP's close consideration of the risk for serious influenza complications, the availability of intranasal vaccine, and safety concerns before so recommending.
- Humiston *et al* 2001, University of Rochester: This national survey of 458 pediatricians and family physicians about universal vaccination of 12-35 month-olds achieved a 66% response rate. With the assumption that LAIV spray and TIV were both available for use, 54% thought a recommendation to be justified, but 77% expected the up-front cost to be a major barrier. Another 76% thought that implementation would be feasible, but 46% thought that would be less so if only TIV

- were available for 6-11 month olds.
- Gary Freed *et al*, NIP/University of Michigan, did a 2002 national survey of VFC pediatricians and family practitioners. They estimated, where vaccine was covered for all children, that 54% of VFC and 53% of privately insured children would be vaccinated. Where the vaccine was covered for VFC children only, they projected 43% of VFC and 34% of privately insured would get vaccinated. They also surveyed large VFC practices in six states to estimate future vaccine coverage. The responses indicated that 48% of 6-23 month-olds, 68% of 2-18 year-old high-risk children, and 53% of 2-18 year-old household contacts would be vaccinated, indicating a willingness to vaccinate under the encouragement.
  - A 2003 Gallup (CDC/NIP) survey of 251 pediatricians (reported later in this meeting).
  - Vanderbilt University (Poehling *et al*) conducted three parent surveys:
    - 1999, survey of 154 parents of children aged 6 months-3 years hospitalized with fever or ARI (published 2001) showed 32% at high risk and 14% of these were healthy vaccinated children. A physician's recommendation was highly predictive of who was vaccinated (70% versus 3%).
    - 2001-02 season: 295 parents of hospital-based outpatients aged 2 months to 5 years, 5% vaccinated; similar physician recommendation impact (unpublished).
    - 2002-03 season: Vaccination rates of healthy children increased under the recommendation; again, physician recommendation was important (unpublished).
  - Szilagyi *et al*.
    - 2002, Burden on Practices. A time and motion study of 92 children aged 6 months to 18 years with visits for influenza vaccination in 7 Rochester area practices in 2000-01 season indicated: a two-minute median time to vaccinate and a 14-minute median time for the total visit. But 80% of the patient time was spent waiting in exam rooms and waiting areas, suggesting separate influenza vaccine hours or clinics are needed.
    - 2003 study of an insurance database including >70% of Rochester area children during three seasons (1998-2001) estimated that extra visits would be needed under an expanded recommendation. If vaccination occurred only during well-child care visits from October to December, an estimated 74% of all 6-23 month-olds would need one to two extra vaccination visits. This calculated out to 800 extra visits for a typical group practice with 500 newborns/year and 160 extra visits for a solo practice.

#### *Intervention Projects*

- Zimmerman *et al*: Intervention study in nine inner city health centers (presented later in the meeting)
- Kempe/Daley *et al*, U Colorado (unpublished data): intervention studies in five Denver area pediatric practices
- 2002 season: vaccinations of 10-45% of healthy 6-23 month-olds across five practices; 1000-2500 doses per practice. Three held influenza vaccination clinics, two had nurse-only visits; all found it a doable proposition.
- 2003 season: preliminary data of a randomized reminder/recall study of influenza vaccination including 5200 healthy 6-23 month-old children and 491 parents surveyed pre-season (60% response). Of those, 65% said the vaccine is safe, 36% would have their child vaccinated, 32% were undecided, and 70% said their providers did not discuss the vaccine with them. About 500 parents will be resurveyed after the influenza season.

The conclusions from this review were that the implementation data will probably remain limited until a full ACIP recommendation is issued. Providers seem to be willing to try to vaccinate 6-23 month-olds but are concerned about the related cost and feasibility. A full recommendation may impose a potentially large burden of patient visits, implying that practices likely need to have separate influenza clinics, use all possible visit opportunities, keep vaccinating throughout the season, and evaluate all potential implementation strategies.

## **National Survey of Pediatricians about Influenza Vaccinations**

Presenter: Mr. Alan Janssen, NIP

To assess the current understanding of pediatricians' knowledge, beliefs, intentions and behaviors regarding influenza recommendations, and their intentions to immunize for influenza in the 2003-04 season, NIP and the Gallup organization conducted a survey. The Gallup poll staffers were also mothers who followed up vigorously with the 251 pediatricians surveyed, contributing to an excellent 89% completion rate. The respondents were practicing pediatricians who on average were immunizing >5 children per week for childhood immunizations. The data were collected from September 4-22, 2003, and the margin of error was 6.3% overall with a 95% confidence interval. Pediatricians were chosen as the primary providers of childhood vaccinations and a key stakeholder group in terms of implementing pediatric influenza immunizations. Pediatricians alone were chosen in view of the short time frame and in pursuit of the statistical power of a more limited sample (i.e., than if family/general physicians were also included).

The questions and their responses, were:

1. Based on your understanding, would you vaccinate or not vaccinate the following groups?
  - a. 7-year-old child with cystic fibrosis: 99%
  - b. 26-month-old child with well controlled asthma on low dose corticosteroids: 97%
  - c. 10-year-old sibling of a child with cystic fibrosis: 96%
  - d. 16-year-old child with an HIV infection: 84%
  - e. 18-month-old child with recurrent otitis media: 78%
  - f. 8-month-old child with a pregnant mother: 64%
  - g. 5-year-old child entering kindergarten: 51%
  
2. Awareness of AAP and/or ACIP position on the routine use of flu vaccine for children aged 6-23 months: 96%.
  
3. How well do you know the content?
  - a. Very well: 36%
  - b. Somewhat well: 57%
  - c. Minimally well: 7%
  - d. No knowledge: 0%
  
4. Understanding of AAP/ACIP Position (i.e., what is the current position?)
  - a) AAP/ACIP encourages, when feasible, that all children, 6-23 months, receive an annual influenza vaccination, unless contraindicated: 51%
  - b) AAP/ACIP recommends all children, 6-23 months, receive an annual influenza vaccination, unless contraindicated: 44%
  - c) AAP/ACIP does not recommend nor encourage an annual influenza vaccination for children 6-23 months old unless a child has a medical condition that increases risk of complications from

influenza or lives with a person at increased risk: 5%.

5. Relationship between self-reported level of knowledge and AAP/ACIP Position
  - 41% of respondents who stated that they knew the position “very well” believed that routine influenza immunization was “recommended.”
  - 57% of respondents who stated that they knew statement “somewhat well” believed that routine influenza immunization was “encouraged when feasible.”
6. Beliefs regarding VFC reimbursement, Fall 2003/Winter 2004: Will VFC provide reimbursement for:
  - a) Children, 6 months and older, with high-risk medical conditions, such as asthma -- 84% said yes, correctly.
  - b) Healthy household contacts of children with high-risk medical conditions, such as asthma -- 58% said yes, correctly.
  - c) Healthy children, 6-23 months old -- 49% said yes, correctly.
  - d) Healthy HH contacts of high-risk adults (e.g., adults 65 years old and older, heart disease) 46% said yes, correct if they are under 18 years old.
  - e) Healthy household contacts of children aged 0-23 months -- 33% said yes, correct if the contacts are under age 18 years.
7. Pediatric vaccination intentions, Fall 2003/Winter 2004 season (Respondents asked to select one)
  - Routinely offer the vaccine to all children aged 6 months and older: 67%
  - Routinely offer the influenza vaccine to children older than 6 months with high-risk medical conditions: 28%
  - Provide vaccination only if parents ask: 3%
  - Not vaccinate children aged 6 to 23 months: 0.4%
  - Don't know: 1.0 %
8. Relative importance of factors in pediatricians' decisions to implement routine flu immunization of 6-23 month olds
  - Safety of the vaccine: 96% Important, 3% Not Very Important
  - Efficacy of the vaccine: 95% Important, 2% Not Very Important
  - Severity of influenza disease in children: 95% Important, 6% Not Very Important
  - Adequate resources (money, staff): 90% Important, 10% Not Very Important
  - Parents asking for the vaccine: 88% Important, 11% Not Very Important
  - Parents' knowledge about the flu vaccine recommendation: 83% Important, 16% Not Very Important
  - Workable system for second dose: 81% Important, 17% Not Very Important
  - Availability of VFC Reimbursement: 77% Important, 21% Not Very Important
  - Availability of thimerosal-free vaccine: 65% Important, 34% Not Very Important
9. Relative appeal of factors that could facilitate implementation of routine pediatric flu immunization
  - Your (i.e., physician's) personal encouragement: 92% Desirable
  - Parent education materials: 91% Desirable
  - Use of a Reminder/recall system: 84% Desirable
  - Offering vaccine only during office hours: 71% Desirable
  - Reducing the cost of vaccination (e.g., charging only an administrative fee, no office visit charge): 69% Desirable
  - Providing vaccine in collaboration with health dept., school clinic, etc. 66% Desirable
  - Providing standing orders to vaccinate all eligible children in your practice: 62% Desirable

- Offering vaccine during non-office hours at your practice location: 41% Desirable
- Referring to outside agency (e.g., health dept., school clinic, etc.): 38% Desirable
- Referring eligible patients to pharmacies: 13% Desirable

10. How satisfied are you with your practice's ability to meet community needs for pediatric vaccination?

- Extremely satisfied: 13%
- Very satisfied: 34%
- Satisfied: 38%
- Not too satisfied: 12%
- Not satisfied at all: 3%

Preliminary conclusions of the survey were that:

- Almost all pediatricians report they are currently vaccinating children with high-risk medical conditions and children who are household contacts, but only about two out of three report routinely vaccinating healthy 6-23 month olds;
- Self-reported awareness of the current AAP/ACIP position is very high. However:
  - 6 out of 10 characterized their knowledge as somewhat well (rather than very well)
  - Only about half were able to identify the correct statement
- Similar to last year, about two-thirds of pediatricians expect to routinely offer flu vaccine to all children 6 months old and older, and just less than a third are planning only to vaccinate those children with high-risk medical conditions.
- The decision to provide routine flu vaccination of children was most influenced by perceptions/beliefs regarding: 1) safety of the vaccine; 2) efficacy of the vaccine; and 3) the severity of influenza in children.
- Having adequate resources, including parent education materials, is also a critical factor in the decision.
- Physician encouragement, parent education materials, and reminder/recall systems are the top three factors for facilitating implementation of routine pediatric influenza immunization.
- Pediatricians are a) most interested in providing routine pediatric flu vaccination inside their practice; b) open to collaborating with other entities, such as health departments; and c) least interested in referring patients out.
- A large amount of education, directed at providers as well as parents, will be needed to successfully implement routine pediatric influenza immunization.

### **University of Pittsburgh Feasibility Study**

Presenter: Dr. Richard Zimmerman, University of Pittsburgh

This study was funded by a CDC-ATPM Cooperative Agreement. It was undertaken to address several issues: immunization rates have plateaued for childhood immunizations in terms of series completion, and racial disparities persist across all ages. This is true despite systematic reviews and meta-analyses of effective methods to raise rates, suggesting that there is a real issue about translating research to real world applications.

The study of hundreds of office practices by Crabtree, Miller, Stange, *et al*, reflected great complexity and diversity of practice, the importance of understanding the internal operating models and their core values, and of tailoring interventions to those differences.

Therefore, this study looked for interventions that were feasible in the hard-to-reach communities. The

idea was to initiate influenza immunization among 6-23 month-old children, increase influenza immunization among 2-17 year old high-risk children, and determine if this had any impact on other childhood immunizations. The settings involved were nine inner-city Pittsburgh health clinics serving the great proportions of minority children and in the greater general population of Allegheny County. Five organizations participated, one center with two sites, one center with five sites and three centers with one site each. Human subjects approval for the intervention and the evaluation were granted by the University of Pittsburgh's IRB and the Children's Hospital of Pittsburgh IRB, respectively.

The methods used included introductory meetings with each site to present a menu of options from which the clinics would choose and provider education, including interventions effective in raising rates. The sites were encouraged to choose interventions the staff believed to be most effective and feasible, given the center's staffing, systems, and patient population. The investigators helped with the implementation (e.g., patient mailer designs and use of ICD9 codes to identify high risk patients, clinic posters, etc.) held educational meetings and nursing staff "pep rallies" to encourage them to promote vaccination, and developed an algorithm with which to identify eligible patients (i.e., what does it take to vaccinate a 6-23 month-old?). They spoke with informatics experts familiar with clinic-based systems and set the birth date criteria to define "6-23 month-olds," using birth dates from 12/1/00 through 4/1/02. That needed to be clear for the lists pertinent to mailings and evaluation. The contributions of the Children's Hospital of Pittsburgh and the activities chosen at each site were itemized.

The statistical methods used were chi-square tests for comparison of immunization rates, and assessment of the impact on age at vaccination for other vaccines, skewed distributions and medians (non-parametric tests).

Samples sizes were shared for children aged 6-23 months, and for high-risk children aged <2 years. Thousands of children were involved. Intervention and pre-intervention influenza vaccination rates were charted for each of the five sites:

- Children aged 6-23 months: two sites went from zero to 17% and 38%, one from 4% to 17%, one from 6% to 49% and one from 7% to 42%.
- For influenza vaccination rates for high-risk children (typically those with asthma) who were at least 2 years old, the impact was less. Increases ranged from 8-12% pre-intervention, to 13-43%. Two sites statistically raised their rates and the others just had marginal improvements.
- Influenza vaccination rates overall for the first to the second doses showed a fall-off (e.g., 42% to 13% and 49% to 29%). Keeping the momentum for dose two, needed by the 6-23 month-old children getting their first dose, remains a challenge.

The results overall not only showed no harm, but a benefit correlated with influenza vaccination. The statistical cut-points used were a chi square for MMR, DTP, and Polio 2, which showed a consistent improvement in other vaccinations. For example, one site had 97% vaccinated for MMR within the grace period, versus 92% among those not receiving the flu shot; 85% received DTP3 versus 79% among those who not receiving the flu vaccine; and the same trend was seen for Polio 2.

The study's limitations included a single city setting and involvement of only two racial groups (although there was a substantial number of minorities), the lack of a full ACIP recommendation for support, and the unknown sustainability of follow-up phone calls, unless autodialers are used.

Conclusions were that:

- Inner city clinics, including those serving the most disadvantaged patients, can implement 6-23-month-old influenza vaccination.

- A tailored approach is effective.
- Uptake varies by site and effort.
- A drop-off in the second dose was still seen.
- There is no evidence of harm to completion of the routine childhood immunization series.

*Discussion* included:

- Dr. Anders<sup>1</sup> [SAME ISSUE ON COI] appreciated this report, a reflection of what he does daily. He stated that implementing this to 6-23-month-olds is easy once one puts one's mind to it. But an ACIP statement confirming that doing so is important, and will ensure that it is done. Pediatricians educated about and believing in the product and the value of the service will ensure that families/children do so as well. He added that dose 2 can be given in the early morning with little interference in the practice.
- Dr. Plotkin noted that education is needed about the common use of the word "flu" by practitioners and families. That could lead to a belief that influenza vaccination will eliminate all respiratory infections in winter. Perhaps a new name such as myxoma virus, or grippe, should be promoted.
- The lower (e.g., 40-50%) post-intervention vaccination rates reached in some clinics were attributed to a few factors: the deliberate choice of the most difficult sites (since if the intervention works there, it will work elsewhere); the lack of buy-in from nursing staff in some clinics; and the absence of a VFC purchase backup. This was the first year, and the sites are still being educated, but there is a sense that they now feel this to be more routine. It is year 2, VFC coverage is in place, and they have heard about it from multiple venues.
- *Was there any difference seen in response from the faith-based versus other clinics?* The rates varied, and Dr. Zimmerman would hesitate to make conclusions. A comparison cannot be made between, for example, a residency program with doctors in training and a practitioner with a small staff. Certainly, the faith-based clinics were committed to their communities and trusted.

### **Implications of Influenza Vaccination Program to VICP**

Presenter: Dr. Geoffrey Evans, HRSA

The Vaccine Injury Compensation Program (VICP) covers the vaccines that are recommended by the ACIP for pediatric use and, in some cases, mandated by states for school or day care entry. A Vaccine Injury Table (VIT) lists the covered vaccines, medical conditions, and relevant time intervals for coverage. This can be modified through a regulation, rule-making, and/or publication of notices in the Federal Register.

The VICP claim process requires filing with the federal system before seeking remedies in civil court. The vaccine must be on the VIT and can have been administered at any age. The alleged effects must have lasted six months, except for rotavirus vaccine.

The 1986 originating law and implementation of the VICP in 1988 provided no mechanism for adding vaccines. A 1993 addition did so, through Executive Branch action (via DHHS) publication of notice, public comment, and final rule publication in the Federal Register. A two-year window allows the addition of existing and newly licensed vaccines after CDC recommendation of routine administration to children. The VICP coverage is official after CDC's *MMWR* publication and Congress's imposition of an excise tax to fund payment of any claims.

Current vaccines listed on the VIT are:

*Pre-1988:*

Diphtheria, tetanus, pertussis (DTaP, DTP, DTP-Hib, DT, Td, TT)  
Measles, mumps and rubella (MMR, MR, M, R)  
Polio (IPV and OPV)

Details of later additions were provided. In 1996, these included *Haemophilus influenzae* type b (Hib), hepatitis B (HBV), and varicella (VZV). In August 1997, a “flat” excise tax was enacted to cover all three vaccines added in 1996, and a two-year filing window was provided for the “older” claims.

*Rotavirus vaccine* (RV) was added in 1999. Licensed in August 1998, its excise tax was imposed in October 1998 for vaccines against rotavirus disease. CDC published a general use recommendation in March 1999 and the VICP published notice of coverage July 1999. Rotavirus vaccine was added to the VIT with no condition specified as a claim requirement.

*Pneumococcal conjugate* is likely to be the vaccine most analogous to the influenza vaccine process. Congress approved its excise tax in December 1999, before its licensure, to cover “conjugate vaccines against streptococcus pneumoniae” under the VICP. CDC published its general use recommendation in October 2000, which allowed provisional VICP coverage (Box 13) to go into effect for “no condition specified.” The VICP final coverage rule was published in July 2002 and added PCV as a distinct VIT category.

*Hepatitis A* was recommended by CDC in a modified general use recommendation in October 1999, for use in those states with twice the national average of hepatitis incidence. With that recommendation, the VICP’s Advisory Commission on Childhood Vaccines (ACCV) voted to cover hepatitis A upon imposition of the excise tax. A bill to do so passed the House in 2003, but not the Senate. The inactivated vaccine is licensed for use in children aged six months and older. Its “encouragement” for use, is not equivalent to “routine” use for VICP purposes. The latter would require new language to specifically recommend it for routine or universal use. In contrast to the live attenuated product, the current license is approved only for ages 5 to 49 years. In the future, it probably will be allowed in younger children. That would then make it VICP-eligible, or if the CDC recommendation expands into an older age group. So, as with the pneumococcal conjugate vaccine, the excise tax may have language covering only the inactivated product, which probably would be the one used to change the recommendation. Future coverage will depend on the tax language. It may cover the inactivated product only or both products. If the former, and if use of the live attenuated vaccine expands later, that could then be included in routine childhood schedule and added to the VICP and VIT.

*Discussion* included clarification that high-risk children would not be covered by the VICP for influenza vaccine, since the recommendation is only for their use rather than for routine use. When the universal recommendation for those considered at high risk because they are aged >65 years was noted, Dr. Evans confirmed that the VICP coverage extends beyond childhood vaccines. He acknowledged that there is an inconsistency when a recommendation for one high-risk group will extend to all ages, but not that for another high-risk group. This is likely to be included in future discussions of changes to the excise tax language

### **AAP Position**

Presenter: Dr. Margaret Rennels, Chair, AAP Committee on Infectious Disease

The AAP’s Committee on Infectious Diseases (COID, or the Redbook Committee) makes recommendations on vaccine policy, as ACIP does for the CDC. The Redbook Committee agrees that the disease burden of influenza is moderately high; that the vaccine safety data are satisfactory; and that

the efficacy data indicate that it is moderately effective. The AAP would like to have more data but that will not be in hand for years, as it would require 35,000 to 70,000 children, years of research and great cost. The CE seems to be no more costly to society than vaccines already administered and the vaccine may also offer the added benefit of an under-estimated herd immunity effect. The Pittsburgh feasibility study and Gallup poll data were very reassuring that the implementation of a universal recommendation is logistically feasible.

“Encourage to the extent feasible,” the current language, confuses practitioners and the public, and the lack of VICP coverage is a serious issue. Particularly in light of the probability that there will be no important new data in the next several years, the ACIP should move beyond “encourage” to “recommend.” But this should be done gradually, to begin in the 2004-05 season, and to include the contacts of those aged 6-23 months. That is the best way to prevent hospitalization of children aged <6 months. Dr. Baker, also representing the AAP, agreed.

Discussion included comment that the COID would retain its harmonization of schedules with the CDC/ACIP, recommending after the ACIP and before the next season. The legal implications, if uptake is slow, would be the same as other vaccines (e.g., hep B and varicella). Dr. Peter thought that a vote could be effected without a board meeting by using an e-mail vote. While the Academy has to file an intent for a statement to be reviewed by multiple committees, it can move fast in emergency situations. He encouraged the COID to move quickly to get through the first stage and expected that the board would be impressed by the survey reported today. Dr. Rennels agreed, but also offered the caveat that the COID is only advisory, like the ACIP for CDC. Its advice is not always taken, as occurred in the case of smallpox.

### **AAFP Position**

Presenter: Dr. Martin Mahoney, AAFP

The AAFP’s recommendations for influenza vaccination parallel those of the ACIP. They advise it for persons at increased risk of complications (e.g., age 50-64 years, medical conditions, being in nursing homes, or for pregnant women); for persons who can transmit the disease, such as healthcare workers, care providers, and household contacts of persons at high risk, and for those desiring vaccination.

Specifically, the AAFP’s states that children <23 months are at increased risk for influenza-related hospitalization. Vaccination is encouraged when feasible for their household contacts and out-of-home caregivers, particularly for contacts of children aged 0-5 months, because influenza vaccines have not been approved for use among children aged <6 months.

The challenges to protecting young children from influenza include the need for education that sends consistent messages to parent and clinicians, assurance of insurance coverage, and other logistical concerns. The latter include defining the best practices in delivering the vaccine, conducting a systematic literature review, and empowering physicians to achieve high coverage rates in the community.

He noted that the pediatrician survey, although encouraging, was not quantitative. Other concerns include unresolved financial considerations, logistical concerns about implementation (borrowing from other disciplines--study of health behavior could help); and methods of delivering best practices in office-based clinics and community-based clinics. Dissemination of AAFP vaccine recommendations is done through their website; the Director’s newsletter; the “AAFP This Week” electronic newsletter, and the “FP Report” and the “Family Practice” print news media.

Dr. Greenburg referenced the related topic of pandemic influenza preparedness, the cornerstone of which

is immunization of school-age and pre-K children to prevent disease spread to the community at large. The further that is put in place and the learning curve is followed, the better the response capacity will be to a pandemic situation.

## **VOTE ON INFLUENZA RECOMMENDATION**

Presenter: Dr. Keiji Fukuda, NCID

The Committee was presented with two decision points:

- 1) Timing: whether to vote at this meeting or those held in February, June or October 2004. The latter two would be too late for the 2004 season.
- 2) Whether the ACIP should move from “encouragement” of influenza vaccination (when feasible) to a full “recommendation” for children aged 6-23 months. Implementation of the recommendation would be the fall of 2004.

*Discussion* included:

- Mr. Philip Hosbach of AventisPasteur stated that the influenza vaccine supply is expected to exceed demand this year. AvP would be ready to act on a full recommendation. But they preferred to know as soon as possible since the vaccine preparation process for the following season usually begins in March. AvP expects a gradual uptake, but could handle a 60%-70% uptake.
- The annual birth cohort of 4 million, with the 6-24 month-old population of ~6 million brings the total influenza vaccination cohort to double digits. This would be a small increment, within the wastage of current vaccination. However, if vaccination of household contacts is also recommended, those numbers would be increased.
- Influenza vaccine is already covered by the VFC when it was added to the “encouraged” group of vaccines. It would not be expanded except perhaps for the secondary groups cited in the recommendation.

*Pro:*

- Mr. Salamone thought a universal recommendation to be common sense. Immunization of children aged 6-23 months is in their best interest; the risk is limited; parents will accept it if their physicians recommend it; and physicians will accept it if AAP and others recommend it. He supported issuing a recommendation at this meeting and letting the physicians decide when to implement it.
- Other points voiced in favor cited the emergence of SARS and the difficulty in delineating between the two, especially with contact issues, which might indicate the need for prompt initiation of vaccination. No further data were likely to arise and the current safety and efficacy data are acceptable for this age group.

*Con:*

- Additional factors, however, were that the January 2004 childhood schedule was ready, according to the old recommendation. And, while there are two manufacturers for TIV, only one is licensed for this age group. Additionally, while the schedule could be changed, as was done for varicella, issuing the recommendation now could be construed as a recommended implementation for 2003.

Dr. Zimmerman moved that ACIP change “encouragement” of influenza vaccine administration to a full recommendation for vaccination of children aged 6-23 months of age, with full implementation to be done in the fall of 2004. Dr. Birkhead seconded the motion.

Further discussion included Dr. Poland's suggestion to add that "full implementation may not occur until fall 2004." Concerns about sensitivity to the timing needs of the AAP and AAFP to make their own recommendations, and the expressed concerns about the physicians' vaccine supply and liability issues were raised. Regardless of CDC's recommendation, implementation will take time and practitioners will need to gear up. Dr. Evans reported that after a vaccine is added to the VICP, eight years of retroactive coverage is included. Anyone giving the vaccine under the encouragement recommendation would be covered. He also noted that the full recommendation document will list the high-risk groups for whom vaccine is recommended, as well as language for people in close contact, healthcare workers and household contacts. Dr. Bridges suggested also listing "out-of-home caregivers."

Dr. Zimmerman repeated his **motion to move that "ACIP move from the 'encouragement' to full recommendation for children 6 to 23 months of age. Effective implementation is the fall of 2004."**

**Vote:**

Conflict of interest with AventisPasteur: None

In favor: Birkhead, Campbell, DeSeda, Finger, Gilsdorf, Hanson, Salamone, Zimmerman, Poland, Levin

Opposed: None

Abstained: None

**The vote passed.**

**IOM VACCINE FINANCING REPORT**

Presenter: Dr. Frank A. Sloan, Chair, IOM Committee on the Evaluation of Vaccine Purchase Finance in the United States. Pre-publication Report Issuance: August 4, 2003

The prepublication draft of "Financing Vaccines in the 21st Century: Assuring Access and Availability," released by the Institute of Medicine's Committee on the Evaluation of Vaccine Purchase Finance in the United States, was in the meeting materials. The committee was asked to examine the current arrangements for purchase and distribution of vaccines in both public and private health sectors; to identify strategies to ensure vaccine access and offer incentives for new vaccine development, and to develop recommendations to guide related federal, state, and congressional decision-making.

The rationale for the study was based on the importance of vaccines to the nation's public health. An overview of the multi-disciplinary and multi-sectoral committee and its study process was provided. The committee surveyed state health officials nationally and conducted eight independent studies of vaccine market structure and trends, pricing trends, insurance practices and coverage levels, and disparities in access to vaccines. Expert industry (vaccine, insurance) and public health panels were held, as well as other informational interviews and meetings with key experts and stakeholders. Gaps in the evidence base included data in some areas such as vaccine production cost and revenues, and on the impact of insurance coverage and cost sharing on immunization rates.

The national immunization system is one of the U.S.' most important public health investments. But, despite vaccination rates at all-time highs, childhood vaccination rates are stalled at 74% nationally and considerably lower for adults, especially those at high risk of disease. Recent data showed 49% influenza coverage for those at high risk. Structural and financial problems have interrupted the vaccine supply and concentrated vaccine production firms. The number of manufacturers dropped by 50% from 1966-77 and continues to fall. Several vaccines, including MMR, polio and tetanus, have single producers. It could take years for the supply to recover from a long-term production shut down by any one of these

companies. Vaccine delivery is hampered by the non-coverage of insurance policies or rising co-pays and deductibles. Today's more effective vaccines are also more expensive (e.g., \$50 for pneumococcal conjugate), making such cost-sharing shifts more significant. Vaccine delivery in the public health system is fragmented and variable, reimbursement rates for immunizations are below par, and practitioners are challenged to stock multiple products according to who pays for what. All told, these factors result in many missed opportunities, and immunization referrals by private physicians to public clinics are already rising.

The past successes of the national immunization system are closely tied to a healthy and competitive private vaccine market. The NIP purchases >50% of the childhood vaccine market, but any greater growth in that share with its related discounts could reduce industry motivation to develop new vaccines.

The IOM committee tried to balance the need for strong investment in future vaccines against current access to reasonably priced vaccines now while, at the same time, reducing the fragmentation that is currently so disruptive. Many strategies were considered to arrive at three recommendations, which would substantially redesign the system of vaccine purchase and distribution. They are:

1. *Establish a mandated immunization system subsidized by vouchers.*
  - a) Mandate and subsidize (the latter is essential) immunization coverage by all public and private insurance plans, acknowledging the importance of its link to medical care in a federally funded mandate. The purchase and administration costs of mandated vaccines would be federally subsidized to ensure that all receive them.
  - b) A voucher system would cover those children and adults who are under- or uninsured to ensure their seamless coverage. They could receive immunization from their own provider, who would be reimbursed for vaccine and its administration. The voucher returned to the government will be assigned to the proper program for reimbursement.
  - c) Vaccine development would be subsidized, to the amount calculated with the use of an objective benchmark. This would factor in the total societal benefit of the vaccine and whether it is a current vaccine, an improvement on the latter, or a new vaccine, each level involving an escalation of cost. The incentives provided will likely be more modest to maintain investment and current capacity, promote development of better versions of old vaccines, and stimulate additional firms to enter the field. Thus, the subsidy formulas for current and future vaccines would be slightly different. This would increase vaccine prices, on average, which are currently undervalued by society. The committee believed that more, not less, should be spent, "perhaps several times as much as we do today."
  - d) To "sell" this challenging concept, vaccines must be placed in context. One aspect of this is that the value of entire vaccine global market about equates to just one of the blockbuster drugs. Another is that the cost savings of immunization outweigh the expenditures, making it a good investment. Using this approach could well induce companies to focus their attention on new vaccines that would benefit society the most. But to be effective, the subsidy must be credible to industry, with assured payments free of budgetary whim. The subsidy process must be transparent, determined by an independent body, and have a methodology consistent across vaccines. If the private market supports a price above the subsidized amount, the subsidy can be foregone.
2. *Reorganize the composition of the Advisory Committee on Immunization Practices (ACIP).* The ACIP's recommendations on vaccines have substantial fiscal implications (e.g., the addition of PCV in 2000 increased federal expenditures by half a billion dollars over two years). It is independent and its process is transparent, but it currently lacks the expertise to address vaccine cost effectiveness. Its expertise should be expanded to include health insurance, healthcare delivery, consumer issues, health economics and finance, and manufacturing. Vaccines with strong spillover effects (i.e., those conveying

herd immunity) would be included in the mandate/subsidy program for research and implementation support. Those without those effects (e.g., for diabetes or cancer) are most likely to be covered by private and public insurance programs. Current vaccines without spillover effects such as tetanus would be grandfathered into the program. Aside from the science, the ACIP would use the data of vaccine cost/benefit implications to support its recommendations. The ACIP could be two bodies, one purely scientific and the other economic, or could have the input of an industry body to advise it in those areas.

3. *Provide a public process of stakeholder deliberations* on the full implication of the proposal and to address technical design issues.
  - a. Convene regional/national meetings (e.g., by NVAC) with multi-sectoral representation (public health agencies, insurers, providers, employers, industry and consumers).
  - b. Develop a research agenda and evaluation strategy to ensure that the proposal achieves the desired objectives.

To address the long-term systemic problems that threaten the public health process, CDC sought the IOM's help. These proposals were the committee's response, providing a blueprint, strategic framework to which many details would have to be applied. The IOM looks forward to working with CDC, NVAC and the ACIP further to meet these challenges.

*Discussion* included:

- Dr. Orenstein agreed that the system is not working completely well. For example, last year PCV was distributed in 19 states through two-tier systems. VFC-eligible children could get pneumococcal conjugate vaccine at a health department clinic, while other children would be sent home. This is a matter of concern as more vaccines are added to the childhood schedule, and as adult immunization efforts increase.
- Dr. Plotkin complimented IOM on its boldness. Its already-developed priority list of vaccines could help identify those which should be promoted. ACIP's similar recommendation in advance would be even more helpful. Spillover of herd immunity and protection of others is hard to predict (e.g., it is still unclear with HPV vaccine). Although herd immunity is a bonus, he thought it to be a poor criterion for a recommendation. He preferred to replace a subsidy *a priori* with an *a priori* recommendation to indicate future markets to manufacturers and to avoid a disastrous lack of a market. For the latter, he cited the Lyme disease vaccine experience, which he thought failed at least in part due to ACIP's lack of enthusiasm for it, despite public demand.
- Dr. Peter reported the NVAC/NVPO review of this report and their informal discussion of the proposed regional/national meetings. While commending the IOM's acknowledgment of vaccines' importance, the NVAC regretted its incomplete address of the public health infrastructure that has successfully advanced the nation's immunization status. However, the previous IOM report, "Calling the Shots," did so. NVAC is forming a small workgroup to recommend a process to approach and implement these recommendations.
- Dr. Birkhead agreed about the lack of a public health role. The VFC gives his health department free access to physicians' offices and the resulting interactions; and the health department is a central source in times of shortage for information and direction of supply. These aspects are important but are not in this report. He asked how what works well now could be retained in a radical redesign. Dr. Sloan responded that this report just addresses areas not in "Calling the Shots," which the committee certainly endorsed, to focus on the areas not working well, such as R&D, procurement policy, and coverage concerns. It was hoped that fixing the financing would turn the focus to the third, public health area. All need to be balanced. The solution may not be cheap, but they tried to limit the cost by limiting the vaccines to be included to those addressing infectious disease. There is a gray area between these and the others addressed by various insurance programs.
- Dr. Birkhead noted that the ACIP approved influenza vaccine, which may not be cost saving, and

asked how the new process would price such a vaccine? Dr. Sloan said that cost offsets would be factored in, such as deferred hospitalizations and quality of life from freedom from the flu,. To evaluate such non-pecuniary benefits, the committee would have to think about what values are used to judge this and ask for surveys to gather explicit data on that, rather than suppositions.

## **SMALLPOX SESSION**

### **Update on the Civilian Smallpox Vaccination Program (SVP)**

Presenter: Dr. Ray Strikas, NIP

A chart of the preparedness of CDC's national Smallpox Vaccination Program (SVP) demonstrated a good status for the vaccine supply, clinician education, lab diagnosis, vaccine safety screening, and adverse event reporting. Detection and reporting and disease surveillance are improving, but more work is needed on hospital care, response team vaccination, and vaccine clinic planning.

A performance measure or scorecard for state and local areas receiving federal bioterrorism funds is being developed by a CDC workgroup. This will provide a baseline preparedness and management level from which to address terrorism incidents (e.g., biological, chemical, or radiologic events). Another workgroup of external public health partners was meeting on this day, and on November 6, the IOM's SVP Committee plans to discuss specific scorecard measures:

- Voluntary vaccination, training of key responders
- Early detection, reporting, isolation, treatment of cases
- Laboratory capacity to confirm smallpox disease and to rule out other rash illnesses
- Vaccine supply management
- Drills and exercises to test proficiency
- Data and information management
- Rapid investigation and prophylaxis of contacts
- Mass vaccination (e.g., the entire population vaccinated within 10 days of first confirmed case)
- Delivery of critical messages and materials to the public before, during, and after response.

A law passed in May 2003 provides benefits for public health and healthcare team members, or public safety response team personnel, who are injured after smallpox vaccination. This was placed on the VIT in August, but the compensation program is not yet in place. Final rules are pending in the very near future, but those vaccinated as part of the SVP since January 24 will be covered when the final rules are in place. Dr. Evans hoped that the interim rules and procedures would be in place in 4-6 months.

At least one worker has been vaccinated at each of 2,174 hospitals (44% of U.S. acute care hospitals) and ~190,100 doses of vaccine are available in states. From January 24 to October 10, 2003, the SVP has vaccinated 38,542 individuals, of whom about 66% are healthcare workers and 33% are public health workers. Of these, 64% are female and 25% are primary vaccinees. Ages range, but 80% are >40 years old. The take response for all vaccinees has been 92%; 90.3% in primary vaccinees and 92.5% in revaccinees. There have been no reports of eczema vaccinatum, erythema multiforme major, fetal or progressive vaccinia, or of vaccinia transmission to contacts. Charts were shared to demonstrate the cumulative and weekly vaccination rates, along with maps showing the status by vaccinated state of individuals and state response teams.

Data from Lane *et al* and Neff *et al* were charted to compare current versus historical rates of adverse events after vaccination. Other than the zero cases reported above, generalized vaccinia and post-vaccinial encephalitis paralleled 1960s rates for primary vaccinees.

As the SVP progresses, challenges include public complacency due to reduced threat perception since the end of the Iraq war and the resulting low priority assigned to smallpox attack preparation. The public health and hospital workforce is not fully engaged, is skeptical about the threat credibility, and is still confused about vaccination risks and available protections. A licensed vaccine for citizens who insist on being vaccinated is expected in 2004. Current access to clinical trials is limited. No other program has been begun and demand is very small to date. The DHHS' action plan is to increase national awareness of the threat and the safety of vaccine, to measure state and local preparedness, to work to add smallpox and bioterrorism preparedness standards into the hospital accreditation process, to weigh other techniques to speed post-attack vaccination (including deployment of vaccine stocks to local/regional facilities and gathering other federal agencies as SVP partners), and to develop options to make vaccine available to citizens who insist on vaccination.

### **Update on DOD SVP**

Presenter: Dr. John Grabenstein, Col., DOD

*Vaccination status.* Since the President's December 2002 announcement that troops will be vaccinated before an attack to ensure their protection and the accomplishment of their missions, ~502,000 have been vaccinated in three stages: smallpox epidemic response teams (SERTs), medical teams for hospitals and large clinics, and mission-critical forces, especially central command. Most vaccinees are male (mean/median age 27 and 29 years; 67,000 aged >40; 12,000 >50) and ~61,000 (12%) are female. About 350,000 are primary vaccinees and 150,000 are revaccinees. The median follow-up time from vaccination is eight months, and 90% are within five months.

*Dermatokinetics.* The DOD has been studying dermatokinetics, tracking the evolution of a smallpox vaccination site in 1,151 respondents to a telephone or e-mail data collection system. One result already apparent is that the site scab, presumed to fall off on days 14 to 21 post-vaccination, remained on day 28 among 40% of the participants. Either the presumed scabbing period is not evidence based, or the current standard of site coverage and bandaging is more occlusive than in the past.

The kinetics of vaccination site symptoms was also charted. In general, only 10-20% reported symptoms (streaking, warmth, local rash, swelling and bandage reaction); itching (~73%) and leaking fluid (~34%) were also reported. The kinetics of systemic symptoms were similarly charted. Swollen lymph nodes spiked at about seven days. Similar peaks were shown from days 7 to 10 for eye infection and chest pain (1%-3% of reports; no medical care was sought for chest pain); muscle ache, headache, and joint ache peaked at ~14%, 12% and 9%, respectively.

Generalized vaccinia cases totaled 34, all very mild. Distributions were charted of inadvertent infection of the self (e.g. skin, eye) and of contacts. As compared to 504,000 cases of no vaccinia spread to another person, 28 cases did spread, mostly to spouses and adult sexual partners, and in a few cases of sports-related contact, to friends. No vaccinated healthcare workers transmitted vaccinia to a patient, nor did vaccinated patients do so to unvaccinated healthcare workers. VIG has been used twice, and only one encephalitis case occurred, very early in the program.

Ten HIV-positive individuals were inadvertently vaccinated. Among those, there were ten takes and ten heals, with no eczema vaccinatum, progressive vaccinia, or deaths attributable to the vaccine. Three heart conditions were previously discussed and are under ongoing evaluation. Follow-up data on 35 of the 58 myopericarditis cases previously reported indicated that 80% had a complete clinical recovery (based on echocardiogram and stress tests) eight weeks after diagnosis. In the remaining 20%, intermittent chest pain was the only symptom, and 6% had non-specific ECG changes. Follow-up of these 58 will be done for a year.

*Pregnancy.* Outcomes among women inadvertently exposed to smallpox vaccine early in their pregnancy, or just pre-conception, were studied through data from the National Smallpox Vaccine in Pregnancy Registry, a DOD/CDC collaboration.

In first trimester outcomes, the observations fit expected rates: vaccination during or just before pregnancy had no apparent effect on pregnancy outcomes. Of 149 military women so exposed (mean age 23), 128 progressed to the second trimester. Of the balance, 13 had miscarriages, five had elective abortions, and two had ectopic pregnancies. Viral culture and/or PCR positive samples were obtained in 19 out of 19 cases. The rate was somewhat above historical rates, but that may be because there are now so many more vaccinia-naïve people in the population that a historical comparison is only of limited value.

The study conclusion was that the primary transmission risk is to people who share the same bed, and secondarily, a failure to bandage.

*Discussion* included that the HIV-positive status of those 10 vaccinees was unknown. Their CD4 count, when tested, was about 300-700, so they were not immunosuppressed. They were relatively recently infected. The demographics of the 58 myocardial or cardiac outcomes of immunization were all primarily Caucasian, young, male, and primary vaccinees. The disproportion of these was statistically significant, indicating that something was going on, but exactly what is not yet resolved.

### **Report of the ACIP Smallpox Vaccine Safety Workgroup**

Presenter: Dr. John Neff, Chair, Armed Forces Epidemiological Board

This multidisciplinary workgroup evaluated vaccine safety data and the vaccine safety monitoring and treatment system, with a secondary, focused on the use of VIG and cidofovir. The workgroup met weekly, beginning in January 2003, and held emergency ACIP teleconferences on the myocarditis and the ischemic cardiac deaths. They recommended screening, rather than exclusion from vaccination, of persons with known cardiac disease and at least three risk factors. They found no definitive causal link between vaccination and the ischemic and inflammatory cardiac events, but there was a biological possibility, based on the military data. They did not favor expansion beyond the ACIP's pre-event smallpox vaccination recommendation.

Since June, four cases of dilated cardiomyopathy were identified 3-5 months post-vaccination. Five sentinel case review teams were created to look for unidentified or advantageous agents in either the vaccine or the recipients.

The vaccinated civilian population is much smaller in number and the reverse in characteristics to the military cohort. Only 25% are primary vaccinees, more (65%) are female, and the age group is older by at least a decade. The military program vaccinates ~2,000 people per week, and the rate has been fairly level since May. The civilian vaccination rate peaked early on and also is flattening out, at about 25 primary vaccinations per a week.

The low number of adverse health outcomes is a success for the program as currently designed, but Dr. Neff offered a caution. The amount of time (45-60 minutes) spent on the current screening process would likely not be possible in a massive population vaccination program, and if done, it will not be as effective as to date. There also are the unanticipated events of myopericarditis (80 possible cases, 62 probable and two confirmed with biopsy evidence), and the two cases of dilated cardiomyopathy in each of the civilian and military cohorts. All four are revaccinees, male in the military cohort and female in the civilian. All

of them are ~10 years older than the average age of vaccinees. The onset is gradual, over 3 to 5 months after vaccination, and all are severe cardiomyopathy. They are surviving; none have had transplants yet.

The Workgroup concluded that investigating *adventitious agents* would be costly in funds and time, due to the required open-ended and resource-intensive process. It could divert resources from other areas that are of higher priority and is unlikely to provide timely information to help inform the population on the vaccine's safety. They preferred to follow the current clinical and epidemiological investigations to best protect and inform the public. They recommended continued development of epidemiological data; identification of risk factors (underway); conducting good clinical case follow-up and evaluation of the rate of residual impairment; and extensive investigation of inflammatory and cardiac reactions during the vaccine trials. They concluded that any exploration of adventitious agents should have very specific protocols, goals and timelines, with clear cost analysis, how that would be interpreted, and possible resulting investigations.

*Sentinel case review* is in process through subgroups on Unreviewed Deaths (no association found to the vaccine), Chest Pain/Dyspnea/Fever Syndrome (4 cases, one death), Dilated Cardiomyopathy (4 cases, report in process), and Neurological Adverse Events (no cases identified to date). The Dermatology group has just begun review of all cases of generalized vaccinia and other associated rashes. The review objective is to better define the rashes and how many of them are actually generalized vaccinia. This diagnosis probably has been greatly overused among individuals with an intact immune system.

Data on *vaccinia transfers to contacts* reflect the predominance of primary vaccinee transmitters and support emphasis on the lack of nosocomial transmission among health workers. The contacts were predominantly unvaccinated young adults, half of them family members. The characteristics of the transmission setting are also important. None were at work and none nosocomial. Person-to-person transmission requires a very intimate body contact; bed partners are at highest risk. And, although contact transmission had no long-term morbidity or mortality, it generally caused many lesions in vulnerable eye, nose, mouth, and genital regions.

A larger vaccination program, especially one in response to an event, will have mostly primary vaccinees with largely immunologically susceptible contacts in a home setting, where infection control practices are inconsistent. That means that better attention to the site management issues is needed, including analysis of fomite transmission risk, how to provide complete containment of drainage without causing increased maceration to the site, and determining the appropriate site bandaging, particularly at home.

*Pregnancy registry.* The pregnancy registry includes 160 women, most in the military. The observed rate (2:1000 female vaccinees) of pregnancy was much less than that expected (8-11:1000 vaccinees). Of those inadvertently vaccinated, 70% were immediately pre- or post-conception, when pregnancy tests may not be positive. The outcomes of all the pregnancies will be known in about February. Currently, the rates of spontaneous abortion and ectopic pregnancies are not higher than anticipated for the ages for the risk factors involved. There was no vaccinia identifiable in the three products of conception that were available for testing.

Dr. Neff advised continuation of the sentinel case review process, renewed efforts to prevent contact transmission and site management, and continued follow-up on the cohort of women exposed to vaccinia during pregnancy to determine the pregnancy outcome.

### **Consideration in the Timing of Smallpox Revaccination**

Presenter: Dr. Julie Gilchrist, NCID

Markers of cellular and humoral immunity are needed to determine adequate immune response to smallpox, and how often response team members should be revaccinated to maintain their immunity. The technology to explore cellular immunity did not exist in the smallpox era, so historical data are absent. There are no laboratory measures of immunity. Several studies have explored neutralizing antibody, but protective levels remain unclear.

*Laboratory Studies.* A historical review of related laboratory studies revealed that:

- Cell mediated immunity develops rapidly after vaccination and has an important role in recovery from infection, as demonstrated by the two-day revaccination study of Pincus and Flick (Journal of Pediatrics 1963;62:57-62). Other researchers have demonstrated that inactivated virus can generate a vesicular response in a previously vaccinated subject but not a naive one, supporting the idea that cellular immunity occurs.
- Vaccinia virus-specific CD4<sup>+</sup> and CD8<sup>+</sup> CTL persists in persons immunized 4 years earlier (Demkowicz WE Jr., Ennis FA. J Virology 1993; 67:1538-1544). However, 50% of those vaccinated <3 years previously had CD8<sup>+</sup> CTL activity and low level CD4<sup>+</sup> activity (Erickson AL, Walker CM. J Gen Virol 1993; 74:751-754). All three showed no detectable response *in vitro* had been vaccinated as children, while only one of the three who responded had been vaccinated as a child. I ALSO FIND THIS CONFUSING.
- CD4<sup>+</sup> and CD8<sup>+</sup> memory vaccinia virus-specific CTL activity was measured in persons vaccinated 35-50 years previously, and produced one in 66,000 cells (Demkowicz WE Jr., Littau RA, Wang J, Ennis FA. J Virology 1996; 70:2627- 2631).
- Using a lack of local skin response to revaccination as an indication of immunity:
  - Less than 10% of those with neutralizing antibody titers of >1:10 exhibit primary type reaction, compared with >30% of persons with titers <1:10 (McIntosh K, Cherry JD *et al.* J Infect Dis 1977;135:155-66).
  - More than 95% of primary vaccinees will have neutralizing antibody titer of >1:10 (Cherry JD, McIntosh K *et al.* J Infect Dis 1977;135:145-54).
  - Titers of >1:10 persisted for over ten years in 75% of those vaccinated, after the second dose, and up to 30 years after the third (Lublin-Tennenbaum T, Katzenelson E. Viral Immunol 1990;3:19-25; El-Ad B, Roth Y. J Infect Dis 1990;161:446-8).
- Other studies show a >55% reduction of the variola pock count for ten years following a primary vaccination; a >70% reduction for 20 years following a revaccination; and >75% reduction in the pock count for at least 20 years in vaccinated patients following exposure to smallpox, demonstrating the booster effect of revaccination.
- *Israeli Defense Forces Study.* Antibody persistence after vaccination was examined in an Israeli study of neutralizing antibodies using a plaque reduction assay. Two groups were involved, one of 65 recruits aged 18 years who were previously vaccinated at ages 1 and 8 years, and a group of 20 reservists vaccinated at 0, 8, and 18 years of age. Both received the Elstree (Lister) strain. Results showed a decrease in neutralizing antibody from the 23rd day post-vaccination to the test given three years after vaccination, but no further titer decrease 30 years later. The Israelis concluded that only a primary vaccination and two revaccinations are necessary in the absence of direct exposure risk.
- American studies of antibody persistence after vaccination include a trial of 80 previously vaccinated volunteers aged 32 to 60 years compared to ten never-vaccinated volunteers aged <31 years. The preboost titers of neutralizing antibody in the 80 participants were comparable to the titers in the comparison cohort six months after vaccination.

*Epidemiologic studies* to date have focused more on mortality than incidence of infection.

- Hanna (Hanna, W. 1913, Studies in Smallpox and Vaccination. Bristol, Wright) studied 1163 smallpox cases based on their age and vaccination status. No fatal cases occurred in those

vaccinated 0-14 years prior. The case-fatality rate increased with time since vaccination. For the vaccinated cases, severity of illness was directly related to time since vaccination, and there were no severe cases in those 0-14 years since vaccination.

- Mack (Mack TM. J Infect Dis 1972;125:161-9) studied 680 cases of variola major in Europe after eradication of endemic smallpox (~1940 on). Again, the fatality rate related to time since vaccination. These data support persistence of the long-term antibody and cell-mediated immunity, paralleled by similar clinical outcome data and indicated protection from death perhaps for >20 years.

#### *Past recommendations:*

- 1964 WHO Expert Committee on Smallpox made recommendations for on those at special risk and in endemic areas:
  - For non-endemic areas, maintain a sufficiently high level of immunity in the general population to minimize the risk of serious complications upon revaccination (recommended at 5-10 year intervals).
  - For endemic areas, revaccinate every year.
  - For those at special risk (e.g., hospital and public health personnel), ensure a level of immunity to avoid risk of smallpox upon exposure by revaccinating every three years and more frequently if exposure is probable.
- The 1966 ACIP recommendation advised vaccination with fully potent vaccine for a high level of protection for at least 3 years and substantial but waning immunity for >10 years. Further protection against death appears to extend for perhaps decades. Revaccinate at 3-year intervals for those potentially exposed and every 10 years for those not so.
- Other recommendations: 1978 ACIP (for lab workers); 1985 CDC/NIH (added animal care workers); 1991 ACIP (health care workers); 1993 CDC/NIH biosafety guidelines updated the 1985 ones to recommend revaccination every 10 years. In 2001, ACIP recommended revaccination every 3 years for those workers handling the more virulent non-variola orthopoxviruses (e.g. monkeypox), halted vaccination of those working only with highly attenuated or non-human pathogenic strains (MVA, NYVAC, ALVAC, TROVAC), and advised vaccination for all others (cowpox, vaccinia) every 10 years.

#### ***Considerations for Revaccination of Response Team Members at the Outset of Outbreak Control Activities***

Presenter: Dr. Melinda Wharton, for Dr. J. Michael Lane, MPH

Dr. Lane recommended revaccination of everyone going in or out of the door in the event of an actual smallpox incident. As support, he cited the uncertain duration of immunity and the problems encountered with reactions in the last year, which involved Type 1 and Type 2 errors that could indicate persons are immune when in fact they are not. Any healthcare or public health worker who has contraindications to vaccination should not be seeing smallpox patients or working on these investigations anyway. And, if they do not have such contraindications but have a recent major reaction, there is no risk to repeat vaccination.

The Workgroup suggested several options to maximize protection and minimize risk:

- Option 1: Revaccinate response team members every 3 years, and consider “out the door” revaccination when feasible (i.e., be vaccinated on the way out to respond to an outbreak rather than waiting for a reading to ensure that the take was accurate).
- Option 2: Revaccinate response team members every 10 years with universal “out-the-door” revaccination.

The workgroup members had noted that if the recommendation to revaccinate every three years was effected, “out-the-door” vaccination would not be necessary, but Dr. Lane’s comments were counter to that. His position was that, in the event of an outbreak, the risk of infection outweighs any other consideration. The Workgroup had some skepticism of the “out-the-door” option, but Dr. Lane had not been present to comment. The Workgroup had questions about this policy and had recommended vaccination every three years.

*Discussion* included:

- Dr. Poland noted that the DOD data discounted assurance of no risk if vaccinated beforehand, even though the subjects were distant vaccinees. And there are no current data on myo/pericarditis, etc., among those vaccinated ten years earlier.
- Dr. Grabenstein was concerned about those vaccinated with only one dose, since there are no data on their protection 3-10 years afterward. He suggested an Option 3, stratifying by interval those who had one dose in life or more, which may be an important variable.
- Dr. Neff appreciated the sense of Dr. Lane’s thesis that logistics in an epidemic prevent sorting out who has been vaccinated how many times; it is easier to just vaccinate. Dr. Orenstein agreed that vaccinating everyone in response to village outbreaks in India did not always show a take, but the 30% death ratio of the infected made the vaccination risk minimal.
- Dr. Poland thought a vote on this would be premature. He suggested separating the revaccination and out-the-door vaccination decisions, since the timing of revaccination presents different issues in the absence of a possible exposure.
- *How often did field staff in India who saw smallpox every day get revaccinated, and were there ever cases of smallpox workers with documented vaccination who developed smallpox?* Dr. Orenstein recalled the recommendations at the time to probably be for revaccination every one to three years. All the field staff were vaccinated and were revaccinated annually. The recommendation for lab workers was to be vaccinated regularly if they worked with variola, but there are no data on resulting adverse events. Dr. Grabenstein offered to share any of the limited relevant DOD data available. The Workgroup might be able to get data from USAMRIID’s special immunization program.
- Public health workers could be sent to investigate febrile vesiculopustular disease that might be chicken pox and should not be vaccinated literally out-the-door. In the event of a suspect case of smallpox, they could still be vaccinated very quickly

Dr. Levin asked for clarification from the Workgroup on the options suggested, either at this or the next meeting.

### **Contraindications Policy in Post-Event Mass Vaccination Campaigns**

Decision/Presenter: Dr. Ray Strikas, NIP

The question must be answered of how to deal with contraindications in the event of smallpox outbreak anywhere in the world. This poses more distinct risk/benefits than in the current situation. One or more identified cases likely indicate that more cases are incubating in other locations. When the first case is detected, it will not be known how many more will occur or where, and an unnatural spread (i.e., an attack) may occur. The U.S. has sufficient vaccine for the entire population and a high-level decision has been made that it would be offered to the population at large in the event of a confirmed case anywhere in the world.

In June, the ACIP stated that preparedness efforts for smallpox must include plans for mass vaccination of large population groups, up to the entire population, in a short period of time. In view of that, several questions were asked for the ACIP’s consideration:

- In the setting of a smallpox outbreak anywhere in the world and vaccine offered to the U.S. public, what contraindications or exclusions should there be for persons not known to have been exposed to smallpox?
- Should there be differing recommendations for persons in an affected area (with smallpox cases), compared to persons in an area without cases?
- What should be recommended for healthy persons who have household contacts with contraindications?

The U.S. population currently with smallpox vaccination contraindications includes:

- Eczema or atopic dermatitis (E/AD): c. 20 million, 36 million households
- Immunosuppressed: ~8 million, 14.4 households
- Pregnant women and breast-feeding women: ~5 million
- Heart disease or risk factors: ~28-30 million people
- Total: ~50 million, or ~20% of the population affected by contraindications or exclusions, as well as those who are their household contacts (calculated by multiplying 1.7 by the number of persons with contraindications or exclusions).

*Risk.* The risk of selected complications after smallpox vaccination was compared to historical data, which reflected them as being similar to or lower than in the current program, except for myocarditis and pericarditis. However:

- 30%-40% of persons with atopic dermatitis/eczema (AD/E) may not acknowledge the condition in themselves or their contacts (Naleway *et al.*, *Annals Int Med* 2003). Taking the 0.8% estimated prevalence of AD/E of their Marshfield Clinic cohort and extrapolating that to 518,000 current vaccinees, and if all acknowledging AD/E were deferred from vaccination, then (.3 or .4 x .008 x 518,000) or 1243-1658 at-risk persons were vaccinated with no resulting eczema vaccinatum.
- Tasker *et al* (2003 IDSA #820) reported the vaccination of eight asymptomatic HIV-infected individuals in the military, with no sequelae. Of 15,738 records in the database of the vaccinated civilian program, ~ 77 people (0.5%) reported contraindications after the fact, only 17 of those being mild adverse events, local or mild systemic reactions.

Screening procedures have clearly limited the number of civilian (and presumably military) vaccinees with contraindications, but a large-scale post-outbreak vaccination program would have less time and opportunity to screen potential vaccinees. Recommendations for such vaccination would include "exclusions," (chosen by the Workgroup rather than "contraindications," where one does not offer vaccine at all unless there is exposure). "Exclusions" could equate to the general understanding of the "precautions" taken, where vaccine is not offered before counseling is provided about the risk of adverse events.

**Exclusion options** to consider for vaccination of the unexposed public in a smallpox outbreak in several areas were offered:

*Affected (cases identified) areas:*

- No exclusions: Vaccine is offered to all, with information about the risks of adverse events for those with contraindications or exclusions
  - Advantage: Avoids public concerns about discrimination in recommendations.
  - Disadvantage: Highest risk for adverse events.
- Limit exclusions to immunosuppressed persons.
  - Advantage: Immunosuppressed persons are at highest risk of a severe event and also may not respond well to vaccination; eczema vaccinatum can be treated with a

- good chance of recovery.
- Disadvantage: Some will likely still demand vaccination.

*Unaffected Areas* (no cases):

- No change in those listed for exclusion (former contraindications).
  - ℞ Advantage: Lowest risk of adverse events.
  - ℞ Disadvantage: Public may demand vaccination regardless of recommendation.
- Limit exclusions to immunosuppressed persons.
  - Advantage: Immunosuppressed persons are at highest risk of severe event and also may not respond well to vaccination; eczema vaccinatum can be treated with VIG with good chance of recovery
  - Disadvantage: Some will likely still demand vaccination.
- No exclusions: Vaccine offered to all, with information about the risks of adverse events for those with contraindications or exclusions
  - Advantage: Avoids public concerns about discrimination in recommendations
  - Disadvantage: Highest risk for adverse events

*Discussion* included:

- Cases appearing anywhere in the U.S., let alone in a neighboring state or city, will probably prompt public demand for vaccination. That will make screening very difficult, if not impossible. And, with unnatural transmission, public health will probably not be able to reassure the public with any degree of certitude that a case elsewhere would not impact other communities.
- Dr. Halsey suggested that, beyond stating contraindications, ACIP could issue an advance statement noting the risk of serious adverse events, to support that not everyone should be vaccinated and to avoid a panic upon determination of a case. The statement would be based on any information made available to the CDC that would enable it to guess fairly rapidly if this were a natural or unnatural transmission. Dr. Neff added the ethical question: presuming that a case in the U.S. would not be the only one in the world, what about vaccinating the entire U.S. population when vaccine would be needed to stop an epidemic elsewhere?
- Dr. Poland suggested using this as an opportunity to develop plans for different scenarios, perhaps even for different viruses in the orthopox family (e.g., a high-dose bioterror attack with monkeypox or camelpox). Populations to include are children aged <1 year, those who are immunosuppressed and pregnant women.
- Dr. Modlin reported that children's issues were discussed in the Workgroup's teleconference. They noted that children have an increased risk of encephalitis from vaccine and perhaps other complications. The sense of the discussions was to address children as is done for the immunosuppressed unless there is a high risk of exposure. Dr. Zimmerman agreed with this approach and **moved to limit the advised precautions to those who are immunosuppressed and to include children aged <1 year.**
- However, Dr. Poland preferred to state that there is always some degree of risk, explicitly state the risks and the threshold, and let people in an outbreak area make their own vaccination decision. Dr. Modlin pointed out that the current pre-event program already offers fairly explicit definitions of who would be considered immunocompromised, and the workgroup foresaw no further delineation.
- Although time for counseling in an outbreak will be limited, it was expected that there will be a lot of local and individual decision making. But Dr. Birkhead stressed that the liability issues around *not* giving vaccine must be very clear. Dr. Strikas added the need to clearly define "affected" and "unaffected" areas. Dr. Livengood expected that CDC would publish such a list, and the local areas may decide as well (e.g., in view of commuters, New York City may include Philadelphia as well as its own outlying areas). However, this could risk a thinning of efforts in

the areas of need in order to address those of less need. Dr. Orenstein suggested that “affected” would be the areas where CDC would do surveillance and containment.

Dr. Levin approved of the latter definition of “affected” as the areas where CDC would do surveillance and containment, with that determination to be made by someone in authority. The committee’s conclusion was that in the *unaffected areas* (i.e., no identified cases), vaccination would not be given to immunosuppressed persons and those aged <1 year. In *affected areas* (i.e., cases have been identified) there would be no exclusions. The vaccine would be offered to all, with precautionary information provided about the risks of adverse events for those with contraindications.

### **SVP Issues for Workers Outside Healthcare Settings**

Decision/Presenter: Dr. Melinda Wharton, NIP

The SVP poses issues relevant to workers outside of the hospital settings already addressed. The current recommendations about site care for healthcare workers are to cover the site with gauze, a semipermeable dressing and a layer of clothing until the scab separates; to change dressings as needed to prevent exudate buildup, and to examine the dressings daily and change them if needed. Outside the patient care settings, the site should be covered with a porous dressing; if transmission is a concern (e.g., with children present), a layer of clothing should be added.

There has been no nosocomial transmission, but there have been some contact transmissions that were, in general, associated with intimate contact. To determine the compliance with ACIP site care recommendations in the civilian SVP, three states’ practices were requested. Tennessee left the practices up to the individual clinics, and they ranged from no bandaging to semipermeable dressings. Texas advised coverage with gauze if there would be no patient/client contact, and New York advised the use of gauze for those outside healthcare settings. These indicate that, in general, the ACIP recommendations have been influential in practice.

Since some states may include persons on response teams who are outside those groups included to date (e.g., first responders), the ACIP was asked if the current recommendations for site care are sufficient, or if additional guidelines are needed for these occupational groups. In response, the committee indicated its satisfaction with the current recommendations.

**OCTOBER 16, 2003**

### **INVASIVE PNEUMOCOCCAL DISEASE SESSION**

#### **Pediatricians’ Knowledge of/Adherence to PCV7 Shortage Recommendations**

Presenter: Dr. Karen Broder, NIP

The preliminary findings of a U.S. survey of the outcomes of the childhood vaccine shortages, 2000-2003, were presented. The information was provided to assist an ACIP consideration of changing its strategies during future vaccine shortages.

A review was provided of the shortages, which lasted for 20 months from 2000-2002: 17 months for DTaP (2001-2002), 11 and 10 months for varicella and MMR, respectively (2002), and 20 months for

PCV7 (2001 to May 2003). The PCV7 shortage was used as a specific example. Licensed in February 2000 and recommended that June by the ACIP, it was in short supply by September. CDC issued shortage recommendations in September and ACIP did so that December. The shortage did not end until May 2003, when CDC so advised the field.

The recommendations issued by CDC to address the shortage were as follow:

**PCV7 total dose schedule for healthy children by shortage level** (On the basis of shortfall from a 4 dose series) THE PARENTHESSES FOR THE “NO OR MODERATE” ARE THE SAME AS FOR THE “SEVERE” COLUMN

<b>Age (months) First PCV7</b>	<b>Pre-shortage Reference</b>	<b>No or Moderate Shortage (26%- 50% Shortfall)</b>	<b>Severe Shortage (26-50% shortfall)</b>	<b>More Than Severe Shortage (&gt;50% Shortfall)</b>
<b>6</b>	<b>4 Doses</b>	<b>3 doses</b>	<b>2 doses</b>	<b>Prioritize based on assessment of risk</b>
<b>7-11</b>	<b>3 Doses</b>	<b>3 doses</b>	<b>2 doses</b>	
<b>12-23</b>	<b>2 Doses</b>	<b>2 doses</b>	<b>1 dose</b>	
<b>24- 59</b>	<b>1 Dose (optional)</b>	<b>None</b>	<b>None</b>	

There are a few reasons why these recommendation might not be effective: they are complex and long; there may be multiple other vaccine shortages; there is a potential for different vaccination practices and supplies among public and private patients, and a potential conflict between the public health interests of children outside a practice and interests of patients within a practice.

To determine the effect of the shortage on pediatricians and their patients (i.e., the proportion of pediatricians who experienced a PCV7 shortage, or whether children in the public and private sectors were vaccinated differently), a survey explored knowledge/adherence to the ACIP PCV7 shortage recommendations by pediatricians. The methods included a survey mailed during the shortage to 2500 randomly-selected AAP members who provided primary care to children and used PCV7. The survey collected data on the demographics of the practice and the PCV7 supply shortage experience, and provided clinical immunization scenarios to assess adherence. A short follow-up of 122 random non-responders (by fax/phone) was also conducted.

Results were as follow:

- *Participants.* Of the 1412 surveys returned, 946 (67%) were eligible. Of those, 83% were in private practice or an HMO; 80% had both public and private sector patients, and 85% were in urban or suburban settings. Two percent vaccinated only public sector patients and 4% only those in the private sector; 70% vaccinated both and 24% vaccinated neither.
- *Shortage experience.* The shortages were fairly evenly distributed across the public and private sectors. However, more private practitioners reported moderate shortages than those in the public sector, who reported more severe shortages and more depletion of their PCV7 vaccine supply. Seventy-nine percent of the responders experienced the shortage and were out of stock at some point.
- *Vaccination practices.* Pediatricians with little or no shortage were asked to give dose 3; those with severe shortage were asked to defer the PCV dose 3. Of those serving both public and private sectors, 70% vaccinated both and 24% vaccinated neither. Only 2% of public sector practitioners delivered dose 3, and 4% of those serving the private sector alone.
- *Recommendation knowledge/compliance.* Some level of awareness of the recommendations was reported by 94%; 85% adhered to them always or most of the time, and 86% found them to be

- applicable to their practice.
- *Barriers.* The top barrier to using the immunization recommendations (cited by 95% of respondents) was inadequate vaccine supply. That was followed by multiple vaccine shortages and concern over ability to recall patients, at 84% and 82%, respectively. Among other barriers cited were parental pressure and confusion about the recommendations.
- *Adherence* was reported by pediatricians as minimal (done <70% of the time) by 37%, occasional (70-89%) by 28%, and complete (90%) by 36%. Ninety-one percent of pediatricians vaccinated their high-risk patients and patients with sickle-cell anemia.
- *Fourth PCV7 dose administration* at the 12-15 month well-visit for healthy children who received all infant doses was, correctly, never done by 33% of respondents; 18% did so rarely, 19% did so sometimes, and 30% always gave the fourth dose. Of the latter, 30% of both public and private providers with PCV7 shortages did so, as did 67% and 72%, respectively, of those with no shortages. The reasons cited for giving dose 4 ranged in priority from the child being in childcare (65%), diagnosis of OM (53%), parents' request (43%), child's race (16%), child's insurance status (14%), or other (5%). It is noteworthy that none of these reasons were in the ACIP shortage recommendation.
- *Recall capacity* was nonexistent for 36%; 50% did manual records checks; 6% used a computerized system; 5% used registries, and 4% used some other system.

The study concluded that:

- Most pediatricians experienced a PCV7 shortage and were aware of the shortage recommendations.
- Pediatricians vaccinated children in the public and private sector in a similar manner during the shortage.
- Most pediatricians partially adhered to the recommendations, but pediatricians without a shortage were less likely to limit PCV7 use.
- Contrary to recommendations, half of pediatricians sometimes or always gave the fourth PCV7 toddler dose.
- Over one-third of pediatricians did not track their deferred patients.

NIP suggested the following questions for ACIP discussion:

- Should the recommendations be less complex?
- Is tailoring them to the level of shortage too confusing?
- Can provider adherence be improved, particularly among those practices without shortages?
- Would providing more information to clinicians be useful? Would parental education about a shortage?
- What information or tools could be provided to help clinicians track deferred patients?

*Discussion* included:

- *Are there data on health department compliance or on the characteristics of practice staff (e.g., age, size of practice, presence of an NP, etc.) to tailor the educational efforts? The practicing community has many misunderstandings of the ACIP recommendations.* Health department adherence was not directly assessed, but they were asked if they followed any recommendations other than ACIP's. About 10% did so, indicating that most pediatricians did not have an alternative recommendation to follow. The demographic predictors were also not fully explored. This was designed to pick up a national sample of pediatricians, mostly urban or suburban, but the data could be re-reviewed to check gender, age, practice for >10 years, etc. The comprehension problems are a communication issue. More pediatricians thought they were adhering to the recommendations than actually were, according to the scores. The complexity might factor in here.
- *The 85% of practitioners with a cumbersome tracking system, or none at all, is discouraging.*

- Registries would help.* Some software could be developed to be user-friendly, but the 50% using a manual system may not use it even if it were free.
- *Pediatrician self-report does not always match reality; will you check records? And is there any way to measure the percent of children who had not received at least one dose by 6-12 months?* CDC will follow up with a chart audit, through the new vaccine surveillance network in Cincinnati, OH, to see if practices match what was reported. The recommendation was designed to ensure equal distribution and at least partial vaccination among as many children as possible, but whether that happened remains unknown. The NIS data may be able to assess to some degree how many children received the vaccine, adherence to these recommendations, and the response to the DTaP4 shortage as well.
  - Mr. Phil Hosbach, of AventisPasteur, commented on the importance of the clarity and frequency of CDC messages to the states about vaccine supplies and schedules. The increase of influenza vaccination supports that.
  - *What will be the process if there is another shortage, and what can be prepared to respond faster and better?* Dr. Wharton cited the NIP's success in convening the committee on short notice to address such issues. When not possible, CDC issued recommendations and advised the committee as soon as possible when a shortage occurred. This episode also teaches that asking providers to assess the severity of the shortage is less effective than giving clear prescriptive guidance. Dr. Orenstein agreed; the former was too complicated and many physicians did not realize they had a shortage until an order failed to come on time. But the NIP's funding to build stockpiles should have them in place by 2006 for all childhood VPDs.
  - Dr. Levin noted that the ACIP needs education in order to advise on such decisions. He hoped to have the relevant information as soon as possible, and some things could be done in advance. For example, work on recall could be done not only with physicians but also the nurses who often make these decisions and work at the computer). And, if physicians are making decisions on OM and the third or fourth dose, relevant advice could be provided them earlier. He also noted that in Colorado, some public health funded multi-practice audits have been done, and those large databases could provide some of the data suggested on this day. Finally, he asked the academies if they could do anything specific differently, aside from promulgating the recommendations, to better reach their members. Dr. Rennels responded that the NIP website was helpful, but the issue was that the pediatricians could not know if they would have a moderate or severe shortage.
  - Dr. Mahoney lamented another missed opportunity to work with family physicians to answer the question of whether the message is getting through. He emphasized the need to collaborate. Dr. Broder agreed; the need for speed to collect data during the shortage also prevented collaboration with midline practitioners such as nurses and physician associates. The focus on pediatricians was because most children are immunized by them.
  - *Once the shortage is corrected, how long would it take to get back to the regular schedule? Many pediatricians are still operating as if there is a shortage.* The Cincinnati study will look at adherence with catch-up recommendations, but perhaps not at resuming the regular schedule. The NIS might indicate that. Mr. Mason noted the publication (weekly and biweekly) of vaccine-specific updates. All vaccines are currently available, except for some specific package presentations (e.g., syringe or vial).
  - Mr. Hosbach suggested use of the manufacturers' reach, by placing the *MMWR* announcement in with their shipments to states. That could be forwarded to the physicians with their shipments as well.
  - Dr. Zimmerman noted the disparity of beliefs reported about reminders and recalls by practice staffs. This may be because they remember doing so for one vaccine (e.g. influenza one year but not the next) and interpret that as standard policy. The answer to such uncertainty is standing orders.
  -

## **Post-licensure Effectiveness of Heptavalent Pneumococcal Conjugate Vaccine in U.S. Children**

Presenter: Dr. Tamara Pilishvili, NCID

*Background.* A case-control study was done to examine the effectiveness of the seven-valent pneumococcal conjugate vaccine (Prevnar™) in U.S. children. It was licensed for use in infants and young children in early 2000, and the ACIP recommended its use that fall. Controlled clinical trials demonstrated high efficacy of the vaccine against invasive disease when given as a four-dose regimen to infants.

It is particularly important to assure vaccine effectiveness during a supply shortage. To assess that in real life settings of missed doses and catch-up regimens, CDC examined the post-licensure data on effectiveness against invasive disease among children aged 3-23 months. The secondary objectives were to: 1) measure the effectiveness of the vaccine against disease due to seven vaccine serotypes both individually and as a group; 2) measure effectiveness against disease due to serotypes not included in the vaccine but for which vaccine may provide some protection; 3) assess evidence of vaccine leading to higher risk of invasive disease due to non-vaccine (replacement) serotypes; and 4) to measure effectiveness when vaccine is given as “catch-up” regimens.

Cases of invasive pneumococcal disease were identified at eight of the nine routine data collection sites of CDC’s Active Bacterial Core surveillance (ABCs) system. These data are population- and laboratory-based. Surveillance staff regularly contact laboratories to identify new cases and collect isolates for data aggregation at CDC.

The methods used included: a case definition of pneumococcal disease (isolation of pneumococcus from a normally sterile site), selection of the vaccine cohort (3-23 month-olds) and three controls each (identified through birth records by DOB and zip code), data collection, and analytic methods (conditional logistic regression and vaccine efficacy adjusted for the presence of underlying conditions).

To date, 318 cases and 1002 matched controls have been enrolled. Of the cases, 131 match the vaccine serotype and 59 were vaccine-related types (serogroup but not serotype). Isolates for the 15 more possible cases are pending. At least one dose of conjugate vaccine was received by 55% of the cases and 79% of the controls, and 29% of cases and 37% of controls received 3 or 4 doses.

Data were charted to demonstrate the statistically significant VE:

- Overall VE was 77% against invasive disease and 94% against disease due to the seven vaccine serotypes. These findings parallel clinical trial efficacy data: identical for all vaccine types and very close serotype-specific estimates. This was interesting since nearly all the children in the Kaiser clinical trial received a full 4-dose regimen, while many of those in this study had incomplete schedules.
- VE for all vaccine-related serotypes was measured at 70%, and for specific serotypes ranged from 40% (but with wide confidence intervals) to 87%. No effect was seen against serotypes not in or related to the vaccine, inferring that replacement disease was not a significant problem to be expected.
- VE was 87% with two doses for those children starting vaccination at 12-23 months of age, and 100% with three doses for children on the ACIP catch-up schedule.
- In addition to evaluating the ACIP recommended “catch-up” schedules, vaccine effectiveness for children immunized with 3-dose infant schedule and other incomplete infant regimens was also evaluated.
- VE was 96% for children immunized with a 3-dose infant regimen, as well as those receiving two doses before 6 months of age. For those who received only one dose at <6 months, VE was ~78%. Although this last VE estimate is lower than the first two, the difference is not statistically

significant.

*Conclusion.* In summary, Prevnar™ was shown to be highly effective in preventing invasive pneumococcal disease (IPD) due to the vaccine serotypes and the vaccine-related serotype 6A, but not 19A. No increase in risk of disease due to non-vaccine serotypes was found, and the vaccine is effective when given on a catch-up schedule. The study's findings added important new information on the effectiveness of catch-up schedules. It demonstrated that, while fewer than recommended doses may be adequate in protecting against invasive disease, receipt of a full series may be needed to reduce pneumococcal carriage and for other important vaccine effects.

### **Epidemiology of IPD in the U.S.**

Presenter: Dr. Cindy Whitney, NCID

In 1998 and 1999, before Prevnar™ was licensed, children aged <1 year had the largest disease risk for Invasive Pneumococcal Disease (IPD), at ~210 per 100,000, followed by those aged >1 year (~170/100,000). These rates dropped 80% and 70%, respectively, by 2001. And in 2002, a 72% decline in risk occurred among those <2 years old, as well as significant declines not seen in 2001 for those aged 3 (29%) and 4 years (39%).

The changes by vaccine type showed a reduction of 92%, from 156 per 100,000 to 12/100,000, and 50% for vaccine-related disease. Interestingly, late trends indicate a significant increase in non-vaccine-type disease. But the rates increased only from 12 to 16/100,000, and while statistically significant, it is not significant from a public health standpoint.

Similar declines were charted for those ≥65 years, down 29% in 2002; down 20% for those aged 40-64 years; down 46% for those aged 20-39 years; and down 23% for those aged 5-19 years. Transmission is interrupted; these data indicate a real herd effect. The evidence is even stronger by serotype. In 65 year-olds, vaccine-type disease dropped from 134 to 18 per 100,000 (-47%), THIS PERCENTAGE LOOKS WRONG FOR THE NUMBERS PRECEDING with little change in non-vaccine-type or vaccine-related disease. In those aged 20-39, the drop was 64%, again with little change in non-vaccine-type or vaccine-related disease.

*Discussion* included:

- *Were declines also seen in the <1 year-old age group who were not yet vaccinated? That might support the herd effect.* There are so few cases in that age group, an effect is hard to see, but a small one is evident.
- *Did you control for changes in prevalence in vaccine receipt among those aged 65+ years?* Two lines of evidence show that this is not an effect from the polysaccharide vaccine. The types only in the polysaccharide vaccine and not in the conjugate have fairly constant rates of disease. And, just by doing the math, it is clear that during the time of the study, a 10% increase in coverage (from 50% to 60%) of a 50% effective (polysaccharide) vaccine that covers 80% of serotype would show a few percent points change at most.
- *The VE study showed 1-2 doses to be effective, but was this from a short post-vaccination period (1-2 months) or longer duration of follow-up?* This analysis involves a younger age group (3-23 months), so the duration of protection is very short after the last dose. Extended duration of protection is not known. *It would be interesting if one dose protected to 23 months as opposed to just the period between the 2- and 4-month dose.* Children were enrolled from the time of case onset, so the only period available for analysis is that between vaccination and case onset. Different regimens could be examined. Most regimens will be a longer period to the next dose.

## **Pediatrician Non-Adherence to National Immunization Recommendations after PCV Introduction**

Presenter: Dr. Karen C. Lee, Harvard University

*Background:* Previous studies have examined whether children were up to date with their immunizations. But none tried to determine pediatricians' own adherence to national immunization recommendations for routine infant vaccines. Also unknown is the effect of an increasingly complex infant immunization schedule on pediatricians' immunization practices.

To answer these questions, a study was done with two objectives: 1) to characterize pediatrician adherence to 2001 national immunization recommendations after the introduction of pneumococcal conjugate vaccine (PCV), and 2) to describe the impact of PCV introduction on recommended health care utilization and delivery of existing vaccines.

A survey was mailed in summer of 2001 to 691 randomly selected pediatricians in Massachusetts. A universal purchase state, the state health department provides all vaccines used by both public and private providers, but not the combined Hib-HBV vaccine. The survey was done a year after PCV was introduced and before any shortages. The response rate was 71% (N=393 providers).

The survey questions and responses were as follow:

- Were routine visits added because of PCV, and if so, what type? 15% said yes; 22% for well-child visits, 67% for vaccine only, and 6% for both.
- Were other vaccinations moved to other visits because of PCV, and if so, were they moved earlier or later? 38% did move some, usually hep B, and to later visits.

Using these data, the projected impact of PCV on preventive health care costs was estimated. With the addition by 15% of pediatricians of at least one routine visit due to PCV, an estimated 570,000 of the 3.8 million annual birth cohort will have at least one additional visit. Nationally, this could add at least \$20.8 million per year to health care costs, without including the remaining 5% of pediatricians who added some "other" type of visit.

The physicians were given a grid of the recommended childhood vaccines to see if their self-reported immunization practices matched the recommendation. They were asked to check off the ages of routine infant immunizations given (0,1,2,4,6,9,12,15,18 months). The 2001 harmonized recommendations were not sent along. The respondents were not advised to refer to them or other guidelines, nor were they explicitly discouraged from doing so.

The 2001 national immunization recommendations could involve over 10,000 possible combinations for giving all seven routine vaccines. Not surprisingly, the 381 responses reported 209 different schedules for all of them.

Nonadherence to the recommendations for *specific* vaccines was defined if either an inappropriate number of doses of a given vaccine was reported, or doses at unrecommended ages. Pediatricians were classified as nonadherent to *overall* recommendations if their reported schedules were inconsistent with recommendations for at least one routine childhood immunization.

So many pediatricians reported nonadherent patterns for PCV (21%) that the study also looked at nonadherence to non-PCV recommendations (i.e., inconsistency with at least one immunization recommendation other than PCV). PCV led with 21% nonadherence, but pediatricians were also nonadherent for HBV and Hib (11%); and DTaP and IPV (5%).

To demonstrate pediatrician nonadherence, DTaP patterns of immunization were used as an example. The first three doses should be given at 2,4,6 months, and the booster dose at 12-15-18 months. Of 20 respondents, 12 were mostly adherent to this schedule but did not report giving a booster dose. The others reported giving the first dose at 1 month; the 2<sup>nd</sup> and 3<sup>rd</sup> doses late, the whole series early, the primary series early, the first 2 doses early with no booster doses, or only 2 of 4 doses.

Overall, 36% of pediatricians' schedules were not adherent for at least one childhood vaccine; 27% were nonadherent to guidelines (not including nonadherence to booster doses of PCV, DTaP, and Hib). Movement of other vaccination earlier or later might have resulted in nonadherence. Of those who moved the hep B vaccination, 21 of 27 reflected deviations that were consistent with the directions in which HBV had been moved, and similar patterns were seen for DTaP, Hib, and IPV.

A univariate analysis revealed the factors associated with non-adherence:

- Movement of other vaccines and addition of routine visits because of the introduction of PCV.
- Offering to give shots later when multiple injections are due.
- Proportion of Medicaid patients.
- Each additional decade elapsed since medical school graduation raised the respondents' likelihood of nonadherence by 1.5-1.7 times.
- Practice setting and predominant payment method (fee for service versus capitation) were not significantly associated with nonadherence.

The study conclusions were that:

- More than one-third of pediatricians were nonadherent to national immunization recommendations for at least one routine infant vaccine.
- The addition of PCV may have had unintended effects on well-child care, including the addition of routine visits, movement of other vaccines to generally later visits, and potentially decreased adherence to national immunization recommendations.

The study limitations included:

- The study's findings may be generalizable only to all Massachusetts pediatricians. They cannot get the combined Hib-HBV vaccine through Massachusetts' universal purchase program, so they might have been more likely to add visits or move vaccines than those in other states where this combination vaccine is used. On the other hand, since there is only one vaccine formulary in Massachusetts, there may be even greater variation in immunization practices among providers in other states.
- The study did not assess the participants' pre-PCV immunization practices; "educated inferences" were made about the actual impact of PCV on recommendation adherence.
- Self-reported behavior may not match actual clinical practice.
- If the respondents gave socially-acceptable answers that would bias against variability in reported practices, the study may have underestimated. Conversely, it may have overestimated nonadherence if a substantial number of participants did not carefully complete the survey; missing data may have classified them as "nonadherent."
- Pediatricians who need to consult the guidelines may have been less able to describe their immunization practices without doing that.

*Discussion* included:

- Dr. Peter cited an NIP study indicating that only 10% of all children receive all recommended vaccines at the scheduled age, so adherence is historically low. And, in view of the fact that Massachusetts in 2002 had the highest rate of completion for vaccinations of 2-year-olds, the issue is whether PCV will lead to a lower completion of the schedule. Preliminary 2002 data indicate that it will not, but he was also interested in the experience of other states. Dr. Lee

- reported another multicenter study being done to evaluate whether immunization rates dropped due to PCV introduction. Preliminary data also indicate no effect.
- A different geographic area and methodology than this study, the Rochester study, also reviewed medical records. Its preliminary data also indicate an increased number of injections given with PCV, no delay to other vaccines' administration, and no decrease of total or well-child visits.
  - Dr. Martin Myers agreed that extrapolating from pediatricians does not reflect all vaccine delivery to children. Thought is needed about different delivery venues as well, and about whether some vaccines are more important than others. Perhaps the ACIP should advise on priorities of which ones should be delayed in a shortage, to help vaccinators develop a practical schedule. With influenza vaccine being introduced, and the impact of PCV, unintended consequences need to be avoided (e.g., DTaP being given in a nonadherent fashion).
  - Dr. Orenstein commented that this study was done before Pediarix™ was introduced; it would be interesting to know what difference that would make. And, with VPDs at near-record lows for rubella, tetanus, and polio, a good look at what is necessary to change things is needed before doing anything radical (e.g., advising on which to delay). Dr. Wallace added that pertussis rates have been stable for the last two decades.
  - Dr. Paradiso commented that Wyeth's data on utilization rates for booster doses in the second year indicate the lowest compliance with fourth dose. There is no guidance about which vaccine should be given, and when, over an 18-month period.
  - Dr. Santoli raised the study's findings on the impact of PCV on acute care, especially among febrile infants, and the use of blood cultures. NIP feels reassured by disease rates that are not rising, but it is important to know what physicians are doing about blood cultures. Dr. Lee reported that physicians were asked how they would deal with a well-appearing 8 month-old girl with fever (102.5°F) for two days, no focus of infection on exam nor history of exposure to viral infection, no chronic conditions, stable family and reliable follow-up, both before and after PCV was introduced (assuming she had received three doses). Providers were less likely to order blood or urine cultures or CBC than they were previous to PCV's wide use. This has implications for surveillance of invasive infection. And the fact that providers reported a change in urine testing, in view of the fact that PCV has no known effect on urinary tract infections, is also of concern.
  - *Did you ask the pediatricians surveyed if they knew the child had or had not received PCV?* Two back-to-back questions in the same survey were asked of the same respondents: how they would approach this infant a year ago before PCV's wide use; and then, for a child who had received it, how the respondent would have managed the febrile infant.
  - Dr. Levin asked several clarifying questions of Dr. Lee, revealing the survey's assumption that the reason for the extra visit was because the caretakers did not want the child to receive an extra shot. The survey did not ask if there was a computerized system to indicate needed immunizations, which would help, nor did it determine if the nurse practitioners interviewed were in the same office as the pediatrician. It would be interesting to know if they provided different answers. And finally, it was assumed that the physicians treating a higher proportion of Medicaid patients might be in less affluent areas or more likely to be at academic health centers. But the effect of Medicaid followed no trend regarding adherence or nonadherence for those seeing 25-50% Medicaid patients, so that would not necessarily prompt any recommendations. It might have been hypothesized that those in academic health centers or HMOs with centralized guidelines might be more consistently adherent to recommendations. The study may have been underpowered to find those differences in the practice setting, but they did find the greatest magnitude of decreased testing in the management of a febrile infant in those settings.
  - Dr. Modlin was concerned to hear that pediatricians might be altering their practice for febrile infants due to the introduction of PCV. Any survey involves changes in answers based on prompting; it is an important issue to find out to what degree practices might have changed. The NIS should be able to survey actual practice through its full records for ~2,000 children each

- year.
- *Is there any hope for a computerized program to help practices immunize?* Dr. Pickering said yes, but challenges include the compatibility of present hardware in physician offices to download software and the need for programs able to address the multiple reasons a child may be behind on immunization. There is still a lot of software development and hardware acquisition to be done, as well education to the physician on how to use it. Anything offered would have to be clearly helpful and easy to use. Dr. Birkhead added that many states are moving toward web-based applications that do not require software, but can be available to anyone using a Web browser.
  - *Please comment further on the physician's age aspect in the findings; and do you expect similar events to the PCV findings when influenza vaccine is introduced for those aged 6-23 months, or will you do a comparative study?* It is disconcerting that time since training was most strongly associated with nonadherence. There could be focused efforts towards those pediatricians in practice longer to support continuing medical education, perhaps more rigorous board certification, etc. And there are no current plans to do an influenza vaccine introduction study. Hopefully, the ACIP discussion will adequately prepare physicians for pending recommendations.
  - Mr. Hosbach stated that AvP will publish best practices to help pediatricians implement the full recommendation for influenza vaccination.
  - *How much influence on current immunization practices does a recertification exam have on physicians?* Dr. Mahoney stated that this is on the exams, but the breadth of knowledge is so extensive that this is only a small component. This aspect is another opportunity for the AAP and AAFP to develop and disseminate such collaborative materials as computer programs.

## **FEBRUARY ADVISORY STAKEHOLDER ENGAGEMENT SURVEY**

Decision/Presenter: Dr. John R. Livengood, Acting Executive Secretary

The General Services Administration (GSA) contracted an evaluation of Federal Advisory Committees by the Gallup organization. They surveyed selected members, recipients of their advice, and other stakeholders in the process. Intra-agency and government-wide comparisons were made of scientific and other types of committees. The idea was to establish a plan to continue to improve the advisory committee process and its outcomes. For the survey of the ACIP, the members were asked to select one or two areas of focus on improvement for the next year, which then will be reported annually.

The survey included 25 items that were grouped into measures of people, process and outcomes. Eight respondents from ACIP were polled and individual responses were confidential. A rating scale of 1 to 5 was used, with 5 being strong agreement that the attribute applied to the ACIP.

*Overall Results.* The one universal agreement was that the work of this committee should be made widely available to others. The ACIP ranked well above other agency and other government-wide committees with a mean average of 4.55. Particular strengths were in overall satisfaction (75% strongly agreed), and 88% would work with the Committee again. The people and outcomes associated with the ACIP were rated more highly than the committee process itself. ACIP was rated by the GSA as a “best practices” committee. One possible ACIP activity could be to determine what factors so qualified it, and disseminate that.

The items with a *low* proportion of “strongly agree” responses were: meets often enough (38%) at three times per year; the recommendations are used effectively (50%); the committee helps to make the agency more effective (50%); the committee has access to adequate resources (57%); sufficient feedback is provided from CDC (57%); and that the operating procedures are fair (63% – this related mostly to the

expression of minority opinions).

The mean scores of items with a “low” score (but still well above the mean satisfaction level of other departmental and government-wide committees) were that the committee has access to adequate resources (4.14), meets often enough (4.25), protection of majority and minority opinions (4.25), is provided sufficient feedback (4.29), has the right mix of individuals as members (4.38), and makes the agency more effective (4.38).

A chart was provided (an Importance-Performance Leverage Analysis) to correlate primary and secondary priorities and major or minor strengths of the committee. This visually charted which drivers were most correlated with satisfaction with the overall process, that is, those with higher performance ratings. It also demonstrated the drivers with lower performance ratings in terms of major/minor strengths, but still of high priority. Of these, four stood out: that recommendations are used effectively, the committee helps to make the agency more effective, fair operating procedures, and the right mix of individuals. Dr. Dixie Snyder, who remains the ACIP Executive Secretary, requested particular attention to the last. It may be that fewer state and health department representatives are needed on the committee. The charter requires that committee membership be fairly balanced in terms of points of view and adhere to term limits. It was recently amended to prevent members from serving more than 180 days after the end of their term, rather than remaining until they are replaced. DHHS policy is to avoid excessive individual service and to reduce the waiver requests submitted to date. The guidelines require that members serve no more than 4 years on any committee, no more than 8 years out of 12 on any committees, and be on no more than one committee at a time.

*Discussion* included:

- State and local representation has continued to decrease over time. CDC’s previous suggestions of additional such members in the next round of appointments were not well received by the DHHS. The committee ranked this issue quite high on the survey, but its ability to influence membership is questionable.
- Dr. Modlin raised the committee’s ability to meet by teleconference between meetings or before or after the formal meeting. The committee can extend the hours as necessary. He thought it unlikely that the members would be willing to sacrifice more than three weekdays to attend. He appreciated the committee’s great strength of its broad representation, including an entire spectrum of individuals, groups and organizations with state immunization programs. More of the same would only further the ACIP’s mission.
- Dr. Finger stressed the need to preserve areas in which ACIP ranks high and to ensure that they are not threatened. The IOM’s suggestion of a significant change in how the ACIP operates was of concern to him. It must be ensured that the science base of this committee’s reputation is not diluted or disrupted. The membership rated itself high on this; that alone could be used as a response.

Specific suggestions were:

- Dr. Zimmerman hoped for attention to clarify the role of the workgroups, including the responsibilities of the Chairs, more guidance for them, and the resources available to them.
- Dr. Birkhead commented that knowing if and how the ACIP recommendations are used is of interest, in terms of the ACIP’s scientific mission (i.e., if they are clear or confusing and how effective they are).
- Dr. Levin hoped to reduce the time lag between member nomination and approval, and for earlier provision of information (e.g., options and their rationale) related to the decisions likely to be requested at the meeting. They often do not have full input until the day a decision is needed. That kind of efficiency also is measurable.
- Dr. Finger asked for a quicker release of the meeting minutes, perhaps about mid-cycle. This

would fall under the feedback category. Dr. Foster asked for the minutes and meeting materials (e.g., handouts) on a CD ROM rather than hard copy.

- Dr. Myers suggested that the meeting agenda be posted on the website, an element of “communicates effectively.”

*New members.* Dr. Livengood outlined the nomination/appointment process. A solicitation of nominations will be sent out for the four positions to be open in 2004. After conflict of interest screening of the nominations received, a packet of nominees is sent to DHHS by the end of January. Once that is advanced, it is unclear how the process works. The names are returned as approved, or requests are received for nominees with certain attributes, or names of other nominees may be received from Washington. To broaden the reach for committee members, the White House has requested specific actions to ensure balanced points of view and to term limit adherence, as outlined previously. CDC will try to avoid waiver requests for members, but it is ironic that a committee commended for its best practices still needs to change them. However, there may be ways to work with this, such as re-inviting a member after a period of absence from the committee.

Dr. Gellin reported that NVAC works under the same rules and term limits, and asked for nominations as well (letter and CV) for that committee.

## **RECOMMENDED ROUTINE AND CATCH-UP SCHEDULE FOR 2004**

Decision/Presenter: Dr. Greg Wallace, NIP

The Recommended Childhood and Adolescent Immunization Schedule for the United States, 2004, was presented. The committee’s opinion was requested on:

- *Influenza:* the preferred abbreviation for the inactivated trivalent influenza vaccine (TIV or IIV), and on changing from the current “encouragement” to a full recommendation. If the latter, the following sentence would be inserted with the appropriate *MMWR* citation: “Beginning in the Fall 2004, healthy children age 6 to 23 months are recommended to receive influenza vaccine.”
- *Influenza vaccine abbreviation.* Historically, “trivalent” was included in the TIV acronym used, although at that time a monovalent was used. IIV may be better, but it may look like a Roman numeral. Dr. Levin agreed and preferred TIV, which Dr. Rennels also noted is most used by the AAP. Dr. Deborah Wexler, of the Immunization Action Coalition, reported their use of “LAIV” for the live attenuated trivalent influenza vaccine. That could be confused with TIV, which may be why “IIV” was chosen for the inactivated vaccine. Dr. Baylor noted that TIV is used in the vaccine package insert and advocated consistency.

*Decision:* The consensus was to use TIV.

Considerations on implementation included the need for AAP board approval, which is difficult to get before the schedule is due at the printer by January. Dr. Wharton thought that adding the recommendation to a lengthy footnote would have little effect. If the committee wishes to communicate this recommendation in the fall, it would be better to reformat the 2004 schedule to show the routine recommendation for 6-23 month-olds in anticipation of the influenza season, and moving it above the schedule’s red line to list it as a recommended vaccine. There was some question as to whether the current schedule could be changed in time for approval at the January meeting. The schedule would be changed in June 2004 to begin in July, with the title changed to either January to June or January to September.

Dr. Wexler stressed the need to be clear that the “I” in TIV stands for “inactivated,” as specified in the

package insert, and not “influenza.” Dr. Curlin asked what would happen if a live attenuated vaccine is developed for the younger age group. The schedule language may have to be changed again. Dr. Wharton responded that both vaccines would be addressed in the footnote; the chart just shows the need for influenza vaccine.

*Conclusion.* The conclusion was to label the recommendation for the first half of 2004. A new schedule harmonized with the academies will be addressed at a subsequent ACIP meeting.

Dr. Zimmerman suggested that the schedule title validate the schedule to September, since the AAP and AAFP boards could not approve the harmonization until June. Dr. Mahoney reported that the AAFP can expedite a recommendation within a couple of months, but perhaps not the AAP’s structure. Dr. Rennels reported that the AAP’s process involves other committees’ review before a proposal goes to the board, but this probably could be done within six months.

Mr. Hosbach noted that AvP’s vaccine ordering process begins in March, so the faster the recommendation is communicated, the better. Dr. David Newman, of the National Partnership for Immunization, noted that April includes National Infant Immunization Week, when it would be easier to communicate the influenza recommendation.

Dr. Wallace suggested dating the schedule for January to June; the next one could be issued earlier than June if desired. Dr. Orenstein expected no major changes, mostly the schedule would be rearranged. The Workgroup could be empowered to approve the minor changes anticipated without having to go back to full committee.

*Conclusion:* The sentence about influenza will not be inserted in the schedule. Other small changes from the June meeting were to include changing the bar for PCV, add a sentence about VAERS, adding a sentence about the timing of the last dose for DTaP, Hib and PCV, and adding language about LAIV. All were agreed to in June.

*Catch-up Schedule* There were no changes from last year.

## **MENINGOCOCCAL WORKGROUP UPDATE**

Presenter: Dr Reginald Finger, Chair, Meningococcal Workgroup

*Background:* The latest ACIP statements on meningococcal polysaccharide vaccine (MPV) were published in 1997 (general) and 2000 (for college students). The latter is probably the cause of the gradual increase in MPV uptake. The ACIP reached consensus in June 2003 to encourage clinicians to educate parents about the disease and vaccine.

Conjugate vaccines have been and are likely to be more effective than polysaccharide vaccine. The monovalent Group C vaccine is being used with success in the United Kingdom, but several meningococcal conjugate vaccines are in development in the U.S. At least one licensure application is expected to be submitted before the end of 2003.

Formed after the June ACIP meeting, the Meningococcal Work Group was charged to follow up on the June consensus decision and to prepare for arrival of meningococcal conjugate vaccines. It has three voting members of the ACIP, several liaison meningococcal expert members, and other organizational representatives. A conference call was held in August and the Workgroup had met on this morning. The issues being considered are:

- Who will implement the education campaign and how will it be paid for? (NIP is addressing this

now.)

- What happens if education about MPV is highly successful but there is inadequate availability of or accessibility to the vaccine? (Not solved; the Workgroup is addressing this.)
- How fast are the MCVs going to become available? (The Workgroup will write to the five manufacturers known to be working on it to request a slide set on their progress. This will be used to educate the Workgroup via a computer-assisted conference call and to begin forming policy in preparation for FDA licensure. The Workgroup will report on that in February. Dr. Finger suggested that Dr. Rosenstein and her EIS officer, Dr. Winger, give a presentation with a more complete account of the epidemiology of meningococcal disease
- Is adolescent vaccination with MCV conceived as a “catch-up” or a long-term phenomenon? (The Workgroup expects that this vaccination may be longer-term than expected, as seen with hepatitis B vaccine.)
- What is the best venue for pulling together the latest and most accurate information about the MCVs? (The conference call will begin that process).

*Discussion* included:

- Dr. Trudy Murphy suggested that the Workgroup define what constitutes “adolescence” and also consider the best way to protect infants and neonates from meningococcal disease.
- Dr. Pickering hoped that the presentation to the ACIP would include the successes of those vaccines in the countries where they are utilized, as well as their availability.
- Dr. Paradiso recalled ACIP discussion in years past of what age to target for meningococcal vaccination. That involves different serogroups, which affects the epidemiology of disease control in the U.S.
- Dr. Bill Atkinson, of the NIP, stated that the *MMWR* article about vaccination of microbiological workers dealing with occupationally invasive meningococcal disease was vague. That led to interpretation by lab directors to vaccinate all lab workers, which he feared was unnecessarily using a lot of meningococcal vaccine.
- Dr. Levin requested more details about the educational program in the upcoming presentation. Dr. Gellin suggested that the Workgroup check with Dr. Salisbury, ACIP’s liaison from the London Department of Health, for the U.K.’s experience.
- Dr. Baker suggested beginning the education within the context of the current ACIP recommendation to “encourage” education of college students. Whether or not to expand that target group could be discussed later.

## **HEPATITIS SESSION**

### **Corrections to VFC Hepatitis B Resolution**

Presenter: Dr. Bill Atkinson, for Dr. Eric Mast

*Background:* The ACIP’s February VFC resolution (#02/03-1) contained unintentional inconsistencies with current ACIP recommendations for the use of hepatitis B vaccines. Its purpose was to incorporate the use of Pediarix™ into hepatitis B vaccine schedules.

Changes made to correct these since then were as follow:

- Throughout the document, changed all hepatitis B vaccination scheduling options from “weeks” to “months” to be consistent with ACIP recommendations and the previous VFC resolution for hepatitis B vaccine (10/01-2).
- Page 2: Changed the title of “Option 1\*” with the asterisk as a footnote to “Option 1 (Preferred)” to highlight the ACIP’s preference for a birth dose of hepatitis B vaccine.
- Page 3: In the section on Infants born to HBsAg-negative mothers, deleted “The 3<sup>rd</sup> dose of

PEDIARIX™ should be given at least 16 weeks after the first dose, preferably at 6 months of age but not before 14 weeks of age” to be consistent with the amount of information given for COMVAX™ and the minimum intervals presented on a separate table. The same change was made for infants born to HBsAg-positive mothers and infants born to mothers with unknown HBsAg status.

- Page 4: Changed the Table footnote for infants born to woman whose HBsAg status is unknown, from: “Only a single antigen hepatitis B vaccine is given at birth. Hepatitis B immune globulin (HBIG) should also be given to all infants within 12 hours of birth – 0.5ml administered intramuscularly at a site different from that used for vaccine,” to “Single antigen hepatitis B vaccine should be given within 12 hours of birth. Maternal blood should be drawn as soon as possible to determine the mother’s HBsAg status. HBIG (0.5mL) should be given as soon as possible (no later than 7 days) if the mother tests HbsAg-positive.” This was done to be consistent with existing ACIP recommendations for management of infants born to mothers with unknown HBsAg status (*MMWR* 1991;40[No. RR-13]:1-25).
- Pages 6-7: Updated the section on Contraindications and Precautions to be consistent with the existing ACIP General Recommendations on Immunization (*MMWR* 2002;51[RR-02]:1-36).

One conflict remains. The minimum age for dose 3 on page 6 states that it not be given before 24 weeks of age, while the General Recommendations say not before 6 months of age. The Division of Viral Hepatitis strongly believed that there are sufficient data to support a dose at 24 weeks as opposed to 6 months.

*Discussion* included:

- Ms. Diane Peterson, of the Immunization Action Coalition, pointed out that the harmonized schedule just approved provides a minimum age of 6 months for the third dose, but this resolution states 24 weeks. When computers are programmed, 24 weeks (168 days, with a 4-day grace period allowed, or 164 days) and 6 months (182 days or with the grace period, 178 days), a discrepancy of four days is a big issue, especially for registries.
- The Division had data to present on this issue, but an agenda change prevented that from happening. Dr. Zimmerman was uncomfortable with making a policy decision without seeing supporting data. Dr. Wexler observed that children do arrive a week early for the six-month last dose of hepatitis B vaccine, so it would not be counted as valid, but the four-day period provides some flexibility. The minimum interval table in the General Recommendations allows other vaccines such as DTaP dose 3 and IPV to be administered up to four weeks earlier than six months of age. She advised against a more rigid schedule that would make hepatitis B vaccination’s four-day window the only outlier on the schedule.
- Dr. Orenstein asked, given the 90% coverage for the hep B dose 3, what epidemiological gain would come from using a different interval for this vaccine. Dr. Atkinson cited the opportunity to avoid unnecessary fourth doses. Dr. Mast had assured him that no data support 6 months as a magical time period, but it does increase parents’ and providers’ flexibility to vaccinate early arrivals. In the absence of anything wrong with 24 weeks, this is a cost and recall issue; it does not matter in terms of seroconversion or titers.
- This was a time sensitive issue, due to the need to update the heavily-used VFC statement. However, the 24-week issue could be revisited. The harmonized schedule was settled in February, and the footnote has been noticed. Provider flexibility was increased and there have been no negative data since then.

Dr. Zimmerman **moved to approve the amended VFC resolution as presented**. Dr. Birkhead seconded the motion and there was no further discussion.

## **VOTE: VFC RESOLUTION**

Conflicts: Drs. Poland and Levin were conflicted with a vote involving Merck and GlaxoSmithKline. Since that prevented a quorum, the ex-officio representatives were asked to vote.

In favor: Birkhead, Campbell, Deseda; Finger, Gilsdorf, Zimmerman, Curlin, Phillips, Green, Gellin, Groom, Evans.  
Abstained: Baylor, Poland, Levin  
Opposed: None

**The vote passed.**

## **Hepatitis B Data Relevant to the Immunization Schedule**

Presenter: Dr. Eric Mast, NCID

The VFC resolution contained other edits to the contraindications and precautions. These were minor changes to be consistent with the General Recommendations on immunization, and were to be distributed to the Committee.

The Division of Viral Hepatitis had always supported a minimum age of 24 weeks for immunization to allow clinicians to give that dose at the six-month visit. That is how the recommendation was over time, but there was some confusion about that between the VFC documents, the General Recommendations and what is in other ACIP statements.

There are immunogenicity data from the many countries worldwide that vaccinate at a 6, 10, 14-week schedule. Those data showing equivalent seroprotection with lower antiHBs titers provided from such earlier intervals. The schedules abroad could support efficacy at that use, and the presence of high antibody levels after 24 weeks. There are no long-term protection data with those schedules for vaccination at <4 months of age. The programmatic issue of defining 6 months of age led the Division to advocate a footnote say specifying >24 weeks and placing 6 months on the chart, as done by the AAP.

Registry system algorithm coding would have to change to avoid immunization too early. However, agreeing to 24 weeks would exclude less children and avoid unnecessary fourth doses. Dr. Groom reported that the IHS is finalizing their coding. This is not an insignificant process, but it is done, and the forecaster used in the system is able to change along with the recommendations. She thought the 24-week option to be in the best interest of eliminating missed opportunities and unnecessary fourth doses.

## **HIV Vaccine Workgroup Update**

Presenter: Dr. Guthrie Birkhead, Chair

The HIV vaccine working group held its second meeting on October 14. They heard updates on the Vaxgen gp120 U.S. trial analysis, the Vaxgen gpP120 trial in Thailand, a presentation on the new Alvac Phase III trial in Thailand, an update on other candidate vaccines in development. They also reviewed lessons from the implementation of the hepatitis B high risk recommendations to inform how to approach the development and implementation of HIV vaccination recommendations or guidelines.

### **Vaxgen gp120 U.S. Trial Analysis**

The U.S. government sponsored an analysis committee with representation from NIH, CDC, and others, to: 1) verify the Vaxgen trial results (completed and verified), 2) correct for the multiple comparisons done by Vaxgen in the course of examining groups (complete: the chance of VE found by minority status was 8%; VE by chance for black population status was 22%); 3) examine the randomization process to ensure equal distribution of risk factors between the vaccine and placebo groups (done – none were

found); and 4) examined differential loss to follow-up or other underlying explanations for the unexpected finding (done: the VE was higher in those with higher risk and among those with better immune response, but neither explained the higher VE found in minorities). The workgroup's conclusion was that there was no apparent biological explanation for the apparent higher VE in minority groups. There is still a very real possibility that this occurred by chance alone. NIH will host a broad consultation in December to try to reach final conclusions of the Vaxgen data's meaning.

Other HIV vaccines in development are:

The Vaxgen gp120 Thai (Vax003) trial data are expected by the end of the year.

- The Alvac Thai Phase III trial, by the U.S. Army Medical Research and Materiel Command, of a recombinant canarypox vector (Aventis) with Vaxgen's B/E strains (more common in Asia) given at 0,1,3, and 6 months, and with a boost at 3 and 6 months. Several sites in Thailand have been selected and the first vaccinations should begin in October.
- Several other vaccines are in development and should begin either Phase IIB (proof of concept) or Phase III trials by 2005 or 2006.

To begin to develop guidance for an HIV vaccine, the workgroup reviewed the experience of the hepatitis B high risk vaccination recommendations. These have not had wide acceptance or use in STD clinics, correctional facilities, drug treatment programs, or the targeted high risk adolescents, etc. CDC Hepatitis Integration Projects have begun to provide an opportunity to learn how to approach HIV vaccine implementation strategies. They are working to fund and start up hepatitis B vaccination, incorporated into drug treatment, prison and other settings. This should prove to be helpful in indicating potential HIV vaccine implementation strategy barriers, and how to address them.

The Workgroup conclusions at the end of its day-long meeting were:

- Although a licensed HIV vaccine is probably years off, preparatory steps for its use should begin now.
- CDC should work with community HIV planning groups (which have valuable community advisory committees) to educate/prepare them for the advent of HIV vaccines
- CDC should continue the hepatitis integration projects and support studies of registries or other data systems with which to track adults to aid in the implementation of the likely six-shot HIV vaccination protocol, including boosters).
- The FDA will need to anticipate issues that may arise around licensure of a partly effective vaccine approved for use among only a limited number of groups.
- Planning is needed now on methods of vaccine financing to determine how a vaccine with likely limited initial availability will be prioritized and distributed to populations.
- The ACIP HPV and HIV vaccine workgroups should work together, in light of the similar issues they face (e.g., adolescents and targeting to high-risk groups), or perhaps even merge.
- The HIV Vaccine Workgroup should liaison with the NIH HIV Vaccine Communication Workgroup and identify other appropriate groups with which to coordinate.
- The workgroup should begin work on a document to lay out the issues and a foundation for a future HIV vaccination program to describe related principles and to leave guidance for future (new) ACIP members.

*Discussion* included comment by Dr. Wexler, to Dr. Birkhead's agreement, that the low acceptance of and access to hepatitis B vaccine has little to do with the desire for it (that is demonstrated) and a lot to do with financing it.

Presenter: Dr. Rachel Barwick, NCID, for Dr. Martin Cetron

The yellow fever vaccine was released about a year ago. A slide was presented of the suspect and confirmed vaccine-associated viscerotropic cases reported to VAERS since 1990. Confirmed cases were so identified with the workgroup's case definitions. The suspect cases were so defined normally because there was no appropriate specimen available, but the cases were temporally associated with the vaccine and were otherwise clinically compatible with previous cases. This year, three new viscerotropic cases occurred, all fatal and all positive for the vaccine antigen. This was within the expectations of about four cases per 1 million doses distributed and 20-21 cases per million doses distributed among those over age 65.

The Workgroup's case definition for neurotropic disease enabled the identification of five more yellow fever cases that were initially diagnosed as Guillain-Barré Syndrome. Two other cases reported to VAERS presented as demyelinating disease; one was suspect and the other was confirmed yellow fever. About four cases per million doses are expected and 15-20/ million for adults aged >60 years.

The Workgroup will continue to refine these estimates. When asked if the ACIP wished to strengthen the wording of its recommendation for vaccine for those aged >60, there was no response.

## **AGENCY UPDATES**

***Department of Defense.*** Dr. Stephen Phillips, the new DOD liaison to ACIP, reported that their influenza vaccination program began this week and is required for all in the armed forces. DOD does not anticipate any supply problems. Beginning this year are new DOD influenza surveillance sentinel sites in the Middle East operations theater. Finally, he noted that some of the uptake of meningococcal vaccine may be due to military use, an immunization also required, as well as its use among students.

***Food and Drug Administration.*** Dr. Norman Baylor reported that there would be no VRBPAC meeting held in November. The next will be in February, 2004, and will focus on selecting the influenza vaccine strain selections for the 2004-2005 season.

***National Institutes of Health/National Institute of Allergies and Infectious Disease.*** Dr. George Curlin shared a few slides of the collaborations underway in NIAID's Biodefense Research agenda. This includes more than 50 major initiatives to stimulate biodefense research,

Industry partnerships include the Cooperative Research and Development Vaccines program, currently funding 54 awards, of which 13 are to industry. The Biodefense Partnerships program includes large industry as well as universities and small companies. The partnerships are executing the NIAID contracts for the next-generation MVA and rPA vaccines. Progressing work on a safer smallpox vaccine for use in the general population also suggests that the Smallpox Vaccine Workgroup should perhaps be restarted.

Another bad season for West Nile Virus is expected. Several NIAID-sponsored research projects were outlined. They are conducting basic research on the disease pathogen, the maintenance of WNV in nature, and on preventing and controlling its spread. Work is underway at the University of Alabama on antiviral screening to test intravenous immune globulin in a clinical trial, but recruitment is very slow for this Phase I/II random placebo-controlled trial. NIAID has also begun the first volunteer clinical trial of malaria vaccine in Mali, which was described. Eighty-four malaria vaccine constructs are under consideration in an all-department approach. The vaccine is of great interest abroad and for U.S. travelers. Finally, NIAID's cooperative research agreement helped in the formation of the FluMist™ vaccine, the first such vaccine approved by FDA.

**National Vaccine Program Office:** Dr. Bruce Gellin thanked NVPO's Atlanta staff for its work during the NVPO office's transfer to Washington, D.C. Staff positions are being filled now. NVPO's new tasks include the NVPO's task from the IOM Vaccine Financing Report to gather stakeholder input. The Vaccine Supply Workgroup will review the reports of that National Vaccine Advisory Committee's (NVAC) Vaccine Supply Workshop (held in 2001) and the General Accounting Office's vaccine supply report, to see what has occurred since these were issued. The proposal of the Wingspread Conference group was presented to NVAC, which formed a workgroup to evaluate its and other potential proposals to improve public participation in the formation of vaccine policy. NVAC/NVPO workshops in planning will explore innovative vaccine delivery modalities, led by the Office of Emergency Public Health Preparedness. In other areas, the immunization standards both for adults and for children and adolescents were published. Influenza pandemic activity has been brisk, spurred by SARS and bioterrorism concerns. NVPO has met with vaccine and antiviral manufacturers on this. Hopefully, a plan will be announced soon, as this year is the 25<sup>th</sup> anniversary of pandemic influenza preparedness. Finally, the first international neonatal workshop will be held early in March 2004 in Washington, D.C.

**Vaccine Injury Compensation Program.** Dr. Geoffrey Evans reported the escalating number of VICP claims in FY03 (2,592 versus 957 for the previous fiscal year), most (94%) of them due to the autism/thimerosal Omnibus proceeding previously described to the ACIP. The short form filing for the Omnibus hearing is proceeding and a decision applied to those cases is hoped for in 2004. At question is whether many of these cases will pass the statute of limitations of three years from the time of vaccination. Otherwise, the program is proceeding normally on its 150 other non-omnibus hearing filings. Only one pre-1988 claim remains; they should all be closed out before the year's end. An estimated \$900 million was paid in all those settlements. The Trust Fund has a \$1.8 billion balance.

Thimerosal litigation in the civil sector includes >300 individual and uncertified class action suits filed in many states against vaccine manufacturers and the vaccine administrator (the physician). The types of lawsuits are traditional tort claims alleging that a specific child was injured and seeking lifetime care for him/her (medical monitoring, no current vaccine effects). There are also derivative claims by parents or legal guardians or spouses. Both derivative and monitoring cases are not covered by the VICP and are therefore in the tort system.

The individual cases are supposed to first file with the VICP. But in all cases, the attorneys are arguing that they can be filed because they are not "vaccine-related:" 1) the claimant was injured because the thimerosal was allegedly an adulterant or contaminant, which is not covered by the VICP; 2) the medical monitoring claims are for less than \$1000 each and therefore qualify, and 3) the third party derivative compensation is not covered by the VICP. Most of the decisions on the adulterant claim have put these back into the VICP system. The other claims have produced variable decisions and remain in the courts. There has been no decision yet on the causation issue. Industry has reported that their legal fees have reached the tens of millions to defend against these suits. It is interesting that similar litigation going in the U.K., in which the claims were initially funded by the government, has had that funding support withdrawn on the basis of no evidence to support a successful claim.

*VICP-related legislation* in the past few years has tried to address some of the loopholes used to bring these ongoing cases. That advanced by Sen. Bill Frist and Rep. Greenwood have contained user-friendly program process revisions. There are about a dozen or so others, as well as some very important provisions that would address the legal situation with these tort suits. But whether there will be further action before the end of the session is unclear.

*Discussion* included comment that, in view of reassuring new research, perhaps a formal or informal ACIP statement could be issued on the matter. The last ACIP statement could be seen as worrisome.

The IOM report of 2001 found insufficient evidence, but some plausibility that thimerosal as a mercury-containing product could cause neurodevelopmental disorders. New data from at least three new studies have been published, and there are more data on the question of ethyl- versus methyl mercury effects.

With the industry's move to remove thimerosal from vaccine and the new evidence suggesting no harm, Dr. Zimmerman suggested that ACIP state that the new data suggests no causal link, as a formal part of the in ACIP minutes documents, and request an update and discussion. Dr. Evans noted that the IOM will revisit the evidence and policy on thimerosal in the spring, and NVAC is addressing the related policies. Such an ACIP comment could be helpful. He added that there is a waiting period of 240-280 days, after which the claimant can file directly against the vaccine manufacturer, but most are just staying in the process. Dr. Braga reported for Aventis that such claims would be paid out of their self-insurance, not that carried by insurance companies, making it a real expense.

**National Center for Infectious Disease.** Dr. Alison Mawle reported that the previous NVAC meeting included a workgroup report on polio lab containment. Part of the global eradication plan is certification of all wild poliovirus resideing in labs. NCID is charged to develop the database documenting that for NVPO, which is leading this work for the nation. Phase I is almost complete. Over 30,000 labs were surveyed and 91% responded. Those with potential versus no such material can be delineated. Diagnostic labs that can grow culture are most likely to have it, so most laboratories (90%) fall in the "least likely" category. By the time the database is closed, NCID expects to have 100% of the "most likely" and "may have" labs. A draft report has already been given to NVAC, and the formal report will probably be presented at its next meeting.

**National Immunization Program.** Dr. Orenstein reported with sadness the unexpected death of NIP Deputy Director and former ACIP member Dr. Natalie Smith on August 22, 2003, after short battle with cancer. She had directed the California Immunization Program for seven years and was one of the first directors of the Association of Immunization Managers. She was replaced by Dr. Steven Cochi, a long-time CDC staffer. He was Chief of the Section when the Vaccine Safety Datalink was developed, played a major role in the program to eliminate rubella, and most recently directed the Global Immunization Division.

**Measles.** A measles outbreak occurred in the Republic of the Marshall Islands and >20 NIP staff worked on the response. This was the largest outbreak in any of the NIP's 24 grantees since 1994. Midway between Hawaii and Australia, the RMI has 29 atolls and 5 main islands over a huge ocean area. As occurred in the U.S., the RMI was lulled into complacency by the absence of disease for several years. As of October 1, 752 lab- or clinically-confirmed cases had been reported, 99% on Majoro atoll. These resulted in 84 hospitalizations and three deaths. The cases spread from there to Guam (5 cases), Palau (1), Hawaii (10) and to one traveler to California and Canada. Supplies of state and territorial immunization grantees were drawn down to send 50,000 doses of MMR vaccine to the RMI. In all, 30,626 doses were delivered to individuals aged from 6 months to 40 years. The epidemic is now declining. Attack rates were highest in young infants aged <1 year, infecting almost 20% of all the infants on the island for an incidence of 206.9/1,000. That was followed by a 47.6 rate for those aged 1-4 years that declined with age thereafter.

The causes were the dense population of Majoro (25,000 people in 3.75 square miles); the importation of measles virus, most likely from Asia (this genotype is seen in Japan and China); and low immunization coverage (<70%) that allowed susceptible persons to accumulate in the population. To prevent future outbreaks, coverage monitoring will be improved among pre-school children; it will be assured that children entering school are vaccinated, with records kept at school; and NIP is considering assigning a public health advisor for the Pacific islands to manage programs and support the global effort toward measles control, to prevent importation.

The lessons learned from this event are that:

1. Measles disease is a serious, leading global cause of vaccine-preventable death for children under 5 years of age. The WHO estimates that about 745,000 died of it in 2001-2.
2. The absence of disease over long periods can lead to a false sense of security.
3. Immunization coverage is key. Disease surveillance cannot be the primary tool used because by the time the outbreaks occur, it is already too late. Continued support of global measles control efforts is essential.
4. The stockpile was valuable in helping to control this outbreak. It must be ensured that there are stockpiles available for other kinds of outbreaks of vaccine-preventable diseases including measles.

Data from the Pan American Health Organization (PAHO) indicate that >10 months have passed since indigenous measles transmission has occurred in the Americas. However, an current outbreak in Mexico City also appears to be an importation.

*Rubella.* Since PAHO announced a hemispheric goal of eliminating rubella and general rubella syndrome, 42 of the Americas' 44 countries have introduced rubella-containing vaccines into their childhood programs. Mass adult campaigns have been conducted in several countries. Surveillance is in place, particularly for measles control, that enables an estimation of rubella incidence. The U.S. had only 18 cases of rubella reported in 2002, a low rate attributable to prevention in the U.S. and in Latin America and decreased measles importations. In 2002, there were only 44 cases, down from >27,000 in 1990. THE TWO PRECEDING SENTENCES DO NOT AGREE. NIP will sponsor an annual National Immunization Awareness Week that in April 2004 will be coordinated on a hemispheric basis.

*Coverage.* The national immunization coverage results were released. The national coverage in 2002 was 75% for children born between February 1999 and May 2001. Immunization goals are 90% coverage for individual vaccine for two year-olds and 80% for the combined series. A few states reached that goal and some are close to that. The entire series' coverage among children aged 19-35 months in the New England states, North Carolina and Georgia, and three midwestern states is 80-89%, according to the 2002 National Immunization Survey.

A chart was shared of progress in the individual vaccines. Coverage of three or more doses of DTP was <80% from the 1960s through the early '80s, below the target 90%, but it now meets the 2010 goal. Measurement stopped due to budget cuts in 1985, after which measles reappeared. Measurement of coverage is the primary prevention tool, beyond surveillance. MMR coverage is at ~90%, as it is for polio and hepatitis B. *Haemophilus influenza B* exceeded 90% and varicella coverage is the highest ever at 80%.

*Racial and ethnic disparities* in immunization coverage have been markedly reduced for childhood vaccines, almost to a leveling-off. MMR is close to 90% for all groups and varicella coverage among some minorities are exceed the estimates for whites. NCID data show the virtual elimination of the big disparities in pneumococcal disease after introduction of PCV, particularly between blacks and whites. However, some disparities persist, particularly true of the continuing shortfall in the fourth dose of DTP, which continues to lower the percentages of the combined series.

Public comment was solicited to no response. With no further comment, the meeting adjourned at 2:35 p.m.

I hereby certify that these minutes are accurate to the best of my knowledge.

---

Myron J. Levin, MD, Chair

---

Date

## **ATTACHMENTS**

**CENTERS FOR DISEASE CONTROL AND PREVENTION (Final)  
 ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES  
 MARRIOTT CENTURY CENTER HOTEL  
 ATLANTA, GEORGIA  
 OCTOBER 15-16, 2003**

**AGENDA**

<b>AGENDA ITEM</b>	<b>PURPOSE/ACTION</b>	<b>PRESIDER/PRESENTER(S)</b>
--------------------	-----------------------	------------------------------

**October 15**

8:30	Welcome	Dr. J. Modlin (Chair, ACIP) Dr. J. Livengood (CDC, OD)
------	---------	---

**INFLUENZA SESSION**

9:00	Introduction	Information Dr. K. Fukuda (NCID) Dr. R. Zimmerman
9:10	Impact of influenza in young children	Information Dr. T. Uyeki (NCID) Dr. W. Thompson (NIP)
9:25	Influenza hospitalization of young children	Information Dr. M. Griffin
	Discussion	
9:45	Vaccine effectiveness and safety in young children	Information Dr. K. Neuzil
	Discussion	
10:35	<b>BREAK</b>	
10:50	Evaluation of inactivated influenza vaccine in children aged 6-23 months old	Information Dr. D. Greenberg
	Discussion	
11:15	Vaccine Adverse Event Reporting System and influenza vaccination of 6-23 months old	Information Dr. J. Iskander (NIP)
11:30	IOM Report on Influenza Vaccines and Neurological Complications	Information Dr. K. Stratton
	Discussion	
11:40	Economic evaluation of influenza vaccination of children	Information Dr. L. Prosser
	Discussion	Dr. M. Meltzer
12:25	<b>LUNCH</b>	
1:25	Feasibility of influenza vaccination of 6-23 months old	Information Dr. M. Iwane (NIP)
1:35	National survey of pediatricians on influenza immunization	Information Mr. A. Janssen (NIP)
1:45	University of Pittsburgh feasibility study	Information Dr. R. Zimmerman
	Discussion	
2:00	Implications for Vaccine Injury Compensation Program	Information Dr. G. Evans
2:10	Statements by AAP and AAFP	Information Dr. M. Rennels Dr. M. Mahoney
2:20	Discussion	Dr. J. Modlin (ACIP, Chair)

**SMALLPOX SESSION**

2:50	Smallpox Update on Civilian Program	Information Dr. R. Strikas (NIP)
3:05	DoD Smallpox Vaccine Update	Discussion Dr. J. Grabenstein (DoD)
3:20	Consideration in the timing of revaccination for smallpox	Discussion Dr. J. Gilchrist (NCIPC) Dr. M. Lane
3:50	Report from ACIP Vaccine Safety Working	Discussion Dr. J. Neff

	Group	Information	
4:20	BREAK		
4:40	Contraindication policy in post-event mass vaccination campaigns	Discussion	Dr. R. Strikas (NIP)

AGENDA ITEM	PURPOSE/ACTION
PRESIDER/PRESENTER(s)	

5:25	Site care for non-health care workers	Discussion	Dr. M. Wharton (NIP)
5:55	Briefing on IOM Report “Financing Vaccines in the 21st Century: Assuring Access and Availability”	Information	Dr. F. Sloan (IOM)

6:25 ADJOURN

**OCTOBER 16**

8:00	Unfinished Business from Previous Day		
8:30	Pediatricians knowledge of and adherence to pneumococcal conjugate vaccine (PCV7) shortage recommendations: US survey findings	Information Discussion	Dr. K. Broder (NIP)
9:00	Effectiveness of pneumococcal conjugate vaccine against invasive disease: results of a case-control study and updated surveillance data	Information	Dr. C. Whitney (NCID)
9:30	Pediatricians clinical practices and adherence to National Immunization Guidelines after introduction of pneumococcal conjugate vaccine	Information	Dr. Karen Lee (Harvard Univ.)
10:00	BREAK		
10:30	Federal Advisory Stakeholder Engagement Survey Results	Information Discussion Decision	Dr. J. Livengood (CDC)
11:30 (NIP)	Recommended Childhood and Adolescent Immunization Schedule, 2004 & catch-up Schedule	Decision	Dr. G. Wallace
11:45	LUNCH		
12:45	Corrections to the VFC resolution for Hepatitis B	Information Discussion VFC Vote	Dr. E. Mast (NCID)
1:15	HIV Vaccine Workgroup Update	Information	Dr. G. Birkhead
1:45	Meningococcal Workgroup Update	Information	Dr. R. Finger
1:50	Yellow Fever Vaccine Safety Workgroup Update	Information	Dr. M. Cetron (NCID)
1:55	UPDATES		
	Department of Defense	Information	Dr. S. Phillips (DoD)
	Food and Drug Administration		Dr. N. Baylor (FDA)
	National Institutes of Health		Dr. G. Curlin (NIH, NIAID)
	National Vaccine Program Office		Dr. B. Gellin (NVPO)
	Vaccine Injury Compensation Program		Dr. G. Evans (HRSA)
	National Center for Infectious Diseases		Dr. A. Mawle (NCID, OD)

2:55 National Immunization Program  
Public Comment

Dr. W. Orenstein (NIP, OD)

3:20 ADJOURN

## ATTENDANCE

### ACIP MEMBERS

Guthrie S. Birkhead, MD, MPH  
Judith Campbell, MD  
Jaime DeSeda-Tous, MD  
Reginald Finger, MD, MPH  
Janet R. Gilsdorf, MD

Celine I. Hanson, MD  
Myron J. Levin, MD, Chair  
Gregory A. Poland, MD  
Mr. John Salamone  
Richard Zimmerman, MD

### EX-OFFICIO MEMBERS

Centers for Disease Control and Prevention Representatives  
John Livengood, MD, Acting Executive Secretary  
Alison Mawle, MD, NCID  
Walter Orenstein, MD, NIP  
Melinda Wharton, MD, NIP

### Ex-Officio Representatives

Norman Baylor, for Karen Midthun, Food and Drug Administration (FDA)  
George Curlin, National Institutes of Health (NIH), National Institute for Allergy and Infectious Diseases (NIAID)  
Geoffrey Evans, National Vaccine Injury Compensation Program (NVICP)  
Bruce Gellin, Director, National Vaccine Program Office (NVPO)  
Randolph Graydon, Centers for Medicare and Medicaid Services (CMS)  
Amy Groom, Indian Health Services (IHS)  
Kristin Nichol, Department of Veterans' Affairs (DVA)  
Stephen Phillips, Department of Defense (DOD)

### LIAISON REPRESENTATIVES

Carol Baker, American Academy of Pediatrics (AAP)  
Martin Mahoney, American Academy of Family Practitioners (AAFP)  
Stephan Foster, American Pharmacists Association HIS FIRST NAME IS DIFFERENT HERE THAN ON PG 69  
Geno Germano, Pharmaceutical Research and Manufacturers of America (PHARMA)  
Jody H. Hershey, National Association of County and City Health Officers (NACCHO)  
Jose Ignacio Santos, National Immunization Council and Child Health Program, Mexico

Rudolph E. Jackson, National Medical Association  
Samuel Katz, Infectious Disease Society of America (IDSA)  
Monica Naus, Canadian National Advisory Committee on Immunization  
Kathleen Neuzil, American College of Physicians (ACP)  
Georges Peter, National Vaccine Advisory Committee (NVAC)  
Margaret Rennels, American Academy of Pediatrics (AAP)  
Robert Scalettar, American Association of Health Plans (AAHP)  
William Schaffner, Infectious Disease Society of America (IDSA) and Guide for Adult Immunization  
Jane Siegel, Hospital Infections Control and Prevention Advisory Committee (HICPAC)  
Litjen Tan, PhD., American Medical Association (AMA)  
James Turner, MD, American College Health Association (ACHA)

Liaisons absent: Drs. Paul McKinney, Richard Clover, Steven Gall, and David Salisbury

#### AGENCY STAFF

#### CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

Epidemiology Program Office (EPO): Richard Dixon

National Center for Birth Defects and Developmental Disorders (NCBDDD): Jennita Reefhuis

National Center for HIV, STD, and TB Prevention (NCHSTP): Chuck Vitek

National Center for Infectious Diseases (NCID):

Niranjan Bhatt	Keiji Fukuda	Erin Murray
Rachel Barwick	Julie Gilchrist	Michele Pearson
Michelle Basket	Scott Harper	Michelle Russell
Craig Borkowf	Alan Janssen	Stefanie Steele
Caroline Bridges	Deva Joseph	Theresa Tursh
Maria Cano	Kristin Kenyan	Tim Uyeki
Joanne Cono	Kim Lane	Teri Wallis
Nancy Cox	Martin Meltzer	Cynthia Whitney
Roz Dewart	Ann Moen	

National Immunization Program (NIP):

William Atkinson	Gary Euler	Cindy Knighten
Norman Allred	Susan Farrall	Andrew Kroger
Roger Bernier	Dan Fishbein	Brock Lamont
Linda Brown	Darla Guris	Karen Lees
Louisa Chapman	Wendy Heaps	Peng-Jun Lu
Bob Chen	Beth Hibbs	Tasneem Malik
Susan Chu	Sonya Hutchins	Dean Mason
John Copeland	Marika Iwane	Mehran Massoudi
Margaret Cortese	Alan Janssen	Mike McNeil
Gustavo Dayan	Laurie A. Johnson	Elaine Miller
Rex Ellington	Allison Kennedy	Zack Moore
	Katrin Kohl	Trudy Murphy

Rick Nelson  
Huong Nguyen  
Diane Z-Ochoa  
Dennis OÆMara  
Ismael Ortega-Sanchez  
Brian Pascual  
Kristin Pope  
Lisa Prosser  
Donna Rickert  
Valerie Robinson  
Lance Rodewald

Sharon Roy  
Jen Reuer  
Tammy Santibanez  
Jeanne Santoli  
Kari Sapsis  
Ben Schwartz  
Judy Schmidt  
David Shay  
Kris Sheedy  
Irene Shui  
Jim Singleton

Nicole Smith  
Vishnu Priya-Snellor  
Ray Strikas  
Fran Walker  
Sabrina Walton  
Donna Weaver  
Eric Weintraub  
Eddie Wilder  
Carla Winston  
Skip Wolfe

Office of the CDC Director: Larry Pickering

Office of General Counsel: James Misrahi

DEPARTMENT OF DEFENSE (DOD): John D. Grabenstein , Steve Jones

FOOD AND DRUG ADMINISTRATION (FDA): ChrisAnna Mink, Dorothy Scott

NATIONAL INSTITUTES OF HEALTH (NIH): NIAID: Barbara Mulach

MEMBERS OF THE PUBLIC OR PRESENTERS to the committee in attendance were:

Lynn Bahta, MN Department of Health  
Bryan Bechtel, Infectious Diseases in Children  
Wyndolyn C. Bell, MedImmune, Inc.  
Eric Benning, Fulton County Department of Health and Wellness  
Valerie Berry, Solvay Pharmaceuticals  
Damian Braga, Aventis Pasteur  
Andrew Bowser, freelance medical writer, Brooklyn, NY  
Pat Cannon, Wyeth, Newnan, GA  
Dan Casto, Merck and Co., Inc.  
Kathleen Coelingh, MedImmune Vaccines  
Terry Cleveland, Cingular Wireless  
Sherri D. Coffee, Medimmune  
Keli M. Coleman, MedImmune  
Lenore Cooney, Cooney/Waters, New York, NY  
Dack Dalrymple, Dalrymple & Associates/Pink Sheet, Washington, D.C.  
Roberto Debbag, FUNCEI Argentina, Buenos Aires  
Michael Decker, Aventis Pasteur/Vanderbilt University  
Penelope H. Dennehy, RI Hospital/Brown University  
Iris de Bruijn, Solvay Pharmaceuticals  
Richard Dinovitz, Wyeth Vaccines  
S. Douthwaite, GSK  
David Dwight, Chiron Vaccine  
Antonia Farrell, NJ DHSS  
Steven Foster, American Pharmacist Association  
Johanna Garcia, NJ Department of Health  
Diana Gaskins, GA Immunization Program, Atlanta, GA  
Bob Giffin, IOM  
Ruth Gilmore, GA Immunization Program

David Greenberg, Children's Hospital of Pittsburgh  
Jesse Greene, South Carolina Department of Health and Environmental Control  
Marie R. Griffin, Vanderbilt University  
Jill Hackell, Wyeth  
Neal Halsey, Johns Hopkins University, Baltimore, MD  
Claire Hannan, Association of State and Territorial Health Officers (ASTHO)  
Richard A. Haupt, Merck Vaccine Division  
Phil Hosbach, Aventis Pasteur  
Tracy Ingraham, GA Division of Ph  
Karen Jacobs, Reuters  
Melonie Jackson, Georgia Chapter, AAP  
Peter Khoury, Baxter BioScience  
Charlotte Kroft, GlaxoSmithKline  
J. Michael Lane, ORISE, Oak Ridge, TN  
Jim Lathrop, Chiron Vaccines  
Sheila Leader, Medimmune  
Karen C. Lee, Harvard University/Massachusetts General Hospital  
Clement Lewis, Chiron Vaccines  
Harold W. Lupton, Aventis Pasteur  
Marie-Michele Leger, American Academy of Physician Assistants, Alexandria, VA  
Jeff Levine, Ketchum, Washington, D.C.  
Lugene Maher, Wyeth  
Susan Malone, CC Health Department, Savannah, GA  
Geoff McKinley, Baxter Vaccines  
Claudia Miller, MN Department of Health  
John Modlin, Dartmouth Medical School  
Tracy Montrella, Merck Vaccine Division  
Marie Murray, Recorder, Atlanta, GA  
Viera Muzithras, Wyeth  
Martin Myers, UTMB, Galveston, TX  
Anders Nelson, Chinchilla, PA  
Peter Paradiso, Wyeth Vaccine, West Henrietta, NY  
Kate Paxton, Ketchum  
Diane Peterson, Immunization Action Coalition, St. Paul, MN  
Stanley Plotkin, MD, Aventis Pasteur, Doylestown, PA  
Greg Poland, Mayo Clinic  
James Ransom, National Association of City and County Health Officers (NACCHO)  
Lynn Redwood, Safe Minds, Tyrone, GA  
Fred Ruben, Aventis Pasteur  
Carol Ruppel, Every Child By Two  
Brent Rutland, Aventis Pasteur  
Judith Shindman, Aventis Pasteur Ltd.  
Dr. Alan J. Sievert, AAP  
Eric Skjeveland, Merck Vaccine Division  
Parker Smith, International Medical Newsgroup  
Andrew Stevenson, Solvay Pharmaceuticals  
Jennifer Stevenson, Swarthmore College  
Jeffrey Stoddard, MedImmune  
Kathleen Stratton, IOM  
Stacy Stuerke, Merck  
Nuredin Sule, Mercer Pharmacy School

Karen Townsend, GA Chapter, AAP  
John Trizzino, Henry Schein, Inc.  
David Wahlberg, Atlanta Journal-Constitution  
Ted Tsai, Wyeth  
Miriam E. Tucker, Elsevier, Rockville, MD  
Tom Vernon, MD, Merck Vaccine Division, West Point, PA  
Peter Vigliarolo, Cooney Waters, New York, NY  
Martin Wasserman, GSK  
Deborah Wexler, Immunization Action Coalition, St. Paul, MN  
Emily White, Acambis, Inc.  
Steve Wilson, WXYZ TV, Detroit  
Celia Woodfill, CA Department of Health Services  
Daniel Yee, Associated Press, Atlanta, GA  
Greg Yoder, Merck  
Laura York, Wyeth Vaccines  
John Zahradnik, Aventis Pasteur

.

2