Table of Contents NEEDS FORMATTING TO ALIGN COLUMNS

JUNE 23, 2004 1
Opening Comments 1
Hepatitis A Update 2
Progress in Hepatitis A Prevention 2
Merck Presentation: Hepatitis A Vaccine (VAQTA® 4
GSK Presentation of Hepatitis A Vaccine 5
Alaska Study of Interference With Maternal Antibody 6
IOM Immunization Safety Review Report 7
Public Comment 9
Influenza Program 9
Influenza-Associated Mortality/Encephalopathy in Children 9
Influenza Vaccine 2005-05 Supply Update 11
Kaiser Pediatric Vaccine Effectiveness Study, ... 12
Influenza Vaccine Effectiveness, University Student Population 14
Case-Control Influenza VE Study, Persons Aged 50-64 Years 15
Update: National Influenza Vaccine Summit 17
Priming and the Pediatric Influenza Immunization Dosing Schedule 18
Update: Pandemic Influenza Preparedness and Response Plan 20
Statement on Influenza Immunization of Health Care Workers 22
Adult Immunization: NFID/National Coalition Presentation 25
Adult Immunization Schedule 2004-2005 25
Vote 26
Pilot Project to Enhance Public Participation 26
Agency Updates 29
Public Comment 31
JUNE 24, 2004 31
Healthcare Worker Influenza Vaccination Recommendations 31
Vote 34
Meningococcal Disease: Meningococcal Workgroup Report 34
Cost Effectiveness of Meningococcal Vaccine Use in the U.S. 35
Scenarios of Meningococcal Vaccine Use 38
Public Comment 41
Smallpox: National Smallpox Vaccine in Pregnancy Registry Analysis 41
Smallpox Workgroup Report 43
Influenza: Vaccine Efficacy of Partial Vaccination Schedules 43
Prevnar Supply Status 44
High Risk Groups Who Should Receive Four Doses 44
Pertussis: Newer Macrolide Antibiotics in Treatment/Prophylaxis 46
Combination Vaccine Recommendations 47
Workgroup Updates 48
Closing Comments 51
Public Comment 51
Certification 52

CENTERS FOR DISEASE CONTROL AND PREVENTION
NATIONAL IMMUNIZATION PROGRAM
ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

MINUTES OF THE MEETING
June 23-24, 2004

JUNE 23, 2004

A meeting of the Advisory Committee on Immunization Practices (ACIP) was convened by the Centers for Disease Control and Prevention (CDC) National Immunization Program (NIP) at the Atlanta Marriott Century Center Hotel in Atlanta, Georgia, on June 23-24, 2004. Membership announcements included the rotation of three new members onto the committee and the reappointment of Chair Dr. Myron Levin for another year. Certificates of appreciation were provided to retiring members Dr. Jaime De Seda and Dr. Richard Zimmerman.

The meeting agenda (posted on CDC's Website, http://www.cdc.gov/nip/) addressed influenza, meningococcal disease, immunization of health care workers, adult immunization, the enhancement of public participation in vaccine policy formation, smallpox vaccination, the vaccine supply, pertussis, and updates by the ACIP workgroups. The meeting was convened by ACIP Chairmen Dr. Myron Levin at 8:50 a.m. Those present are listed on the attached sheets (Attachment #1).

Opening Comments
Acting ACIP Executive Secretary Dr. Steven Hadler made several announcements:

- New ACIP members at this meeting were Ms. Lisa Stinchfield, NP (replacing Dr. Celine Hanson). Dr. Jonathan Abramson's term was extended for another three years. Dr. Tracey Lieu and Dr. Julie Morita will attend as of the October meeting.
- New liaisons were Dr. Jonathan Temte (AAP), Dr. Romeo Rodriguez (National Immunization Council/Child Health Program, Mexico), Dr. Dennis Brooks (NMA) and Dr. Charles Helms (NVAC)
- ACIP Workgroups to confer at this meeting were those to address influenza, HPV, evidence-based recommendations, pertussis, meningococcus, and MMR/VZV
- The ACIP home page is www.cdc.gov/nip/acip; e-mail is at acip@cdc.gov.
- ACIP Protocol: The quorum of ACIP members must be maintained to conduct committee business. The ACIP Charter allows the Executive Secretary to temporarily designate ex officio members as voting members in the absence of a quorum (eight appointed members) of members qualified to vote. If voting, they are asked to disclose any potential conflicts of interest. Meeting time is reserved for public comment at scheduled intervals, but may also occur during open discussion if a speaker is recognized by the Chair. ACIP members with potential conflicts of interest are asked to disclose all vaccine-related work and financial interests, and to refrain from any discussion or vote that is related to such matters. When needed, however, limited waivers of such conflicts of interest are granted, to enable members' expertise to be provided in their service on the Committee. Waivers may be issued, for example, to members who also conduct clinical vaccine trials or serve on Data Monitoring Boards (DSMB).

The members and liaisons then introduced themselves (see Attachment #1). Those reporting potential conflicts of interest were Dr. Abramson (a one-time consultation for Merck in 2003), Dr. Poland (Merck and VaxGen), Dr. Treanor (Protein Sciences Corporation, Viscount, MedImmuune and VaxGen, and Dr. Levin (clinical trials for GlaxoSmithKline [GSK], Merck, and Merck's DSMB).

AGENDA ITEMS

Hepatitis A Update
Overview: Summary of progress of hepatitis A prevention in the United States: recommendations, epidemiology, incidence, vaccine manufacture, study of interference with maternal antibody.

Progress in Hepatitis A Prevention
Presenter: Dr. B. Bell, NCID

Overview: Background/rationale for current recommendation; hepatitis A epidemiology in the vaccination era, CDC modeling study estimates of vaccination impacts; future options.

The success of hepatitis A immunization was demonstrated by a radical decline in incidence from the baseline year of 1980 to 2003. Incidence from baseline declined by 89% in areas where vaccination was recommended, by 93% where its consideration was advised, and 53% in areas without a recommendation to routinely vaccinate children. From the 1980 baseline of slightly more than 12 cases per 100,000 population, the 2003 provisional rate was 2.6 cases, a 76% overall decline.

Prior to vaccination, most hepatitis A was transmitted from person to person in households and extended family settings during community-wide outbreaks. Asymptomatic infection among children aided its spread. There was no risk factor identified for almost half the cases, and the known risks were variable. Since there was (and is) no formulation available for routine infant vaccinations, the strategy to reduce overall incidence and to advance herd immunity among all age groups became vaccination of children. From 1980 to 1999, the estimated incidence of hepatitis A was about sixteen times higher for children to age five years, and during that period, ~60% of the estimated 271,000 infections per year occurred in children aged <10 years; ~75% occurred in children aged <5 years.

Therefore, CDC began an incremental routine hepatitis A vaccination policy for children. In 1996, the ACIP recommended vaccination for children living in communities shown to have a high rate of hepatitis A (e.g., African-Americans and Alaskan natives). While that strategy was demonstrably successful in those communities, a 1998 analysis of overall notifiable disease rates showed hepatitis A still leading all other vaccine-preventable diseases.

Therefore, CDC directed the next immunization phase to those states and counties with historically and consistently elevated rates, which accounted for most cases nationally. In 1999, the ACIP recommended routine state-wide vaccination for children in states, counties or communities with >20 cases per 100,000 population (twice the national

average, true in 11 states) during the period 1987-97; and urged consideration of routine vaccination of children in areas with a case rate above the national average of >10/100,000 (six states). These state categories represented a third of the U.S. population, but almost two-thirds of the hepatitis A cases.

The 2003 data of the National Immunization Survey (NIS) showed, among children aged 24-35 months, a 50% coverage rate (CI of 6%-73%) for at least one vaccine dose in the states where it was recommended, and 25% (CI of 1%-32%) in those where its consideration was advised, as opposed to 1% in the rest of the country. Vaccination differences by race and ethnicity were seen, with rates higher among Hispanics than Caucasians or African-Americans. First-dose coverage was higher among older children (26-73 months) registered at six CDC sentinel sites, and one large HMO site had a 98% coverage rate. A map of the U.S. showed highly variable implementation of the CDC recommendation.

Charted data of the National Notifiable Diseases Surveillance System (NDSS) showed a rapid decline in hepatitis A incidence among all age groups. However, this occurred mostly among children to age 18 years (a decline of 82-90%) and 70% among adults. The decline was also true of all racial/ethnic groups, including among American Indians and African-Americans. This was dramatically mapped among the previously-high rate states, showing a precipitous drop in rates per 100,000 population in 2003, compared to baseline. Declines of 89% were seen in states with recommendations; 93% in those considering the vaccination; and 53% in other states. Rates by age group and region were also charted. The regional picture had reversed, in fact, with the areas providing nearly 67% of cases earlier now providing only a third in 2003.

A Poisson regression analysis was done of the observed hepatitis A incidence, adjusted for under-reporting, with vaccine sales data used as a surrogate to estimate coverage. The incidence estimates included both the direct vaccination effect and also the indirect herd immunity effect provided to others not vaccinated. The predicted incidence declines paralleled the actual rates of states with no recommended statewide vaccination. Two analyses included, and then ignored, vaccination in the 17 states where vaccination was either recommended or urged for consideration. When not included, the observed declines exceeded predicted incidence; when included, the modeled incidence was similar to what was observed. An estimated 97,800 cases were prevented by vaccination from 1995 and 2001, and ~39% were prevented in 2001 (including 72% of predicted cases in recommending states). A strong herd immunity effect was seen to have prevented about 33% of cases.

Thanks to a voluntary policy implementation, overall national rates in 2003 were at an unprecedented low and the predominant epidemiology of the disease had shifted fundamentally from children to high-risk adults. The latter now constitute ~81% of cases, higher in recent years among adult males. Of those who are contracting hepatitis A from 2000-2003, about 10% occurred among international travelers, and ~20% of those were children. Another 10% occurred among other adults at increased risk, such as illegal drug users or men who have unprotected sex with men.

Future plans. CDC plans studies to further characterize the impact of vaccination coverage in older children (expected to be finalized this fall). This will evaluate the

economic impact of various vaccination strategies, including universal childhood vaccination (expected by year's end), and evaluation of the acceptability of routine childhood hepatitis A vaccination to providers in those states not currently vaccinating.

Several options through which to further reduce incidence were outlined. These included improved implementation of current vaccination recommendations for children and high-risk adults (the latter historically difficult to do) and extension of vaccination to children nationwide. Considerations relevant to the latter include the unknown final impact of the current recommendations. Hepatitis A incidence is periodic, and vaccination will likely lengthen the inter-epidemic period. Some discussion is needed of the ultimate goal, whether to lower incidence or eliminate transmission, as is consideration of the ability to sustain the currently geographically-based recommendation. Cost effectiveness is always a consideration, as are the feasibility and acceptability to the public and whether a licensed hepatitis A vaccine for children aged 1 year will be released in the near future.

Discussion included a question of whether any appreciable reduction in mortality due to hepatitis A had been seen. The present surveillance data did not answer that, but Dr. Bell hoped to be able to report on that in October.

Merck Presentation: Hepatitis A Vaccine (VAQTA®) for Children Aged ≥1 Year
Presenter: Dr. Barbara Kuter

Overview: Data developed by Merck, and filed with the FDA, on the use of the hepatitis A vaccine VAQTA® among children aged 1 year and older. All such hepatitis A vaccines are currently licensed for use from age 2 years.

Earlier vaccination against hepatitis A would provide earlier protection and could prevent more severe disease in adults, since children are a reservoir for infection. Vaccine licensed from age one year could also be incorporated into the routine childhood immunization schedule.

While response to vaccine can be blunted by maternal hepatitis A antibody persistence, this has been shown to decay in the first year of life (Lieberman et al, *Pediatr Infect Dis J*, 2002; 21(4): 347-8). A chart of seropositivity showed a consistent decline from 2, to 4, to 6 months, and then a sharp decline to 12 months. While about 30% of infants measured were still seropositive at 12 months, the GMT cutoff was very close to ten, which is the level at which Merck defines seropositivity.

Based on that, Merck studied VAQTA® use at 12 months of age. The objectives were to ascertain that VAQTA® would induce responses similar to those observed in 2- to 3-year-olds who received two doses, six months apart, and that it would be well-tolerated and immunogenic when administered either alone or with other routinely administered vaccines (i.e., MMR, Varivax®, DTaP [Tripedia] and OPV or IPV).

Design: Open, randomized, multi-center study of 617, 12 month-olds with negative history of hepatitis A. Four treatment groups all received 25 micrograms of VAQTA® at 12 months with or without another vaccine. Safety follow-up was done 42 days after receipt of any live virus vaccines and 14 days after receipt of all other vaccines. Serologic follow-up was done at vaccination, six weeks after the first dose of VAQTA® and four weeks after dose 2. Results

indicated that hepatitis A responses were comparable to those of historical controls of 2- to 3-year-olds (as were responses to MMR2, Varivax® and DTAP) and the study control (concomitant vs. non-concomitant). There was no formal comparison done of the polio co-vaccination data. The maternal antibody at 12 months was shown to be low as to not interfere with the vaccine's immune response when given at that age. Hepatitis A immune response in this regimen was comparable between children either initially seronegative and seropositive.

Safety: VAQTA® provided alone at 12 months of age was assessed for injection site tenderness and soreness, fever, upper respiratory infection (URI), and irritability. Low rates of adverse experiences were found, with a slightly higher rate (but still very low) of fever after the first dose (~12%) and second dose (~8%).

For immunogenicity, concomitant administration of VAQTA® with MMR2, Varivax, and Tripedia® at 12 and 18 months showed virtually identical GMTs whether delivered alone or concurrently. The polio responses showed a 30-fold increase in GMTs for all three types. And, except for varicella and pertussis, the immunogenicity rates were similarly comparable at 12 and 18 months to historical rates. However, the varicella response rates differed greatly between 2000 (86%, which met acceptability criteria of GMT antibody ≥ 5) and 2002 (50%). The 2002 difference was probably a sample handling issue, rather than interference. Similarly, the response to DTaP administered at 2, 4, 6, and 18 months involved different timing of the dose 3 pre-dose bleeds between the study and historical controls. That difference was found to relate to study design, rather than interference, since the higher prevaccination titer at 13.5 months than at 18 months decreased the likelihood of a four-fold rise.

Safety was assessed for concomitantly administered VAQTA® doses 1 and 2 in relation to vaccination site pain, tenderness or soreness, URI and otitis media. Again, results were comparable except for slightly higher rate of URI in the non-concomitant group. The reverse was seen for otitis media rate, which were higher in the concomitant group. No unusual reactions were reported. Dose two results also were comparable between the two groups.

The conclusions were that VAQTA® can be administered as early as 12 months of age. It is highly immunogenic and generally well-tolerated, whether administered alone or with other vaccines. There was no impact of low levels of maternal antibody on the immune response, suggesting good priming in this age group. The safety and immunogenicity of VAQTA® in 12-month-olds was comparable to 2- to 3-year-olds.

Discussion included that there are no comparative data available for Hib; it was not examined. Regarding pertussis, the study criterion that was not met was the four-fold rise that was expected in 80%; only 74% reflected that. However, that was thought to be related to a difference in the kinetics of sample collection. The earlier, the better the antibody level; later collection is less likely to attain a four-fold response. But there was an eight-fold increase between the pre- and post-sample, regardless, a significant increase in antibody response. There was no real explanation for the two-fold difference in the otitis media rate between the groups, but that is seen in many pediatric vaccine studies.

GSK Presentation of Hepatitis A Vaccine

Presenter: Dr. Andrew Trofa, GlaxoSmithKline (GSK)

Overview: Hepatitis A recommendations; vaccines produced; clinical relevance of

vaccination of children aged <2 years old.

GSK has two hepatitis vaccine products in the U.S.: Havrix®, pediatric formula, and Twinrix®, licensed for use from age 18. Worldwide sales include, Amberix® (hepatitis A and B), and Hepatyrix® (hepatitis A and typhoid). Havrix® was licensed in 1992 (1995 in the U.S.), and was recommended by the ACIP in 1996 for use in selected groups, and in 1999 in high-rate areas.

A phase III trial for Havrix® use under age two began in 2003. Vaccinating before two could increase vaccination compliance and coverage by decreasing the required number of immunization visits. It would provide an opportunity for co-administration to better protect children and their contacts. Issues involved included maternal antibody and the effect of co-administration with other vaccines. The initial study reviewed co-administered DTaP and Hib to children aged 11-25 months. The ongoing studies examine ages 15-18 months to minimize the potential effect of maternal antibody and to explore the integration of hepatitis A vaccination into the existing immunization schedule. There also are fewer vaccinations in that age range.

Design. The three ongoing studies co-administer Havrix® with PCV (HAV-220), MMR and varicella (HAV-231), and DTaP and Hib (232), to ~3480 children. Children aged 11-13, 15-18, and 23-25 months received Havrix® alone and two other 15-18 month old groups had it co-administered. The primary objective was to achieve the desired GMC after dose two, and secondarily, after dose one.

Endpoints. Both primary and secondary objectives for HAV-210 were met, showing anti-HAV GMC ratios (95% CI) meeting the pre-defined limits for age 15-18 and 23-25 months, singly- or co-administered, after dose 2. The GMCs after dose 1 were lower for the younger group and did not meet the secondary objective, but the seroprotection rates for DTP and Hib were 100%. For pertussis, the secondary objective's vaccine response was met, although it was for FHA and PRN.

The conclusions for safety were that redness and pain were the most common solicited symptoms four days post-vaccination, as was irritability for unsolicited (30 days post-vaccination) symptoms. Grade three symptoms were uncommon in all groups. Serious adverse events (42) were seen in 38 subjects, with one febrile seizure suspected to be related.

In summary, all primary and secondary objectives were met except for the anti-PT vaccine response. The study established safety record for Havrix®. The subject age does appear to affect the antibody persistence after first dose, especially for those at 13-15 months of age. However, this study demonstrated the feasibility of hepatitis A vaccine at <2 years. Additional Havrix® co-administration studies are ongoing in children aged <2 years, and evaluations in younger age groups are under consideration.

Alaska Study of Interference With Maternal Antibody; GSK Vaccine

Presenter: Dr. Beth Bell, NCID

Overview: CDC cooperative agreement study of maternal antibody interference done with the Anchorage, Alaska Native Medical Center, to compare anti-HAV responses among children with and without passively transferred antibody (PMA) as infants. The study was done before the varicella vaccine went into use. There may be enough specimens to look at that as well, but the sample size is small.

The GSK vaccine is safe and immunogenic among infants without passively-transferred maternal antibody. All vaccinees responded in the presence of maternal antibody, but their immune response was blunted. To identify the optimum dose and schedule to overcome the effect of passively-transferred maternal antibody, this single-blind clinical trial randomized infants to three groups (6-12, 15-18, and 12-21 months) to receive different two-dose vaccination schedules (which were charted). A blood draw was done in each of the groups at 13 months of age to allow inter-group comparisons to determine vaccine interference, since one of the groups would not have received it prior to their 13-month blood draw.

Anti-HAV concentrations over time were charted for both groups with sero-positive or -negative maternal antibody. They track exactly in parallel at baseline and months 1, 7 and 12. The 13-month draw results also showed no difference in percent positive response to other vaccines at the 13-month blood draw for anti-HBs, measles IgG, anti-Hib PS, pertussis PT IgG, PRN IgG, diphtheria or tetanus. All the children but two also responded to one or more polio vaccine antigen. Both of those children were in the group that had received no other vaccines.

Discussion included:

- All the children were enrolled and randomized at age <6 months to one of the three groups. Analysis began when the sample size was sufficient for power to detect a two-fold difference in GMC between the children of sero-positive and -negative mothers. The mothers were naturally infected. There are no data on a small group (~20) of children whose mothers had been vaccinated, all of whom appeared to respond to the vaccine.
- There are little data available on viral shedding after exposure by an immunized child, something relevant to herd immunity. Some, from the first Thai vaccine trial, suggest only that the vaccine prevented infection.
- Dr. Plotkin commented that there is evidence that T-cell responses occur, despite the absence of T-cell responses to the first dose. The second dose reacts that, taking advantage of the T-cells' sensitization. And, the herd immunity may be similar to other vaccines, in that immunizing infants can prevent hepatitis among adults. As adolescent vaccination is discussed, perhaps hepatitis A might be included to prevent secondary circulation among adults.

Subsequently, the ***ACIP agreed to form a workgroup to discuss the options relevant to the hepatitis A (and hepatitis B) vaccine*** issues to come.

IOM Immunization Safety Review Report
Presenter: Dr. Kathleen Stratton

Overview: The IOM Vaccine Safety Review Committee's final report was developed, in view of new data and in response to the Interagency Vaccine Group. It addressed the hypothesized association between vaccines and autism, focusing on MMR vaccine and autism spectrum disorders (ASD), and thimerosal-containing vaccines and autism. It did not focus on other neurodevelopmental disorders.

The committee's findings for scientific causality were that fourteen large, well-designed epidemiological studies consistently showed no association between the MMR vaccine and autism, favoring rejection of a causal relation. That finding was consistent with the 2001 IOM report on MMR and autism, which focused on broader set of neurodevelopmental outcomes.

The 2001 study concluded that the evidence was inadequate to accept or reject a relationship between thimerosal containing vaccines and neurodevelopment disorders. Significantly more research has been published since then to verify or deny. While a potential biological mechanism does exist for those outcomes by way of analogy with methyl mercury, it does not for autism. For thimerosal and autism, five large, well-designed epidemiological studies in different countries provided significant evidence of no association with autism.

Potential biological mechanisms which could explain how vaccines might cause autism are:

- The release of chemicals into the brain due to disruption of intestinal function by the MMR vaccine.
- Triggering of abnormalities in the immune system that are indicative of vaccine-induced damage to the CNS.
- Increased accumulation of and decreased excretion of mercury from the brains of a subgroup of children.
- The effects of thimerosal on a variety of biochemical pathways.

The evidence comes from *in vitro* experimental systems, clinical observations, and analogies between rodent behavior and human behavior. While the laboratory observations of the toxic effects of mercury are important, these observations do not explain how specific exposures in a rapidly developing infant affect certain tissues but not others when these mechanisms are also active. Laboratory studies also have not shown how these effects lead to autism. The committee did not dispute that mercury-containing compounds, including thimerosal, can be very damaging to the nervous system. But the question remains whether the observed effects of ethyl mercury are related to the development of autism.

The committee concluded that, in the absence of experimental or human evidence that either the MMR vaccine or vaccines containing thimerosal affect metabolic, developmental, immune, or other physiological or molecular mechanisms that are causally related to the development of autism, such hypotheses generated to date remain only theoretical.

Recommendation: Because autism can be such a devastating disease, any speculation that links vaccine and autism makes this a significant issue. For that reason, the committee found good reason to survey autism spectrum disorders as exposure to thimerosal declines.

- There already are indications that autism reports are declining since thimerosal was removed from vaccine. A good epidemiology study will allow proper interpretation of those data.
- Standard and accepted case definitions and assessment protocols for ASD should be used to conduct clinical and epidemiological studies of sufficient power to identify risk factors and biological markers of ASD.
- The surveillance of adverse events should be strengthened (e.g., standardize case definitions of adverse events; established guidelines for use of VAERS; continued use of large linked databases and other tools; further development of the CISA system).

The committee's recommendations for public health response were that:

- No significant investment in studies of the theoretical vaccine-autism connection is needed.
- A public health response should fully support an array of vaccine safety activities.
- Available funding for autism research should be channeled to the most promising areas.
- No policy review of the licensure of the MMR vaccine or thimerosal-containing vaccines and/or of the current schedule and recommendations for administration of those vaccines

is necessary.

Public Comment was provided by Ms. Lyn Redwood, RN, of the advocacy group Safe Minds. She shared a document with the ACIP from Congressman and physician David Weldon, who had read the IOM vaccine safety report. She *asked that a transcription of the report, which was read into the Congressional Record, be included in both the transcription and summary minutes of the ACIP meeting* (see Attachment #2). She found the IOM's recommendations to be contradictory. While the report recognizes "provocative findings" it did not recommend study of the theoretical link of vaccines to autism, even though they could not shown that these effects were not connected. Safe Minds will continue to study these issues.

Dr. Zimmerman, as a father of a child with autism and an ACIP member, suggested that the ACIP accept the IOM Vaccine Safety Report in an official vote, as done for other IOM reports in the past. This would ensure that this report would continue to play an important role in ACIP decisions and support the attention of the medical and other communities to it.

Dr. Levin summarized consensus by the ACIP to accept the IOM report and call for this report's publication.

Influenza Program

Influenza-Associated Mortality/Encephalopathy in Children
Presenter: Dr. Niransjan Bhat, NCID

Overview: Summary of influenza-associated mortality and encephalitis in children 2003-04 among U.S. children aged <18 years.

Pediatric influenza-associated deaths are not nationally reportable, but statistical modeling estimated ~92 influenza-related deaths annually among children aged <5 years in the U.S. Influenza-associated encephalopathy in children has been reported in Japan. The U.S.' 2003-04 influenza season started early in October, and deaths and encephalopathy in children were reported. The predominant influenza subtype was H3N2, known to be more severe, and the vaccine was not optimally matched to it. Worse, there were spot shortages of the vaccine stocked.

In response to the perceived severity of influenza among children, the ACIP recommended vaccination of children aged ≥6-23 months at mid-season 2003-04. CDC asked states to report pediatric influenza-associated deaths, as well as demographic, clinical, laboratory and autopsy data. The following picture emerged:

- As of April 16th, 145 deaths from 40 states were reported to CDC.
- 51% of reported deaths were male; 65% were white, 22% black, and 26% Hispanic.
- The median age of reported deaths was 3 years, with a range of 12 days to 17 years.
- 28% were 6 to 23 months and 63% were less than 5 years old.
- 40% of influenza-related deaths were in children aged ≥2 years; 61% were <5 years old.
- Of the 145 reported pediatric influenza-associated deaths, 43% were among previously healthy children.
- 42% of deaths occurred among children recommended for influenza vaccination.
- 44% of these were healthy children 6-23 months of age and 56% were children with ACIP-defined high risk conditions.

- 58% of deaths were among children not currently recommended for vaccination.
- Of the 103 children with known vaccination status, 22% received ≥1 dose of influenza vaccine in the 2003-04 season; only 6% of them were adequately vaccinated.
- 56% of deceased children were unvaccinated this season; 13% of the children were partially so, and only 2% of the children were fully vaccinated according to the recommended schedule.

Influenza-related encephalopathy data was defined as altered mental status lasting >1 day and onset of neurological symptoms within 5 days of fever onset. The collected data of 108 reports revealed that:

- 50 cases from 26 states met the case definition; 58 did not and were excluded.
- 28 (56%) were among males
- 51% of reported deaths were male; 65% were white; 22%, black, and 26%, Hispanic.
- The median age of reported deaths was 3 years (range 12 days to 17 years).
- 28% were aged 6-23 months; 63% were less than 5 years old.
- Of the 145 reported pediatric influenza-associated deaths, 43% were previously healthy children.
- 42% of deaths occurred among children recommended for influenza vaccination.
- 44% of these were healthy; 56% were children with ACIP-defined high risk conditions.
- 58% of deaths were among children not currently recommended for vaccination.
- Of the 103 children with known vaccination status, only 6% were adequately vaccinated; 22% received ≥1 dose of influenza vaccine in the 2003-04 season.
- More than half the cases survived without neurological sequelae. Of the remaining 14 cases, 7 survived with some kind of neurological impairment and 6 children died.

In summary, 135 influenza-associated pediatric deaths and at least 39 influenza-associated cases of encephalopathy occurred during the 2003-04 influenza season. Younger children (<4 years) were most affected. At least 50% of affected children had some underlying medical condition and at least 30% of affected children had a neurologic or developmental disorder. Most children (67% of deaths and 74% of encephalopathy cases) were either previously healthy or had an underlying medical condition that prevented routine vaccination during the 2003-2004 influenza-season. At least 38 cases of influenza-associated encephalopathy occurred, half among those aged <5 years, but older children were also affected. More than 40% had severe outcomes, including death or neurologic sequelae.

Study limitations included the use of a passive surveillance systems and non-inclusion of unconfirmed cases; an unknown degree of state participation in voluntary reporting; potential absence of early-reported cases; variable amounts of the clinical data received; and lack of similar national data which precluded comparison to previous seasons.

Next, data collection and analysis will be finalized. The CSTE has made influenza nationally reportable, and CDC is working to collect data on pediatric influenza-associated deaths for the 2004-05 influenza season, under the rubric of the Emerging Infections Program (EIP). NIP plans to spend $40 million to provide influenza vaccine through the VFC and is discussing with the ACIP the expansion of groups targeted for influenza vaccination, or possible universal vaccination of children.

Discussion included:

- There are some Japanese data on acute necrotizing encephalopathy (ANE), but not from

the U.S. this past or previous season. Data analysis of the clinical symptoms and pathophysiology of the American and Japanese experiences is pending; current work is the preliminary examination of clinical information. Data available for encephalopathy (the definition of which is in process) include total number of affected patients. Data were collected retrospectively, so refined methods such as neuroimaging, lumbar puncture, etc., are not available to adequately judge each case in the same way. But basic criteria are being developed for use (e.g., signs of brain inflammation on imaging, etc.). An analysis of a convenience sample of autopsy reports (N=20) was available, but with variable data quality. Of those, >50% listed influenza on the autopsy report, but also respiratory failure or pneumonia, invasive bacterial infection, sepsis, and CVD.

- One outlier (an influenza B case) was reported in April, but the epidemic curve was flat. The season was closed, but data still being solicited.
- Delineation of possible/probable cases to better estimate the burden of disease will improve with national reporting. The modeling estimates examined the annual mortality trends and measured the influenza season's excess mortality, as validated by neurologic data. But influenza-related mortality is rare, with large CIs. An estimated 92 cases/year occur among those aged <5 years; reports were received of 96 children of that age.
- There was no viral PCR testing of brain tissue, but there was some of spinal tap fluid. None were positive for influenza.
- There are no data on maternal encephalopathy for the reported 16 deaths and two cases of encephalopathy in those aged <6 months. Anecdotally, a couple of cases had RSV and pertussis co-infection identified.
- CDC hopes by the end of the coming influenza season to have developed a protocol and tool for prospective surveillance, as opposed to clinical data.
- Dr. Neuzil reported consistent agreement of the published Tennessee data with CDC's data, although the CIs are wide. There are no data on international pediatric deaths. What exist are from developing countries such as the Congo, which also have high mortality rates.
- Dr. Tim Uyeke, of NCID's Influenza Branch, reported anecdotal (unpublished) reports in Europe this past season of sudden deaths in children. Some U.S. state/local health department autopsy specimens from children with unexplained deaths also showed suspicious infectious disease etiology. He expected that histochemical staining would find evidence of influenza A virus infection in upper airway tissue in the "unexplained" cases.

Influenza Vaccine 2004-05 Supply Update

Presenter: Dr. Gregory Wallace

Overview: Past and expected influenza vaccine production and distribution.

Of the 95 million vaccine doses manufactured in 2002, 83 million were distributed; of the 86.9 million produced in 2003, 83.1 million were distributed. The timing was graphed of the fall and winter vaccine distributions since 1999. In 2003, most was distributed by November. This paralleled the "usual" distribution years (e.g., 1999, 2002) and differed from the years of distribution delays in 2000 and 2001.

The three manufacturers expect to produce >100 million doses for the next season, two producing inactivated vaccine and the other, live attenuated. About 6.3 million of the 8 million doses produced for the public contract will be purchased, exceeding the 4.1 million purchased

last year (not including stockpiled vaccine). The 2004 projections anticipate surpassing the 2003 demand, based on the public's knowledge about last season's early start and the new VFC recommendations to vaccinate children aged 6-23 months. There is no national data base of coverage for all age groups. In January 2005, a national module of the BRFSS state survey will assess coverage among those aged 6 months to 17 years. The 2003 NIS data are being evaluated for coverage among those aged 19-35 months.

The current recommendation includes 83 million individuals at increased risk. These include the 6-23 month-old cohort, plus ~2 million children that will become 6 months old during the influenza season (October to March). An additional 102 million at risk are also targeted (e.g,. health care workers, those aged <2 or >65 years, household contacts of those at high risk; those aged 50-64 years).

An additional $40 million will flow through the VFC to purchase ~4 million to 4.5 million doses for routine influenza vaccination. Distribution options are being developed based on expected demand scenarios. Half will be available by September and the balance, by January 1.

Discussion included that the vaccine expires after the season. If demand does not increase, what to do with that vaccine is a challenge for the stockpile as well as routine immunization. The expected 100 million influenza dose production includes about 21 million doses of the LAIV produced by MedImmune.

Kaiser Pediatric Vaccine Effectiveness Study, Kaiser Permanente Colorado

Presenter: Dr. Debra P. Ritzwoller, Kaiser Permanente Colorado

Overview: Study evaluating vaccine effectiveness (VE) of the 2003-4 influenza vaccine in preventing medically attended influenza-like illness (MAILI) among Kaiser Permanente Colorado (KPCO) member children aged 6 months to 9 years and 6-23 months.

In 2002, after the ACIP's encouragement to vaccinate children aged 6-23 months, KPCO began routine vaccination for children age <2 years. This continued in 2003-04, when the influenza season began earlier. Especially among children, it began before RSV activity and declined just as RSV appeared.

Dr. Kathy Edwards had presented to the ACIP the small amount of safety data available on the use of inactivated split virus influenza vaccine in children, and the small cohorts involved. Most studies did not focus on the safety aspects, other than the absence of severe reactions. The Neuzil follow-up study (unpublished) also was presented to ACIP, which reanalyzed Edwards' five-year study data comparing the use of the inactivated vaccine (N=635) to the live attenuated vaccine and a control group aged 1-15 years. The analysis indicated increased induration and decreased fever with age, and no severe reactions. Clearly, more epidemiologic information on the vaccine's safety among children was needed.

The KPCO of Denver/Boulder area began a study to evaluate the effectiveness of the 2003-04 influenza vaccine in preventing medically attended influenza-like illness (MAILI) among its member children aged 6 months to 9 years and 6-23 months. Ten percent of its 380,000 members are children aged <10 years. The study used KPCO's electronic immunization tracking system and electronic medical record system. KPCO's technical infrastructure allowed rapid

identification of vaccination status and ILI-related outcomes.

As of October 18, 2003, >50,000 shots had been given at the region-wide KPCO influenza clinics. Walk-in vaccinations were given through December 31. ≥146,000 members were vaccinated during the 2003/04 season. Estimated vaccine coverage by December 31 were 58.8% for children aged <2 years and 38.3% for 2-9 year-olds. The study limitations included the lack of a laboratory confirmation and that the more narrow definition of ILI could be biased if physician knowledge of the child's vaccination status influenced coding decisions. This was also an observational study, and could involve selection bias regarding who obtains vaccination.

Study methods. Age at enrollment: 6 months to 9 years on October 1, 2003, of children continuously enrolled in KPCO from October 1 to December 31, 2003 and one prior KP encounter. Vaccination status was determined as fully vaccinated (two flu shots ≥14 days before ILI); partially vaccinated (one flu shot in fall 2003 ≥14 days before ILI and no record of prior influenza vaccinations); and unvaccinated (no shot in 2003).

MAILI and the pneumonia/influenza codes were defined. Adjustment variables for the analysis were age, gender and prior disease categories, which were determined from KPCO disease management registries. In the survival analysis, vaccine status was included as a time-varying variable. Other models were run for a subset of 6-23 month-olds. Demographics and prior disease categories, vaccination status of pediatric members, the multivariate Cox proportional hazard model and the hazard model for 6-23 month-olds were charted.

The study conclusions, despite suboptimal antigenic match between the vaccine and the circulating influenza strains, were:

- Fully vaccinated children aged <10 years were 27%-50% less likely to present with a MAILI (depending on definition) than unvaccinated children.
- Fully vaccinated children aged 6-23 months were 49% less likely to present with pneumonia or influenza than those unvaccinated.
- For all children aged <10 years, partial vaccination (1 shot) was significantly less protective than two shots (0.73 vs. 0.49).
- However, partial vaccination was not found to be protective for children 6-23 months.
- A significant protective effect was more likely to be found using a more narrow definition of MAILI or ILI.
- KPCO's electronic medical record enabled a demonstration of vaccine effectiveness in a year when RSV and influenza did not co-circulate.
- The laboratory confirmation will be more important in other years with limited influenza circulation and high levels of non-influenza virus co-circulation.

This study suggested substantial operational challenges to vaccinating large numbers over a short time period, something likely to worsen with a universal ACIP vaccination recommendation for all children (or all Americans). KPCO's experience last season, as a result of the media coverage, of being inundated in a very few months (especially in their primary care clinics) supported that study's conclusion about the challenges upon a universal recommendation.

Discussion included:

- "Fully vaccinated" meant immunization in the two separate falls of 2002 or 2003.
- Dr. John Modlin commented that the only data available for efficacy among children with chronic conditions were for those with underlying asthma. The number of those in that

single population might be sufficiently large for analysis, or the sum total of children with chronic underlying conditions. When Dr. Ritzwoller said that the latter analysis could be done, Dr. Modlin encouraged that, since influenza vaccine efficacy among children with chronic conditions is a controversial topic.

- Dr. Walter Orenstein noted substantially different vaccine uptake between children with- and without underlying conditions. He asked, since vaccine efficacy this past year differed from previous years, if there were enough vaccinations given in 2003 or before that, which could support that same analysis. Dr. Ritzwoller was uncertain that this was possible. There are enough data, but the absence of laboratory confirmation and the different seasonal peaks, involving co-circulating viruses such as RSV, parainfluenza, etc.), may not allow certain ascertainment of ILI.

Influenza Vaccine Effectiveness, University Student Population

Presenter: Dr. James C. Turner, University of Virginia

Overview: Vaccine effectiveness study done early in the 2003-04 influenza season, evaluating a population of mostly young, healthy adult students at the University of Virginia.

Dr. Turner began with a tribute to Dr. Barry M. Farr, who he had hoped would have been able to give this presentation. His career is ending at age 53 due to an illness, after a career of nearly 26 years at the University of Virginia (UVA). He applauded Dr. Farr's world-class career and his hundreds of publications. He will be greatly missed by the field.

Knowing the mismatch between the influenza vaccine and the circulating strain, the UVA studied vaccine effectiveness (VE) early in the 2003-4 influenza season. They evaluated a population of mostly young, healthy adult UVA students. High transmission rates of respiratory pathogens have been documented among students living and congregating in dormitories, and VE is usually maximal among young, healthy adults.

Methods. In this retrospective cohort study, student health computer records were mined for influenza vaccination administered (from 10/3/03 to 12/1/03) and ILI diagnosed (from 11/3/03 and 1/5/04). ILI cases diagnosed <2 weeks after vaccine were excluded. A sensitivity analysis was done with an incidence density comparison that accounted for several factors: 1) assignment to the control group of vaccine recipients who were not immune until 17 days after the onset of the study period, as well as cases occurring <2 weeks after vaccination. That left 66% of vaccine recipients who had received vaccine >2 weeks before the analysis (accomplished by the final 12 days of the study). For the remaining unallocated cases, the vaccine group was assumed to be half immune and half non-immune, and the latter were assigned to the control group. ILI was defined. Rapid antigen screens were used first to confirm epidemic influenza, after which classical cases were diagnosed without screens. (Only equivocal cases were screened.) Vaccine availability was publicized to students and given to them on their request.

Results. During the study period, ILI was diagnosed in 266 (1.75%) of 15,163 unvaccinated students. Of the 3,473 who received inactivated influenza vaccine, 19 (0.55%) developed ILI >2 weeks after vaccination. Eighty-eight (36%) of 244 flu screens were positive during the first 2 months of the outbreak, and five (6%) of those positive tests were among those vaccinated.

A sensitivity analysis compared incidence density between an unadjusted (50/50) immune/non-

immune group. The vaccine group had 19 ILI >2 weeks after vaccine among an estimated 142,321 person-days (1.3/10,000 person-days). The control group had 282 ILI among 1,050,383 person-days without vaccine <2 weeks after vaccine (2.7/10,000 person-days), for a relative ratio of 0.497 (95%CI, 0.30-0.79). When allocated by 25/75 immune/non-immune, the rates were 1.45/10,000 person days for the vaccine group and 2.65/10,000 person days for the control group, for an RR of 0.546 (95%CI=0.32-0.87).

A parallel study of flu vaccine and ILI in UVA hospital employees (11/3/03-1/5/04) involved 3800 employees with patient contact, of whom 3085 (81.2%) were vaccinated. During the study period, 17 (0.45%) reported ILI. Nine (53%) of those cases were tested, and five (56%) the nine were positive. Of those five, one (20%) was in a vaccinee, but symptoms began within 2 weeks of vaccination. The study suggested VE, although lower than some years, of an RR of 0.31, while the Colorado data suggested no efficacy (RR=0.87).

Conclusions were:

- The vaccine was associated with a 50%-69% relative reduction in ILI among the university students during the first two months of the 2003-2004 season.
- Although this was a lower VE than in most years, significant efficacy occurred even though the presence of the Fujian strain was documented in Virginia.
- Student Health data (young, healthy adults) may allow rapid assessment of maximal VE during the early phases of a community epidemic.
- 15.6-fold more ILI cases (and higher statistical power) were available in Student Health than in Hospital Occupational Health over same period.

Discussion included:

- Dr. Nichol observed that a reduction of 50-70% is consistent with other efficacy trials that examined lab-confirmed ILI. If even 75% of the students with medically-attended ILI actually had influenza, the efficacy for reducing influenza would be even higher, so a rate of 50-69% is not lower than seen in other published studies. Some showed a reduction of medically-attended ILI of 30%-45%.
- Dr. Neal Halsey cited crowding as a risk factor for both acquisition and, potentially, increased severity of influenza. That has not been analyzed, but these studies may add that as another factor to adjust for analyzing efficacy study. Dr. Turner said that on- and off-campus residency could be determined, and that might relate to intensity of exposure. College students do not necessarily spend time at their dwelling, but it could be assumed that people living in the same dorm room could transmit, based on other illnesses. But in this case, on- and off-campus students are served by the same healthcare system, so the results probably were not biased.

Case-Control Influenza VE Study, Persons Aged 50-64 Years, Colorado 2003-04.

Presenter: Dr. Guillermo A. Herrera, NIP

Dr. Herrera began with a warm recollection of past friends who were intent on making the world a better place, many of whom did not survive to do so. He called for the use of evidence to make the world that better place, noting that life is too short to not do so.

Overview: Case-control study of the VE of 2003-04 influenza vaccination against medically attended, laboratory-confirmed influenza illness among persons aged 50-64 years, Colorado. The analysis focused on persons vaccinated <2 weeks prior to

influenza onset.

CDC conducted a study to estimate the vaccine effectiveness (VE) of 2003-2004 influenza vaccination against medically attended, laboratory confirmed influenza illness among persons aged 50-64 years. Laboratory confirmation was facilitated by the Colorado Health department's requirement to report positive influenza tests (although not for case contact information). Of the >10,000 cases reported by December 31, 2003, >500 were aged 50-64 years. Because of the age group and the characteristics of laboratory based reporting, serious cases are more likely to be tested and reported. Data was collected from the case individuals (random digit dialing) on demographics, illness onset/duration, vaccination/timing, doctor visits, hospitalization, and use of antiviral medication. Those who did not recall an influenza test or illness from November to December 2003, were excluded from the analysis.

Three controls were matched to each case. Frequency was matched by telephone exchange and gender. A logistic regression model was used for analysis. Persons vaccinated <2 weeks prior to influenza onset were considered unvaccinated and excluded from the analysis.

Results. Out of 574 reported cases, 330 were interviewed, and most of the balance could not be located. Control recruitment and demographics were presented. The cases and controls were fairly evenly matched in age (79% were 55-64), gender (40% male), insurance coverage (88%-90%), most (76%-79%) were vaccinated, and white (86%-91%). Such matching was not true of high-risk conditions, however, with 50% the cases reporting that versus 21% of the controls.

- Of those hospitalized (32.5% overall; 47.9 at high risk and 19% not at high risk), 42% were vaccinated overall; 55% of those were at high risk and 32% were not.
- For those excluded with ILI 1-13 days before illness onset, 45.9% overall were vaccinated; 55.5% of those were at high risk and 35.8% were not. The percentage hospitalized was 32.4% overall, 48.4 for high risk and 15.8 for not high risk.

The limitations of this retrospective study included the non-random allocation of vaccine; that controls were not tested for influenza, and that excluding persons with ILI also may have excluded persons with influenza. Vaccination status was self-reported and recall bias was possible concerning the dates of vaccination and illness onset. Persons without phones could have been under-represented, and lab-reportable cases generally over-represent patients who are more ill and hospitalized. The case-cohort method provided wide VE confidence intervals, and the overall vaccination rate at the time of case illness onset was unknown due to early season. Finally, historical vaccine coverage estimates would overestimate VE. A case-control study is underway.

The study concluded that estimated VE against medically attended, laboratory confirmed influenza, 33% of whom were hospitalized, was 52% for those not at high risk and 38% for those at high risk. These results were comparable to several other studies, which showed VE ranging from 15%-38% when the vaccine was a suboptimal match to the circulating strain; and a 50% VE for lab-confirmed influenza.

The study's recommendations:

- Supported the CDC/ACIP recommendations to continue to encourage vaccination even when the vaccine match is suboptimal
- Prospective, timely vaccine effectiveness surveillance is needed and ideally should be

conducted annually with a comparable methodology and population each year.

- Efforts to raise vaccination coverage should be continued.

Discussion included:

- The study used the term "effectiveness" as opposed to "efficacy" because CDC only uses the latter for RCT studies.
- Dr. Decker reported a recent Canadian report that found little or no apparent efficacy against ILI among selected long-term care institutions reporting outbreaks in season. But a 45% reduction in radiologically confirmed pneumonia and a 39% reduction in deaths among long-term facility residents were observed. The authors concluded no significant effect since the CI included 1.0, but Dr. Decker thought that to be a sample size artifact. The estimates of major effectiveness outcomes are comparable to those seen among other years in populations offering larger sample sizes.
- Dr. Neuzil cited Dr. Edwards' 5-year study reported in the *JID* in 1994. An RCT, this compared ILI and lab-confirmed influenza and demonstrated that ILI will always be underestimated. That study also had two matched and two mismatched years for influenza A viruses, and showed a higher VE (>70%) estimate than the Bridges study. She commented that "match" is a relative term that changes year to year.
- Having VE information is helpful mid-influenza season, but information on its lack of effectiveness is not. The methodology of these large databases should be standardized to allow rapid feedback during the influenza season and help the drive to get more people vaccinated. Dr. Fukuda reported that CDC is trying to put those prospective studies in place to accomplish that.

Update: National Influenza Vaccine Summit

Presenter: Mr. Dennis O'Marah, NIP, for Dr. L.J. Tan, AMA

Overview: Summit meetings to discuss vaccine demand, crisis planning, improving health care worker vaccination rates, universal vaccination, and improving vaccine uptake.

These summits have been co-sponsored by CDC and the AMA since 2001, in response to influenza vaccine production/distribution delays. They have broad representation from the vaccine industry, government, relevant professional organizations, public health, health care and community immunization providers and institutions, business, insurance and managed care, consumers and advocacy groups. A number of workgroups have been formed to address the issues of physicians, occupational and community-based vaccination providers, payment, vaccine distribution and reallocation, and consumer education. Workgroups are planned to develop a steering committee and to address issues of vaccine communications and long-term care.

The 2004 Summit proceeded from the premise that demand drives vaccine supply. This involves public and provider education and requires the delivery of a consistent message. It was acknowledged that the definition of "demand" requires clarification, relevant to both consumers and pre-ordering. An extension of the vaccination season was supported. It was agreed that crisis planning must be both proactive and timely. The input of stakeholders is critical, including the development of tiered recommendations to target vaccine to those at risk in periods of shortage, and vaccine reallocation procedures.

The Summit developed a list of areas in which it could help to advance immunization. For example:

- The Communications Workgroup in development looks to improve routine communications, create a year-round approach to influenza communications and to "put a face" on influenza. This involves the development of a "message map" to defeat the myths about influenza vaccination and to create a single, simple, unified voice for all its aspects.
- To improve vaccination rates among health care workers, model programs and relevant templates will be identified. The Summit will work with the JCAHO and NCSL to create new standards, regulations, and legislation to help make influenza vaccination mandatory for health care workers. The latter's goals will be approached collaboratively, and activity will build on the "Call to Action" and monograph published by the NFID.
- The move to universal vaccination will be supported, and a realistic timetable will be developed. Dialogue with Canadian and Australian colleagues will continue. A Summit Universal Vaccination Working Group will be created.
- To improve influenza vaccine uptake, promotion/support of "late-season" vaccination will be strengthened. Pediatric vaccination will be promoted, as will vaccination of women in concert with ACOG. Businesses will be educated on vaccination's benefits and urged to incorporate vaccine coverage into their health plans. Improved payment rates for vaccine/vaccination will be supported and private insurance outreach will be improved.
- In a broader concept of influenza prevention, the Summit will advocate for improvements in respiratory hygiene by health care workers, diagnostic testing, and use of anti-virals.

The National Influenza Vaccine Summit is perceived as a permanent but informal organization at the national level that works year-round on the issues. As a flexible entity, it can respond to contingencies, and it could expand attention to a broader array of adult vaccination issues.

There were no subsequent questions or discussion.

Priming and the Pediatric Influenza Immunization Dosing Schedule

Presenter: Dr. Katherine Neuzil

Overview: Data from first year of a two-year study comparing two influenza vaccine schedules used among 6-20 month-old children. The study is a collaboration of the University of Washington, the Madigan Army Medical Center, and the Duke University Medical Center.

Two doses of trivalent inactivated influenza vaccine (TIV) are recommended when a child first receives vaccine, but doing so in the fall before influenza season is challenging. This study compared TIV vaccine reactogenicity and immunogenicity among children aged 6-23 months in two groups: those who received an initial dose of TIV in the spring and the second dose in the fall, and another who received the standard regimen of two TIV doses in the fall.

Methods. Healthy children aged 6-20 months were randomized to one of the two experimental groups described above. Another open-label, control group of 40 children was enrolled in the fall. The schedule for vaccination and blood draw (twice for each patient) was presented for each group and exclusion criteria were outlined. Reactogenicity was monitored by telephone call at 3-4 days and parental diaries for 5 days, and daily temperatures were taken. All children

received two doses of TIV in the fall, in accordance with standard of care guidelines. Children in the early group (spring/fall vaccination) received a total of three TIV doses. Vaccines had no preservative and included antigens for H1N1 Moscow/10/99, A/H3N2 New Caledonia/20/ 99 and B Victoria-like. Immunogenicity was assessed by hemagglutinin inhibition (HAI). Adverse events assessed were injection site redness, swelling, fever (mild, moderate and severe), and drowsiness, irritability, vomiting and change in appetite.

Reactogenicity results. In all, 259 children enrolled in the early (114), standard (105), or control (enrolled in the fall, N=40) groups. Since no significant differences in age, sex, or time of vaccination was found between the standard and control groups, their results were combined in this presentation. The early group received their first TIV dose at a significantly younger age (11 months) than the other two groups (15 months, P<.001).

Complete reactogenicity data was available on >93% of participants after their first, second or third dose. These showed:

- No significant difference in fever (>100.1°F) among the groups, or in children after TIV doses 1, 2 or 3, nor for rates of reaction in the first 3 days post-vaccination.
- No influence according to age of vaccination on rates of fever, redness, or swelling.
- No differences in rates of fever, pain, or redness with increased time interval between shots (~4-6 months vs. 1 month between first and second TIV)
- No significant differences in other symptoms among groups (irritability, drowsiness, appetite)
- No significant difference in the percent of children who received two TIV doses according to different schedules (dose 2 administered in October or December, with influenza season beginning in November, 2003).

The study conclusions were that:

- Initial and repeated doses of TIV were well tolerated, with little fever, pain, redness, or swelling noted and no significant change in reaction rates with subsequent TIV doses.
- Similar rates of antibody titers >1:32 by HAI were seen to all three influenza antigens following the second TIV dose, regardless of when the first dose was given.
- Children given the first dose of TIV in the spring were immunized against influenza earlier and had fewer office visits than the Standard/Control group.

Further studies are underway to evaluate this schedule using a primary spring vaccine. This will have a different antigenic composition due to the changed H3N2 and B components this year.

Discussion included:

- Dr. Abramson observed that this study confirms that only one dose is needed in year two. He asked if any data indicated whether a dose at 6 months still primed the child for the next season, or if someone could be primed at <6 months of age (e.g., at age 3 months in spring and then given full protection in fall). Dr. Neuzil presented as the ideal, giving the first dose of vaccine year-round. Only 20-25% of the study children were vaccinated by 6 months, too few to draw any conclusions; but that analysis might be possible this year. A subset could be primed at age 3 months and earlier, and given dose 2 in the fall.
- The 1:32 cutoff is good for comparing immunogenicity among the groups, but analysis of the distribution of antibody titers (now being analyzed) would be more sensitive.
- Dr. Martin Myers reported data presented to VRBPAC last fall on two groups of children aged 15-23 and 6-15 months. The magnitude of responses to each of the antigens

differed, as assayed at FDA and at CDC. He asked if younger children's immune response is less. Dr. Neuzil repeated that the numbers prevented such a breakdown. However, she thought that the age would bias against the early group vaccinated in spring. The standard groups were always vaccinated at age 4-5 months older.

- The expiration of vaccine in June should be extended if year-round vaccination becomes a reality.
- When a strain changes and the first dose is the old vaccine and the second dose is the new vaccine, Dr. Plotkin asked if the responses would be equal to two new-vaccine doses. He advised doing a neutralization test as well as an HAI test for specificity for strain utilization.
- Mr. Hosbach, of Aventis, said that the expiration date deliberately ends in June in anticipation of the next season, to avoid the co-circulation of two different vaccines, but there are data that support its continued viability beyond that date.
- Dr. Katz raised the issue of diagnostic testing. He asked what Dr. Neuzil had heard from parents whose 6-12 month-olds develop RSV or adenovirus, etc., after vaccination, and asked how their confidence in the vaccine's effectiveness could be maintained. Dr. Neuzil agreed that this is a challenge, more so in pediatric than internal medicine practices. Care is needed to educate parents that this vaccine will not protect against all respiratory illness in the winter time.
- Dr. Fred Rubin, of Aventis, commented that the neutralization test only enhances the sensitivity of detecting additional antibodies, over the already-specific HAI.
- Dr. George Peter asked if the first dose must be strain specific, or if it could be generic. The reason children receive two doses is because they are not primed by natural infection. If that is true, the strain antigen of the first dose might not matter. Dr. Neuzil agreed. Any vaccine could be given to a child aged >6 months at the beginning of the influenza season.
- Dr. Schaffner called attention to an NFID announcement in the meeting materials about its development of a toolkit to help pediatricians and family physicians reach the 6-23 month-olds to be immunized. The toolkit is also available electronically.

Update: Pandemic Influenza Preparedness and Response Plan

Presenter: Dr. Ben Schwartz, National Vaccine Program Office (NVPO)

A mockup of the planned pandemic plan Website was shared, which will be regularly revised and updated. The U.S. pandemic plan has been developed and cleared by DHHS. After it is reviewed by other departments, it will be released for a 60-day public comment period. That input is important, as it will provide fresh perspectives on decision-making on currently unresolved issues, and help identify and improve unclear (or missing) areas of information.

The core plan describes the roles of national coordination and decision-making in the event of a pandemic. An overview of key preparedness issues and an outline of response actions at the national, state, and local levels are provided. Two independent guides aid planning by state and local health departments and health care systems. The lag behind public health in planning. Ten annexes provide more detailed and technical information on key preparedness/response issues.

Three annexes to the pandemic plan were highlighted at this meeting: a strategy to decrease disease transmission early in the pandemic (when sufficient vaccine may not be available), lessons learned from the swine influenza program (a pandemic that never occurred), and the

preparation of a plan based on the similarities and differences between influenza, smallpox and the SARS outbreaks which are relevant to all public health emergencies.

The current plan describes federal coordination (command and control) activities, particularly by DHHS agencies; provides the legal authorities for pandemic response actions; describes the currently available infrastructures and technologies, and gives guidance on strategies for response actions and supporting roles. It does not (yet) address a public/private sector mix for pandemic vaccine purchase and distribution, define priority groups for vaccination (the goals for that definition are being developed), have indemnification or liability issues, or provide such specifics as who could provide essential community services, or how to run a mass vaccination clinic or supply education and communications materials. Key issues not yet included in the plan are how to gather public and expert (e.g., ACIP) input, particularly on: 1) on the decision making process for unresolved issues; 2) definition of unclear or incomplete plan areas; and 3) additional guidance of what other materials might be useful.

Aside from the plan's development, CDC has enhanced surveillance and expanded its surveillance collaborations in Asia and with the WHO. To ensure the security and supply of vaccine, DHHS funding has been allocated to assure year-round egg availability and to expand and diversify U.S. influenza vaccine production with cell culture technology. The NIH is obtaining and testing pilot lots of H5N1 vaccine, an Oseltamivir stockpile will be established, and bioterrorism funds supported state and local pandemic planning.

Discussion included:

- ACIP and its Influenza Workgroup will review and comment when the plan and the Website are released.
- The Canadian plan also is available for review. Dr. Poland suggested a case study to see why, in view of what is known, it took almost 30 years to develop a pandemic plan.
- Dr. Marcuse wished for discussion of vaccination prioritization in a pandemic. DHHS has discussed this at a recent meeting of the CSTE, whose input was requested.
- In view of increasing influenza vaccine production and related VFC funding, the Influenza Workgroup suggested that the ACIP encourage CDC to enhance its national influenza vaccination campaign (e.g., through a coordinated national plan to promote influenza vaccination). This relates to the need for effective communication strategies and partnering to get the word out, particularly when the supply status is known after Thanksgiving.
- Mr. Hosbach reported Aventis's anticipation of producing 48-50 million doses, most to be distributed and delivered in September and October. Dr. Pada also urged a push to continue vaccination at least into the season and perhaps through it. This could help to avoid last year's wastage of 12 million of the 90 million doses produced, when vaccination stopped in mid-November. Dr. Kathleen Coleman reported MedImmune's expectation that 1-2 million doses of LAIV will also be available in October for the season.
- Dr. Abramson urged emphasis on vaccination of household contacts.
- Changing the June 30 expiration of the current vaccine probably could not be addressed in time by the FDA. Aside from the issue of having two vaccines co-circulating, FDA needs the stability data to support extension beyond June. Mr. Hosbach reported that the Aventis vaccine is usually licensed in July to allow supply for cases (e.g., in Alaska). Study of vaccine stability >12 months is needed.
- Dr. Deborah Wexler reported the last Influenza Summit's development of a laminated

card ("Pocket Guide for Influenza Vaccination"). It was endorsed by 15 medical associations and the 500,000 print run was depleted. They hope to issue it again this year.

- The ACIP will discuss 1) the use of end-of-season vaccine to prime young children (more information is needed), which could be adopted as an ACIP approach; and 2) the immunology issues related to potentially having two vaccines available. Those issues will be referred for discussion to Dr. Fukuda and others, who will report back at the October meeting. Dr. Hadler asked that recommendations be forwarded to him, Dr. Cochi, and Dr. Chapman.
- Dr. Marcuse commented that the risk of ensuring an adequate vaccine supply even with unpredictable factors is now carried by the manufacturers, who decide how much to produce. There should be a different partnership between government and industry to ensure the supply, share the risk, and provide some accountability for demand. Dr. Levin reported that NVAC would consider those issues in its following week's discussion of the IOM report on financing the vaccine supply. The latter's content paralleled Dr. Marcuse's points.

Statement on Influenza Immunization of Health Care Workers

Presenter: Dr. Jane Siegel

Overview: Rationale for improving healthcare worker vaccination rates; proposed evidence-based recommendations; likely results.

The rationale for improving health care worker vaccination rates includes: 1) the extensive documentation of influenza transmission in health care settings; 2) study data with serologic evidence of influenza infection during the winter among 23% of healthy adults; 3) the importance to prevention efforts of influenza vaccination of patients/residents and staff; and 4) that health care worker vaccination coverage remained flat (at ~38%) from 1997-2002.

To address this, evidence based recommendations are needed on the influenza vaccination of healthcare workers. A literature review was done to investigate the evidence on the following.

The impact of vaccination on healthcare worker absenteeism.

- Wilde (*JAMA* 1999; 281:908) showed an 88% and 89% reduction, respectively, in influenza A and B after vaccination, 29% fewer days absent due to febrile URI and 53% less days absent.
- Saxen (*PIDJ*; 1999: 779-83) showed a 28% reduction in total sick days due to URI and in days the worker felt unable to work, fewer days of respiratory illness or symptoms, and fewer antimicrobials prescribed. There was no difference in absenteeism among health care workers with or without direct patient contact.
- Among healthy working adults, Nichol (*NEJM*, 1995) showed a 25% reduction in URI episodes and related 43% and 44% reductions in sick leave days and physician visits, respectively. The direct and indirect cost savings were calculated to be $46.58 per person vaccinated.
- Bridges (*JAMA* 2000; 284: 1655-63) showed a 50% reduction in lab-confirmed influenza in the 1997-98 season and 36% in 1997-98; a negative effect (-45%) in lost work days 1998-98, but a 32% reduction in 1998-99. Societal costs in 1997-98 were calculated at $65.59/person and $11.17 in 1998-99.
- Demicheli (Cochrane Library, 2004) showed 0.4 (95 %, CI 0.1-0.8 days) fewer lost work days among healthy adults.

- Nichol (*JAMA* 1999; 282: 137-44) showed LAIV producing a 19-24% reduction in severe febrile illness and febrile URI, an 18-28% reduction in work loss days, and a 43-47% reduction in the number days of antibiotics.

The impact of health care worker vaccination on nosocomial influenza transmission.

- Potter (*JID* 1997; 175: 1-6) compared vaccination of health care workers and patients in long-term care facilities. They indicated decreased mortality from pneumonia-related deaths in patients with health care worker vaccination; greater than that from patient vaccination.
- Carman (*Lancet* 2000; 355: 93-7) followed up on that to compare institutions where the health care workers were vaccinated (coverage 51% when offered) or not (5% coverage). Crude patient mortality was significantly decreased in the former. PCR results of living patients did not differ in percent positivity, but those of patients who died in facilities with vaccinated workers showed a significant decrease in PCR positivity. Another analysis of functional level showed the same differences in mortality.

The impact of influenza vaccination of healthcare workers on patient safety.

- The Stevenson (*CMAJ* 2001; 164: 1413-9) surveys of Canadian long-term care facilities reviewed staff vaccination and outbreak rates. The overall staff vaccination rate in 1998-99 was 35% (median per facility 40%) and the resident rate was 83 (median 90%). The resident vaccination rate was significantly inversely related to outbreak incidence. Staff vaccination rates overall had no significant effect, but did when stratified by facility size.

Remaining questions include how to use data from outbreak control to determine:

- Whether TIV shedding data indicate asymptomatic viral shedding in immunized individuals, and if so, if it has clinical significance. Two studies offering inactivated vaccine showed less shedding among the vaccinees.
- How the valid it is to extrapolate data from healthy, working adults or from experience in long term care facilities to the overall health care worker population.
- Whether evidence-based ratings of recommendations should be issued.

Relevant to the latter, the HICPAC system of recommending based on evidence was shared. These recommendations are based only on the peer-reviewed literature:

- Category 1: "Everyone do it." 1A levels are strongly recommended for implementation and strongly supported by well-designed experimental, clinical or epidemiologic studies; 1B, strongly recommended for implementation and supported by some experimental, clinical or epidemiological studies and a strong theoretical rationale; 1C, required by state or federal regulations, rules or standards (with or without supporting data).
- Category 2: "Do it if you want." Suggested for implementation and supported by suggestive clinical or epidemiological studies or a theoretical rationale.
- No recommendation: "No one knows what to do." This is an unresolved issue of practices for which insufficient evidence or no consensus regarding efficacy exists.

Among strategies to improve health care worker vaccination, several types of recommendations are possible:

- All health care workers should receive influenza vaccine annually to protect patients (Potter 1997, Carman 2000, Stevenson 2001) and decrease absenteism (Nichol 1995, Bridges 2000, Saxen 1999, and perhaps Wilde 1999).
- All healthcare workers should be provided with the rationale to support universal

participation in the annual influenza vaccination.

- All healthcare workers and students of healthcare professions (Nichol 1997; Watanakunokorn 1993; Bryant [in press]) should be provided influenza vaccine at no cost.

Additional strategies to enhance vaccine acceptance by healthcare workers could be:

- Monitoring of influenza vaccine uptake during the annual campaign; providing feedback and focusing education and vaccine delivery activities in deficient areas.
- Compiling unit- or group-specific reports using appropriate denominators.
- Using mobile carts or "influenza deputies."
- Role modeling by institutional leaders.

Other high-risk areas involving healthcare workers are those involving contact with healthy children aged <2 years, with the elderly, and pregnant healthcare workers. After this presentation, next steps to be addressed included development of recommendations for review by HICPAC and ACIP and the publication of recommendations in MMWR by the fall of 2004.

Discussion included:

- If a recommendation is to be published in time for this season, it would need to be drafted and voted on at this meeting, using the HICPAC rating scheme until the ACIP's is fully developed. Waiting for the latter would delay a recommendation to the 2005 season. There was consensus to issue something for this fall and then updating later according to the ACIP evidence-based format.
- Related issues identified included who would pay if it is recommended that medical students receive the shot at no cost, and if allied health school students were included in the recommendation. Listing this as a strategy for success, to remove the cost of the influenza burden, might be an approach. Making this statement as strong as possible was endorsed, since this is a safety issue for healthcare workers and a clinical issue for patients. The data on this are "clear and unambiguous."
- Vaccination is already recommended and most hospitals already offer it to their staff, but compliance is still poor. The data are not strong that this vaccine creates a safer environment, but that is also true of measles and rubella vaccination. Research into why healthcare workers resist vaccination is needed, to overcome those reasons.
- In Canada, the Potter study helped produce an authoritative statement which produced a significant change among healthcare workers. Factors contributing to high and low coverage in facilities included the facility director's strong support and the ease of vaccination on all shifts. But problems remain in large acute care hospitals that have high casual staff turnover and poor resources. That is an issue of resources, not the recommendation, but the latter requires "teeth" in terms of fallout for an unvaccinated healthcare worker, as well as resources to implement those guidelines in the facilities.
- After four decades of recommendation and little compliance, something is needed to push the goal further. A separate, stand-alone statement targeting healthcare workers has value.
- As a nurse, Ms. Betsy Fraser, of Birmingham, defined the bottom line: influenza can be transmitted 48 hours before symptoms emerge. Health care workers demonstrating by example that the shot is safe provide a strong lead for their patients. She advised simplifying the message to ensure that busy, distracted healthcare workers will hear it. Many studies indicate that healthcare workers are "clueless about the rationale for" the vaccination. Education is the first step, perhaps by professional organizations that this is

expected of healthcare workers.

- Publicizing vaccination rates has been shown to be an effective impeller, but there must be a measurable data point.

A statement was prepared overnight and presented on the following day. CDC staff advised on the perspectives of policy and adult immunization.

Adult Immunization: NFID/National Coalition Presentation
Presenter: Dr. Kristin Nichol

The National Foundation for Infectious Diseases (NFID) presented its Call to Action for influenza immunization of healthcare workers to the ACIP last February. It has been endorsed by multiple organizations. Many of the latter are considering action to improve vaccination rates. The NFID also issued a document, "Improving Influenza Vaccination Rates in Healthcare Workers." This addresses the overall impact of non-vaccination, the lack of knowledge of the vaccination's rationale by healthcare workers, and its potential impact. Since non-vaccination is associated with outbreaks, a comprehensive, concerted effort is needed by health care providers and institutions, insurers, and employers to improve vaccination rates. The report outlines three specific strategies for three intervention areas to do so: 1) increase demand, 2) enhance access, and 3) reduce provider barriers. Employer support of vaccination, provision of easy access, and education of the care worker to dispel myths, are critical.

Adult Immunization Schedule 2004-2005
Presenter: Dr. Gregory Poland, Chair, ACIP Adult Immunization Workgroup

Overview: Update on adult pneumococcal revaccination and the adult immunization schedule. The workgroup hoped to present data on immunogenicity, reactogenicity, and safety data at the next meeting.

One adult immunization schedule is color-coded and organized by age group and then by medical/other indications, another is coded by vaccine. Small changes were outlined: an added chart row for health care workers; removal of the cautionary footnote against using influenza vaccine in pregnant women in the second and trimester (and noting approval of that vaccination by ACIP, AAP and ACOG). The updated influenza vaccination footnote would now be consistent with the 2004 recommendations released.

The workgroup discussed the pro's and con's of July- versus October schedule release. Feasibility issues require an October release to allow parents to prepare vaccination programs, order vaccine and allow timely reminder for college entrants to be vaccinated in fall. Also discussed was the schedule's complexity versus the desire to have the format match the childhood harmonization schedule (ease reference by family practitioners consulting both). They considered whether more risk-based groups should be added, versus simplifying the schedule's appearance by age, and whether it is too much or too little information. The concept of offering a life-span schedule was discussed. The schedule was reviewed by focus groups conducted by Dr. Gary Freed of the University of Michigan. He found that the vaccines were not being routinely administered by clinicians, and the schedule seemed to improve the knowledge of needed vaccinations.

The ACIP was asked to approve the presented adult immunization schedule, to be released this fall or perhaps in July. Also presented were the potential childhood/adolescent schedule, the adult immunization schedule, and those two merged. All were age- and condition-based.

Dr. Birkhead moved to approve the recommended adult schedule as presented. Dr. Zimmerman seconded the motion. There was no discussion.

Vote
In favor: Zimmerman, Womeodu, Traenor, Gilsdorf, Finger, DeSeda, Campbell, Birkhead, Abramson, Levin, Poland.
Opposed: None
Abstained: Marcuse, Stinchfield

The vote passed.

Dr. Marcuse noted that influenza and perhaps hepatitis B are vaccines that could be given electively to people to reduce their disease risk. The color scheme was found to be clear only for persons at risk (e.g., from a medical exposure). Considering the universal influenza vaccination recommendation to come for children, there should be a class of vaccines that might be "encouraged" as done in footnote 5, perhaps with references. The same issue will pertain to hepatitis B vaccination.

The ACIP was in consensus to support the merging of the childhood, adolescent and adult schedules so that they could be used either in combination or as stand-alone schedules.

Pilot Project to Enhance Public Participation; Keystone Center Offer
Presenter: Dr. Roger Bernier, NIP, Mary Davis-Harris, Keystone Center (by phone).

Dr. Bernier provided a background on the Wingspread Public Engagement Planning Group conference, which developed a proposed Vaccine Policy Analysis Collaborative (VPACE). This resulted from a special assignment to explore how the immunization community might enhance public engagement in decision making about vaccines. The assumptions on which this effort was based were to bring together all the interest groups that normally do not interact, to work together to create a supportable proposal, in the hope that this achievement would attract wider interest in the immunization community and funding support.

The current levels of public participation were outlined, as were the organizations involved in the initial Wingspread planning group. The rationale for involving the public was summarized as "the right thing to do," to share decisions; "the best thing to do," to allow better decisions, and "the useful thing to do," to result in supported decisions. More importantly, doing so would build relationships and trust, the key outcomes.

The key features of this enhanced process were outlined. Participation would involve stakeholder groups and the general public in two phases (Tiers 1 and 2). A "safe harbor" environment and a "not strictly partisan" ethic would be the mode of operation for its activities (dialogue, analyses of pending decisions, tracking). Pending government decisions would be discussed, to produce a list of options with pros and cons. VPAEC would not be a new advisory committee, as it would not issue recommendations. It was intended to enhance such present activities as public hearings. It would be a time-limited demonstration project to explore how to

engage and increase constructive dialogue in vaccine research and policy decisions. The IOM Vaccine Safety Review Committee recently recommended that as well. The potential benefits were large and the risks were low.

VPACE's discussions would involve issues of technology and values, cross-cutting programs and implementation. The government would consider the VPACE report and provide feedback. Funding of $75,000 to support a three-year pilot of this work was proposed by the Keystone Center. The pilot involved the parallel work of a standing NVAC Workgroup (Chaired by NVAC member Ruth Katz) and that of an IOM Roundtable. The IOM had agreed to work as a convener and to supply an expert on vaccines.

Ms. Davis-Harris related the endorsement of this idea by Keystone's steering committee. They suggested that the optimal use of meningococcal vaccine might be an appropriate pilot project. It is a current and timely issue, and an ACIP workgroup was discussing a universal versus more-selective recommendation. She asked if ACIP was interested, if they agreed that meningococcal vaccine was an appropriate issue to address, and if they would consider and provide feedback on the pilot's results. Other issues that also could be suitable for address were hepatitis A vaccine, and pandemic influenza priorities, etc. There was a time constraint on Keystone's offer, however, in that they wished to identify an issue in the next two weeks in order to submit to their Board at their meeting the first week of July.

Discussion included:

- Dr. Gellin reported that the NVAC workgroup headed by Ms. Katz is looking at this proposal, as well other models through which to engage public participation, at its September meeting. They are not seeking issues to address; there could be a long list (e.g., there will not be enough influenza vaccine to meet the pandemic influenza plan). Dr. Bernier clarified that the NVAC workgroup had only the original "blueprint" of this concept. This funding could put that as a real-life application to assist NVAC in its discussions.
- Dr. Gellin remained unclear as to how much the pilot would cost, who would lead it (e.g., a Fellow?), or who would be involved and how they would be chosen. Ms. Davis-Harris reported the assumption that the $75,000, plus donated time from IOM and other public engagement groups would pay for this pilot on one issue.
- Dr. Bernier clarified further that a group such as the Wingspread participants would be involved, and probably involve many of those persons. They were selected to be neutral, involving both critics and supporters of vaccine. A two-day session would be convened to discuss options that would then be fleshed out with an analysis as rich as possible. Beforehand, a broader public engagement would be done to inform the stakeholders' two-day meeting, and the latter would be reported to ACIP.
- Dr. Wexler stated that vaccine support organizations such as P-KIDS and the IAC withdrew after the first meeting when agreement was requested to the VPACE concept. All public organization representatives were not involved, so the process was not "outside in." She heard from others that the NVAC lead was welcomed by those who continued. She asked who the group steering committee members behind this $75,000 project were, as this project was not discussed at Wingspread. She suggested a poll of the Wingspread invitees to assess their support of the VPACE concept as the ultimate model for public engagement. Dr. Bernier identified the Lounsbery Foundation as the funding source, and the steering committee was listed on the back of the VPACE proposal cover. Its members included several ACIP members and attendees at this

meeting, who were named. In all, ~10 people from the original steering committee participated.

- Dr. Plotkin observed that there seemed lingering dissension to this concept and perhaps a lack of enthusiasm from industry. He advocated public engagement through NVAC. It was established, at least in part, to allow that, and unlike the ACIP, it addresses policy matters that benefit from external input. Dr. Abramson found the meningococcal vaccine proposal interesting and thought that NVAC could propose that to ACIP. Dr. Nichol thought that structured input on certain themes (e.g. vaccination cost utility; political, medical, or legal implications; issues of distributive justice, etc.) could be useful.
- Dr. Bernier explained that the pilot proposal was designed not to bypass NVAC, but to provide it with real-time input. As an ACIP workgroup topic (as are hepatitis A and pandemic influenza vaccination), it was presented to ACIP first.
- Dr. Peter stated that the NVAC workgroup was formed in response to the VPACE proposal a year earlier, when NVAC endorsed the concept of public participation. He was cautious about the two-week deadline, noting that Keystone could use the funding to do this independently. ACIP would always be interested to hear the results, but he felt that the requested endorsement was premature. Dr. Hess agreed and added the importance of the satisfaction of those involved in the process, without which the process would ultimately founder.
- Dr. Levin clarified that endorsement was not being requested, only an examination of the work product and ACIP's opinion of the usefulness of the VPACE concept.
- Dr. Thomas Zink, of GSK, was proud to have participated in the Wingspread conference, which he termed an enjoyable and educational experience. However, he would have preferred to not proceed with the process until such details as raised by Drs. Gellin and Wexler were worked out. He stated the importance to GSK that this process be done correctly, and approved NVAC as the right place to do it.
- Dr. Marcuse favored this as an NVAC pilot, since public participation is most needed when questions of values are addressed (e.g., in prioritizing influenza vaccine in a pandemic, weighting individual and public health, such as limiting spread from children or saving the lives of the elderly). Such a discussion can help to provide guidance. Dr. Evans thought that all, NVAC members included, would benefit from seeing such a model in process.
- The length of time anticipated by Dr. Bernier to deliver a product was 3-6 months, which could allow the processing of 2-3 issues a year.
- Dr. Abramson stated that ACIP should not select the issue to be addressed; NVAC should.

Dr. Zimmerman moved to stop trying to achieve consensus and to proceed with the agenda. Dr. Treanor seconded the motion. Although it seemed a reasonable plan to him, he did not know enough about it to make an informed decision. Dr. Finger stated that the Meningococcus Workgroup would seek an ACIP decision on that in October 2004 or February 2005 at the latest. That would not be linked to the funded pilot. Dr. Levin summarized ACIP's willingness to review the project's work product, if it is done. Dr. Bernier accepted that, and said Ms. Davis-Harris, although Keystone would prefer to have the legitimacy conferred by ACIP agreement that this is an important issue on which to deliberate and give feedback. Dr. Zimmerman withdrew his motion and Dr. Levin summarized ACIP consensus to consider the VPACE project product. Selection of the topic was left up to the Wingspread group. Dr. Bernier hoped that some NVAC workgroup members would participate, especially those who were not at Wingspread, as well as interested ACIP members.

Agency Updates

Department of Defense. Dr. Phillips deferred reporting on the DOD smallpox program, as it was to be presented the following day.

Food and Drug Administration. Dr. Baylor reported that he would inform the ACIP of the agenda for the upcoming VRBPAC meeting.

National Institutes of Health. Dr. Curlin reported that the NIH is maintaining a vigorous vaccine research agenda. Issues germane to the ACIP are discussed in workgroups that include ACIP membership.

National Vaccine Program Office. Dr. Gellin announced an NVAC Vaccine Financing Workshop to be held on the following week. Its pandemic planning process and public participation workgroup processes had already been presented. At the February NVAC meeting, the Acting Assistant Secretary of Health, Dr. Biato, asked the committee how pandemic influenza planning could be better done. NVAC has three workgroups addressing that.

Vaccine Injury Compensation Program. Dr. Evans reported the VICP's status, now in its fifteenth year of operation. To date, 2004 vaccine compensation claims total 787, versus 2589 at this time in 2003. Most (90%) of the latter were due to the autism/thimerosal omnibus proceedings. A quarter of the non-omnibus pending claims involve DTaP; another 25%, MMR; HBV involves 20%. Of the 4000 vaccines administered before 1988, all but one claim have been adjudicated. The VICP awards total $1.4 billion to date, of which ~$900 million went to pre-1988 claims. More than $575 million paid post-88 claims. The Trust Fund has $2 billion.

In VICP-relevant legislation, a bill to add hepatitis A and influenza vaccines to the list of taxable vaccines has passed the House and Senate. When the Secretary publishes a Notice of Coverage in the *Federal Register*, the vaccine will be listed provisionally on the VIT as new vaccines recommended by CDC for routine administration to children. That was published on May 29, 2004 for routine vaccination of 6-23 month-olds against influenza. After the Notice of Coverage conveys the effective (publication) date, injury claims can be filed. The Secretary will publish a Notice of Proposed Rule-Making, which includes a 180-day public comment period. Upon publication of the final rule, these vaccines will be added to the VIT under a distinct listing that would cite any applicable injury defined by the Secretary.

Any trivalent vaccine against influenza will be covered by the VICP. However, a pandemic product would not be covered, as that would be monovalent and would have to have its own liability resolution.

> *Civil thimerosal litigation* includes at least 350 ongoing individual suits for injured children, but all the suits requesting medical monitoring due to thimerosal adulteration of vaccine have been dismissed. Derivative claims proceed, depending on state laws. The first cases on the merits of causation, involving Merck, are likely to go on trial in Baltimore in early 2005. In the thimerosal omnibus autism proceedings, the discovery process that was to end 7/1/04 was indefinitely extended by the federal claims. With the IOM's definitive report on vaccines and autism, it is hoped that that process will end soon. Only a few claims have opted out of the VICP program (which is allowed after 240

days in the VICP program) to seek remedies in the tort system.

Discussion included:

- *When does the process begin to add the meningococcal vaccine to the VIT? Upon a recommendation for its use in children or adults, how fast could the VICP process cover that vaccine?* Once CDC publishes the recommendation, even if it does so for only one age group, then Congress imposes an excise tax. The Secretary does nothing until there is an excise tax date, but overall activity can begin with CDC's published recommendation.
- LAIV will be covered as well as the inactivated vaccine.

National Center for Infectious Disease: Dr. Alison Mawle updated the ACIP on the Division of Global Migration and Quarantine's work in Cote d'Ivoire to assist refugees fleeing the civil war there. At least 8000 of those refugees were settled in the U.S., but beforehand, CDC responded to three large outbreaks. These outbreaks highlighted the constant opportunities for re-introduction of diseases now controlled in the U.S.

- *Varicella and measles among the U.S.-bound refugees*. (Refugees need not be vaccinated before coming to the U.S.; they can be vaccinated at arrival.) When case isolation and restricted movement could not resolve the outbreaks, CDC distributed varicella and measles vaccine donated by Merck and UNICEF. An EpiAid done by NCID characterized a new strain of varicella. Working with the Cote d'Ivoire Ministry of Health, the State Department, U.N. High Commission on Refugees, WHO and others, NCID evaluated and vaccinated in one week >6000 refugees in 19 different transit centers. That stopped the outbreaks and resettlement was reinstituted in April 2004.
- *Rubella*. Then, in late April, rubella broke out, and further vaccination with MMR purchased by the State Department was administered to >3000 refugees. Post vaccination surveillance is ongoing.

Finally, Dr. Mawle announced, to applause, that CDC's Scientific Research Award for Lifetime Scientific Contribution was given to Dr. Walter Orenstein, former NIP Director.

National Immunization Program. Dr. Steven Cochi reported NIP successes in 2004, which also reflected well on the ACIP's hard work.

- Hepatitis A dropped radically after the 1999 ACIP recommendation for statewide routine hepatitis A vaccination of children. Targeted to areas of highest incidence, 50% coverage was achieved in 11 high risk states. The drop in incidence in those states was paralleled to those areas where vaccination was suggested. Previous racial and ethnic disparities were virtually eliminated.
- Invasive pneumococcal disease incidence is measured by the NCID's Active Bacterial Core (ABC) surveillance system. By the end of 2003, 68% of children aged 19-35 months had received PCV7; that coverage now approaches 94%. A May 2004 *JAMA* article reported a marked parallel decrease in pneumococcal disease. By 2003, reductions ranged from 77% among <1 year olds, 83% among 1 year-olds, 64% among 2 year-olds, 60% among 3 year-olds, and 46% among 4 year-olds.

Among the challenges to NIP's work is vaccine financing. The $45 cost in 1985 to fully immunize a child in the public sector rose to $186 in 1999; it is now $472 to do so. The 150% rise by 2004 in the cost of the full vaccine series was paralleled by only a 60% appropriation increase since 1999. In fact, funding decreased slightly in the last 2-3 years. The number of

children who could receive the full series from the Section 317 program dropped from 787,000 in 1999 to an estimated 467,000 in 2004. Nineteen states still have a two-tiered policy in which PCV is not offered in public clinics to children who are not eligible for the VFC program. Paradoxically, while poor children covered by the VFC get that service, under-insured children served by state public immunization systems, do not.

Dr. Cochi shared, but did not elaborate upon, the new CDC organizational chart. Earlier in June, CDC Director Dr. Julie Gerberding convened a two-day meeting of a multi-representative panel Blue Ribbon Panel on Vaccine Safety (e.g., AMA, AAP, AAFP, AAHIP, PhRMA, academia, advocacy groups, government agencies and advisory committees). Its objectives were to:

- Review the structure, function, credibility, effectiveness, efficiency, and support of CDC's vaccine safety program and assess how it could be maximized and sustained.
- Review the intramural and extramural collaborative activities of the vaccine safety program and determine their effectiveness and efficiency.
- Determine the optimal organizational location for vaccine safety activities within the CDC to ensure scientific objectivity, transparency, and oversight while at the same time ensuring that program priorities are established appropriately and are relevant to the immunization program and stakeholder needs. This objective was particularly crafted to address conflict of interest, or any perception of same.

The panel, which expressed a strong appreciation of the existing vaccine safety infrastructure, will report its findings to Dr. Gerberding. A draft summary of the meeting will be on the CDC Website, probably in early- to mid-July, which will summarize the major discussion points and ideas. Comments were invited.

The panel agreed that the NIP is the best organizational location of vaccine safety activities. NIP stressed the need to retain those strong activities in its Epidemiology and Surveillance Division. They agreed that there was a need to address the perception of conflict of interest, to optimize the program's effectiveness, to more systematically develop the research agenda, and to enhance the extramural research program. Research would benefit from the oversight of an external scientific advisory group, perhaps including members of the ACIP, HICPAC, NVAC, and VRBPAC. Dr. Cochi hoped that a dialogue on that would begin soon.

Discussion included a question of whether the 70% pneumococcal coverage involved a disparity between those not receiving it in VFC clinics versus those who do. Dr. Cochi reported analyses underway to determine that and hoped to report back with hard data.

Public Comment was solicited. Ms. Lynn Bozof had signed up to speak, but was not present. With no other comment, the meeting adjourned at 6:00 p.m.

JUNE 24, 2004

Healthcare Worker Influenza Vaccination Recommendations

On the following morning, Dr. Zimmerman reported the previous evening's work by himself and Drs. Jane Seward and Ray Strikas on the HICPAC/ACIP healthcare worker recommendations. They reviewed the current ACIP healthcare worker recommendations; the CDC/ACIP recommendations on MMR and varicella that pertain to state laws; the current HICPAC pneumococcal and isolation recommendations; and the input from the previous day's discussion. Input from stakeholders will be needed. Seven issues and proposed options were presented:

1. Current ACIP wording: "Healthcare workers should be vaccinated against influenza annually."
   – *Proposed addition:* "All eligible healthcare workers should be vaccinated against influenza annually to protect their patients, themselves, their families and their communities and to decrease healthcare worker absenteeism."

Discussion: There is no evidence to support that vaccinating healthcare workers protects the community; that can be deleted. This is in the current statement because healthcare workers are essentially community workers. "Communities" could be retained, or changed to "families" to avoid misinterpretation; "household members and families" should be added, a healthcare worker concern.

1. Current ACIP wording: "Efforts should be made to educate healthcare personnel regarding the benefits of vaccination and the potential health consequences of influenza illness for themselves and their patients."
   – *Proposed wording:* "Healthcare facilities should educate healthcare workers regarding the benefits of vaccination and the potential health consequences of influenza illness for themselves and their patients. Such education includes epidemiology, modes of transmission, diagnosis, and means of preventing the spread of influenza, in accordance with their level of responsibility in preventing healthcare-associated influenza."

Discussion: "Patients" should be listed first. "Efforts should be made to educate healthcare personnel" should be changed to "healthcare facilities should educate"... Both the AAP and OSHA provide refusal forms for parents to sign (OSHA for hepatitis B), a strategy generally agreed to be wise. HICPAC also added a declination statement.

The current ACIP recommendation on MMR ("ACIP recommends that states implement immunization requirements for school entry for 2 doses of MMR or …") related to two issues, #3 and #4, which follow.

1. Options for state level administrative measures:
   A. No statement
   B. "ACIP and HICPAC recommend that states consider a requirement that all healthcare workers participate in an influenza prevention program that includes education and provides annual vaccination."
   C. Defer recommendation until the 2005 ACIP recommendations.

Discussion included the need to discuss this with ASTHO. If this is pursued, input from state officials will be needed. There was general consensus to support option B.

1. Institution level administrative measures:
   – *Proposed wording:* "ACIP and HICPAC recommend that all health care facilities require that all healthcare workers participate in an influenza prevention program which includes education and provides annual vaccination."

Discussion. The proposed wording was adopted by consensus.

1. Current wording: "Facilities that employ healthcare workers are strongly encouraged to

provide vaccine to workers by using approaches that maximize immunization rates. All healthcare personnel should be provided convenient access to influenza vaccine at the work site, free of charge, as part of employee health programs."

– *Proposed addition:* "Strategies include mass vaccination clinics, mobile carts, flu deputies (i.e., peer vaccinators), vaccination access during all work shifts, role modeling and support by institutional leaders, and incorporating influenza vaccination programs into the institution's patient safety and occupational health programs."

Discussion. There was consensus to accept the proposed additional language, and to add to it language on signing a refusal form.

1. *Measuring/reporting vaccination rates.* Current wording: "Healthcare workers' influenza immunization rates should be regularly measured and reported."

   – *Proposed wording:* "Recognizing the importance of measurement and feedback, healthcare workers' influenza immunization rates should be regularly measured and reported to entities such as patient care units and the institution's administration. If the healthcare worker declines, the healthcare worker should sign a statement of declination."

Discussion included:

- The refusal language would be better inserted here, as it would stand out more.
- It will not be long before all states specify what must be reported to the public, and HICPAC is working on guidance for public reporting.
- Nurse assistants and people with minimal education have the most patient contact, and they have the same opinion as the community that the vaccine causes influenza. *Informed* refusal is important, and when documented, the burden is clearly placed on the healthcare worker.
- The insertion of "barring medical contraindications" could be considered.
- Dr. Poland suggested "If the healthcare workers refuse, consideration of antiviral prophylaxis when appropriate and/or informed declination should be documented." However, Dr. Neuzil preferred to approach this from a non-punitive perspective. Most hospitals offer vaccination to all their patients and simply document those who accept and decline. Rather than "refuse," the language was suggested that "healthcare workers who decline should sign a document (or statement) of declination."
- Since many healthcare workers do not care for patients, the text should be clear for hospitals that this is for direct patient care providers, not for site administrators. Perhaps, as OSHA does, the background should define healthcare workers as those with "regular patient contact." SARS demonstrated that many more workers have patient contact than might be expected.

7. *Provision of evidence levels* to support the recommendation. Two options were proposed: to provide none, or to use HICPAC's 1A and 1B evidence level categories (see previous delineation), which are based only on the peer reviewed literature.

Discussion included:

- ACIP was urged to adopt a system like HICPAC's, in which 1A represents strong evidence, study design, and rationale; 1B involves more epidemiologic study designs; and category 2 involve more consensus opinion when the evidence is not sufficient for a

strong recommendation . The presence of supportive data in general could warrant a 1A recommendation; there are at least two RCTs (Foster, Carmon) specific to healthcare workers.

- HICPAC ranked healthcare worker vaccination as supported by 1A evidence.
- There was some discussion about leaving the statement as is and not rating the evidence until the ACIP rating system workgroup finished its work. On the other hand, use of the HICPAC system was not deemed likely to prejudice ACIP's later decision for its own use, especially since this would be a joint document. It also was not certain that HICPAC would agree to a joint statement without evidence ratings. A footnote could note that ACIP is developing its own system and the rating could be clearly defined as HICPAC's.
- Different ratings are likely to be needed in different parts of the statement. The workgroup could determine which category 1 issues should be A or B levels. Another perspective was that, since the evidence is mixed, it need not be ranked at all.

General discussion included:

- Somewhere in the statement, make the point that absenteeism has, as the nurse-to-patient ratio drops, mortality rises.
- Some of these changes could potentially and profoundly affect different parties and that is generally addressed in broader discussion with affected groups. But this recommendation was desired to be done now in order to be in place for the next influenza season, and this was the last chance to vote before the October meeting on a joint HICPAC/ACIP statement. Except for the language about the states, the HICPAC guideline just released includes the rest.
- Stronger rules, beyond guidelines, could be needed, but that is another discussion.
- The evidence rating would not do any harm and may do some good.

Dr. Levin suggested that the ACIP version be accepted and sent back to HICPAC, with some ACIP members deputized to agree with HICPAC on the final joint document. Drs. Zimmerman and Dr. Poland volunteered to do that.

Dr. Poland moved to accept the 7 issues as discussed and Dr. Birkhead seconded the motion.

Vote (no conflicts applied)
In Favor: Womeodu, Traenor, Poland, Marcuse, Gilsdorf, Finger, DeSeda, Campbell, Birkhead, Abramson, Levin, Zimmerman
Opposed: None
Abstained: Stinchfield

The vote passed.

Meningococcal Disease: Meningococcal Workgroup Report
Presenter: Dr. Reginald Finger, Workgroup Chair

The Workgroup's activities were outlined. They included commentary on the NCID meningococcal cost-effectiveness study and on Wyeth's presentation of vaccine production issues. They also listed four possible policy options for the use of MCV-4 in adolescents and young adults and discussed the possible future approaches to the use of MCV-4 and MCV-B in infants. Meningococcus B predominates in infants. Several manufacturers are working on a

vaccine for Group B that involves antigens other than those in the polysaccharide vaccine.

NCID funded and planned a late September meeting on the status, awareness and vaccination options of meningococcal disease. The Workgroup reviewed the epidemiology of meningococcal disease. Since its incidence differs by age group, they arranged policy options by that category.

"Hot topics" of discussion related to this vaccine included: how large a financial outlay to prevent meningococcal disease the nation will accept; what the price(s) will be of MCV-4 (the vaccine for the four serogroups) in the current polysaccharide vaccine; this will be in the conjugate to be released this year) and future MCVs; the willingness of the AAP, AAFP, ACHA, etc., to co-publish a recommendation with the ACIP (that is expected); and how public input will affect the recommendation.

Cost Effectiveness of Meningococcal Vaccine Use in the U.S.
Presenter: Dr. Colin Shepard, Dr. Nancy Rosenstein, NCID

Quadrivalent meningococcal conjugate vaccine (MCV-4) may be licensed in the U.S. in the fall of 2004, for use among those aged 11-55 years. It may be licensed in future for use among infants, and toddlers aged 2-4 years. As yet, no submission has been provided to the FDA for this vaccine's use among infants. Meningococcal disease is relatively rare and MCV-4 is likely to be expensive, so NCID conducted a cost-effectiveness analysis that compared the vaccine's introduction in all three age groups.

Study design. Two hypothetical population cohorts were analyzed, both 3.8 million strong: a U.S. birth cohort and an adolescent/11-year old cohort. Two comparisons of the birth cohort were analyzed: infant vaccination (three doses at 2, 4, and 6 months of age) and toddler vaccination (one dose at age 1 year). Another comparison analyzed the adolescent cohort (one dose to all 11 year-olds) versus no vaccination. The analysis proceeded from a societal perspective (the cost of world cost) over 22 years, the time in which most have started or completed college.

The decision-making model's outcomes measures were five: cost per case and case prevented, cost per death and death averted, and cost per life-year saved. All values were converted to 2003 dollars, and a 3% discount of costs and benefits was used. The decision tree was shared. The possible routes under a no-vaccination program proceeded to either infection (meningococcal disease) or no infection, then to no sequelae or long term sequelae (such as scarring, multiple amputations, hearing loss, neurological disability), or death.

The assumptions and calculations were outlined. The calculation of disease incidence, based on ABCs data, addressed age- and dose-group incidence and an age-specific case fatality ratio. The upper and lower bounds of the confidence intervals were based on the highest and lowest overall annual rates in a ten-year period. To calculate the rates of long-term sequelae, they used the data of Quebec's early-1990s extended outbreak (Erickson and De Wals *CID* 1998;26:1159-64). The median age of the 420 survivors was 2 years for serogroup B and 14 years for serogroup C. For hearing loss, the 8.8% rate came from a study among children with meningococcus, since it was felt that using a rate among survivors of ages like Quebec's might underestimate. (Edwards M, Baker CJ. *J. Pediatrics* 1981; 99:540-45). And, since neurologic disability is such a rare outcome, a meta-analysis of meningococcus sequelae was used, and produced a rate of 2.1%

(Baraff et al, *PIDJ* 1993;12:389-94).

Vaccine-induced protection is full and immediate with one dose among toddlers and adolescents. The duration of protection is assumed to be 22 years, with no decline in efficacy. Vaccine efficacy was based on U.K. data, since group C conjugate vaccination has been done routinely for >2 years. The analysis assumed zero efficacy for those aged 0-4 months; that is, no full protection until five months and two doses of vaccine. There also is a third dose at 6 months.

Vaccine coverage was drawn from NIS and state data, and was assumed to be 93%, 91% and 71% respectively, for infants, toddlers and adolescents. For each of the outcomes, the analysis calculated for several components: acute medical care, parents' work lost, sequelae-specific acute medical care, lifetime costs of sequelae (rehabilitation, long term care), and lost productivity. Excluding costs related to adverse events, the cost per vaccination was estimated to be $80, in a range of $64 to $114.

Results of the analysis were as follow:

- Birth cohort, no vaccination: 1037 cases, 74 deaths.
  - Infant vaccination: 485 cases, 544 prevented; 32 deaths, 42 prevented.
  - Toddler vaccination: 635 cases, 401 prevented; 38 deaths, 35 prevented.
- Adolescent cohort, no vaccination: 541 cases, 72 deaths.
  - Vaccination: 289 cases, 257 prevented; 37 deaths, 34 prevented.
- Median vaccination program cost, in millions (range): Infant $912 (range $767-$1078); toddler: $306 ($236-$380); adolescent: $209 ($143-$375).
- Median cost of disease, birth cohort (0-21 years):
  - No vaccination: median $185 million, $77 million without productivity costs (another 58% added).
  - Infant vaccination: $87 million, $37 million without productivity costs (+57%).
  - Toddler vaccination: $113 million, $50 million without productivity costs (+55%).
- Median cost of disease, adolescent cohort:
  - No vaccination: $138 million, $35 million without productivity costs (+75%).
  - Vaccination: $72 million, $18 million (+75%).
- Median net costs of vaccination program, less saved cost of illness (range in millions)
  - Infant: $813 million ($660-$980 million).
  - Toddler: $232 million ($166-$307 million).
  - Adolescent: $148 million ($88-$271 million).
- Incremental cost per cases and deaths prevented (thousands)
  - Infant: $1142/case prevented, $1438/death prevented (higher due to the multiple injections required).
  - Toddler: $122/case; $1374/death.
  - Adolescent: $61/case; $464/death.
- Average cost per life-year saved, in thousands (excluding cost of productivity loss)
  - Infant: $378 ($402)
  - Toddler: $141 ($168)
  - Adolescent: $92 ($141)
- Average cost per life-year saved for adolescents (excluding productivity) by cost per vaccination (in thousands): $64/vaccination, $97 saved; $75/vaccination, $121 saved; $84/vaccination, $141 saved; $100/vaccination, $177 saved; $114/vaccination, $207 saved.

- Vaccine comparisons of cost per life year saved, in thousands:
  - DTaP, MMR, polio: all cost-saving for children aged <5 years.
  - Pneumococcal conjugate vaccine (PCV, 1997), at $58/dose: $80 per life year saved (excluding cost of productivity loss)
  - Meningococcal polysaccharide vaccine, college students: $62 - $489 per life year saved

Conclusion: The cost effectiveness of toddler and adolescent strategies are essentially equivalent. Adolescent vaccination would not prevent disease in the age groups where meningococcal rates are highest. The cost of productivity losses comprises the majority of the cost of disease, especially in the adolescent cohort. Because MCV-4 does not cover serogroup B, about 33% of U.S. cases would not be preventable regardless of age group vaccinated.

Discussion included:

- The analysis' calculation of lifetime productivity loss accounted for a work life >22 years. Dr. Turner suggested analysis to compare this vaccination to other techniques such as Pap smears, colorectal screening, etc. Dr. Martin Meltzer of NCID reported that targeted screening can involve very large ranges (e.g., mammograms in women aged 40-50 years can be >$100,000/life year saved). It is also very difficult to compare a vaccine to a diagnostic screening strategy to prevent disease, as they are different. The life saved by a mammogram or Pap screening is very different from dollars per life year saved by a vaccine. Dr. Turner agreed, but pointed out that for public health, a widely used intervention such as a Pap smear is well understood and if possible would be a good comparison.
- Dr. Plotkin asked if foreign CE studies had been considered or used. Dr. Shepherd responded that in general, the input points are too different to allow comparison, but data points from the U.K. are often used. The differences include the epidemiology, rates of disease, and different vaccines used (and their costs) and campaigns (e.g., the U.K. had a massive catch-up campaign of all ages to 18 years).
- *If PCV becomes the gold standard at an $80,000 cost per life year saved, can the necessary cost of vaccination be extrapolated to make the average cost of life saved by meningococcal vaccine equal to PCV?* That could be done. An analysis with the cost of vaccination <$64 has not yet been done.
- In the U.K., everyone to age 22 (the age where carriage rates are highest) was vaccinated. That was followed by a 60% decrease in other age groups, suggesting an impact on herd immunity. In the U.S., there is no real-life model whereby only adolescents or toddlers were vaccinated, to allow an analysis of herd immunity. While this could be hypothesized over 10 years for an adolescent strategy and over 20 years for one for infants/toddlers, in the absence of data, that was not done.
- "Adolescent" in this model means beginning vaccination at age 12 years, not doing the catch-up. That would add substantially to the cost.
- Opinion of the 71% coverage estimated for adolescents varied; some thought it an underestimate, since coverage is typically in the 95% range for school entry; others though it optimistic, based on HDS data (50% or lower). However, the latter depends on how long after mandate it is measured; it rises with time to very high rates.
- The cost per quality adjusted life year (QALY) will be estimated next. Given the significant sequelae, the cost per QALY is likely to drop significantly compared to what was presented at this meeting.
- *Was the cost of vaccinating college students with the polysaccharide removed, since that*

will not be necessary? No, but that is a good point, and could be done.

Scenarios of Meningococcal Vaccine Use

Presenter: Dr. Nancy Rosenstein, NCID

Overview: Advantages/disadvantages of polysaccharide and conjugate vaccines; discussion of the Workgroup's issues related to routine vaccination of adolescents and college freshmen and a catch-up campaign.

The licensure of the meningococcal vaccine is expected in December, but it will be presented to the FDA in September. In October, Aventis Pasteur and the Workgroup will present the findings on the vaccine's scientific data on immunogenicity and safety to the ACIP. The vaccine will be available in 2005, so the joint release of recommendations (ACHA, AAFP, AAP) should occur in early 2005.

The current polysaccharide meningococcal vaccine is efficacious for use among high-risk groups and in outbreaks, but is not recommended for routine administration due to its lower efficacy among young children. It provides a long duration of protection (at least 5-years in adults and older children), but no booster effect and no herd immunity. It is not easy to operationalize in routine vaccination, and its higher cost is not "acceptable." The serogroup C conjugate meningococcal vaccines used in the U.K. works well in young children, and its duration of protection is at least 10 years (perhaps life-long). It has a booster effect and provides herd immunity, is easier to operationalize, and the U.K. found its cost acceptable for their immunization strategy.

The first vaccine expected to be licensed in the U.S. is a quadrivalent conjugate vaccine by Aventis Pasteur for use among those aged 11-55 years. The available data suggest good safety and immunogenicity; those and the U.K. data indicate efficacy and herd immunity. The duration of protection is assumed to be 10+ years. But the cost is likely to be high and the infrastructure for its delivery may not exist in the U.S. There is a strong public advocacy for a vaccine to prevent meningococcal disease.

Key questions and pros/cons debated by the Workgroup revolve around whether ACIP should recommend:

1. *Routine adolescent vaccination*. Pro: It prevents disease in a relatively high risk group and provides an opportunity to promote/enhance the adolescent visit. Con: Its cost is relatively high per life-year saved; it is likely to have a low impact on meningococcal disease short-term if only 11 year-olds are vaccinated; and the adolescent visit is not fully established. *The Workgroup* ***consensus was to recommend adolescent vaccination.***

1. ***Routine vaccination of college freshmen in dormitories.*** Pro: The current permissive recommendation to educate such freshmen

debated by the Workgroup revolve around whether ACI
recommend:
1. *Routine adolescent vaccination*. Pro: It prevents disease in a relatively high risk
and provides an opportunity to promote/enhance the adolescent visit. Con: Its c
relatively high per life-year saved; it is likely to have a low impact on meningo
disease short-term if only 11 year-olds are vaccinated; and the adolescent visit is
established. *The Workgroup* ***consensus was to recommend adolescent vaccinat***

Conclusions Analysis of Registry information to date revealed: no cases of fetal vaccinia, no observed increase in pregnancy losses, and no increase in early diagnosed birth defects. But it is challenging to draw early conclusions on individual defects, given the small population. Enrollment of women and follow-up of pregnancy outcomes continues.

Discussion included Dr. Gall's comment that these were the first data in the literature in about 50 years on smallpox among pregnant women, and that the data parallel those of the New York City outbreak

Smallpox Workgroup Report
Presenter: Dr. Gus Birkhead, Workgroup Chair

Dr. Birkhead reported the Smallpox Workgroup's review of studies. The overall conclusions were that the data are reassuring: there were no cases of fetal vaccinia reported, no increase of spontaneous abortions or congenital abnormalities. However, the Workgroup was uncertain about the interpretation of individual cases of birth defects, due to the small numbers. They recommended continued enrollment of women and follow-up of outcomes, and continued efforts to improve the already effective screening program. The Workgroup will continue to meet for near future to address any smallpox issues.

Pneumococcal Disease Vaccine and Shortage

Influenza: Vaccine Efficacy of Partial Vaccination Schedules
Presenter: Dr. Cynthia Whitney, NCID

Overview: Evaluation of the outcomes since licensure of Prevnar® in February, 2000.

The ABC data through 2003 indicate that Prevnar® is working well in its target age group (<5 years old), with rates dropping 80% in those aged <2 year-old and leveling off. A herd effect was seen in adults over same period.

Serotyping was done for cases (n=318), which were defined as pneumococcus isolated from a sterile site among children aged 3-59 months at the culture date. Of the 318, 131 were vaccine serotype cases and another 59 were vaccine-related (serogroup but not serotype); 113 were neither. Serotyping was pending for the remaining isolates. Three controls per case, matched by age (+/- 14 days) and zipcode, were identified through birth certificate records. Most of the study children were under partially-vaccinated. Fifty-five percent of the cases and 79% of controls received at least one dose of conjugate vaccine; 29% of cases and 37% of controls received 3 or 4 doses of the vaccine.

Vaccine effectiveness for children immunized with a 3-dose infant schedule and other incomplete infant regimens was also evaluated. Analysis showed VE of 96% for children immunized with a three-dose infant regimen. The same was true for those vaccinated twice before age 6 months of age and 78% for only one dose prior to age 6 months. However, the higher effectiveness estimates for those receiving two or three doses compared to one dose were not significantly different. These results were very similar to the Kaiser trial (Black et al, *PIDJ* 2000), indicating that the schedule for this vaccine may be less important than for others. The VE of three- versus four doses was also evaluated by a proportional hazards analysis that

incorporated the time since vaccination. While it indicated that a fourth dose booster at 12-23 is better, three doses were already highly effective.

The conclusion was that pneumococcal conjugate vaccine is highly effective in preventing the invasive disease caused by the vaccine's serotypes. It provides similar protection from the vaccine related serotype 6A, but has very low VE to prevent disease from type 19A. No evidence was found of an increased risk of disease due to non-vaccine serotypes. The vaccine is highly effective in preventing invasive disease when given as a "catch-up" regimen. However, the data to date do not definitively indicate how many doses are needed to interrupt carriage. Further analysis is ongoing,

Prevnar Supply Status

Presenter: Dr. Gregory Wallace, NIP

Overview: Prevnar® distribution from February 2000 to date; survey of pediatricians regarding vaccine shortage; CDC response; future supply/recommendation changes.

Prevnar® distribution was chaotic. The production from January to April of this year has been equal to the need for about half of the four-dose schedule. An AAP survey of its members two, four, and eight weeks after the ACIP recommendation showed high awareness and implementation of the schedule. CDC actions in response to the shortage, which resulted from high uptake of the new vaccine, included weekly calls with the manufacturer and relevant agencies (FDA, NVPO, AAFP, AAP), updates issued on the lot production, releases, and distribution; projections of future production/distribution, and inventory assessment. Three lessons learned from this experience were that: 1) improved communication results in improved responses to shortages; 2) routine vaccine supply continues to be vulnerable; and 3) production redundancy is needed to help prevent supply issues.

While the Prevnar® supply is improving, more "real time" data might allow an earlier relaxation of the stringent recommendation. Recommendations will be based on reliable production and distribution information, but it remains hard to judge the reality at the provider level. The question is whether the recommendation should be stepped to move from three to four doses, or if four doses should just be recommended. The advantage of a three-dose schedule would be to relax the recommendation sooner; the disadvantage is that providers want simple messages to direct them. While waiting to recommend the four-dose schedule could delay uptake, that would be simpler for providers to follow.

High Risk Groups Who Should Receive Four Doses Regardless of Shortages

Presenter: Dr. John Moran, NIP

Overview: Data relevant to whether, despite the Prevnar ® shortage, the ACIP recommendation of four doses to high risk groups should be expanded to include Alaskan Natives and American Indian adults, due to their higher rates of invasive pneumococcal disease (IPD); presentation of new data.

In 2000, an analysis comparing the annual incidence of invasive pneumococcal disease (IPD) among children aged <42 months revealed it to be much higher in certain groups. These groups included children with chronic conditions (e.g., sickle cell disease) that make them more

susceptible to invasive pneumococcal infection, and those who, when infected, are more susceptible to severe disease (i.e., children with chronic heart or lung disease). Groups identified as involving such children (Alaskan Natives, American Indians, African-Americans, and day care attendees) were exempted from the ACIP's two-dose recommendation during the shortage.

Recent data were presented from the National Hospital Discharge Survey (NHDS) on IPD in children aged <24 months. While these data indicated that the burden of PCV7-preventable IPD increased since 2000 among Alaska Natives, among whom the ratio to the general population rose from 2.4 to 3.6, as well as among Navajos (2.8 rising to 6.8), and Apaches (9.6 to 10.0). However, it did not rise among African-Americans, and the evidence did not support an increased risk of IPD among *all* Native Americans. There also was no evidence that Alaskan Natives or American Indian children responded less well to a two-dose schedule compared to other children. These data suggested that perhaps the ACIP recommendations should be re-thought.

While Alaskan Native and certain American Indian children may retain higher vaccine-preventable IPD rates than children in the general population, the evidence does not indicate that they respond less well to the two-dose series than other children. However, four doses may provide more lasting protection, more herd immunity, and better protection against non-invasive disease. One option might be to redesignate the high-risk groups to cite those which specifically should continue to receive four Prevnar® doses during a PCV shortage.

A recommendation was suggested that "Alaskan Native and American Indian children in areas with a demonstrated risk of IPD more than two-fold higher than the national average (Alaska, Arizona, New Mexico, and the Navajo populations in Utah and Colorado) are at high risk of invasive pneumococcal disease and should receive the standard four-dose PCV7 series during the current PCV shortage."

Discussion included that the relative risk of children at medical high risk depends on their condition. Immunocompromised children's rates are much higher (e.g., more than ten-fold for sickle cell anemia, but closer to the differences just presented for others). Dr. Vo reported the IHS' expectation that the Prevnar® shortage would resolve shortly, but their concern that it could reoccur. For that reason, the IHS hoped that the ACIP would designate specific groups of American Indians and Alaskan Natives in whom the demonstrated risk is greater than twice the national average, and listed them as a high risk group for Prevnar® vaccine use during the shortage.

Dr. Zimmerman moved to approve the Prevnar® recommendation as presented and was seconded. However, Dr. Hadler found that unnecessary, since the presentation was just to help the Workgroup recommending during the shortage (which was about to end) by asking the committee's advice/sense of what should be done. Dr. Moran confirmed that there was no suggestion to change the language about African-Americans.

Dr. Rodriguez' asked if there were data on giving two doses at <6 months and a booster at 12-15 months. Dr. Whitney reported that few children in the study were vaccinated on that schedule. The point estimate from other places, and reports in the literature, indicate that it is a reasonable thing to try, but there was little the CDC could say about it. Dr. Paradiso reported Aventis' serological data showing good response to two doses, comparable to three doses, for four of the five serotypes, but not for 6B and 23F. Three doses are needed for the latter two serotypes. The

question is the burden of disease for those types, and the potential of cross-reacting antibodies for 6B to 6A, from two- versus three doses. Also noted that schedules differ around the world (e.g., Canadians use 2+1 for all their vaccines).

Without ACIP objection, the Work group will recommend the four doses for these groups, so CDC will have that advice should another shortage occur. Dr. Ivey stated the IS desire that the recommendation be permanent in case these shortages recur, and to have the fall schedule released as soon as possible for these high risk groups. Dr. Levin summarized ACIP's agreement to that, and the committee's consensus to approve the proposed advice.

Pertussis: Newer Macrolide Antibiotics in Treatment/Prophylaxis
Presenter: Dr. Tejpratap Tiwari, NIP

Overview: Compliance/safety data for Erythromycin®, the recommended antibiotic for treatment/prophylaxis for pertussis; data on the newer macrolides, Azithromycin® and Clarithromycin®, comparative to Erythromycin®.

After its normal 14-day treatment course, Erythromycin® provides >99% of patients with negative cultures for *B. pertussis*. However, ~20% patients discontinue treatment or prophylaxis due to frequent gastrointestinal side effects (~3%) and the need for frequent doses (3-4 per day for 14 days). Infants <6 weeks old who are given Erythromycin® for pertussis are also at increased risk for acquiring idiopathic hypertrophic pyloric stenosis.

Two new macrolides, Azithromycin® and Clarithromycin® are licensed in the U.S. Compared to Erythromycin®, they have good *in vitro* activity against *B. pertussis*, are more resistant to acid pH, are better absorbed, and are widely distributed in the body. They provide a greater tissue concentration and have a longer plasma half-life. Thanks to the foregoing, they require fewer daily doses (1 for Azithromycin® and 2 for Clarithromycin®) and a shorter course of treatment (5 and 7 days, respectively). However, they are also considerably more expensive than Erythromycin®.

Six studies of these new drugs were published in the last ten years, but comparison of four of them was confounded by small sample sizes and dissimilar enrollment/control criteria. However, those four did show a trend for efficacy similar to Erythromycin®, with fewer and milder adverse events. The two more definitive studies were outlined:

- Halperin et al (40th annual ICAAC Meeting, October, 2002; Abstract 169; in press, *Pediatrics*, 2004) compared Erythromycin® and Azithromycin® in a multi-center, randomized equivalence trial involving 477 children with suspected pertussis, aged 6 months to 16 years. Of those, 238 received one Azithromycin® dose of 10 mg/kg on day 1 followed by a 5mg/kg single daily dose from days 2–5. The other 239 received Erythromycin® estolate in three divided doses of 40 mg/kg daily, for ten days.
  - *Results:* Of the Azithromycin® group, 18% reported gastrointestinal adverse events, significantly different from the 40% who reported that in the Erythromycin® group.
- Halperin's team also conducted an efficacy study among 11 of the previous study's children with culture-confirmed pertussis. Complete post-treatment bacterial eradication was equal between Azithromycin® and Erythromycin®, and nonrecurrence one week post treatment was virtually equivalent for cases with available cultures (90% power to detect equivalence, 6.2% failure rate).

- Lebel et al (*PIDJ*, 2001;20:1149 –54) compared Clarithromycin® to Erythromycin® in a single center, randomized, safety and efficacy study of suspected pertussis cases among 153 children aged one month to 16 years. Of those, 77 received three daily Erythromycin® estolate dose of 40 mg/kg (to a maximum of 1 gram daily) for 14 days. The other 76 received two, 15 mg/kg per day (maximum 1 gram daily) of Clarithromycin® for 7 days.
    - Results: Again, the GI complaints were significantly different, reported by 32% of the Clarithromycin® group, versus 44% of the Erythromycin® group.
- Lebel et al also analyzed efficacy among culture-confirmed pertussis cases, and found similar post-treatment bacterial eradication between the Clarithromycin® group (31/31) and the Erythromycin® group (22/23). However, the small sample size prevented the demonstration of treatment equivalence.

Neither of these two drugs are indicated for treatment of infants aged <6 months. There are no data on Clarithromycin®'s use in that age group, but limited data on Azithromycin® indicate no association with idiopathic hypertrophic pyloric stenosis (IHPS) in infants. Similarly, no well-controlled safety trials have been done of their use during pregnancy. However, animal studies indicate no adverse fetal effects, and available data showed no anomalies among infants born to women who were exposed to either of these drugs. FDA assigns Azithromycin® to a Category B label, and Category C for Clarithromycin®. They may be used if alternative therapy is not appropriate and the potential benefits warrant their use despite the potential risks.

Discussion included comment that five days of Azithromycin® achieved better compliance than that for Erythromycin®. The Halperin study showed a 90% treatment completion rate versus 55% for Erythromycin®.

Combination Vaccine Recommendations
Presenter: Dr. William Atkinson, NIP

Overview: Consultation with the ACIP on the current childhood schedule's combination rule.

NIP develops training materials for providers, translating the recommendations to practical application. In 2003, 40,000 people attended training courses, and 8000 e-mails (66% from providers) were responded to.

The current combination rule can be interpreted as allowing off-label use of certain vaccines without specific ACIP authorization. Since 1997, the schedule has stated that "Licensed combination vaccines may be used whenever any components of the combination are indicated and the vaccine's other components are not contraindicated."

TriHIBit® is the DTaP-Hib combination licensed for dose four of the Hib series after age 12 months. The potential interpretation that TriHIBit could be used for all those series was resolved in a footnote two years earlier specifying its use only for dose four. But now, Pediarix,® the DTaP-IPV-HepB combination, apparently is being used off-label by clinicians for the fourth and fifth DTaP doses. Its license is only for doses 1, 2, and 3 (and, for the hepatitis B case). This is a common question heard by the NIP at least 30-40 times in the last month.

ACIP published (*MMWR* 1999; 48 [RR-5]:2) a statement that "The use of licensed combination

vaccines is preferred over separate injection of their equivalent component vaccines." ACIP's past other "off-label" recommendations were summarized in a table provided to the committee. The exceptions given to the latter have related to the age of the dose, minimum age, minimum intervals during pregnancy, etc. Finally, the ACIP's 1999 combination vaccine statement explicitly stated that the use of combinations might be justified if products with only the desired antigens are not available and the child's potential benefits outweigh the risk of adverse events associated with the extra antigens. However, using Pediarix® for DTaP doses 4 and -5 could result in as many as six doses of hepatitis B vaccine, and the available safety data only extend to dose four.

Three options were offered:

1. *Do nothing* and allow the combination vaccine rule to create off-label use situations not specifically approved by ACIP. This is simplest, but FDA's Center for Biologics Evaluation and Research (CBER) would likely object due to the sparse safety or efficacy data for such uses.
2. *Modify the combination vaccine rule's wording* in the schedule to indicate it may only be applied when a vaccine is approved by FDA for that dose. This would not require ACIP action for every new combination vaccine and would assure compliance with FDA indications. However, it creates yet another rule and could lead to missed opportunities for certain doses if the single antigen is available. Possible wording offered was:
   – "Licensed combination vaccines may be used whenever any components of the combination are indicated, the vaccine's other components are not contraindicated, *and the vaccine is approved by the Food and Drug Administration for that dose of the vaccination series."*
1. *Request specific ACIP approval for every off-label circumstance encountered*. This would require repeated *MMWR* Notices to Readers.

Following the ACIP's feedback, the NIP will refer this issue to the General Recommendations Workgroup to examine in detail, focusing on the science and policy issues, and then returning for later ACIP deliberation. Until ACIP advises otherwise, the NIP prefers to err on the side of caution, advising the use of a vaccine antigen only when approved for that dose in a schedule, unless this would lead to a miss opportunity and the withholding of a needed vaccine.

Discussion included:

- This had been discussed in past, with agreement that the General Recommendations Workgroup should address.
- Dr. Birkhead approved of the NIP's (Option 2) language, but would add that providers should not make giving a combination as a routine practice in the absence of another vaccine for a fourth dose. Dr. Wexler advised keeping this as simple as possible for the clinician.
- NIP has always had the position that, as long as the use of the vaccine has been endorsed by groups like the ACIP, AAP, AAFP, etc., the clinician is covered for liability. When questioned about issues of such antigen-positivity, NIP refers the inquirer to the VFC language. .

Workgroup Updates

MMR-V Workgroup

Presenter: Dr. Judith Campbell, Workgroup Chair

Overview: Varicella vaccine coverage; reduction in cases, hospitalizations, deaths; lessons learned from outbreaks; Workgroup activities.

Varicella vaccine was licensed, and AAP/ACIP general recommendations were approved and published, in 1995-96. These were updated in 2000 to address the vaccine's use for child care and school entry, outbreak control, post-exposure, children with HIV, adults and adolescents at high risk for exposure/transmission. When the Varicella Vaccination Program was updated for the ACIP last year, the MMR-V Workgroup was formed to review current recommendations and to prepare for a potential MMR-V vaccine.

The Workgroup focused its discussion on varicella; an MMR policy revision will be addressed in future. The topics being reviewed by the Workgroup have included an overview of the varicella vaccination program (consideration of going beyond the current program goal of >90% disease reduction to elimination) and the current epidemiology of varicella, including outbreaks and breakthrough infection.

Varicella vaccination coverage rose from ~26% in 1997 to 81% in 2002; it is expected to be >90% by 2010. Concurrently:

- Data of the National Notifiable Disease Surveillance System (collected in Texas, Michigan, West Virginia, Illinois) from the second and third quarters of 2003 charted rapid declines in reported varicella cases (down by 76% to 88%) alongside rising coverage rates (from 70%-83%), from the baseline 1995-96 pre-vaccination era data.
- Reductions were similarly charted overall and by age group from data of the Antelope Valley, CA, surveillance site (86% case decline) and the West Philadelphia surveillance site (89% reduction).
- Reduction of severe disease and hospitalization was charted from the 1995-2003 data of the Varicella Active Surveillance Project, from a high of 3.5/100,000 population in 1997 to <1.0/100,000 in 2003.
- Mortality, similarly plummeting (down 75%) from 1995-2001, was charted according to National Center for Health Statistics (NCHS) data. The 1995 average of 107 deaths annually dropped, consistent with incidence data, to only 26 varicella deaths in 2001.

Lessons learned along the way include that:

- Ongoing outbreaks occur even among highly-vaccinated school children (93%-99.5% coverage). A recent California outbreak occurred among unvaccinated sixth graders despite an 85% school coverage rate.
- Breakthrough cases are mild, but infectious, and outbreaks lasted an average of 2 months. In the latter, the attack rate of those vaccinated ranged from 7%-17%, and the outbreak VE estimates ranged from 83%-85%.

Topics being reviewed by the Workgroup include the transmissibility of breakthrough infections. The AAP and other groups are concerned about waning vaccine confidence among clinicians, with a VE of ~80%. Risk factors that may relate to vaccine failure are being studied by the Workgroup (e.g., age at, or time since, vaccination; medications taken by children). Further analysis of Phase IV post-licensure surveillance and outbreak data will be done. Other issues addressed by the Workgroup include correlates of protection against varicella and waning immunity, and the cost effectiveness of varicella vaccination programs. The latter involves the role and severity of breakthrough disease over time and the role of environmental boosting in

maintaining immunity. Another presentation, on the cost effectiveness of the two-dose strategy, compared no varicella vaccination to the two-dose program. The latter was found to be cost effective from a societal perspective. A one-dose versus two-dose program might not be CE considering marginal benefits, but the analysis did not include variables such as outbreak control.

Future presentations by the Workgroup to the full committee will include the current status of the vaccination program and the impact of the vaccination strategy. They will include varicella epidemiology, reports on outbreaks and vaccine effectiveness; data on one- versus two doses relative to safety, immunogenicity, efficacy and cost effectiveness; correlates of infection; and the MMR-V vaccine.

Discussion included report of one study of breakthrough disease that looked longitudinally over 10 years as well as the 6 week post-vaccination period. In that study, the correlate of protection seemed to be a GP ELISA value ≥5. Dr. Jane Seward stated that age and perhaps time since vaccination need to be examined in a more robust data set. The time since vaccination could potentially be correlated to age and degree of infection during outbreaks. The breakthrough rate and severity seem not to be associated with waning immunity. A report is planned for the October meeting. The reported loss of provider confidence, however, has not been paralleled by any reduction of vaccine coverage.

HPV Workgroup Update

Presenter: Dr. Janet Gilsdorf, Workgroup Chair

Overview: Workgroup tasks and plans; candidate vaccines; clinical trial data.

This Workgroup was formed in 2002 in anticipation of a vaccine to prevent human papilloma virus (HPV), but has only recently become active. The natural history of HPV, which causes cervical cancer, was noted from one to 20 years after initial infection. Most cases, perhaps even 90%, of this very common infection spontaneously disappear, but some individuals have persistent infection that may or may not develop into CIN-1 (cervical epithelial neoplasia) lesions. A few develop to CIN level 2 or 3 epithelial neoplastic lesions, and a few of those go on to cancer. The length of time for this process makes the study of cancer as an endpoint of vaccine efficacy studies a problem, so the focus has been on the CIN endpoints.

The Workgroup's core tasks are to 1) review and monitor the progress in HPV vaccine development; 2) identify gaps in information needed to formulate vaccine recommendations; 3) determine the appropriate time for formal presentation to the entire ACIP; and 4) provide a framework for the discussion of HPV vaccine recommendations.

At its first meeting in February of this year, Merck and GSK presented their candidate vaccines, which use HPV L1, a major capsid protein which self-assembles into virus-like particles (VLP). The vaccine candidates have been evaluated in animal models and shown an efficacy that is associated with development of neutralizing antibody. Phase I and II studies also showed good safety and tolerability.

The results of the Merck and GSK RCT clinical trials were outlined.

- Merck's monovalent HPV serotype 16 (a known high risk serotype for cervical cancer) uses an aluminum adjuvant. Its proof of concept study (*NEJM*, November 2002) showed 100% VE: none of the vaccine recipients developed HPV 16 infection, compared to 41 of

the placebo recipients. And in a subset of the persistent infection group, none of the vaccine recipients developed CIN compared to nine placebo recipients.

- The data of GSK's bivalent HPV 16/18 proof of concept study (*NEJM*, 2002) also showed 100% VE; no vaccinees developed persistent serotype 16 or 18 infections, while 16 placebo recipients did.

Three trials are underway, for:

- GSK's HPV 16/18 is given at 0-, 1-, and 6-months. It uses an AS04 adjuvant, which improves the immunogenicity of the viral-like particle. The multinational Phase III study will involve women aged 15-25 years (N=13,000), and another population-based study in Costa Rica will involve 15,000. The endpoints are HPV infection, both incident and persistent, CIN 2, CIN 3, and cancer. Enrollment began this year.
- The Merck trial is of a quadrivalent vaccine addressing serotypes 6, 11 (both high-risk for anal-genital disease), 16 and 18, which is given on a 0-, 2-, and 6-month schedule. It uses an aluminum adjuvant. This Phase III study is also multinational, involving 17,800 women aged 16-23 years. Its endpoints are HPV 6/11-related genital warts, HPV 6/11/16/18-related CIN, and HPV 16/18-related CIN 2/3 or cancer. Enrollment is completed. Additional studies that are ongoing and planned for this HPV 16/18/6/11 candidate vaccine include an efficacy follow-up study using the Nordic Cancer registry. Another study is of outcomes of vaccination during pregnancy; one is of immunogenicity and adverse events in adolescents aged 9-15 years; and others include vaccine efficacy studies among men.

The target groups for these vaccines are pre-adolescent girls and boys (Merck) and pre-adolescent girls (GSK). Merck expects to file for licensure with the FDA in March 2005, and GSK anticipates doing so in 2008.

The next steps for the Workgroup include determining the framework for developing recommendations, defining the key issues regarding recommendations, and defining the elements to be considered in the recommendations.

Dr. Hadler, filling in as Acting Chair after Dr. Levin's departure, commented that the HPV vaccine will further strengthen the adolescent vaccination program.

Closing Comments

Dr. David Neumann announced that August is National Immunization Awareness Month. This was established to call attention to immunization across the life span, capitalizing on public and provider interest in back-to-school immunizations. At a press conference to be held in Washington D.C. on July 29, CDC will release its new data from the 2003 National Immunization Survey. Family experiences of complications among children who survived influenza and meningococcal disease will be described to draw public attention to those vaccines and to immunization in general, for healthy adults as well as those at high risk. Awards will be given to various community groups and a seminar will be conducted on Capitol Hill on the importance of immunization. Consumer materials have been developed, and are available on the NCAI Website, www.partnersforimmunization.org.

Public Comment was solicited, and the meeting adjourned at 1:15 p.m. The next meeting will be held on October 27-28, 2004

Certification

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

Myron J. Levin, MD, Chair

Date

Attachment #1: Attendance

ACIP Members

Jon S. Abramson, MD
Guthrie S. Birkhead, MD, MPH
Judith R. Campbell, MD
Jaime Deseda-Tous, MD
Reginald Finger, MD, MPH
Janet Gilsdorf, MD
Myron J. Levin, MD
Edgar K. Marcuse, MD, MPH
Gregory A. Poland, MD
Patsy Stinchfield, NP
John J. Treanor, MD
Robin J. Womeodu, MD
Richard Zimmerman, MD

Members absent were: Dr. Ban Mishu Allos, Mr. John B. Salamone

Ex-Officio Members

Centers for Disease Control and Prevention

Stephan Cochi, MD, NIP
Stephan Hadler, MD, NIP, Acting ACIP Executive Secretary
Alison Mawle, MD, NCID
Gina Mootrey, MD, NIP
Charles Vitek, MD, NCHSTP

Ex-Officio Representatives of Other Federal Agencies

Norman Baylor, MD, Food and Drug Administration (FDA), for Dr. Karen Midthun
George T. Curlin, MD, National Institute for Allergy and Infectious Diseases (NIAID)
Geoffrey Evans, MD, National Vaccine Injury Compensation Program (NVICP)
Bruce Gellin, MD, Director, National Vaccine Program Office (NVPO)
Kristin L. Nichol, MD, Department of Veterans' Affairs (DVA)
Stephen Phillips, DO, MPH, Department of Defense (DOD)
Linda Murphy, RN, Center for Medicare and Medicaid Services (CMS)
Amy Groom and Steven Holve, Indian Health Service (IHS)

Liaison Representatives

Carol J. Baker, MD, and Margaret Rennels, MD, American Academy of Pediatrics (AAP), Committee on Infectious Diseases (COID)
Peter Paradiso, MD (for Dr. Gio Germano), Pharmaceutical Research and Manufacturers of America
Dennis A. Brooks, MD, MPH, National Medical Association (NMA)
Richard Clover, MD, and Jonathan Temte, MD, American Academy of Family Practitioners (AAFP)
Romeo S. Rodriguez, MD, National Immunization Council and Child Health Program, Mexico
James Randolph Farris, MD, Centers for Medicare and Medicaid Services (CMS)
Stephan L. Foster, PharmD, American Pharmacists Association (ApharmA)
Stanley Gall, MD, American College of Obstetrics and Gynecology (ACOG)
J. Henry Hershey, MD, MPH, National Association of County and City Health Officers (NACCHO)
Samuel Katz, MD, Infectious Disease Society of America (IDSA)
Clement Lewin, PhD, MBA, Biotechnology Industry Organization (BIO)
W. Paul McKinney, MD, Association of Teachers of Preventive Medicine (ATPM)

Monica Naus, MD, National Advisory Committee on Immunization, Ontario, Canada
David A. Neumann, PhD, National Coalition for Adult Immunization (NCAI)
Kathleen M. Neuzil, MD, MPH, American College of Physicians (ACP)
Charles Helms, MD, National Vaccine Advisory Committee (NVAC)
Robert Scalettar, MD, MPH, American Association of Health Plans (AAHP)
William Schaffner, MD, Guide for Adult Immunization
Jane Siegel, MD, Hospital Infections Control and Prevention Advisory Committee (HICPAC)
James C. Turner, MD, American College Health Association (ACHA)

Liaisons absent: David M. Salbury, MD, London Department of Health; Litjen Tan, PhD, American Medical Association (AMA)

Agency Staff

Agency for Toxic Substances and Disease Registry: Kris Bisgard

Department of Health and Human Services (DHHS)

Centers for Disease Control and Prevention (CDC):

No C/I/O identified: Erin Burns, Chris Casey, Janet Cilu, Katrin Kohl, Mimi Larzelere, Tasneem Malik, Anjella Vargas Rosales, Sally Schofeldt, Maxine Spence, Stephanie Steele, Skip Wolfe

Epidemiology Program Office (EPO): Andrew Kroger

National Center for Infectious Diseases (NCID):

John Barson	Keiji Fukuda	Ann Moen
Niransjan Bhat	Scott Harper	Trudy Murphy
Stephanie Bialek	Marika Iwane	Michelle Pearson
Oksana Bilukha	Rima Khabbaz	Colin Shepard
Caroline Bridges	Anna Likos	Cynthia Whitney
Lynette Brammer	Harold Margolis	Ian Williams
Joanne Cono	Eric Mast	Jennifer Wright
Roz Dewart	Martin Meltzer	

National Immunization Program (NIP):

James P. Alexander	Bakary Drammfa	Peng-Jun Lu
Curtis Allen	Kristi Elgusne	Jonathan Mertin
Norma Allred	Gary Euler	Lynne McIntyre
F. Averhoff	Peg Haeriz	Mike McNeil
Achal Bhatt	Jim Harrison	Pedro Moro
Karen Broder	Wendy Heaps	Erin Murray
Cedric Brown	Sonya Hutchins	Rick Nelson
Scott Campbell	Laurie A. Johnson	Pekka Nuorti
Sandra Chavez	Alison Kennedy	Dennis O'Mara
Bob Chen	Elena Khromova	Suzanne Pickering
Gary Coil	Tamara Kicera	Bette Pollard
Margaret Coleman	Katrina Kretsinger	Vitali Real

Jan Reuer
Marty Roper
Sharon Roy
Ismael Ortega Sanchez
Tammy Santibanez
Jeanne Santoli
Judy Schmidt
Jane Seward
Kristine Sheedy
Irene Shui
Suzanne Silver
Jim Singleton
Nicole Smith
Vishnu Priya-Sneller
David Sniadack
Margarita Sniadack
Ray Strikas
Marie Teldovich
Tejpratap Tiwari
Claudia Vellozzi
Heather Voner
Fran Walker
Greg Wallace
Donna Weaver
Melinda Wharton

National Institutes of Health (NIH): David L. Klein

National Vaccine Program Office (NVPO) Sarah Landry, Ben Schwartz

Department of Defense (DOD): John D. Grabenstein, Margaret Ryan

Members of the public or presenters to the committee in attendance were:
Michelle Alcorn, National Meningitis Association
Lisa Amrani, Merck
Paula Annunziato, Merck Research Laboratories
Lynn Bahta, MN Department of Health
Michele Bailey, ASHA, Durham, NC
Wendolyn Bell, MedImmune, Inc.
Joan Benson, Merck & Co., Inc.
Gursha Bindra, Aventis Pasteur
G. Bland, Mayo Clinic
Dean Blumberg, UC Davis Medical Center, Sacramento, CA
Anita Bosé, Cohn & Wolfe, New York
Andrew Bowser, freelance medical writer, Brooklyn, NY
Lynn Bozof, National Meningitis Association
Kim Bush, Baxter
Kathleen Coelingh, MedImmune Vaccines
Kelly Coleman, MedImmune
Lenore Cooney, Cooney/Waters, New York, NY
Dack Dalrymple, Dalrymple & Associates/Pink Sheet, Washington, D.C.
Anna DeBlois, ASTHO
Michael Decker, Aventis Pasteur/Vanderbilt University
Carmen Deseda, Hato Rey, PR
Richard C. Dinovitz, Wyeth
Jag Dosanth, GSK
Monica Farley, Emory University
Betsy Frazer, AQAF, Vestavia Hills, AL
Len Friedland, GSK
Diana Gaskins, GA Immunization Program, Atlanta, GA
Greg Gilmet, Aventis Pasteur
Ruth Gilmore, GA Immunization Program, Atlanta, GA
Cleveland Grady, Jr., GSK
Erik Greenbaum, Merck
Amy Greene, Association of State and Territorial Health Officers (ASTHO)

Jesse Greene, South Carolina Department of Health and Environmental Control
John Grindley, Kelly/Grindley., Wheeling, WV
Linda Grindley, Kelly/Grindley, Wheeling,
Jill Hackell, Wyeth
Jeff Hackman, MedImmune
Neal Halsey, Johns Hopkins University, Baltimore, MD
Claire Hannan, Association of State and Territorial Health Officers (ASTHO)
Rick Haupt, Merck & Co., Inc.
Philip Hosbach, Aventis Pasteur
Barbara Howe, GlaxoSmithKline (GSK)
Johnny Im, GSK
Peter Khoury, Baxter BioScience, Belsville, MD
Ariyaradi N. Krishnarts, Chiron
Charlotte Kroft, GSK
Barbara Kuter, Merck Research Laboratories
Melanie Jackson, Georgia Chapter, AAP
Rudolph Jackson, MD, Morehouse School of Medicine
Karen Kessnick, Acambis
Cynthia Lapel, National Meningitis Association
Tama Lee, National Meningitis Association
Marie-Michele Leger, AAPA
Christian Louce, Acambis, Cambridge
Janice Lovie, California Department of Health Services, Berkeley, CA
Maryn McKenna, Atlanta Journal Constitution, Atlanta, GA
John Modlin, Dartmouth Medical School
Susan Moline, East Health District, Georgia Department of Public Health
Marie Murray, Recorder, Atlanta, GA
Martin Myers, National Network for Immunization Information, Galveston, TX
Cheryl Norton, Minnesota Department of Health
Patrice Norton, Pediatric News
Paul A. Offit, Children's Hospital of Philadelphia
Walter Orenstein, Emory University Vaccine Center
Georges Peter, Brown Medical School
Stanley Plotkin, MD, Aventis Pasteur, Doylestown, PA
Jane Quinn, GSK
James Ransom, National Association of City and County Health Officers (NACCHO)
Lynn Redwood, Safe Minds
David Reyes, University of Arizona
Debra Ritzwoller, Kaiser Permanents, Boulder, CO
Brian Rosen, MedImmune
Fred Ruben, Aventis Pasteur
Judith Rusk, Infectious Diseases in Children, Thorofare, NJ
Alan Shaw, Merck
Jerry Shelton, Merck
Judith Shindman, Aventis Pasteur Ltd.
Eric Skjeveland, Merck
Dr. Alan J. Sievert, AAP, East Metro Health District, Lawrenceville, GA
Barbara Slade, Decatur, GA
Ben Sloat, Georgia Immunization Program

Parker Smith, PCS Photo
Nanette Stoback, Aventis Pasteur, Geneva, IL
Jeffrey Stoddard, MedImmune
Kathleen Stratton, Institute of Medicine (IOM), Washington, D.C.
Stacy Stuerke, Merck
Lonnie E. Thomas, Henry Schein, Inc.
Andrew Trofa, GSK
Thomas Vernon, MD, Merck Vaccine Division, West Point, PA
Peter Vigliarolo, Cooney Waters, New York, NY
Beth Ward, Georgia State Health Department
Martin Wasserman, GSK
Barbara Watson, MD, Division of Disease Control, Philadelphia, PA
Deborah Wexler, Immunization Action Coalition, St. Paul, MN
Greg Yoder, Merck & Co.
Laura York, Wyeth Vaccines
Daniel Yu, AP
John Zahradnik, Aventis Pasteur
Thomas Zink, GSK Vaccine, Philadelphia, PA

Attachment #2

Comments made on the House Floor June 18th 2004 by Congressman Dave Weldon, MD, in regards to the Institute of Medicines' report on autism and vaccines.

I would like to take this time to address what I consider to be a very growing problem, the epidemic of autism and neurodevelopmental disorders that are plaguing our Nation.

In January of this year, the Department of Health and Human Services sent out an autism alarm to the Nation's pediatricians. In this alarm, they stated that one in every 167 children born is being diagnosed with an autism spectrum disorder. I will repeat that. One in every 167 children being born in the United States today is being diagnosed with an autistic spectrum disorder. Furthermore, one in seven children is being diagnosed with either a learning disability or a behavioral disability.

Mr. Speaker, something dreadful is happening to our youngest generation, and we must sound the alarm and figure out what is going on with our children.

I had the pleasure of addressing an autism conference in Chicago last month, and I would like to share today some of the thoughts I shared there with about 1,000 researchers, doctors, nurses, educators and, most importantly, parents who were there to seek answers to this growing problem..

I have said repeatedly that the autism community is the 900-pound gorilla that has not had its voice properly heard on Capitol Hill. This is largely due to the endless demands on the time, effort, emotions and financial resources of the parents of these children who are struggling to meet the unique needs of these kids with autism. There is little time, money, energy left to engage in public debates, let alone engage the Congress when one is trying to raise a child with a disability like autism.

However, I see that changing, and last month's Institute of Medicine report I think has had one positive effect. It has united and reinvigorated parents throughout the country in their efforts to get answers to why children are being diagnosed with autism at such a high rate in the United States.

At the outset of my remarks, I want to make it extremely clear that I support vaccinations. I have a six-old son, and he has received all of his vaccinations. Someone in the media recently tried to portray me as a vaccine skeptic. After reviewing my record on this issue and all of my statements in the past, the newspaper printed a retraction. This, however, seems to be part of the pattern, to vilify those who simply ask if our vaccines could be made safer.

I support vaccinations, and indeed, I gave thousands of vaccinations to thousands of my patients when I was practicing medicine full-time prior to coming to the U.S. House. However, I believe it is appropriate to acknowledge that like with any other medical intervention, different individuals respond differently. We are all unique. We all have different genetic makeup, and what may cause no harm to the vast majority of people can cause serious side effects in some individuals.

Since we established the National Vaccine Compensation Program in the late 1980s, several

thousand individuals have been compensated for vaccine injuries. We know that there are adverse reactions, and I believe it is important that we dedicate resources to better understand why some children have these reactions.

For too long, those who run our national vaccination programs have viewed those who have adverse reactions, including those with severe adverse reactions, as the cost of doing business. Furthermore, the vaccine compensation program, which was designed to be a no-fault compensation system, has become so adversarial that only the most obvious cases receive compensation, and too many parents feel that the program is not worth the difficulty of going through it.

The questions I raise are multiple. The number one question has been whether neurologic problems were caused in some children by the high levels of a mercury-containing additive that was included in our vaccines in the 1990s. This mercury containing additive is called thimerosal, and in the 1990s, infants and unborn children were exposed to significant amounts of mercury at a most critical point in their development.

Now, this recent Institute of Medicine report, what exactly is wrong with it? What about it has so many people in the autism community upset?

In my 10 years of service in the U.S. Congress. I have never seen a report so badly miss the mark. I have heard some weak arguments here in Washington., D.C., and I can tell my colleagues that the arguments put forward in this IOM report are indeed very weak.

Let us examine this report in some detail. On January 15th of this year, I wrote Dr. Julie Gerberding, the director of CDC, and I asked her to postpone the February 9 Institute of Medicine meeting and its report because of my concern that this was not an exercise in discovering the truth, but was instead a meeting, and I will quote what I said in my letter, 'being driven by a desire to short-circuit important research and draw premature conclusions."

I said, "If the purpose of this meeting is to seriously consider and address these concerns, then this will not be accomplished."

Quoting further from my letter to Dr. Gerberding, I said, "It appears to me, not only as a member of Congress but also as a physician, that some officials within the CDC's National Immunization Program, the NIP, may be more interested in a public relations campaign than getting to the truth about Thimerosal." I said, "Pressing forward with this meeting at this time I believe will further undermine the credibility of the Centers for Disease Control on matters of vaccine safety and do damage to the reputation of the Institute of Medicine (IOM) . I believe the proposed date of this meeting, which you have the ability to change, is in the best interest of no one who is seeking the truth about a possible association between vaccines and neurodevelopmental disorders, including autism."

Now, I had a follow-up conversation on February 3 of this year with Dr. Gerberding, and she assured me that the Institute of Medicine's February meeting was not an attempt to "draw conclusions," but merely to "update the science," of where we were, basically.

However, it is clear that this report draws conclusions; and what is perhaps the greatest outrage, it goes further to call for the halt of further research.

A public relations campaign, rather than sound science, seems to be the modus operandi of officials at the CDC's National Immunization Program. Why do I say this? Let us look not only at the timing of the IOM meeting in February, the content of the IOM report, but also at studies the IOM used as a basis for their decision.

The Institute of Medicine based their decision almost entirely on five epidemiologic studies. Epidemiology is essentially the statistical analysis of disease in populations. All of these studies were conducted by researchers with an interest in not finding an association. All of the studies had significant shortcomings, all of which the IOM itself declares would miss the association with autism in a genetically acceptable subset of children.

Not only the timing of the IOM meeting raises suspicions but also the narrowing of the scope of inquiry and the emphasis the IOM placed just on epidemiology.

In 2001 the Institute of Medicine concludes: "Exposure to Thimerosal-containing vaccines could be associated with neurodevelopmental disorders." The IOM also recommended that children not be given mercury-containing vaccines.

What was the response of the CDC? For this most recent report, they narrowed the IOM scope to looking just at autism. Does this sound like an agency interested in understanding whether or not Thimerosal is harmful to some children, or does this response lead one to conclude that they are more interested in designing something to reassure an increasingly skeptical public?

Unlike 2001, this time the IOM was directed by the CDC to only consider the possible relationship between Thimerosal and autism rather than neurodevelopmental disorders as a whole. Anyone familiar with the Verstraeten study, a study published looking at Thimerosal and autism, knows exactly why the IOM scope was narrowed, because the 2003 Verstraeten study found associations between Thimerosal and neurodevelopmental disorders in some children with autism may have been misdiagnosed as having speech or language delay. By narrowing the scope, which largely went unnoticed by the media, the CDC has avoided acknowledging that Thimerosal very well may have caused neurodevelopmental disorders in some children.

This latest IOM report is simply part of a PR campaign, in my view. Would we not have had a much more productive report if the CDC had updated the research on possible associations between Thimerosal and neurodevelopmental disorders as a whole? In evaluating Thimerosal's relationship to autism, the IOM relies almost exclusively on these five epidemiologic studies.

The principal authors of all five of these studies have serious conflicts of interest. All five studies were published in 2003, leading up to the IOM's February 2004 meeting. All were conducted while the CDC and the NIH virtually ignored the Institute of Medicine's 2001 biological and clinical research recommendations.

It is critical to note the instructions that the IOM was given, primarily by the CDC, which has been funding the IOM.

Pages 5 and 6 of the IOM report make it clear that epidemiology was to reign supreme. In the absence of epidemiologic evidence to support causality, the IOM was instructed to give biological evidence little consideration and was prohibited from allowing biological evidence to

lend evidence towards causality.

Is it any wonder that the CDC has spent the past 2 years dedicating significant funding to epidemiology while starving funding for clinical and biological research? The IOM notes in their report that the epidemiologic studies they examined were not designed to pick up a genetically susceptible population, and this is the very theory of the link between Thimerosal and autism and autism spectrum disorders. One in 167 becomes autistic. Why do the other 166 not? It is because they do not have the impaired ability to eliminate mercury from their system. We are looking at a genetically susceptible subpopulation. Yet these studies that they base this report on, they admit, were not capable of picking up these subsets in the populations.

Let us look at these studies. The only study done in the United States, the Verstraeten study, was published in the Journal of Pediatrics in November of last year. Much has been written exposing the study's methodological problems, findings, and conclusions. Most importantly, however, is that this study did not compare children who got Thimerosal to those who did not. Instead, its CDC-employed authors focused primarily on what is called a dose response gradient. Those who got less 'Thimerosal later in life had less autism is the theory behind the study.

In addition to the study itself, it is important to note the public relations spin surrounding this study. On the day the Verstraeten study was released, a top CDC researcher and coauthor of the study was quick to declare to the news media: "The final results of the study show no statistical association between Thimerosal vaccines and harmful health outcomes in children, in particular autism and attention deficit disorder."

Let me repeat that: The final results of the study show no statistical association between Thimerosal vaccines and harmful health outcomes in children, in particular autism and attention deficit disorder. The newspaper headlines the day read; "Study Clears Vaccine Containing Mercury," the Associated Press and USA Today. "CDC Says Vaccines Are Safe," the Seattle Times. While that was the spin of the day, allow me to quote from the study:

"We found no consistent significant associations between Thimerosal-containing vaccines and neurodevelopmental outcomes. In the first phase of our study, we found an association between exposure to mercury from Thimerosal-containing vaccines and some of the neurodevelopmental outcomes screened. In the second phase, these associations were not replicated for the most common disorders in an independent population. They did find associations, but they changed the study and most of the associations disappeared.

Furthermore, in January 2004, the lead coauthor was forced to admit that many children in the study were too young to have received an autism diagnosis. He went on to admit that the study also likely mislabeled young autistic children as having other disabilities, thus masking the number of children with autism. The message from the CDC to the media was that there is nothing to be concerned about, but the study said something different. The news media to a large degree took the CDC's spin hook, line and sinker. Largely, they chose not read the study itself.

Five months after that study was published in the Journal of Pediatrics and, I might add, after the IOM report was largely written, Dr. Thomas Verstraeten broke his silence in a letter to Pediatrics stating, "The bottom line is and has always been the same, an association between Thimerosal and neurological outcomes could neither be confirmed nor refuted and therefore more study is required," is what Dr. Thomas Verstraeten said. Dr. Verstraeten, the lead author of this study,

says that an association between Thimerosal-containing vaccines and neurodevelopmental disorders cannot be refuted based on his study.

Yet the IOM in their assessment of that same study states that it is a basis for concluding, "There is no association between Thimerosal-containing vaccines and autism." The IOM acknowledges that Verstraeten would not have picked up an association in a genetically susceptible population. The IOM also noted that the study was limited in its ability to answer whether Thimerosal in vaccines causes autism because the study tests a dose response gradient, not exposure versus no exposure.

I might also add, Mr. Speaker, that the Verstraeten study cannot be validated. The earlier data sets have been destroyed and the only datasets the CDC will make available to outside researchers are the ones they have already manipulated. The raw, unaltered data is not available. Additionally, outside researchers are held to a much more restrictive access to information than are the CDC researchers. Only one independent researcher has been granted access to the CDC's VSD database, and the CDC has kicked that researcher out based on ridiculous reasons. They claim their research methods might infringe on privacy, yet they know the database contains no names and it is impossible to locate the patients from this database.

I want to talk briefly about the other four studies that the Institute of Medicine based its conclusions on. The IOM cited the 2003 Hviid study of the Danish population as one of the key studies upon which it based its conclusions. Let us first consider the conflict of interest of the principal author. Dr. Hviid works for the Danish Epidemiology Science Center, which is housed at the Staten Serum Institute, the government-owned Danish vaccine manufacturer. Also, all of his coauthors either work with him at the center or are employed by the SSI.

The SSI, the Staten Serum Institute, makes a considerable profit off the sales of vaccine and vaccine components and the U.S. is a major market for the SSI.

(Apparent gap in the written statement provided to the ACIP.)

. . . examined critically. It is important to note, however, that Dr. Miller has actively campaigned against those who have raised questions about vaccine safety. We have a person here who is actively campaigning, testifying in lawsuits, against the theory that thimerosal is linked to neurodevelopmental disorders and autism, doing a study supposedly showing there is no link. So what can we conclude about these five epidemiologic studies? We can see clearly why the IOM is on very shallow ground in drawing the conclusion that it did. They based their decision on these five studies, three of them examining genetically homogenous children in Denmark. At least one employee of the Staten Serum Institute serves as coauthor on three of the studies. Only one study examined the U.S. population, and that study did not compare children who had received mercury with those who had not. Four of them are studies of children receiving less than half the amount of mercury that U.S. children received. None of them with any ascertainment of prenatal or postnatal background mercury exposures, none of them considering prenatal exposure which may have been given to the children, none of them have been able to detect a susceptible subgroup in the population, three of them failing to address how the addition of outpatient cases of autism in Denmark might have previously skewed their results. Four of them examined populations with autism rates considerably less than the United States, and one of these studies has never been published. It is impossible to review the data.

Might I also add they are all statistical studies. There have been numerous biological studies suggesting that thimerosal is linked, mercury is linked to autism, specifically mercury studies that show after chelation therapy, children with autism excrete a tremendous amount of mercury in their urine, whereas normal children do not.

And it is important to note that there was a recent report published by Dr. Emili Garcia-Benhou and Dr. Carlos Alcaraz examining statistical errors in medical publications. They found five volumes of Nature and 11 volumes of the British Medical Journal. They found 11 percent of the computations in Nature and the BMJ were incorrect and at least one statistical error appeared in 38 percent of the papers, despite all the biological evidence suggesting there may be a link with thimerosal and autism here and the obvious knowledge that many of these statistical studies are flawed. The Institute of Medicine concluded, and many people in the press believed it, that there is no link.

Mr. Speaker, something needs to be done. The Institute of Medicine report not only looked at the mercury issue. It as well looked at the issue of the safety of the measles-mumps-rubella vaccine. Many years ago a researcher in England, a Dr. Andrew Wakefield, published a report suggesting that some children with autism have measles virus growing in their intestines causing a condition called inflammatory bowel disease, and, indeed, there have been recent reports in the medical literature that some of these children have measles virus particles in their cerebral spinal fluid and elevations of a protein called myelin basic protein in their cerebral spinal fluid, suggesting they have an active low-grade encephalitis being caused by measles virus.

The IOM was asked to look at this issue;. How did they approach this issue? Did they ask for research protocols that attempt to duplicate the Wakefield study? No. What they did was again another epidemiologic study.

SSI has $120 million in annual revenue, and vaccines are the fastest-growing business segment, accounting for 80 percent of its profits. Both the United States and the United Kingdom are important export markets for SSI's vaccines and vaccine components.

Furthermore if Hviid were to find an association between Thimerosal and autism, SSI, with which he and his center are affiliated, would then face significant lawsuits. These facts are important and are critical when evaluating Dr. Hviid's work. Furthermore, this study looked at autism and not at neurodevelopmental disorders.

The important thing in evaluating this study is that exposure in the Danish population to Thimerosal varied considerably from that in the United States. Danish children received 75 micrograms of mercury in their rust 9 weeks of life and then another 50 micrograms at 10 months. By comparison, children in the United States received 187.5 micrograms of mercury by the age of 6 months, nearly 2 1/2 times as much mercury as the Danish population.

Dr. Boyd Haley has said that comparing the exposure of the U.S. children to these children in Denmark is like comparing apples and cows. I think there is a lot of truth to that. Hviid states that the rate of autism went up after they began removing Thimerosal from vaccines in 1992. The numbers in Hviid's study were skewed in that they began to add outpatient autism diagnoses after 1992.

I do not believe how they can use a Danish study as a valid conclusion to say that thimerosal did

not cause the increase in autism and other autism spectrum disorders and neurodevelopmental disorders in the United States even children in the United States received significantly more mercury exposure.

Another study that the Institute of Medicine relied on was the Madsen study. Madsen et al., once again examined virtually the same population, Danish children, Danish children who received significantly less than they. Let us consider the conflicts of interest in the Madsen study. First of all, two of Madsen's coauthors are employed by the same Staten Serum Institute. The study, like Hviid, added outpatient cases into the number of cases of autism after 1995, a methodological flaw. The authors acknowledged that this addition might have exaggerated the incidence of autism after the removal of autism. The IOM acknowledged this but yet used the data anyway.

Another study that the IOM relied on, the Stehr-Green study, examined, guess what, the Danish population again, along with the Swedish population. I will not repeat the problems with the Danish data, but with regard to Sweden it is important to note that the children there received even less thimerosal than children in Denmark, receiving only 75 micrograms by 2 years of age versus children in the United States receiving 197.5 micrograms by 6 months of age.

Furthermore, the authors included only inpatient autism diagnoses in the Swedish population The IOM notes that the ecological nature of this data "limits the study's contribution to causality," but they cite it anyway.

The Miller study also included in the IOM report examines the population of children in the United Kingdom. This study is still unpublished, which limits its ability to be . . .

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I believe that the CDC's conclusion and the Institute of Medicine's conclusion on the MMR is well flawed. I am pleased that finally attempts is underway to duplicate Dr. Wakefield's findings, and hopefully we can get some answers to these questions regarding the safety of the measles-mumps-rubella vaccine.

For the reasons that I have outlined above and other reasons, the Institute of Medicine report I believe is premature, perilously reliant on epidemiology, based on preliminary and incomplete information, and I believe may ultimately be repudiated perhaps in short order. This report will not deter me nor the autism community from our commitment to see that thimerosal and MMR research is properly done. This report will do nothing to put to rest the concerns of parents who believe their children were harmed by mercury-containing vaccines or the MMR vaccine. While this report will lead many clinicians to believe that thimerosal is safe and there are no problems with the MMR, it may contribute further to an erosion of the doctor/patient relationship in the United States.

This report has dragged the Institute of Medicine under a cloud of controversy that has currently engulfed the CDC. Much like the infamous 1989 study by the National Institute . . .

(End of written statement provided to the ACIP).